22/1

PSYCHOPHARMACOLOGY BULLETIN

NATIONAL INSTITUTE OF MENTAL HEALTH

LD [redacted] C
U.S. DOCUMENTS
NEWARK PUBLIC LIBRARY

ECDEU

1960 25 Years 1985

NCDEU

1986
Vol. 22, No. 1

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

HE 20.8109:

Editor-in-Chief:

Nina R. Schooler, Ph.D.
NIMH, Rockville, Md.

Special Features Editor:

Allen Raskin, Ph.D.
Lafayette Clinic, Wayne State University
Detroit, Mich.

Managing Editor:

Lilian Altman
NIMH, Rockville, Md.

Associate Editors:

Jonathan O. Cole, M.D.
McLean Hospital, Belmont, Mass.

Seymour Fisher, Ph.D.
University of Texas Medical Center
Galveston, Texas

Arnold J. Friedhoff, M.D.
New York University School of Medicine

Gerald L. Klerman, M.D.
Cornell University Medical Center, New York

David J. Kupfer, M.D.
Western Psychiatric Institute & Clinic
University of Pittsburgh School of Medicine

Judith L. Rapoport, M.D.
NIMH, Bethesda, Md.

Donald S. Robinson, M.D.
Bristol-Myers Pharmaceuticals
Wallingford, Conn.

The *Psychopharmacology Bulletin* is prepared by the Division of Clinical Research of the National Institute of Mental Health. Its purpose is to facilitate the dissemination and exchange of information among the national and international scientific community. This emphasis is on rapid, informal reporting of work which has not appeared in the more formal literature. In accordance with new policy set forth by our Associate Editors, we are no longer accepting unsolicited papers for publication in the *Bulletin*.

All material published in the *Psychopharmacology Bulletin* is in the public domain unless otherwise noted. Publication in the *Bulletin* therefore does not preclude publication elsewhere.

VOL. 22, NO. 1

1986

PSYCHOPHARMACOLOGY BULLETIN

NEWARK PUBLIC LIBRARY
MAY 1 9 1986
U. S. GOVT. PUBS.
DEPOSITORY 378

Table of Contents

Annual NCDEU Meeting (1985)—Abridged Proceedings

3 **The ECDEU-NCDEU Program**—*Jonathan O. Cole*

Re-Updates: New Perspectives on Long-Standing Issues—

7 Problems With and Promises of Monoamine Oxidase Inhibitors—*Donald F. Klein and Frederic M. Quitkin*

12 New Perspectives on Long-Standing Issues: The Monoamine Oxidase Inhibitors—*Donald S. Robinson*

16 Discussion on the Monoamine Oxidase Inhibitors—*Burtrum C. Schiele*

19 Use of Placebo in Clinical Trials—*Karl Rickels*

25 Scientific and Ethical Considerations in the Use of Placebo Controls in Clinical Trials in Psychopharmacology—*Gerald L. Klerman*

30 The Placebo Control in Clinical Trials (A View From the FDA)—*Paul Leber*

33 Pharmacological Treatments of Schizophrenia—*George M. Simpson*

36 Research Methodology and the Pharmacotherapy of the Chronic Schizophrenias—*Thomas A. Ban, William Guy, and W.H. Wilson*

42 Discussion of Dr. George Simpson's Paper on Pharmacological Treatments of Schizophrenia—*Solomon C. Goldberg*

Multicenter International Clinical Trials—

45 Introduction—*Thomas A. Ban and Jerome Levine*

47 The AMDP System in International Clinical Trials—*B. Woggon, M. Linden, H. Beckmann, E. Krebs, B. Küfferle, B. Müller-Oerlinghausen, B. Pflug, and H.W. Schied*

52 Use of a Standardized Documentation System (BLIPS/BDP) in the Conduct of a Multicenter International Trial Comparing Fluvoxamine, Imipramine, and Placebo—*Giovanni B. Cassano, Luciano Conti, Gabriele Massimetti, Francesco Mengali, Jenifer S. Waekelin, and Jerome Levine*

59 The Design and Conduct of the Upjohn Cross-National Collaborative Panic Study—*Gerald L. Klerman, James H. Coleman, and Robert P. Purpura*

Microcomputers in Clinical Psychopharmacology

65 Why a Statistical Package on a Micro?—*MaryAnn Hill*

73 Microcomputerized Testing of Drug Effects on Divided Attention—*Joe E. Thornton, Joy L. Taylor, Elizabeth L. Gibson, Terry P. Miller, and Jared R. Tinklenberg*

Benzodiazepines—New Indications—

77 The Use of Benzodiazepines for Psychotic Disorders: A Literature Review and Preliminary Clinical Findings—*George W. Arana, Marjorie L. Ornsteen, Fred Kanter, H. L. Friedman, David J. Greenblatt, and Richard I. Shader*

88 New Strategies for the Treatment of Alcohol Withdrawal—*E.M. Sellers and C.A. Naranjo*

93 Benzodiazepines for Treatment of Panic Attacks: A New Look—*Karl Rickels and Edward E. Schweizer*

Cholinergic Mechanisms in the Treatment of Geriatric Disorders—

101 Physostigmine in Patients with Alzheimer's Disease—*Michael Davidson, Richard C. Mohs, Eric Hollander, Bonnie M. Davis, Theresa Ryan, Thomas B. Horvath, and Kenneth L. Davis*

106 Intercranial Drug Administration in Alzheimer's Disease—*Robert E. Harbaugh*

110 The Cholinergic Hypothesis of Memory Dysfunction in Alzheimer's Disease—Revisited—*Nunzio Pomara and Michael Stanley*

Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia—

119 Ceruletide for Schizophrenia: A Review—*Jeffrey A. Mattes, William Hom, and Joseph M. Rochford*

123 Clinical Evaluation of Ceruletide in Schizophrenia: A Multi-Institutional Cooperative Double-Blind Controlled Study—*Hitoshi Itoh, Yasuo Shimazono, Yukio Kawakita, Yoshio Kudo, Yorio Satoh, and Ryo Takahashi*

129 Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia—*Carol A. Tamminga, Robert L. Littman, and Larry D. Alphs*

Fenfluramine Therapy for Autism: Promise and Precaution—

133 Fenfluramine Treatment of Autism: UCLA Collaborative Study of 81 Patients at Nine Medical Centers—*Edward R. Ritvo, B. J. Freeman, Arthur Yuwiler, Edward Geller, Phillip Schroth, Alice Yokota, Anne Mason-Brothers, Gerald J. August, William Klykylo, Bennett Leventhal, Kay Lewis, Leonard Piggott, George Realmuto, E. Gene Stubbs, and Richard Umansky*

141 Short-Term Efficacy and Safety of Fenfluramine in Hospitalized Preschool-Age Autistic Children: An Open Study—*Magda Campbell, Stephen I. Deutsch, Richard Perry, Barbara B. Wolsky, and Michael Palij*

148 Fenfluramine: Neurotoxicity—*Charles R. Schuster, Marilyn Lewis, and Lewis S. Seiden*

152 Fenfluramine Treatment of Childhood Attention Deficit Disorder With Hyperactivity: A Preliminary Report—*Maureen Donnelly, Judith L. Rapoport, and Deborah R. Ismond*

155 The Effects of Fenfluramine on Suicidal Behavior—*Elaine Meyendorff, Anil Jain, Lil Traskman-Bendz, Barbara Stanley, and Michael Stanley*

Free Communications—Session A—

161 The Relationship of Antiobsessional and Antidepressant Effects of Tricyclic Antidepressants—*Matig Mavissakalian, Samuel M. Turner, Larry Michelson, and Rolf Jacob*

167 A Comparison of Alprazolam and Imipramine in the Treatment of Agoraphobia and Panic Disorder—*Ross Rizley, Richard J. Kahn, Douglas M. McNair, and Laura M. Frankenthaler*

173 Taper Withdrawal Studies With Alprazolam in Patients With Panic Disorder and Agoraphobia—*John C. Pecknold and Richard P. Swinson*

177 Amitriptyline and Haloperidol in Unstable and Schizotypal Borderline Disorders—*Paul H. Soloff, Anselm George, Swami Nathan, Patricia M. Schulz, Richard F. Ulrich, and James M. Perel*

183 Open Trial of Buspirone in the Treatment of Major Depressive Disorder—*Edward E. Schweizer, Jay Amsterdam, Karl Rickels, Myron Kaplan, and Marian Droba*

186 A Review of Controlled Studies of Adinazolam Mesylate in Patients With Major Depressive Disorder—*John P. Feighner*

192 Chronic Depression: Demographic and Clinical Characteristics—*James H. Kocsis, Carlyle Voss, J. John Mann, and Allen Frances*

196 Self-Rating of Personality Characteristics and Their Relationship to Treatment Response in Recurrent Unipolar Depressives: A Pilot Study—*Ellen Frank, David J. Kupfer, David B. Jarrett, and Miriam Jacob*

200 The Suicide Assessment Scale: A Scale Evaluating Change in Suicidal Behavior—*Barbara Stanley, Lil Träskman-Bendz, and Michael Stanley*

206 A Retrospective Clinical Analysis of the Overall-Rhoades Classification of Hamilton Depression Scale Profiles—*Robert H. Lenox, Lelon A. Weaver, James E. Shipley, and Stephen Cohen*

214 Understanding the Response Lag to Tricyclics: I. Application of Pulse-Loading Regimens With Intravenous Clomipramine—*Bruce G. Pollock, James M. Perel, Michael Shostak, Seymour Antelman, Barbara Brandom, and David J. Kupfer*

220 Pharmacology of Combined Antidepressant/H_2-Blocking Drug Therapy—*Stephen H. Curry, C. Lindsay DeVane, and M. Michael Wolfe*

Free Communications—Session B—

223 Methylphenidate: Rate-Dependent Effects on Hyperactivity—*Mark D. Rapport and George J. DuPaul*

229 The Therapeutic Effect of Clonidine in Attention Deficit Disorder with Hyperactivity: A Comparison With Placebo and Methylphenidate—*Robert D. Hunt, Ruud B. Minderaa, and Donald J. Cohen*

237 The Use of MK-801, a Novel Sympathomimetic, in Adults with Attention Deficit Disorder, Residual Type—*Fred W. Reimherr, David R. Wood, and Paul H. Wender*

243 The Prevalence of Tardive Dyskinesia in a Mentally Retarded Population—*Mary Ann Richardson, Gary Haugland, Raymond Pass, and Thomas J. Craig*

250 Neuroleptic-Induced Tardive Dyskinesia and Parkinsonism: Changes During Several Years of Continuing Treatment—*Daniel E. Casey, Uffe J. Povlsen, Birgit Meidahl, and Jes Gerlach*

254 Integrating Incidence and Prevalence of Tardive Dyskinesia—*John M. Kane, Margaret Woerner, Michael Borenstein, James Wegner, and Jeffrey Lieberman*

259 A Five-Year Follow-Up Study of Tardive Dyskinesia—*Guy Chouinard, Lawrence Annable, Pierre Mercier, and Andree Ross-Chouinard*

264 Plasma Fluphenazine Levels in Patients Receiving Two Doses of Fluphenazine Decanoate—*Stephen R. Marder, John W. Hubbard, Theodore Van Putten, Edward M. Hawes, Gordon McKay, Jim Mintz, Philip R.A. May, and Kamal K. Midha*

267 An Early Phase II Clinical Trial of Remoxipride in Schizophrenia With Measurement of Plasma Neuroleptic Activity—*Guy Chouinard and L. Turnier*

272 Measuring Adverse Drug Reactions in a Postmarketing Surveillance System—*Seymour Fisher, Stephen G. Bryant, and Ronica M. Kluge*

278 Estazolam in the Treatment of Insomnia—*Roberto A. Dominguez, Burton J. Goldstein, Alan F. Jacobson, and Richard M. Steinbook*

NCDEU Workshop/Microcomputer Interest Group—

281 Microcomputer Database Management Systems Concepts—*David Robert Gastfriend*

287 SAFTEE: Data System for Side Effect Assessment Scale—*Dean J. Clyde*

288 Microprocessor-Based Assessment of Attention Deficit Disorders (ADD)—*Michael Gordon*

291 A Microcomputer-Based Psychophysiology Data Acquisition and Analysis System—*C. Keith Conners, Roy Clymer, and Robert S. Sherrick*

297 A Brain Function Diagnostic and Study Unit for Psychotropic Drug Development and Psychopharmacology Research—*Turan M. Itil, Donald M. Shapiro, Emin Eralp, Ahmet Akman, and Kurt Z. Itil*

301 BMDPC: BMDP Statistical Software for Microcomputers—*MaryAnn Hill*

307 Communications: Microcomputer/Mainframe Interfacing—*Pierre Mercier*

311 Expert Systems in Psychiatry—*Michael Feinberg and Robert K. Lindsay*

317 **Cumulative Index—Psychopharmacology Bulletin—1985—**

Contents Index

Authors Index

B-1 **Psychopharmacology—A Recurring Bibliography—**

Announcements

Allen Raskin, Ph.D., Editor-in-Chief of the *Psychopharmacology Bulletin* since October 1980, has left the National Institute of Mental Health (NIMH) to become Director of the Psychology Division of Lafayette Clinic and Professor of Psychiatry at Wayne State University in Detroit, Michigan. As indicated in the masthead, he will continue his association with the *Bulletin* as "Special Features Editor."

* * *

The new Editor-in-Chief of the *Bulletin* is Nina R. Schooler, Ph.D., who has been a member of the NIMH staff active in both research and administration in psychopharmacology since 1965. In addition to her position of Editor-in-Chief of the *Bulletin*, Dr. Schooler is also Coordinator for Pharmacologic and Somatic Treatments Research and Assistant Chief of the Schizophrenia Research Branch of NIMH.

* * *

We are pleased to announce that the *Psychopharmacology Bulletin* is now being indexed and abstracted by Excerpta Medica.

* * *

ERRATUM

On page 611 of Vol. 21, No. 3, 1985, the second paragraph under *Methods* reads: "For atenolol, patients first received placebo for a week . . ." There was no placebo week, therefore it should read as follows: "Patients were simply started on atenolol, 50 mg/day. If not improved in 1 week, dosage was raised to 100 mg/day." We regret the error.

Annual NCDEU Meeting (1985)—Abridged Proceedings

The annual meeting of the New Clinical Drug Evaluation Unit (NCDEU) program of the Pharmacologic and Somatic Treatments Research Branch of the National Institute of Mental Health (NIMH) took place on May 1–4, 1985, in Key Biscayne, Florida. The program was developed by the staff of the Branch, Nina R. Schooler, Acting Chief, Jack Blaine, Robert Prien, Allen Raskin, Natalie Reatig, Joanne Severe, and Jerome Levine, former Chief of the Branch.

This was the 25th anniversary meeting of the NCDEU program. The program was established in 1959 by the NIMH as the Early Clinical Drug Evaluation Unit (ECDEU) program with 15 grantees. As described below by Jonathan Cole, the early "invitation-only" meetings for these grant-supported investigators developed into the current format of planned symposia and free communications. Sessions focus on recent research findings in psychopharmacology, methodologic problems and advances in clinical trials in this area, and updates or reviews of significant issues in the field.

The 1985 meeting had 340 attendees including 20 from countries other than the United States.

As in previous years, the Winter issue of the *Bulletin* is devoted to summaries of papers presented at the NCDEU meeting. These summaries are designed to provide early availability of the substance of the meeting to *Bulletin* readers. Publication in the *Bulletin* does not prejudice formal publication of the full papers elsewhere at a later time.

The ECDEU-NCDEU Program

Jonathan O. Cole, M.D.[1]

The New Clinical Drug Evaluation Unit (NCDEU) program had its beginning in the early days of modern clinical psychopharmacology when chlorpromazine was still controversial and psychoanalysis was still more popular and accepted than drug therapy. The National Institute of Mental Health (NIMH) had, perhaps slightly reluctantly, recognized that chlorpromazine and reserpine might be effective unique therapies and used its intramural group, led by Dr. Seymour Kety, to develop a special grant to support an evaluation of the new drugs. A major conference was developed by Dr. Ralph Gerard, then of the University of Illinois Medical School via the National Academy of Sciences (NAS), and I was the NAS staff member who did most of the leg work. The conference was held at the Statler Hotel in Washington, D.C., in September 1956 and eventually published in book form as *Psychopharmacology: Problems in Evaluation*.

About the same time, Dr. Nathan S. Kline and Mike Gorman testified to congressional appropriations committees demanding that the NIMH be given two million dollars a year in grant money to finance a multi-hospital collaborative study of drug efficacy in psychiatry. The NIMH reluctantly accepted the extra money and I was hired to run the new program, I believe because no more senior or distinguished individual was available or interested. The Psychopharmacology Service Center was created and staffed, in its early

---

[1] McLean Hospital, Belmont, MA 02178.

years, by Sherman Ross, Dean Clyde, Lorraine Bouthillet, Seymour Fisher, and Sol Goldberg. Gerald Klerman came on board for 2 years to help mount the original nine-hospital collaborative study of phenothiazines in acute schizophrenia.

In those days the Program had the unique problem of having more money than it could spend. For a number of years the team of Kline and Gorman would urge Congress to appropriate still more money earmarked for research in psychopharmacology, and the NIMH administration would very reluctantly acquiesce and accept the new money. All the NIMH grant programs were rich and, believe it or not, the Mental Health Council would specially review the grants with the *lowest* 10% of the assigned priority scores to decide whether they, too, should be paid!

In this fiscal climate it was possible to propose and actually do large-scale collaborative studies, fund a major data analysis and computer facility to handle the data, and consider open-ended program support for early clinical drug evaluation units (ECDEUs).

The initial ECDEU program was designed to provide stable funding for investigators studying new drugs. Many investigators had programs functioning on fitful drug company grants and some state or Veterans Administration money. The Program was intended to provide core support for key staff and allow some kinds of research not possible on drug company money alone.

The Program was approved and advertised; eventually up to 18 such grants were funded. I believe Leo Hollister and Karl Rickels are the only Principal Investigators whose support has continued uninterrupted since the beginning of the Program. As time went by and research became more sophisticated and money got tighter, it became harder and harder for investigators to get continued support for straight-forward clinical trials of various and often unspecifiable new drugs. As review committees became more restrictive the ECDEU grant program, as originally conceived, gradually died a natural death.

However, the ECDEU meetings developed a life of their own. The meetings originally were designed to bring ECDEU grantees together with NIMH staff once or twice a year to discuss drugs they had been studying, to present data, and to compare impressions. Drug company representatives were originally excluded from the meetings entirely or invited in only when their drug was being discussed. Then there developed a second, open phase of the meeting at which drug company staff were allowed in. Gradually the meetings became totally open. Investigators who had lost grant support continued to attend, and gradually any interested investigator was welcome. The Food and Drug Administration (FDA) sent representatives, and foreign investigators often attended; two original ECDEU grantees were David Wheatley of the United Kingdom and Pierre Deniker of France. I believe the availability of this site in Key Biscayne and Burton Goldstein's willingness to continue as a semi-permanent arrangements committee, and the NIMH staff's availability as a secretariat, and the *Psychopharmacology Bulletin's* availability as a publication outlet, have all kept the meetings interesting, friendly, and productive. Jerry Levine, Nina Schooler, Allen Raskin, and Robert Prien, among others, have done a lot to keep the NCDEU meetings alive and well. They are a unique forum, more open and flexible than the American College of Neuropsychopharmacology, where investigators can exchange communications formally and informally with each other, drug company staff, and FDA staff.

The only comparable series of meetings I know of in medical research are those sponsored now by the Committee on Problems of Drug Dependence (CPDD). They go back well into the 1930's and also are attended by a mix of clinical investigators, basic scientists, drug company investigators and monitors, FDA staff, and foreign workers. Whether my early involvement with this drug abuse and analgesic testing group, then at the NAS, was influential in shaping the present NCDEU program, I cannot tell. If it was, we owe a debt to Dr. Nathan Eddy who essentially ran the CPDD program single handed for many years. He even raised money from drug companies to support free grants made by the NAS, now the CPDD, to investigators to carry out drug screening and clinical trials not committed to any particular company's drug. If federal funds continue to decrease and the drug companies to prosper, the NCDEU program could even end up trying this approach to the funding of some kinds of clinical drug studies.

In any event, I have always enjoyed and learned from NCDEU meetings. If I am partly responsible for the development of this unique and excellent program, I'm very glad. The real credit, obviously, belongs to all the participants over the years. I hope the programs are still as interesting and productive 20 years from now.

Re-Updates: New Perspectives on Long-Standing Issues

CHAIR: Robert F. Prien, Ph.D.
Pharmacologic and Somatic Treatments
Research Branch, NIMH
Rockville, Maryland

Problems With and Promises of Monoamine Oxidase Inhibitors[1]

Donald F. Klein, M.D.,[2] and Frederic M. Quitkin, M.D.[2]

We have been asked to discuss the past history of the use of monoamine oxidase inhibitors (MAOIs), the reason for the recent resurgence in interest, and the range of their demonstrated and possible clinical utility.

What are the characteristics that make for a desirable class of drugs that will incite both clinical investigation and application? A partial list would include the following:

They should be safe, especially from irreversible major side effects, such as stroke or hepatic necrosis.

Their lack of safety should not be made dramatically manifest by their being recalled from the market by the Food and Drug Administration (FDA) for deadly side effects, as occurred with tranylcypromine and iproniazid.

They should lack a wide variety of upsetting, even though reversible, side effects, such as orthostatic hypotension, insomnia, anorgasmia, erectile impairment, weight gain, and hypomania.

They should be easily explained to patients without incurring anxiety over potential catastrophies.

They should require no great modification in the patient's normal life processes. Therefore, they should not require that the patient be on a markedly modified diet.

There should be no threat of dangerous drug interactions.

There should be very clear guidelines as to just what foods or concurrent drugs incur what degree of risk.

There should be no class of drugs, such as the tricyclic antidepressants (TCAs), that are believed to be both safer and more effective for the same class of indications.

Finally, the pharmaceutical industry should believe that an investment in these agents may result in a substantial market penetration with a degree of profit which will make their efforts, in supporting clinical investigation and clinical use, profitable.

From the 1960's through the early 1970's the MAOIs failed by every one of these criteria and were generally considered both ineffective and dangerous. Therefore, they were shunned by both investigators and physicians.

We now know that the early research was flawed, primarily by low dose and inappropriate patient samples. We refer to this as a Phase II deficiency. Unfortunately, many pharmaceutical companies do not realize that controlled trials should be preceded by care-

---

[1] This study was supported in part by USPHS Grants MH-30906 and MH-39143-01 from the National Institute of Mental Health.

[2] New York State Psychiatric Institute, New York, NY 10032.

ful study of dose ranging, latency of onset of therapeutic effect, management of toxicity, and identification of patient types responsive to the drug being studied. Neglect of these essential steps has resulted in the history of psychopharmacology being marred by the frequent release of agents at doses far too low to be generally effective and prescribed for trials of inadequate length (Quitkin et al., 1984). Unfortunately, there are no systematic guidelines to determine the necessary information before proceeding to the design of double-blind, controlled randomized trials. Shortening the time to New Drug Application approval and, therefore, lengthening the time of profitable return is often the motivation for rushing to Phase III. Unfortunately, such a rush often proves shortsighted and poor economy since inadequate Phase III studies are the outcome.

With regard to inappropriate patient samples, the widely quoted Greenblatt et al. study (1964) was generally understood to indicate that isocarboxazid (Marplan) was actually worse than placebo and that phenelzine was equal to placebo. However, this state hospital-based study did not even show imipramine to be effective. Further, in the subgroup of neurotic depressives, phenelzine was 100% effective but, since placebo was 86% effective, the drug could not demonstrate specific benefits in this inappropriate population.

A few English psychiatrists held the fort by claiming specific superiority for the MAOIs over the TCAs for a subgroup of patients they referred to as atypical depressives (Sargant, 1960, 1961; West & Dally, 1959). These patients were primarily described as having non-autonomous mood disorder associated with high levels of anxiety, hyperphagia, and hypersomnia.

In 1969, Klein described a group of patients referred to as hysteroid dysphorics. These patients are characterized by flamboyance, seductiveness, and marked vulnerability to interpersonal rejection, with dramatic crashes in mood associated with leaden paralysis, retreating to bed, and often hypersomnia and hyperphagia (Klein & Davis, 1969). This depression was, however, responsive to positive social input, such as a new boyfriend. The description of this syndrome was important because it focused attention on pathologic rejection sensitivity as a predictor of beneficial effect from MAOI. This work also suggests that some aspects of psychopathology, historically attributed to personality or character disorders, may be a manifestation of an affective disorder, and responsive to antidepressants. Unfortunately, neither the English psychiatrists nor Klein (until recently) conducted any systematic comparative trials contrasting MAOIs and TCAs in the management of such patients.

The entire field was essentially turned around by the work of Robinson, Ravaris, Nies, and co-workers (1973, 1974, 1976, 1978a,b; Ravaris et al., 1976). This team focused clearly and definitively upon the question of dosage adequacy, and identified inhibition of platelet MAO as an objective indicator of dose effectiveness.

In 1973, they published an outpatient trial using 60 mg of phenelzine versus placebo, indicating the drug was effective, safe, and well accepted (Robinson et al., 1973). In 1976 they drove the point home in a comparative study of placebo, 30 mg and 60 mg of phenelzine indicating that 30 mg was no more effective than placebo, whereas 60 mg was substantially superior to both 30 mg and placebo (Ravaris et al., 1976).

These findings made more understandable the negative report of a large study published in 1974 that had used a maximum dose of 45 mg of phenelzine (Raskin et al., 1974). In 1977 there was another positive report by Mountjoy in the English literature of the benefits of 75 mg per day of phenelzine (Mountjoy et al., 1977).

In 1979, Quitkin et al. wrote a detailed critical review of the MAOI literature that summed up the persuasive evidence for their effectiveness in what were usually referred to as neurotic depressives and even the possible benefit of these agents for endogenous depression.

The identification of subtypes of depressives who selectively benefited from MAOIs or TCAs was approached by several investigators, the most prominent being Paykel and Robinson (Robinson et al., 1981; Rowan et al., 1982). Both investigators, in a heterogenous group of outpatients, compared MAOIs, TCAs, and placebo. They found similar overall efficacy for both drugs without very much in the way of predictors of specific efficacy. This was somewhat disheartening but was consistent with the failure of statistical methodology to identify specific drug responsive subgroups from heterogeneous groups of patients.

On moving to Columbia University in 1976, Fred Quitkin, of our group, developed a Depression Evaluation Service and promptly noted that a substantial proportion of our patients fit the criteria for atypical depression. We formalized these criteria emphasizing the essential role of non-autonomous mood disturbance associated with two of four frequently associated symptoms: hyperphagia, hypersomnia, leaden paralysis, and rejection sensitivity. This prospective study comparing phenelzine, imipramine, and placebo has been underway for some years now. It includes the efforts of a large team, in particular Fred Quitkin, Mike Liebowitz, Pat McGrath, Jonathan Stewart, Judy Rabkin, and Wilma Harrison (Liebowitz et al., 1984).

In 1981, Raft and Davidson studied a small sample of depressed patients derived from a pain clinic, and showed the superiority of phenelzine to amitryptyline and the superiority of amitryptyline to placebo (Raft et al., 1981). One conceivable drawback to this study was that it was not clear whether some of the patients might have already proven refractory to tricyclic treatment.

The first report of our effort was published in 1984 on a sample of 60 patients showing, as we had hoped, that phenelzine was indeed superior to imipramine which was superior to placebo (Liebowitz et al., 1984). Sub-analysis of these groups indicated the marked superiority of phenelzine for those considered hysteroid dysphorics and also for those who had a history of panic attacks. The relevance of a history of panic attacks to phenelzine superiority was promptly affirmed by Robinson et al. (1985). We are currently analyzing the data on 120 such patients, and our previous findings hold up well.

One major question is: just what are the boundaries of the atypical depressive syndrome? Our decision to require two out of four associated symptoms was quite arbitrary. As our study progressed, we found patients who only had one or even no associated vegetative atypical symptoms and simply manifested a non-autonomous mood disturbance. We entered these patients, also, along separate tracks, into our randomized trials.

Current analyses of the data revealed similar patterns of medication response. Patients with non-autonomous mood disturbance and any of the four atypical features appear to do better on MAOI, but patients with non-autonomous mood and no atypical features did equally well on a TCA or MAOI (Quitkin et al., 1984). These analyses should be considered preliminary.

Other syndromes also share some resemblance to atypical depression. Tim Walsh, who had been studying bulimics in collaboration with Jonathan Stewart of our Depression Evaluation Service, had developed a double-blind, placebo-controlled trial on phenelzine in bulimics that seemed to indicate that phenelzine is an excellent, at least short-term, treatment for bulimia (Stewart et al., 1984; Walsh et al., 1984).

The marked rejection sensitivity of atypical depressives calls to mind the tremendous fears of humiliation and social scorn present in social phobics and, after promising preliminary studies, Mike Liebowitz is now embarked on a placebo-controlled, double-blind trial contrasting phenelzine, atenolol, and placebo in social phobics.

An important heuristic question is whether the MAOI benefit is limited to patients with non-autonomous mood disorder. Pat McGrath of our Depression Evaluation Service has conducted two small open trials on phenelzine and tranylcypromine in outpatient melancholics. These patients had approximately a 75% response rate (McGrath et al., 1984). In other trials, this patient group had placebo response rates of less than 20%. Clearly, a controlled trial is indicated in this group, also.

There are many questions that remain to be answered. Even such simple issues such as whether tranylcypromine has different effects from phenelzine has not received investigative attention. More complex are the heuristic implications raised by the development of specific inhibitors for MAO A and MAO B (Knoll, 1984). A close reading of the literature indicates that the effect of clorgyline is not clearly established (McGrath & Klein, in press). This is somewhat surprising, considering that this drug has its major effects on just those neurotransmitters that are usually considered central to depressive illness. On the other hand, in a pilot study, deprenyl appears effective in atypical depressives (Quitkin et al., 1984). This drug is now being studied in a controlled trial.

On the horizon is a new class of reversible MAOIs. How they will help our patients and our science is quite unclear to date.

Many of our patients are chronic, dating their illness from adolescence. Can their chronic, dysthymic state be reversed by prolonged MAOI treatment? Do they require chronic maintenance treatment with MAOIs or can their improved state be maintained following drug cessation? Quitkin is pursuing this issue, which has substantial public health importance, in a double-blind discontinuation trial.

To sum up, we seem to be entering a burgeoning period of MAOI research and application. That these useful agents should have been ignored for so long is an unfortunate testimonial to the peculiarities of our profit-oriented drug development system and, in particular, the problems created by Phase II failures of adequate assessment.

References

Greenblatt, M., Grosser, G.H., and Wechsler, H. Differential response of hospitalized depressed patients to somatic therapy. *Am. J. Psychiatry*, 120:935–943, 1964.

Klein, D.F., and Davis, J.M. *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore: Williams & Wilkins Co., 1969.

Knoll, J. Deprenyl (selegiline): The history of its development and pharmacologic action. *Acta Neurol. Scand.* (Suppl.), 95:57–80, 1983.

Liebowitz, M.R., Quitkin, F.M., Stewart, J.W., et al. Phenelzine versus imipramine in atypical depression: A preliminary report. *Arch. Gen. Psychiatry*, 41:669–677, 1984.

McGrath, P.J., and Klein, D.F. Heuristically important mood altering drugs. Position paper. Dahlen Conference, Berlin, October 1982. (In press)

McGrath, P.J., Quitkin, F.M., Harrison, W., and Stewart, J.W. Treatment of melancholia with tranylcypromine. *Am. J. Psychiatry*, 141:288–289, 1984.

Mountjoy, M., Roth, R.F., Garside, G., et al. A clinical trial of phenelzine in anxiety depressive and phobic neuroses. *Br. J. Psychiatry*, 131:486–492, 1977.

Quitkin, F.M., Harrison, W., Liebowitz, M., et al. Defining the boundaries of atypical depression. *J. Clin. Psychiatry*, 45:19–21, 1984.

Quitkin, F.M., Liebowitz, M.R., Stewart, J.W., et al. L-Deprenyl in atypical depressives. *Arch. Gen. Psychiatry*, 41:777–781, 1984.

Quitkin, F.M., Rabkin, J.G., Ross, D., and McGrath, P.J. Duration of antidepressant drug treatment: What is an adequate trial? *Arch. Gen. Psychiatry*, 41:238–245, 1984.

Quitkin, F.M., Rifkin, A.E., and Klein, D.F. Monoamine oxidase inhibitors: A review of antidepressant effectiveness. *Arch. Gen. Psychiatry*, 36:749–760, 1979.

Raft, D., Davidson, J., Wasik, J., and Mattox, A. Relationship between response to phenelzine and MAO inhibition in a clinical trial of phenelzine, amitriptyline, and placebo. *Neuropsychobiology*, 7:122–126, 1981.

Raskin, A., Schulterbrandt, J.G., Reatig, N., et al. Depression subtypes and response to phenelzine, diazepam, and a placebo. *Arch. Gen. Psychiatry*, 3:66–75, 1974.

Ravaris, C.L., Nies, A., Robinson, D.S., et al. A multiple-dose controlled study of phenelzine in depression-anxiety states. *Arch. Gen. Psychiatry*, 33:347–350, 1976.

Robinson, D.S., Kayser, A., Corcella, J., et al. Panic attacks in outpatients with depression: Response to antidepressant treatment. *Psychopharmacol. Bull.*, 21(3):562–567, 1985.

Robinson, D.S., Nies, A., Corcella, J., and Cooper, T.B. MAO inhibitors, new biochemical and clinical findings. *Psychopharmacol. Bull.*, 17(3):154–157, 1981.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. The monoamine oxidase inhibitor, phenelzine, in the treatment of depressive-anxiety states. *Arch. Gen. Psychiatry*, 29:407–413, 1973.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Treatment response to MAO inhibitors: Relation to depressive typology and blood platelet MAO inhibition. In: *Classification and Prediction of Outcome of Depression*, Vol. 8. Symposia Medica Hoechst, Stuttgart, West Germany: F.K. Schattauer Verlag, 1974, pp. 259–267.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Clinical pharmacology of phenelzine: MAO activity and clinical response. In: Lipton, M., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978a.

Robinson, D., Nies, A., Ravaris, C., et al. Clinical pharmacology of phenelzine. *Arch. Gen. Psychiatry*, 35:629–635, 1978b.

Rowan, P., Paykel, E.S., and Parker, R.R. Phenelzine and amitriptyline: Effects on symptoms of neurotic depression. *Br. J. Psychiatry*, 140:475–483, 1982.

Sargant, W. Some newer drugs in the treatment of depression and their relation to other somatic treatments. *Psychosomatics*, 1:14–17, 1960.

Sargant, W. Drugs in the treatment of depression. *Br. Med. J.*, 1:225–227, 1961.

Stewart, J., Walsh, B.T., Wright, R.M., et al. An open trial of MAO inhibitors in bulimia. *J. Clin. Psychiatry*, 45:217–219, 1984.

Walsh, B.T., Stewart, J.W., Roose, S.P., et al. Treatment of bulimia with phenelzine. *Arch. Gen. Psychiatry*, 41:1105–1109, 1984.

West, E.D., and Dally, P.J. Effects of iproniazid in depressive syndromes. *Br. Med. J.*, 1:1491–1494, 1959.

New Perspectives on Long-Standing Issues: The Monoamine Oxidase Inhibitors[1]

Donald S. Robinson, M.D.[2]

Monoamine oxidase inhibitors (MAOIs) fell into disuse soon after their introduction into clinical practice 25 years ago. As Dr. Donald Klein points out in the preceding paper, this class of antidepressant drug was supplanted rapidly by the tricyclic antidepressants (TCAs). The MAOIs survived in limited use with a claimed specificity of therapeutic effect for what was termed "atypical depressions" based on experience from uncontrolled studies (Klein, 1969; Sargant & Dally, 1962; West & Dally, 1959). In later controlled trials other investigators (Johnstone & Marsh, 1973; Robinson et al., 1973) confirmed the therapeutic efficacy of phenelzine in the treatment of depression. Recent studies have shown the MAOI phenelzine to be as effective as the TCA amitriptyline in the treatment of depression (Paykel et al., 1980; Ravaris et al., 1980). MAOIs are also at least as effective as existing therapies for phobic and panic disorders (Sheehan et al., 1980). There is little doubt that over the past decade this class of drugs has undergone an impressive resurgence of interest.

Application of modern clinical pharmacologic methods to the study of MAOIs played a role in this recrudescence. Studies based on strict double-blind design, careful baseline evaluation and symptom ratings, with control of critical variables, is essential to clinical psychopharmacology. The importance of these principles was appreciated relatively late in this field and has contributed to conflicting claims about various psychopharmacologic treatments, including the MAOIs.

Burgeoning interest in MAOI research over the past 10 years has resulted in documentation of their effectiveness as general antidepressants. Somewhat unexpectedly, their therapeutic spectrum seems to be broader than the TCAs. Conclusive evidence now exists also for their efficacy in anxiety disorders, including panic disorder and phobic states, and atypical affective disorders such as patients with depression with hysteroid features (Kayser et al., 1985; Liebowitz et al., 1984; Quitkin et al., 1984).

The author's involvement with MAOIs began with development of an assay of *in vivo* MAO inhibition in man which permitted monitoring of the target pharmacologic effect of these drugs in platelets of treated patients (Robinson et al., 1968). This capability proved useful in the clinical pharmacologic study of these drugs, of which relatively little was known, since FDA approval preceded the 1962 amendments to the drug laws. As a consequence, most pre–1962 drugs were lacking in basic knowledge of their pharmacokinetics, therapeutic dose range, or appropriate doses in special populations such as the elderly, and hepatic or renal-impaired patients.

At the time of their approval in 1960, studies in the rat (Gey & Pletcher, 1961) and in man (Ganrot et al., 1962) demonstrated that significant degrees of brain MAO inhibition (75% or greater) were necessary to cause an increase in tissue levels of norepinephrine, serotonin, and dopamine. However, there had been little effort in clinical trials to define adequately the therapeutic dose range, and the prior studies were overlooked. In the early 1970's this led the Vermont group to examine the relationship between platelet MAO inhibition, phenelzine dose, and clinical response of depressed patients (Ravaris et al., 1976). These clinical pharmacologic studies of phenelzine provided a replication of the earlier placebo-controlled efficacy studies (Robinson et al., 1973) and established that the dose of phenelzine is critical in

---

[1] This study was supported in part by USPHS Grants MH–15533, MH–27836, MH–37617, and MH–36179 from the National Institute of Mental Health.

[2] Bristol-Myers Company, Pharmaceutical Research & Development Division, Wallingford, CT 06492.

achieving a therapeutic response. Existing labeling for phenelzine at the time called for inappropriately low doses. The lower end of the therapeutic dose range was found to be 45 mg/day. The data suggested also that the dose-response curve might not be linear. It appeared that a threshold inhibition level of at least 80% (using benzylamine as substrate) was associated with onset of therapeutic effect in depression (Ravaris et al., 1976; Robinson et al., 1978). Subsequently, dosage recommendations have been modified to be 60 to 90 mg/day for most patients.

An important question remaining to be answered is the optimal duration of treatment with an MAOI to maintain a patient in remission following treatment of an index episode. Studies are now in progress at two centers to address this critical issue. Interim results of these ongoing studies are not yet available, but there is early evidence that phenelzine treatment should be continued beyond 6 months for most patients. Selected patients with chronic or recurrent depression may require MAOI treatment for several years.

Studies have shown the optimum daily therapeutic dose of phenelzine to be approximately 1 mg/kg/body weight (Robinson et al., 1978a,b). Recent experience (Lerfald and Robinson, unpublished data) indicates that patients can be started initially at full therapeutic dosage. One would predict it should be possible to use a "loading dose" during the first week of treatment without increased risk of side effects which might accelerate the therapeutic response.

The strategy of employing a multiple fixed-dose design in Phase II studies of antidepressants is an important concept. The advantages of such designs are generation of vital dose-ranging data required for Phase III trials and clinical practice. Such dose-ranging studies, if properly designed, can also provide important efficacy data. Because of the time-consuming and expensive nature of Phase III studies, it is important to define an effective, safe dose as early as possible in the development of antidepressant drugs. Definitive, well-designed studies are key since outcome measures lack precision in psychopharmacology in comparison to many other fields of investigation, and perhaps even more critical is the temporal dissociation between initiating drug treatment, or making a dose adjustment, and the resulting therapeutic effect.

Finally, there is emerging evidence that MAOIs have specific anxiolytic effects in addition to intrinsic antidepressant activity. This possibility is supported by studies in phobic disorders (Solyom et al., 1973; Tyrer et al., 1973), depression with prominent somatic anxiety (Nies et al., 1982), depression with panic symptoms (Liebowitz et al., 1984; Robinson et al., 1985), and panic disorder (Sheehan et al., 1980). Studies by our group have shown phenelzine to have equivalent antidepressant efficacy to amitriptyline in major depression with enhanced antianxiety properties in these patients compared to the TCAs (Robinson et al., 1985). Phenelzine relieves both psychic and somatic symptoms of anxiety associated with depression.

The recent interest in serotonin as a primary neurotransmitter mediating mood and anxiety states (Peroutka & Snyder, 1980; Taylor et al., 1981) has important implications for the MAOIs. This class of drug is known to profoundly affect brain serotonin levels and to inhibit serotonergic neurotransmission (Blier & deMontigny, in press). There is increasing evidence that serotonergic systems may play a central role in modulating anxiety and tension states in conjunction with the noradrenergic systems which mediate outflow from the locus ceruleus. Anxiolytic agents, including the benzodiazepines and buspirone, share a common property of profoundly inhibiting serotonergic neurotransmission in the dorsal raphae nucleus. It is postulated that anxiety agents achieve their clinical effects by inhibiting raphae input to the septo-hippocampal system. However, buspirone, unlike the benzodiazepines, does not inhibit spontaneous firing of cells in the locus coeruleus (Sanghera et al., 1983) and actually mildly enhances noradrenergic firing. This would suggest that a decrease in serotonergic activity mediates a therapeutic anxiolytic drug effect.

An analogous situation may apply to the MAOIs which can markedly increase brain serotonin (Robinson et al., 1979) and inhibit dorsal raphae firing, in addition to their better known effects on noradrenergic systems. Current electrophysiologic and neurochemical studies may provide a basis for understanding the mechanism of action of MAOIs which probably involves a profound effect on serotonergic systems.

Summary

MAOIs are attracting intense interest, both scientifically and clinically, because of a broad spectrum of therapeutic actions. Studies support significant efficacy in the treatment of depression and anxiety disorders. Evidence from recent controlled trials, as well as clinical experience, shows MAOIs to be effective in both endogenous and nonendogenous types of major depressive disorder, atypical depression, depression with hysteroid features, and depression associated with panic attacks. In addition, MAOIs are considered to be one of the most effective treatments for panic disorder. Preliminary evidence suggests some benefit for eating disorders, social phobias, and obsessive compulsive disorder.

Relatively little is known about the need for long-term therapy with antidepressant drugs, including the MAOIs. Until the findings of ongoing studies become available, maintenance MAOI treatment should continue for a minimum of 6 months and probably longer in selected patients with chronic or recurrent depression.

At optimal dosage of phenelzine (1 mg/kg per day) an overall treatment response rate of 85 to 90% can be anticipated in major depression irrespective of subtype. Clinical pharmacology studies of antidepressant drugs can contribute to their rational use in a wide spectrum of mood and anxiety disorders.

References

Blier, P., and deMontigny, C. Serotonergic but not adrenergic neurones in rat CNS adapt to long-term treatment with monoamine oxidase inhibitors. *Neuroscience*. (In press)

Ganrot, P.O., Rosengren, E., and Gottfries, C.G. Effect of iproniazid on monoamines and monoamine oxidase in human brain. *Experientia*, 18:260–261, 1962.

Gey, K.F., and Pletcher, A. Activity of monoamine oxidase in relation to the 5-hydroxytryptamine and norepinephrine content of rat brain. *J. Neurochem.*, 6:239–243, 1961.

Johnstone, E.C., and Marsh, W. Acetylator status and response to phenelzine in depressed patients. *Lancet*, 1:567–570, 1973.

Kayser, A., Robinson, D.S., Nies, A., and Howard, D. Response to phenelzine among depressed patients with features of hysteroid dsyphoria. *Am. J. Psychiatry*, 142:486–488, 1985.

Klein, D.F., and Davis, J.M. *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore: Williams & Wilkins Co., 1969.

Liebowitz, M.R., Quitkin, F.M., Stewart, J.W., et al. Phenelzine versus imipramine in atypical depression: A preliminary report. *Arch. Gen. Psychiatry*, 41:669–677, 1984.

Nies, A., Howard, D., and Robinson, D.S. Antianxiety effects of MAO inhibitors. In: Mathew, R. (ed.), *Biology of Anxiety*, New York: Brunner/Mazel, Inc., 1982, pp. 123–133.

Paykel, E.S., Rowan, P.R., Parker, R.R., and Bhat, A.V. Response to phenelzine and amitriptyline in subtypes of outpatient depression. *Arch. Gen. Psychiatry*, 39:1041–1049, 1982.

Peroutka, S.J., and Snyder, S.H. Chronic antidepressant treatment lowers spiroperidol-labeled serotonin receptor binding. *Science*, 210:88–90, 1980.

Quitkin, F.M., Liebowitz, M.R., Stewart, J.W., et al. L-Deprenyl in atypical depressives. *Arch. Gen. Psychiatry*, 41:777–781, 1984.

Ravaris, C.L., Nies, A., Robinson, D.S., et al. A multiple-dose, controlled study of phenelzine in depression-anxiety states. *Arch. Gen. Psychiatry*, 33:347–350, 1976.

Ravaris, C.L., Robinson, D.S., Ives, J.O., et al. Phenelzine and amitriptyline in the treatment of depression. *Arch. Gen. Psychiatry*, 37:1075–1080, 1980.

Robinson, D.S., Lovenberg, W., Keiser, H., and Sjoerdsma, A. Effects of drugs on human blood platelet and plasma amine oxidase activity *in vitro* and *in vivo*. *Biochem. Pharmacol.*, 17:109–119, 1968.

Robinson, D.S., Nies, A., Ravaris, C.L., and Lamborn, K.R. The monoamine oxidase inhibitor, phenelzine, in the treatment of depressive-anxiety states. *Arch. Gen. Psychiatry*, 29:407–413, 1973.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Clinical pharmacology of phenelzine. *Arch. Gen. Psychiatry*, 35:629–635, 1978a.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Clinical psychopharmacology of phenelzine: MAO activity and clinical response. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Genera-*

tion of Progress, Vol. 2, New York: Raven Press, 1978b, pp. 961–973.

Robinson, D.S., Campbell, I.C., Walker, M., et al. Effects of chronic monoamine oxidase inhibitor treatment on biogenic amine metabolism in rat brain. *Neuropharmacology*, 18:771–776, 1979.

Robinson, D.S., Kayser, A., Corcella, J., et al. Panic attacks in outpatients with depression: Response to antidepressant treatment. *Psychopharmacol. Bull.*, 21(3):562–567, 1985.

Sanghera, M.K., McMillan, B.A., and German, D.C. Buspirone, a non-benzodiazepine anxiolytic, increases locus ceruleus noradrenergic neuronal activity. *Eur. J. Pharmacol.*, 86:107–110, 1983.

Sargant, W., and Dally, P. Treatment of anxiety states by antidepressant drugs. *Br. Med. J.*, 1:5–9, 1962.

Sheehan, D.V., Ballenger, J., and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch. Gen. Psychiatry*, 37:51–59, 1980.

Solyom, L., Heseltine, G., McClure, D., et al. Behavior therapy versus drug therapy in the treatment of phobic neuroses. *Can. Psychiatr. Assoc. J.*, 18:25–32, 1973.

Taylor, D.P., Allen, L.E., Ashworth, E.M., et al. Treatment with trazodone plus phenoxybenzamine accelerates development of decreased type-2 serotonin binding in rat cortex. *Neuropharmacology*, 20:513–516, 1981.

Tyrer, P., Candy, J., and Kelly, D. A study of the clinical effects of phenelzine and placebo in the treatment of phobic anxiety. *Psychopharmacologia*, 32:237–254, 1973.

West, E.D., and Dally, P.J. Effects of iproniazid in depressive syndromes. *Br. J. Psychiatry*, 1:1491–1494, 1959.

Discussion on the Monoamine Oxidase Inhibitors

Burtrum C. Schiele, M.D.[1]

Jonathan Cole gave the keynote address in which he described how Congress was impressed in the 1950's with the great potential of chlorpromazine and other antipsychotic drugs for reducing the morbidity of mental illness. As a result, Congress gave Dr. Cole's Psychopharmacology Service Center 2 million dollars in 1956 to stimulate research. There was a paucity of good research at that time and Jon Cole and his colleagues had to "beat the bushes" for suitable grantees. This probably explains why he told me in 1959 to apply for research money, stating that "you fellows in Minnesota are doing some pretty good work." We received 1.4 million dollars in direct costs over a 12-year period and the University received as overhead about 400,000 dollars. This support resulted in over 150 clinical trials on investigational compounds. The results from most of these trials were published.

More importantly, our Early Clinical Drug Evaluation Unit (ECDEU) operation stimulated similar efforts at other centers such as the St. Paul-Ramsey Medical Center, the Missouri Institute of Psychiatry, and the Veterans Administration Medical Center in St. Cloud, Minnesota. Approximately 50 colleagues participated in these clinical trials. For many, this was a first research effort resulting in publication. Over the years, these colleagues published several hundred additional articles in psychopharmacology. Even those who did not pursue research received lasting benefits through a greater appreciation of what psychotropic drugs can and cannot do, and through familiarity with the scientific measurement of behavioral change developed by psychopharmacologists.

"New Perspectives on Long-Standing Issues" was the title of the first scientific session. Dr. Donald Kline gave a scholarly dissertation on the ups and downs of the monoamine oxidase inhibitors (MAOIs). This class of drugs historically provided the first effective modern antidepressants. The original drug, iproniazid (Marsalid), initially generated great excitement, as it appeared to have potent antidepressant action. Unfortunately, it also produced jaundice and liver damage and was removed from the American market, though it is still commercially available in Canada and the United Kingdom. A number of MAOIs were marketed but only three remain on the American scene: isocarboxazid (Marplan) and phenelzine (Nardil) are hydrazine MAOIs and tranylcypromine (Parnate) is a nonhydrazine MAOI.

The early studies evaluating the effectiveness of the MAOIs were slip-shod and poorly designed by today's standards. Nevertheless, the drugs were widely used until tricyclic antidepressants (TCAs) became available. At this time, the so-called "cheese" reaction, or hypertensive headache crisis, began to appear in patients who were taking the MAOIs. In a short time, these drugs were in disrepute and were rarely used. However, in the late 1970's there was a considerable resurgence of interest in them. This is due to the fact that better designed studies were being conducted. One of the best was a study by Dr. Donald Robinson on Nardil. He demonstrated that the effective dose level was considerably greater than what had originally been recommended, and that patients must be carefully selected. In carefully controlled trials, Nardil proved to be equal in efficacy to the TCAs. Also, a biologic measure of MAO action was available by measuring the platelet MAO content.

A second factor that created further interest in these agents was the advent of several new types of MAOIs based upon the discovery of agents that were highly selective for the two major classes of MAO, Types A and B. A selective MAOI, chlorgyline, acted on

---

[1] Emeritus Professor of Psychiatry, University of Minnesota, Minneapolis, MN 55455.

MAO-A but showed no safety advantage over the already existing MAOIs and is no longer manufactured. One of the more promising drugs is L-deprenyl, which is selective for MAO-B. MAO-A denatures norepinephrine, 5–HT, and dopamine, while MAO-B denatures dopamine and phenethylamine. L-Deprenyl apparently does not alter tyramine and, thus, is considerably less dangerous than the traditional MAOIs. It is marketed in England and other European countries as an antiparkinson drug where it is causing few difficulties and is associated with little orthostatic hypotension.

My main role in this presentation is to discuss Parnate (tranylcypromine). This agent is unlike the other MAOIs in that it has a bimodal stimulating action that occurs very quickly, whereas the hydrazine MAOIs may require several days or weeks before the antidepressant effect is apparent. Parnate has not been associated with liver troubles, tremor, or sweating as have the hydrazine drugs. In the early days, it appeared to be a drug of choice, partly because of its rapid onset of action and high potency. Before long, however, the drug began to show a higher incidence of hypertensive crisis than did the other drugs and so fell into disrepute. This was particularly true in England, where many people eat a whole meal of cheese; patients who were on Parnate often had hypertensive crises after eating ripe cheese or other tyramine-laden foods. A number suffered strokes, and there were some deaths. As a result, in 1964 the FDA threatened to seize the drug and the manufacturer removed it voluntarily from the market. Because of the large number of letters of protest, mostly from physicians who claimed to have patients who were benefiting greatly from Parnate and who had benefited from nothing else, the FDA reversed its decision and the drug was returned to the marketplace within a few months. However, severe restrictions were placed upon its use. The dose was lowered, it was not to be given to people over 60 years of age, and there was a long list of prohibited foods and drugs which should not be used while the patient was taking Parnate.

When the Drug Evaluation Scientific Inventory (DESI) studies were completed, Parnate was given a rating of less than efficacious. The rating has not been changed in spite of the fact that the manufacturer claims to have completed two well-designed studies in the last year that show its efficacy. I understand that new labeling is being developed and that the dose will be raised and restrictions lessened.

Most patients do not respond to Parnate, but it is easy to determine in a few days whether or not they will respond. Of those who do, many demonstrate dramatic improvement. To illustrate, a 43-year-old university graduate had been incapacitated by anxiety and depression for over 20 years. He had failed to respond to psychotherapy, ECT, and many new drugs and had spent the last 10 years in Anoka State Hospital. He had the good fortune to be placed on Parnate while a subject in one of our first double-blind trials under the ECDEU program. Within 3 days he was vastly improved. That Parnate was largely responsible for this improvement is supported by the fact that his fears and anxiety began to return when Parnate was taken off the market. He improved when Parnate supplies were made available to him, and went on to a complete and lasting recovery.

The aforementioned patient is a classical MAOI responder. Some responders, however, may be schizophrenic. One such patient had had florid schizophrenia for many years and had failed to obtain lasting benefit from extensive ECT, many drugs, and years of hospitalization. Surprisingly, she obtained lasting benefits from Parnate. A trial of Parnate (or other MAOI) in treatment-resistant schizophrenics who are tense and anxious or fearful may be worthwhile. A problem is that some schizophrenics may develop more florid symptomatology on Parnate, in which event the MAOI should be discontinued.

The official label says Parnate should be used only in "severe depressions." This wording needs to be improved because most of those who benefit have atypical depression, if they are depressed at all. They often have chronic fears and anxiety, and a few have frank schizophrenia or schizophrenic tendencies.

Parnate is sufficiently different from the hydrazine MAOIs and should not be lumped with these. Studies are needed to compare Parnate against the hydrazine MAOIs. If

Parnate responders would do as well on the hydrazine MAOIs, the latter may be preferred because of a somewhat better safety record.

One of my last ECDEU projects (about the time of my retirement) was an interesting study of Parnate's isomers. Commercial Parnate is a racemic mixture of plus and minus isomers. Dr. Solomon Snyder told us that animal studies suggested that the minus isomer might have greater therapeutic value and less toxicity. Our short-term trial on 11 depressed subjects indicated that he was correct. Unfortunately, as far as I know, no further studies on this intriguing matter have been carried out.

Use of Placebo in Clinical Trials[1]

Karl Rickels, M.D.[2]

It is now almost 40 years since the "Cornell Conference on Therapy" was held (Cornell Conference on Therapy, 1946). It was a "first" in medicine with its primary focus on placebo effects and double-blind methodology. In the late 1940's and early to late 1950's, Beecher and his associates conducted leading research on the patients' subjective response to active drug treatment, primarily analgesics, and to placebo (Beecher, 1955, 1959).

But it was the discovery of chlorpromazine and reserpine, two antipsychotic drugs, in the early 1950's that began to revolutionize clinical research methodology. The discipline of "psychopharmacology" was born.

Psychiatry, a medical specialty that in the early 1950's had almost rejected its medical roots and had embraced a concept of psychological and behavioral causation for most psychiatric illnesses, suddenly found itself with pharmacological tools to modify behavior significantly and to produce frequently lasting improvement. Soon, other neuroleptic agents, as well as drugs to treat anxiety and insomnia, such as meprobamate and the benzodiazepines, drugs to treat depression such as monoamine oxidase inhibitors (MAOIs) and tricyclics, and lithium to treat mania, were also introduced into medicine. The young leaders of this new field of psychopharmacology took the opportunity which was offered to them and forged ahead to develop the discipline of psychopharmacology and make it a leader in clinical research and clinical pharmacology.

The Psychopharmacology Service Center (NIMH-PSC) was created in 1956, changing its name in the early 1960's to the Psychopharmacology Research Branch (NIMH-PRB). NIMH research support multiplied and the judicious support of well-controlled, frequently placebo-controlled clinical trials, conducted both at individual research centers and as collaborative enterprises, carried out with schizophrenic, depressed, manic-depressed, and anxious patients, led to important clinical findings and to advances in research methodology not found, at least at that time, in other medical specialties. Another important driving force behind the excellent clinical collaborative research conducted in the early years of psychopharmacology was the central office of the Veterans Administration.

In these early years of psychopharmacology, industry lagged in its support of clinical research. In fact, most well-controlled studies in the 1960's were government supported. Industry had no real incentive as drugs could get approved rather easily, having to demonstrate only safety but not efficacy.

It is for this reason, but also for the fact that most schizophrenic patients lived in state hospitals and were not treated by private or academic psychiatrists, that much of the early clinical research with neuroleptics and antidepressants was conducted in relatively few State hospitals by such early leaders of psychopharmacology as Fritz Freyhan, Nathan Kline, Milton Greenblatt, Heinz Lehmann, and others.

In 1960, the first NIMH-sponsored collaborative study involving the treatment of anxious outpatients was conducted jointly by NIMH, Johns Hopkins, and the University of Pennsylvania (Fisher et al., 1964; Uhlenhuth et al., 1966), soon to be followed by in- and outpatient studies in depression.

All of these early NIMH and VA-sponsored studies employed already sophisticated research methodology, including the use of placebo and standard controls, randomization, placebo washout, and double-blind design.

---

[1] This study was supported in part by USPHS Research Grant MH-08957 from the National Institute of Mental Health.

[2] Stuart and Emily B.H. Mudd Professor of Human Behavior and Professor of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104.

Since in psychiatry probably more than in any other field of medicine, nondrug or nonspecific factors, including the treatment milieu (Rickels, 1968), exert an important impact on treatment outcome, the use of controls, frequently placebo, became a methodological necessity. The more patients were studied, the more the phenomenon to be studied changed, the well-known Heisenberg phenomenon.

Thus interest in the placebo response in psychiatry intensified during the late 1950's and 1960's and led to a burst of publications including many by the author and his colleagues (Downing & Rickels, 1970; Downing et al., 1981; Honigfeld, 1964). Placebo controls were and are still being used primarily for two reasons: to control for effects due to suggestibility, including milieu or psychotherapy, bias, and enthusiasm of both patient and physician; and also to control for spontaneous symptom change or remission occurring while in treatment but being unrelated to the specific treatment offered.

While the use of placebo is probably more important in evaluating new treatments for anxiety, panic disorder, depression, Alzheimer's disorder, and insomnia, it also plays an important role in drug trials conducted with chronic and acute schizophrenic patients.

The appropriate use of placebo controls in psychopharmacology has been clearly defined in the Food and Drug Administration (FDA) guidelines for clinical trials of psychotropic drugs. These guidelines were drafted by a committee consisting of members of the American College of Neuropsychopharmacology (ACNP) and Early Clinical Drug Evaluation Unit (ECDEU), coming from government, academia, and industry (FDA Guidelines for Psychotropic Drugs, 1974; International Guidelines for Clinical Trials of Psychotropic Drugs, 1978; FDA Guidelines for the Clinical Evaluation of Psychotropic Drugs—Antidepressants and Antianxiety Drugs, 1978; Wittenborn, 1977). In fact, the discipline of psychopharmacology was instrumental in the development of FDA guidelines, not only for psychiatry, but also for other fields in medicine. One of the most important publications relevant to the topic at hand which resulted from close collaboration between members from NIMH and ACNP, many of them also members of ECDEU, should be mentioned here. It is edited by Jerome Levine and was entitled "Principles and Problems in Establishing the Efficacy of Psychotropic Agents" (Levine et al., 1971).

Today it is difficult sometimes to separate activities sponsored by PRB, ECDEU, or ACNP. Yet the PRB and the ECDEU are probably most closely intertwined. It is now 25 years since the ECDEU, later changed to NCDEU, was launched to bring together clinical researchers, scientists, and administrators from academia, government, and industry with the explicit goal to improve communications between those involved in psychiatric clinical research.

Another important factor contributing to improved drug evaluation methodology has been the Kefauver-Harris Amendment to the Food, Drugs, and Cosmetic Act of 1962 (Kefauver-Harris Amendments of October 10, 1962, to the Food, Drugs, and Cosmetic Act, 1962). It mandated that the FDA evaluate not only safety but also efficacy claims for any new experimental agent before approving it for general use.

As a member of the drug efficacy study (National Academy of Sciences/National Research Council, 1969) evaluating psychiatric drugs, a study which was conducted between 1966 and 1968, sponsored by the National Academy of Sciences, and which reviewed for the FDA all drugs introduced between 1938 and 1962, I became clearly aware of industry's frequent lack of interest in controlled research methodology, at times not without reason, as drugs were possibly only of marginal effectiveness. The absence of well-controlled clinical trials could again not be missed (Department of Health, Education, and Welfare, 1978) when I was chairman of the FDA Psychiatric OTC Review Panel in the 1970's.

Since clinical drug trials and the use of experimental drugs and placebo are intimately interwoven with ethical questions involving the protection of human subjects, the USPHS and the FDA independently moved ahead over the years with a number of regulations to assure subject rights and good research methodology. For example, in 1966 the USPHS published its first proposal to establish Institutional Review Boards (U.S. Public Health Service, 1966) and in 1970 the FDA published its first final rules for "Adequate and Well-Controlled Clinical Evaluations" (*Federal Register*, 1970).

Improvement of research methodology and the use of placebo parallels the increasing ethical and methodological concerns regarding the use of placebo in double-blind studies (Helmchen & Müller-Oerlinghausen, 1978).

The conduct of clinical research and the protection of human subjects has been guided since World War II by the Nuremberg Code (Office of the Adjutant General of the United States, 1947), the Declarations of Helsinki (World Medical Assembly, 1964) and Tokyo (World Health Assembly, 1975), and the Declaration of Hawaii (World Psychiatric Association, 1977). This is not to say that ethical concerns regarding clinical research and the use of placebo have not been around for some time. Sir Thomas Percival, for example, discussed placebo use in his 1803 published treatise on "Medical Ethics," and Hooper's "Medical Dictionary," published in 1811, described placebo as "an epithet given any medicine adopted more to please than to benefit the patient." Placebo controls were advocated by Dr. James Lind as early as 1753 when he evaluated the effects of lime juice on scurvy.

More recently, Beecher has given a striking example of placebo effects in surgery (1968). In the 1940's it was an in-vogue procedure to perform a ligation of the internal mammary arteries for the treatment of angina pectoris. Starting in Italy, this surgical procedure entered the United States with great enthusiasm, but when finally a controlled study was evaluated in which half the patients received ligation and the other half simply a skin incision, both groups of patients showed similar levels of improvement.

Over the years, many criticisms of the use of placebo have been voiced (Burkhardt & Kienle, 1978; Freiman et al., 1978; Editorial, 1979). Let us first discuss those voiced on methodological grounds, as placebo is frequently attacked by the statement that "everyone can break the design." To such criticism, Lasagna answered most succinctly many years ago (1971):

1. It is rare for a drug to produce side effects in all patients.
2. It is rare for a placebo not to produce side effects in some patients.
3. The production of side effects is not clearly correlated with desired therapeutic effects.
4. Analyses can always be performed to investigate the possible correlation of side effects and therapeutic success.
5. Coding can and should be done individually so that one code break does not bias all of the subsequent observations.
6. Even an obvious detectable placebo may still serve as a control for spontaneous improvement, unrelated to suggestibility which is at times the main or sole component of the placebo response.
7. Even a partial control on subject and observer bias is infinitely better than no control at all.

There do exist, however, a couple of problems when including placebo control groups. First, patients assigned to placebo studies may tend to be less ill than patients assigned to studies not including a placebo group and thus are not representative of all patients and, secondly, study enrollment will be more difficult.

What are some of the major ethical concerns?

1. Placebo use is a deception.
2. Placebo use withholds otherwise available effective therapy.
3. Placebo use actually endangers the life and welfare of the patient.

Some suggest that one can deal with some of these issues by using a small "ineffective" dose of an active drug as a control. I am against such an approach since I consider it indeed a deception of the patient.

Opponents of placebo use seem to suffer from the delusion that placebos are always ineffective and experimental drugs are always safe and effective. I personally subscribe to the statement made by Lasagna some time ago that "too often the placebo-treated patients turn out to be the lucky ones in a drug trial, deprived only of a toxic and ineffective chemical" (Lasagna, 1970). In fact, it is indeed surprising to me how frequently any, at least potentially, poisonous experimental compound will be readily prescribed to patients without great ethical concerns while a safe placebo will be considered unethical.

This lack of placebo control renders the results of many clinical drug trials meaningless, useful only for drug promotion. I subscribe to Robert Temple's view (Temple, 1984) that an "escape clause" or "easy escape" can be developed for almost any placebo application in situations where it appears to be difficult to use placebo controls for ethical and/or clinical reasons. Many examples could be quoted for such consideration. Suffice it to say that placebo has been meaningfully used in all psychiatric conditions, including schizophrenia and mania.

In some conditions, for example, instead of starting with a parallel group design, one might treat patients only with an experimental or standard agent, and then shift those responding to treatment to either placebo or continued medication. An escape clause should allow a subject to resume active drug therapy only after minimal signs of relapse occur. Such designs have certainly been successfully used in mania, schizophrenia, and depression, to mention only some psychiatric indications.

What are other control options if a placebo is not used? One is the use of "historical controls," an option which in my opinion is not very helpful in most instances. Another option is the use of dose response curves but, in my opinion, even here a placebo group is needed. Finally, the use of standard agents without a placebo control group is recommended. However, unless studies comparing an experimental with a standard agent are of large sample size, involving 100 to 200 patients per treatment cell, only positive but not negative findings are interpretable (Gillings et al., 1984). A failure to include a placebo in such trials may lead to difficulty in interpreting the results. For example, the test drug may turn out to be inferior to the standard drug. Without a placebo, however, it will be impossible to say whether the test drug has any activity at all, a question probably of interest, particularly if the experimental agent has many fewer side effects than the standard agent. In another experiment, the test drug and standard drug may perform equally well. Without a placebo control, however, one does not know whether both drugs are equally effective or ineffective, or whether one was merely dealing with an experimental sample or design unable to discriminate between treatments. Therefore, it is my considered opinion that three treatment groups, namely experimental agent, placebo, and standard agent, are necessary for most appropriate study results interpretation. Here we can compare the experimental drug against the yardstick of standard drug versus placebo response.

Once clinical efficacy has been clearly established, however, I am the last person to demand a placebo group in all additional studies. Yet I know even here of many instances in which the sponsors wished they had included a placebo group. Nevertheless, research questions such as those related to differential drug effects or safety, to the relationship of drug response and drug plasma levels, and many others can be answered without using a placebo control group.

Before concluding, allow me to cite two recent experiences pointing out the importance of placebo controls. In an ongoing trial involving alprazolam, imipramine, and placebo in agoraphobic panic patients, a patient entered the trial who, after gradual increase of dosage during the first 4 weeks, responded with full remission of symptoms, symptoms she had had for many years and which had not responded to psychotherapy and other therapeutic modalities. In fact, the patient was so much improved that she appeared together with me on a radio show and before a class of 165 medical students where she completely upstaged me. Her symptoms clearly responded to treatment and the drug in question appeared to be (to everyone concerned) alprazolam, as the patient described temporary memory problems and sedation with increased dosages but no autonomic nervous system side effects. After 8 weeks, her daily dosage was slowly decreased and when she reached half the daily dosage her symptoms returned. Once a full daily dosage was again established, the patient was symptom-free for about 4 months, at which time she began slowly to relapse, needing increasing amounts of "medication," until finally she demanded to be taken off the study and to know what she was receiving. To our great surprise, when the code was broken, the patient was found to have been on placebo. Thus for more than 4 months the patient responded significantly and better than she had ever before to the supportive milieu of a special panic disorder clinic, an effect not at all drug related.

The second example is a patient suffering from major depressive disorder of the melancholic subtype who participated in a study comparing the use of imipramine, alprazolam, and placebo in depression. The patient showed positive drug response and after the double-blind phase was over and the patient was shifted to a 1 week no-drug schedule, she called her physician 3 days later describing typical withdrawal reactions which included gastrointestinal symptoms, increased sensitivity to sound and light, increased anxiety, distress, and marked lethargy. The patient was seen at once and the psychiatrist evaluating the patient was so sure about the drug the patient was receiving that he did not even request a break of the code. He placed the patient on alprazolam for 2 weeks followed by a slow medication taper without any problems. When the study was completed and the code broken, everyone can imagine our surprise when we learned that the patient had been on placebo the whole time.

In summary, let me state unequivocably my firm belief that no psychiatric treatment method, be it a pharmacological or nonpharmacological one, be recommended for general use unless controlled studies have been conducted which clearly confirm the treatment's claimed efficacy. And in the evaluation of psychopharmacological agents this should always include at least several placebo-controlled studies, some of these also including a standard drug as a third treatment group. This statement holds true not only for the assessment of new agents in the treatment of anxiety, depression, insomnia, pain, and Alzheimer's disease, but also schizophrenia. In all psychiatric conditions, such nondrug factors as milieu change, amount of support, social and familial manipulations and many others, including the mere passage of time, do exert important treatment effects, effects which have to be controlled for in psychiatric drug trials.

References

Beecher, H.K. The powerful placebo. *JAMA*, 159:1602–1606, 1955.

Beecher, H.K. *Measurement of Subjective Responses*. New York: Oxford University Press, 1959.

Beecher, H.K. Placebo effects of situations, attitudes, and drugs: A quantitative study of suggestibility. In: Rickels, K. (ed.), *Non-Specific Factors in Drug Therapy*. Springfield, Ill.: Charles C Thomas, 1968, pp. 27–39.

Burkhardt, R., and Kienle, G. Controlled clinical trials and medical ethics. *Lancet*, 1978/II:1356–1359, 1978.

Cornell Conference on Therapy. The Use of Placebo in Therapy. *NY State J. Med.*, 46, 1946.

Department of Health, Education, and Welfare, Food and Drug Administration. Over-the-counter nighttime sleep-aid and stimulant products. Tentative final orders. *Fed. Register*, 42:25544, 1978.

Downing, R.W., and Rickels, K. The prediction of placebo response in anxious and depressed outpatients. In: Wittenborn, J.R., Goldberg, S.C., and May, P.R.A. (eds.), *Psychopharmacology and the Individual Patient*. New York: Raven Press, 1970, pp. 160–168.

Downing, R.W., Rickels, K., and Ota, K.Y. Evaluation of psychotropic agents with emphasis on the role of the clinical trial . In: van Praag, H.M., Lader, M.H., Rafaelsen, O.J., and Sachar, E.J. (eds.), *Handbook of Biological Psychiatry/Part VI-Practical Applications of Psychotropic Drugs and Other Biological Treatments*. New York: Marcel Dekker, Inc., 1981, pp. 327–358.

Editorial. Controlled trials: Planned deceptions? *Lancet*, I:534–535, 1979.

FDA Guidelines for the Clinical Evaluation of Psychotropic Drugs—Antidepressants and Antianxiety Drugs. *Psychopharmacol. Bull.*, 14(2):45–63, 1978.

FDA Guidelines for Psychotropic Drugs. *Psychopharmacol. Bull.*, 10:184, 1974.

Federal Register, 35:7250, 1970.

Fisher, S., Cole, J.O., Rickels, K., and Uhlenhuth, E.H. In: Bradley, P.B., Fluegel, F., and Hoch, P. (eds.), *Neuropsychopharmacology*. Vol. 3. Amsterdam: Elsevier Publishing Company, 1964, pp. 149–156.

Freiman, J.A., Chalmers, T.C., Smith, H. Jr., and Kuebler, R.R. The importance of beta, the Type II error and sample size in the design and interpretation of the randomized control trial. *N. Engl. J. Med.*, 299:690–694, 1978.

Gillings, D., Grizzle, J., Koch, G., et al. Pooling 12 nomifensine studies for efficacy and generalizability. *J. Clin. Psychiatry*, 45 (No. 4, Sec. 2):78–84, 1984.

Helmchen, H., and Müller-Oerlinghausen, B. *Psychiatriche Therapie-Forschung*. New York: Springer-Verlag, 1978.

Honigfeld, G. Non-specific factors in treatment. *Dis. Nerv. Syst.*, 25:145–156, 225–239, 1964.

International Guidelines for Clinical Trials of Psychotropic Drugs. *Psychopharmacol. Bull.*, 14(1):47–65, 1978.

Kefauver-Harris Amendments of October 10, 1962 to the Food, Drugs and Cosmetic Act, *Code of Federal Regulations*. Washington: U.S. Government Printing Office, 1962.

Lasagna, L. Drug evaluation problems in academic and other contexts. *Ann. NY Acad. Sci.*, 169:503–508, 1970.

Lasagna, L. Decision processes in establishing the efficacy and safety of psychotropic agents. In: Levine, J., Schiele, B.C., and Bouthilet, L. (eds.), *Principles and Problems in Establishing the Efficacy of Psychotropic Agents*. Washington, D.C.: U.S. Government Printing Office, 1971, pp. 29–50.

Levine, J., Schiele, B., and Bouthilet, L. (eds.), *Principles and Problems in Establishing the Efficacy of Psychotropic Agents.* USPHS Publication No. 2138. Washington, D.C.: U.S. Government Printing Office, 1971.

Lind, J. *A Treatise of the Scurvy*. Edinburgh, 1753.

National Academy of Sciences/National Research Council. *Final Report, Drug Efficacy Study*. Washington, D.C.: U.S. Government Printing Office/Food and Drug Administration Publication, July 9, 1969.

Office of the Adjutant General of the United States. *Trials of War Criminals. Volume 2*. Washington, D.C.: U.S. Government Printing Office, 1947, pp. 181–183.

Percival, Sir Thomas. *Medical Ethics*. Manchester: J. Johnson, 1803.

Rickels, K. (ed.) *Non-Specific Factors in Drug Therapy*. Springfield, Ill.: Charles C Thomas, Inc., 1968.

Temple, R. Current issues in the design, conduct, and interpretation of clinical trials. Workshop Proceedings, Washington, D.C., September 10, 1984.

Uhlenhuth, E.H., Rickels, K., Fisher, S., et al. Drug, doctor's verbal attitude, and clinic setting in the symptomatic response to pharmacotherapy. *Psychopharmacologia*, 9:392–418, 1966.

U.S. Public Health Service, *Policy and Procedure Order No. 129, July 1, 1966*. Washington, D.C.: U.S. Government Printing Office, 1966.

Wittenborn, J.R. (ed.). Guidelines for clinical trials of psychotropic drugs. *Pharmakopsychiatrie-Neuropsychopharmakologie*, 10:205–231, 1977.

World Medical Assembly. *Declaration of Helsinki*. Helsinki, 1964.

World Health Assembly. *Declaration of Tokyo*. Tokyo, 1975.

World Psychiatric Association. *Declaration of Hawaii*. Hawaii, 1977.

Scientific and Ethical Considerations in the Use of Placebo Controls in Clinical Trials in Psychopharmacology

Gerald L. Klerman, M.D.[1]

On the occasion of the 25th anniversary of NCDEU, it is appropriate to reconsider the issues involved in the use of placebo controls in clinical trials in psychopharmacology. In the current scene, these issues involve scientific considerations and ethical problems.*

Historical Background

The theoretical and statistical basis for clinical trials had been established for many years, particularly with the work of Fisher and other British statisticians. However, it was not until after World War II that the pace of clinical research accelerated, and clinical trial designs became increasingly utilized in medicine, notably in the evaluation of treatment for cardiac problems, specifically angina pectoris, and in the evaluation of treatments for tuberculosis. Government agencies played a major role in this expansion of the use of clinical trial designs, particularly the Veterans Administration in the United States and the Medical Research Council (MRC) in the United Kingdom.

Although a few clinical trials were attempted in psychiatry in the 1930's and 1940's to assess the claims for the efficacy of convulsive therapy, insulin coma therapy, and even prefrontal lobotomy, it was not until the advent of the newer psychopharmacologic agents in the mid–1950's that clinical trials became involved in psychiatry. The rapid arrival of chlorpromazine and other phenothiazine derivatives, rauwolfia and its derivatives, and meprobamate led to intense controversy and, in partial response to that controversy, a number of controlled clinical trials were begun.

Government agencies in both the United States and the United Kingdom played a major role in organizing these trials of psychiatric drugs. In the United States, credit should be given to the Veterans Administration and also to the National Institute of Mental Health (NIMH). In the United Kingdom, the Medical Research Council initiated a number of trials.

At NIMH, the creation of the Psychopharmacology Service Center in 1956, under the imaginative leadership of Jonathan O. Cole, M.D., stimulated the development of trials, notably the Collaborative Study on the Assessment of Phenothiazines (Cole et al., 1964).

In the 1950's and early 1960's, the scientific issues of design and methodology were in the forefront. There was considerable debate as to the necessity for controlled trials. Experienced clinicians argued that controls were not necessary since they could distinguish placebo effect from drug effect and, by knowing the individual patient well, could identify the specific pharmacologic actions. Doubts were also raised about the feasibility of conducting clinical trials with psychiatric patients because of the variability of their responses, the important role of psychosocial influences on symptom fluctuation, and the absence of objective measures of psychopathology.

These issues dominated discussions in the 1950's and early 1960's, but rapidly receded through the late 1960's with the growing evidence for the efficacy of drugs and the value of clinical trials (Levine et al., 1971).

A powerful governmental impetus to the application of controlled clinical trial designs came in 1962 with the passage of the

---

[1] George Harrington Professor of Psychiatry, Harvard Medical School and Director, Stanley Cobb Research Laboratories, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114. (Now at Cornell University Medical Center, New York, NY 10021).

*Dr. Rickels (this issue) has addressed the major historical background.

Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act. It took 10 years for the Food and Drug Administration (FDA) to implement fully the provisions of that act. During that period, the National Academy of Sciences established the Drug Evaluation Scientific Inventory project (DESI) to review all classes of drugs approved prior to the 1962 Act, including psychopharmacologic agents. That panel was chaired by Daniel X. Freedman, then at the University of Chicago. In addition, the FDA commissioned the American College of Neuropsychopharmacology (ACNP) to participate in the guideline projects, and members of the psychopharmacologic community, through ACNP, participated in developing guidelines for the evaluation of antipsychotic, antidepressant, and antianxiety agents. These guidelines reaffirmed the necessity for controlled studies and, in particular, mandated the use of placebo controls.

By the mid-1970's, the scientific issues around the use of placebo controls subsided and ethical issues began to emerge. In the current scene, the ethical issues are predominant. There are often confounding scientific and ethical issues. Ethical concerns sometimes serve as a rationalization for avoiding the use of placebos. This is particularly so in individuals who advocate evaluating a new drug against some available drug in a two-group comparison design without necessarily using placebo.

The Scientific Consensus

It is useful at this point to restate the consensus arrived at in the 1960's. Why use placebos? Why use control groups? The placebo control group represents a control for a "package" of effects which potentially could obscure and confound the demonstration of drug efficacy.

Do placebo controls control for package of effects? These include:

1. The passage of time, particularly for patients with disorders with an inherent tendency to remit, such as acute depressive reactions, transient stress responses, adjustment disorder with mood, etc.

2. The increased attention given to the patient by the warmth, sympathy, and encouragement of the medical and nursing staff.

3. The patient's expectations and hope for improvement.

4. The psychosocial consequences of being legitimized in the sick role being given the role of patient, often has profound effects on family relations by recasting the patient's problems and behavior into an illness explanation rather than his actions being judged as badness.

In addition, there may be extensive cognitive reframing of the meaning given by the patient to his or her experience through the research interviews, rating scales, and checklists. Being asked to reconstruct the sequence of symptoms and events often gives patients a sense of meaning to the experience and serves to demystify the sequence of symptoms, distress, etc.

The multiple rating scales and checklists may serve as a form of self-monitoring, a behavioral technique shown effective in many forms of behavioral psychotherapy.

There are at least two other important reasons why a placebo control is desirable from a scientific point of view.

1. The placebo control serves as a means of calibrating the skills of the research group. In psychopharmacology, the research group and the research setting are the "instruments" for the detection of change, similar to the use of chemical instruments, such as gas chromatograph in blood assays for drugs. Just as the chemical laboratory would need to calibrate its instruments against blanks and standards on a periodic basis to maintain quality control, so the research group needs to calibrate itself to establish its sensitivity. Can this research group detect the difference between an active drug and a placebo or no-pill? Are they treating a patient population that is sensitive to drug effect? Are they adequately trained? Are they using assessment devices, including rating scales and checklists, which are capable of detecting change? There, the placebo control serves as a test of the sensitivity of the research group.

2. A placebo-washout period between the time the patients enter the study and the initiation of active drug treatment is particularly important in the current scene. In our socie-

ty, a high percentage of individuals are taking psychoactive drugs, including benzodiazepines, sedative-hypnotics, and recreational drugs. Very often patient experiences are symptomatic effects due to the pre-existing drugs, and the placebo-washout period establishes a new baseline for the amount of drug effect. This may particularly be the case in chronically ill patients who are treatment resistant, for example, the improvement noted in chronic schizophrenics when they were discontinued from maintenance treatment with neuroleptics by Paul and Lentz (1977).

Distinguishing Nonspecific Effects From Placebo Effects

Sometimes these effects are called "nonspecific" effects; sometimes nonspecific effects are equated with placebo effect.

It is desirable to distinguish within the package of nonspecific effects, that effect which may be related to pill-taking (i.e., the placebo effect). The optimum way to assess this would be a drug trial in which there was a placebo-pill group, as well as a no-pill control group and an active drug group. Where drugs and psychotherapy are being compared, there may be important reasons to employ both a placebo and a no-pill group, as has been argued by Hollon and DeRubreis (1981). Only a very few such efforts have been undertaken, most notably the trial of drugs and psychotherapy in depression by the Boston-New Haven Collaborative Group (Klerman, 1974). In that study, no effect of placebo pill-taking was noted above the no-pill situation, suggesting that there is no specific effect due to the expectation of pill-taking and prescription over and above the other nonspecific effects listed above.

Ethical Considerations

In recent years, ethical considerations have gained importance in designing trials of illnesses for which standard treatments exist, as in psychoses, or where the control group may have potential adverse effects, as, for example, "sham" electroconvulsive therapy (ECT) with induced unconsciousness, ethical considerations may preclude the use of placebos.

Space does not permit a full discussion of the constraints upon demonstration of efficacy that follow from the ethical restraints on the use of placebo groups. However, it is pertinent to identify a number of solutions that have been proposed and utilized.

On a nonscientific basis, the situation would be improved by increased interaction and communication between investigators and the Institutional Review Boards (IRBs) at their institutions. This communication should be extended to the national scene. A future conference should be planned to provide systematic interchange between scientific groups and representatives of review committees, such as the Editorial Board of IRB, or an organization such as Physician's Responsibility in Medical Research (PRIMR). This might make a useful topic for a future NCDEU meeting.

At the scientific level, a number of design options have been proposed. One is the use of a "treatment on demand" as a control. In this situation, patients are told that treatment is available to them as they feel their symptomatic state may require. Patients who exceeded a certain number of calls or visits per week are then considered treatment failures and removed from the protocol, but treatment is provided to them on a clinical basis. This option has been employed in a study on drugs and psychotherapy in acute depression (Richman et al., 1980).

Second, some investigators have allowed very liberal clinical judgment for removal from the study. Here the decision lies with the clinician. The clinician can remove the patient from the study because of concern for failure to improve, worsening in clinical condition, or adverse effects. In this design, the rate of removal from the study becomes an indirect measure of efficacy of the treatment. At the same time, the patient's clinical needs are adequately met. In order for this design to be adequately executed, it is desirable that the criteria for removal be operationally specified in advance, preferably in quantitative terms. The three categories mentioned above (failure to improve, worsening in clinical condition, adverse effects) are subject to marked variation in clinical judgment and prior agreement as to criteria in terms of rating scale change, or symptomatic or social functioning to enhance reliability and reduce variability among clinicians when the study is conducted across sites or with multiple clinicians at a single site.

Third, is the use of constructive designs. Where an established standard treatment exists, such as neuroleptic treatment for schizophrenics, constructive designs can be used. In these designs, all the patients receive the established treatment and subgroups receive the new treatments. The assumption is that the combination of the standard treatment plus the new treatment will have an additive, synergistic (cocktail) effect (Klerman, in press).

Three recently designed studies employ constructive designs in an interesting way. One, the NIMH study of strategies for the treatment of schizophrenia (Schooler and Keith, unpublished), employs a design in which all patients receive neuroleptic medication; however, the drug sample is divided into a high-dose group and a low-dose group and the design also allows for comparison of two forms of psychosocial intervention, including family psychoeducational efforts. Thus, there is simultaneous exploration of variation in drug dose as it may interact with psychosocial intervention. However, all patients are receiving neuroleptic medication based on the prior demonstration of the efficacy of neuroleptic medication.

Second, the Philadelphia study of drug dependence in the treatment of opiate dependent individuals (Woody et al., 1983) has reported the efficacy of professional psychotherapy. In this study at the Philadelphia VA Hospital, opiate dependent patients in the trial all received a "standard package" consisting of methadone maintenance plus psychotherapeutic counseling by ex-addict peer counselors. One-third of the sample received only the standard treatment, one-third received professional psychotherapy of the cognitive-behavioral type developed by Beck et al. (1979), and the other third received psychoanalytically derived supportive-expressive therapy (Luborsky, 1984). In this study, the two forms of professional therapy showed significant advantage over the standard treatment of methadone maintenance plus peer counseling.

Third, Mavissakalian (1984) has recently reported on treatment of agoraphobia in which the standard treatment involved all patients receiving instruction for in-vivo exposure. Exposure via instruction had previously been shown to have moderate efficacy, helping about 50 percent of patients with agoraphobia. Imipramine or professional exposure therapy was then compared. These constructive designs assume prior demonstration of the efficacy of the standard treatment. The standard treatment may be a drug treatment; as in the case of the schizophrenia study, the standard treatment was a neuroleptic. The standard treatment may be psychotherapy, as in the case of Mavissakalian's study of phobia, or the standard treatment may be a combination as in the Woody study, where the combination of methadone maintenance plus ex-addict peer counseling was the standard.

Conclusions

A scientific consensus has emerged as to the necessity of placebo controls in psychopharmacology. A similar consensus does not exist for psychotherapy research. It is of interest that the placebo group in psychopharmacology includes a package of social psychological factors such as the sick role, and the interaction between patient and therapist expectations. For the psychotherapy research, it is this very package of effects which is among the specific component of psychotherapy and which merits dismantling strategies (Kazdin, in press; Wilkins, 1984).

However, in the current context, the predominant issues regarding the use of the placebo controls in psychopharmacology are not scientific but ethical. The interactions between scientific and ethical considerations continue to be an important area in clinical psychopharmacology. The need exists to explore more fully the principles upon which ethical considerations constrain the use of placebo and in those instances where the ethical issues are predominant, alternative designs need to be developed. A number of promising constructed designs are being employed in conditions where standard treatments exist. The other major design innovation is the use of patient or clinician judgment for removal from the study and using the rate of removal as an indirect measure of efficacy. NIMH should consider the desirability of a conference to promote communication between bioethicists and leaders of IRBs on one hand, and clinical psychopharmacologists, statisticians, and methodologists on the other. Such a conference could provide the arena for intense discussion of unresolved problems and, hopefully, modes of their resolution.

References

Beck, A.T., Rush, J., Shaw, B., and Emergy, G. *Cognitive Therapy of Depression: A Treatment Manual*. New York: Guilford Press, 1979.

Cole, J.O., Goldberg, S., and Klerman, G.L. Phenothiazine treatment in acute schizophrenia. *Arch. Gen. Psychiatry*, 10:246–261, 1964.

Hollon, S.D., and DeRubeis, R.J. Placebo-psychotherapy combinations: Inappropriate representations of psychotherapy in drug-psychotherapy comparative trials. *Psychol. Bull.*, 90:467–477, 1981.

Katz, M.M., and Klerman, G.L. Introduction: Overview of the clinical studies program. *Am. J. Psychiatry*, 136:49–51, 1979.

Kazdin, A.E. Research design and methodology. In: Garfield, S.L., and Bergin, A.E. (eds.), *Handbook of Psychotherapy and Behavior Change*. 3rd ed. New York: John Wiley & Sons. (In press)

Klerman, G.L. Drugs and psychotherapy. In: Garfield, S.L., Bergin, A.E. (eds.), *Handbook of Psychotherapy and Behavior Change*. 3rd ed. New York: John Wiley & Sons. (In press)

Klerman, G.L., DiMascio, A., Weissman, M.M., et al. Treatment of depression by drugs and psychotherapy. *Am. J. Psychiatry*, 131:186–191, 1974.

Levine, J., Schiele, B., and Bouthilet, L. *Principles and Problems in Establishing the Efficacy of Psychotropic Agents*. Washington, D.C.: U.S. Government Printing Office, PHS Publication No. 2183, 1971.

Luborsky, L. *Principles of Psychoanalytic Psychotherapy: A Manual for Supportive-Expressive Treatment*. New York: Basic Books, 1984.

Mavissakalian, M.R. Agoraphobia: Behavioral therapy and pharmacotherapy. In: Beitman, B.D., Klerman, G.L. (eds.), *Combining Pharmacotherapy and Psychotherapy in Clinical Practice*. New York: Spectrum Publishers, 1984, pp. 187–212.

Paul, G.L., and Lentz, R.J. *Psychosocial Treatment of Chronic Mental Patients: Milieu vs Social-Learning Programs*. Cambridge: Harvard University Press, 1977.

Richman, J., Weissman, M.M., Klerman, G.L., et al. Ethical issues in clinical trials: Psychotherapy research in acute depression. *IRB*, 2:1–4, 1980.

Rickels, K. Use of placebo in clinical trials. *Psychopharmacol. Bull.* 22(1):19–24, 1986.

Schooler, N.R., and Keith, S.J. NIMH Protocol for treatment strategies in schizophrenia study. (unpublished manuscript)

Wilkins, W. Psychotherapy: The powerful placebo. *J. Consult. Clin. Psychol.*, 52:570–573, 1984.

Woody, G.E., Luborsky, L., McLellan, T., et al. Psychotherapy for opiate addicts: Does it help? *Arch. Gen. Psychiatry*, 40:639–645.

The Placebo Control in Clinical Trials (A View From the FDA)

Paul Leber, M.D.[1]

In many quarters, placebo controls are maligned; yet, their use is virtually indispensable to the intelligent assessment of efficacy of most psychopharmacologic drug products. It is, therefore, especially gratifying to find the use of placebo resoundingly endorsed by two distinguished investigators, Drs. Rickels (1986) and Klerman (1986). Indeed, their arguments for the use of placebo are so compelling and complete that this discussion must retrace ground they have already traversed.

Federal regulations governing drug product development recognize five types of control conditions that may be employed in clinical investigations intended to meet the regulatory standard of "adequate and well-controlled" investigations (21 CFR 314.126), the standard that must be met if a trial is to be accepted as a source of "substantial" evidence of drug product efficacy. The five control conditions (i.e., placebo, dose-comparison, no treatment, active, and historical), however, vary considerably in the number and nature of assumptions required for their interpretation and, therefore, in their degree of reliability.

The historical control is highly unreliable (Sachs et al., 1982) and, therefore, considered a control of last resort in almost every area of drug development. Because the no-treatment concurrent control does not allow blinding, its usefulness in psychopharmacologic drug development is minimal. Thus, only placebo, dose-comparison, and active control designs which employ prospective and concurrent randomization of experimental and control treatments are of much use in psychopharmacology. In theory, these three designs are capable of generating equivalently persuasive evidence of efficacy; a demonstration of a difference (in the appropriate direction) between experimental and control treatments, provided it cannot be attributed to fraud, bias, or chance, must be attributed to a pharmacologic effect of the experimental drug.

However, as commonly used in psychopharmacologic drug development programs, only placebo-controlled trials have regularly provided this sort of unambiguous evidence of efficacy. Active control investigations rarely document the superiority of an experimental treatment to standard drug and, to date, experience with fixed-dose response designs is so limited that it is impossible to make any informed judgment about their potential usefulness. From a regulatory vantage point, therefore, the placebo control trial has been an indispensable tool for the assessment of psychopharmacologic drug product efficacy.

What accounts for the value of the placebo control? The placebo control allows one to distinguish between true drug effects and improvements due to 1) spontaneous remission; 2) inconstancy of illness course (i.e., if subjects are recruited at a time of symptomatic exacerbation, their subsequent improvement may reflect only a regression to the mean); 3) biased (intentional or unintentional) assessment of outcome; and 4) nonpharmacologic effects of the treatment arrangement or contract (i.e., the placebo effect, per se).

Do placebo control trials have any faults? Of course. One concern is that the very possibility of assignment to a pharmacologically inert treatment may alter the behavior of subjects and investigators in ways that may seriously compromise the external validity of the study. In particular, the chance that placebo may be assigned can affect 1) sample selection (e.g., the very ill may be systematically excluded), and 2) trial conduct (e.g., investigators may be more willing to drop patients who do not immediately respond to their assigned treatment than they would in a trial employing only "active" drugs).

Another shortcoming of studies that employ only a placebo control is that they fail to provide any data about comparative efficacy and safety. While such data are not germane

---

[1] Food and Drug Administration, Rockville, MD 20857.

to a regulatory judgment concerning efficacy, knowledge of the relative utility and risk of treatments is important for drug labeling. Moreover, the interpretation of a trial that fails to discriminate between an experimental drug and placebo can be markedly affected by knowledge of the performance of a standard treatment in that same trial. In particular, if a study fails to discriminate between the investigational agent, standard drug, and placebo, the study can be more readily discounted (i.e., it can be given lesser weight) in the agency's overall assessment of evidence bearing on the experimental drug's efficacy.

Consequently, the clinical trial design that employs placebo, standard drug, and investigational drug is an ideal marriage of the placebo and active control designs. Placebo provides an estimate of what would have been had no pharmacologic treatment been given. Standard drug provides an estimate of both the intrinsic responsiveness of the patient sample to pharmacologic treatment and the sensitivity of the assay system (i.e., the investigator and his assessment methodology). The design offers the same sort of reference points as do the blank and standard solutions in a spectrophotometric analysis.

Overall, it seems fairly obvious that the placebo alone or, still better, combined with a standard drug control, is an essential tool in psychopharmacologic drug development.

This favorable view of placebo, however, is not universally held. Objections to its use have been raised on both practical and ethical grounds.

One practical objection to placebo is that it retards subject recruitment. Physicians and patients are often reluctant to forego or delay treatment with an effective drug, or even a putatively effective one, to use placebo. The objection, however, cannot be fully assessed without reference to the implied comparison; namely, what experimental design is it easier to recruit for? Unless the alternative design has a utility equivalent to the placebo design, the advantage is illusory.

Indeed, many of those who raise objections to placebo appear to assume, albeit incorrectly, that the active and placebo controls provide equivalent protection against error. If this were true, of course, there would be no justification to employ placebo. In fact, however, active controls, as commonly used in psychopharmacology, rarely provide any useful information about efficacy.

When an active control trial fails to distinguish between the effects of an experimental agent and a standard "active" control, it does *not* prove that the two drugs are equally effective. The same result might occur if both treatments were inert, if the study had inadequate statistical power, or if the study were carelessly conducted. Thus, those who argue that a finding of no difference is evidence of efficacy rely upon a series of sanguine assumptions about the conditions under which the active control study was conducted. Many of these assumptions may be unwarranted (Leber, 1985). In particular, the assumption that a standard psychopharmacologic control treatment is "active" in a particular experiment is especially tenuous. Anyone familiar with the nature of psychiatric symptoms, their intrinsic variability, and the variable nature of treatment response among psychiatric patients will recognize why.

Furthermore, the ability to detect a difference between treatments is influenced by both the size of a study and the quality of its conduct. In trials where the goal is to demonstrate a difference, it is in the interest of those who conduct them to increase power and maintain high standards of trial execution. In contrast, in trials where the aim is to fail to show a difference, the incentives, as Temple has noted (1982), are reversed.

Thus, any potential advantage in recruitment rate offered by the active control design would seem to be completely offset by its epistemological flaws. There is no advantage in carrying out a worthless study rapidly!

As noted earlier, objections to placebo are also made on ethical grounds. It seems likely that the failure to recognize the intrinsic flaws of active controls may contribute to the debate about the "ethics" of placebo use. That is, many who object to the use of placebo controls on so-called ethical grounds may do so based on the false belief that the active control is a reasonable alternative to the placebo.

In any case, there are those who believe that the use of placebo is unethical in settings where established treatments exist for the condition for which an experimental drug is being developed (Way, 1984).

This discussant finds this view inconsistent. If one believes that it is unethical to deny a patient immediate access to a known effective treatment in order to assign him to placebo, it should be equally unacceptable to delay his access to definitive treatment in order to assign him to an investigational agent which may not only be ineffective, but dangerous.

In summary, the placebo control is an indispensable tool. If it (or some reasonable substitute for it such as the fixed dose, dose-response control) were not available, we would have to approach each new drug with the skepticism expressed by the 19th century physician who advised his colleagues ". . . to treat as many patients as possible with the new drugs while they still have the power to heal." (Trousseau, quoted by Benson and McCallie, 1979).

Placebo controls are our surest protection against fads and fashions that come and go in pharmacology, against the reckless claims of therapeutic enthusiasts, and, most important, against our own mistaken beliefs and prejudices.

References

Klerman, G. Scientific and ethical considerations in the use of placebo controls in clinical trials in psychopharmacology. *Psychopharmacol. Bull.*, 22(1):25–29, 1986.

Leber, P. The implicit assumptions of active control trials (a critical examination). Presented at the 1983 annual meeting of the Society for Clinical Trials. *Controlled Clin. Trials*. (Submitted, 1985)

Rickels, K. Use of placebo in clinical trials. *Psychopharmacol. Bull.*, 22(1):19–24, 1986.

Sachs, H., Chalmer, T.C., and Smith, H. Randomized versus historical controls for clinical trials. *Am. J. Med.*, 72:233–240, 1982.

Temple, R. Government viewpoint of clinical trials. *Drug Informa. J.*, 10–17, 1982.

Trousseau, A., quoted by Benson, H., and McCallie, D.P. Angina pectoris and the placebo effect. *N. Engl. J. Med.*, 300:1424–1429, 1979.

Way, W. Control placebos. (Letter) *N. Engl. J. Med.*, 311(6):413–414, 1984.

Pharmacological Treatments of Schizophrenia

George M. Simpson, M.D.[1]

As this is an anniversary meeting, it seems appropriate to give some information about the early clinical drug evaluation units (ECDEU), later the NCDEU. This group of investigators was created by the Psychopharmacology Research Branch (PRB) and was exceptionally important for the development of psychopharmacology in this country. In the early days of drug studies, it was reported (perhaps somewhat tongue-in-cheek) that one might receive large bottles of pills, give out handfuls of them, and report that "this is great stuff," and that was the study. Indeed, I once saw an investigator who had a pocket notebook and less than half a page of medium-size handwriting was the sum total information for each patient on his clinical trial. I might also add that his records were much superior to the other studies that I had occasion to see at that time. My own work at that time involved the notion that resting endocrinological measures would predict outcome in major mental illness, specifically schizophrenia. This was funded in the late 1950's by the PRB under the title "Research in Endocrinology and Drugs," later "The Red Project." Spin-offs from this study were trials of triiodothyronine as a treatment in schizophrenic patients with low thyroid tests who were also receiving neuroleptics, trials of Enovid in female patients who showed regular exacerbations of their psychotic symptoms thought to be associated with their menses, papers on the effects of antipsychotic drugs on reproductive function, effects of antidepressants on genito-urinary function, and a publication that showed an increase in spermatogenesis associated with the administration of a monoamine oxidase inhibitor (MAOI). On further consideration, this latter was most likely related to the fact that the two colleagues who happened to get depressed and who had been measuring their own semen count, motility, and morphology weekly for several years also drank quite a bit. The MAOIs may have been less the agent for change than the withdrawal of alcohol which was ordered during the course of this treatment.

At all events, these and other clinical trials outside the endocrinological research ward interested me and led to my applying for a grant and becoming an ECDEU member. There were many drugs available at that time and several new drugs were evaluated in the course of any 1 year. Multiple rating scales were used, many of which are seldom used today. It is not that they were poor scales but that, as ECDEU grew, the Psychopharmacology Research Branch (PRB) developed a data analysis capability, and some standardization of rating scales was essential. Thus, the Brief Psychiatric Rating Scale (BPRS) and Nurses' Observation Scale for Inpatient Evaluation (NOSIE) became standard scales. Many individual and cooperative studies were carried out by these investigators, and the science of clinical trials received a hefty shot in the arm. Diagnosis was, if not frowned on, certainly at a very primitive level in the early 1960's. One saw some very raucous and intrusive people labeled schizophrenics who were textbook manics. Perhaps because of this lack of interest in diagnosis, there were some peculiar ideas about drug actions. The idea of target symptoms was clearly a good one and was incorporated into rating scales, but there was also a notion that target symptoms were individual items and did not belong in groups to syndromes or were unrelated to diagnosis. Thus, the notion that there might be drugs specifically for hallucinations, for example, resulted in a drug marketed for that purpose—Frenquel.

Many clinical trials at this time at ECDEU units studied new drugs in chronic schizophrenic patients. The dramatic effect of chlorpromazine in an open study, coupled with the large number of hospitalized pa-

---

[1] The Medical College of Pennsylvania, Philadelphia, PA 19129.

tients, made this a reasonable strategy. Hospitals had many patients who could not be discharged and who had many positive symptoms when off drugs and made mild to moderate improvement on neuroleptics. Studies invariably took 6, 8, or 12 weeks of active treatment with several weeks of no drug or placebo before and after treatment. Weekly NOSIE, BPRS, Global, and other scales were employed. It was not difficult to demonstrate in such a study that a drug was an active antipsychotic agent. All of the current antipsychotics were first tested in this fashion with the initial findings confirmed in placebo-controlled studies. It is not too surprising, if we consider that all of these drugs were developed from a similar animal model developed after the discovery of chlorpromazine, which worked so well that a variety of chlorpromazine-like drugs was developed. After the production of many, many drugs that differed in their side effects rather than in their therapeutic effects, this procedure reached a dead end. The number of new drugs diminished. There has not been a new antipsychotic drug on the U.S. market since loxapine (1975)—one of the last drugs studied collectively by ECDEU investigators. ECDEU researchers in effect received funds as an investment in them rather than in specific projects. The drop in the number of new drugs left more and more investigators with time to devote to their own pet projects which soon resembled R01 studies, e.g., our staff was involved in studying plasma levels of neuroleptics and in studying tardive dyskinesia at the time the NCDEU change took place.

During this time, psychopharmacology progressed enormously—the sophistication of the methodology, the concern with selection of patients, diagnosis, new rating scales, inter-rater reliability, validity, etc. To an extent, the science of clinical trials which was practically nonexistent in psychiatry was now better developed in psychiatry than in any other medical specialty. Individual investigators also asked many questions about conventional drugs and produced much of the knowledge that supports present-day practices. For instance, during this period we showed that in a double-blind, controlled study one- versus three-times-a-day neuroleptic medication was equally efficacious and resulted in no increase and perhaps even a decrease in side effects if the single dose was all given at bedtime. Later, we studied the same phenomenon but also measured plasma levels. We studied fluphenazine decanoate and showed that it was active at 12.5 mg every 2 weeks. We showed that patients in general responded similarly to repeated administrations of medication, that patients who gained weight did so on each occasion, and patients who did not gain weight did so on both occasions. We showed that the immediate symptoms of withdrawal of antipsychotics were mainly related to the concomitant withdrawal of anti-parkinson agents. Therefore, a patient receiving a neuroleptic plus an anti-parkinson agent should not have both withdrawn simultaneously; the anti-parkinson agent should be continued for at least 1 week in order not to have an upsurge of extrapyramidal reactions. In 1968, we studied "the behavioral and anti-epileptic effects of an iminostilbene derivative," one of the earliest studies of Tegretol in a psychiatric population; and in 1967, a preliminary evaluation of the sedative effects of Catapres, a new antihypertensive agent in chronic schizophrenic patients. A series of papers on extrapyramidal side effects (EPS) resulted in the development of a rating scale for EPS. From this and other studies came our interest in trying to cut down the very high dose of drugs that psychiatrists used and continue to use. In these studies, it appeared that doctors used 300 percent more neuroleptics than were required. In the 1960's began the studies of lithium, studies of naltrexone in chronic schizophrenia, studies of antipsychotics in the elderly, studies with clozapine, and so on. Each ECDEU would have a similar range of different studies that they carried out, all of which added to our knowledge of psychopharmacology.

Nearly all of the investigators were active in teaching and training and so, to a large extent, these units reached a stage where they were perhaps no longer necessary, i.e., there were groups of young psychiatrists who were now being trained in psychopharmacology, the journals were replete with good studies to be read in journal clubs, etc. The introduction of clozapine raised new hopes for the type of different drug that everyone had been looking for, and this remains a not-impossible dream but certainly an unrealized one. In the meantime, use of neuroleptics has advanced the treatment of schizophrenia. It is safe to say that without neuroleptics, social psychiatry and the community mental health movement would have had great difficulties in coming about. The surge of interest in psychosocial treatment of schizophrenia highlights this, since clearly psychosocial interventions are helpful but are not very helpful in the absence of neuroleptic agents. Thus, this anniversary of the ECDEU truly represents the end of a cycle in the search for new treatments in schizophrenia. A substantial advance has been made in the treatment of schizophrenia and, while we have far to go, I feel secure that NCDEU investigators will be in the forefront of the advances to come.

Research Methodology and the Pharmacotherapy of the Chronic Schizophrenias[1]

Thomas A. Ban, M.D., William Guy, Ph.D., and W.H. Wilson, Ph.D.[2]

Introduction

Schizophrenic disorders occur in 0.86% of the general population. This implies that 86 out of 10,000 people randomly chosen from the general population will develop a schizophrenic disorder during their lifetime (Tsuang & Vandermey, 1980). Almost half of all patients diagnosed as schizophrenic will need long-term treatment, and it has been estimated that 30 to 60% of all new long-term patients suffer from one or another form of schizophrenia (Mann & Cree, 1976). There is evidence that 15% of patients who are diagnosed today as suffering from a schizophrenic disorder will become chronically hospitalized at some time in the future. Consequently, it is estimated that one-third to one-half of all psychiatric beds, i.e., one-sixth to one-fourth of all hospital beds—since nearly 50% of all beds are psychiatric—are occupied by schizophrenic patients (Todd et al., 1977).

The prevailing treatment modality for patients with chronic schizophrenia is pharmacotherapy with neuroleptics. This is to the extent that, in a multi-national survey carried out in 768 chronic hospitalized schizophrenic patients, 739 or 96.2% were treated with one or more of 33 different neuroleptics. The total population of this study was contributed by nine centers geographically located in eight countries (Tables 1 and 2) (Ban et al., 1984b).

In spite of their extensive use, it is difficult to demonstrate the therapeutic effectiveness of neuroleptics in chronic schizophrenic patients. This may be due to the lack of sensitive instruments for the assessment of change in this population. An alternative possibility is that chronic schizophrenia consists of a biologically heterogeneous population. In favor of this latter contention is the fact that not every schizophrenic patient shows a similar response to neuroleptics.

TABLE 1

Number and Percentage of Patients Receiving One or More Neuroleptics

Country	*N*	Neuroleptic *N*	Neuroleptic %
Brazil	95	71	74.7
Hungary	59	58	98.3
Italy	93	90	96.8
Japan	200	200	100.0
Nigeria	10	10	100.0
Panama	86	86	100.0
USA	150	149	99.3
Yugoslavia	75	75	100.0
Total	768	739	96.2

TABLE 2

Thirty-Three Neuroleptics Employed in Eight Countries (rank order)

1–11	12–22	23–33
Haloperidol	Promazine	Methylperidol
Chlorpromazine	Clothiapine	Oxypertine
Levomepromazine	Loxapine	Mesoridazine
Thioridazine	Pimozide	Alimenazine
Fluphenazine	Carpipramine	Trifluoperidol
Perphenazine	Perazine	Clopenthixol
Thiothixene	Reserpine	Molindone
Trifluoperazine	Floropipamide	Spiperone
Sulpiride	Fluspirilene	Moperone
Clozapine	Butaperazine	Fluphenazine Decanoate*
Propericiazine	Flupenthixol	Fluphenazine Enanthate*

*The long-acting preparations are not included in the ranking.

Demonstration of Therapeutic Efficacy

Demonstration of therapeutic efficacy is one of the prerequisites for the introduction of a new treatment modality into clinical practice. For drugs which are not causal treatments for a particular disease, e.g., neuroleptics for schizophrenia, this represents a methodological problem which includes the development of an appropriate experimental design and the employment of a discriminative instrument for the measurement of change. It is important that the assessment instrument employed in the measurement of change have the necessary sensitivity to demonstrate differences between the new treatment and the untreated course of the disease (placebo) at the accepted level of probability.

---

[1] This study was supported in part by USPHS Grant MH-35720 from the National Institute of Mental Health.

[2] Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN 37217.

The most frequently employed instrument in the assessment of neuroleptic-induced changes in chronic schizophrenic patients is the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) which consists of 18 items scored on a 7-point scale of intensity.

Since an essential prerequisite for the usefulness of the BPRS in chronic schizophrenic patients is the necessity that the majority of the 18 items (symptoms) be present in a considerable percent of the target population, we have reviewed our data to determine the presence of 18 psychopathological symptoms corresponding to the BPRS items in the same population of 768 patients (Ban et al., 1985).

Data were collected with a specially devised instrument, the Psychopathological Symptom Profile (PSP), developed from the Psychopathological Assessment form of the second edition of the AMP-System by adding items from the Present State Examination (Wing et al., 1974), the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer & Endicott, 1978), and on the recommendation of special consultants. The PSP consists of 176 psychopathological symptoms and includes most items of the Psychopathological Symptoms section of the English edition of the AMDP–III System (Guy & Ban, 1982). Each item is followed by a brief definition and is scored from 0 to 3, indicating whether the symptom is definitely absent (0), probably absent (1), probably present (2), or definitely present (3). Accepting scores 2 or 3 as "present," it was revealed that, of the 176 symptoms of the PSP, 33 were present in at least 40% of the 768 patients (Table 3). We chose the 40% as cutoff point on the basis that any symptom present in a lower percent would not be a useful item in the assessment of change. As shown on Table 4, 8 of the 18 BPRS items are included among the 33 most frequently encountered symptoms of the PSP. While these represent some of the most frequently encountered symptoms of schizophrenia, it is clear that there are a number of significant symptoms which are simply not encompassed by the BPRS. A differently structured instrument would be more suitable in the assessment in order to avoid the possibility of covering up therapeutic changes (Type II or β error) resulting from the administration of neuroleptic drugs.

TABLE 3

Psychopathological Symptom Profile (The 33 Items Present in 40% or More of the 768 Patients)

Rank	Item	*N*	%
1	Lack of insight	717	93.4
2	Blunted affect	632	82.3
3	Asocial behavior	606	78.9
4	Delusions	561	73.0
5	Autistic	553	72.0
6	Unkempt	515	67.1
7	Hallucinations	508	66.1
8	Lack of interest	500	65.1
9	Auditory hallucinations	494	64.3
10	Lack of energy	473	61.6
11	Apathy	458	59.6
12	Derailment (thought)	440	58.5
13	Restricted thinking	426	55.5
14	Inhibition (drive)	426	55.5
15	Concentration difficulties	419	54.6
16	Concreteness (ideas)	411	53.5
17	Thrusts (episodes)	394	51.3
18	Suspiciousness	391	50.9
19	Delusion of reference	390	50.8
20	Impaired attention	387	50.4
21	Emotional rigidity	380	49.5
22	Delusional ideas	377	49.1
23	Persecutory delusions	367	47.8
24	Blocking	341	44.5
25	Mannerisms	334	43.5
26	Incoherent/confused	328	42.7
27	Delusional mood	328	42.7
28	Delusional perception	327	42.6
29	Irritability	315	41.0
30	Thought withdrawal	315	41.0
31	Delusional dynamics	314	40.9
32	Ambivalence	312	40.6
33	Impaired retention	309	40.2

TABLE 4

Corresponding BPRS and PSP Items Present in 40% or More of the 768 Patients

Item No.	BPRS	Item No.	PSP	%	Rank
1.	Somatic concern	33.	Hypochondriasis	–*	50
2.	Anxiety	95.	Anxiety	–	40
3.	Emotional withdrawal	82.	Apathy	59.6	11
4.	Conceptual disorganization	57.	Incoherent/confused	42.7	26
5.	Guilt feelings	111.	Feelings of guilt	–	112
6.	Tension	105.	Tension	–	38
7.	Mannerisms and posturing	127.	Mannerisms	43.4	25
		128.	Posturing	–	97
8.	Grandiosity	70.	Delusions of grandeur	–	72
9.	Depressive mood	98.	Depression	–	70
10.	Hostility	107.	Hostility	–	47
11.	Suspiciousness	106.	Suspiciousness	50.9	18
12.	Hallucinatory behavior	24.	Hallucinations	66.1	7
13.	Motor retardation	115.	Lack of energy	61.5	10
14.	Uncooperativeness	154.	Uncooperativeness	–	34
15.	Unusual thought content	60.	Delusions	73.5	4
16.	Blunted affect	81.	Blunted affect	82.2	2
17.	Excitement	113.	Restlessness	–	35
		118.	Agitation	–	88
18.	Disorientation		Disturbance of Orientation:		
		14.	Self	–	90
		15.	Time	–	73
		16.	Place	–	102
		17.	Situation	–	59

*– = < 40%

Shortcomings of Classification

Introduction of neuroleptics, the most effective single treatment modality employed in chronic schizophrenic patients, has brought attention to the differences in therapeutic responsiveness among patients. In spite of this recognition, which suggests that chronic schizophrenia consists of a biologically heterogeneous population, examination of the nature of this heterogeneity, by studying the natural course of the disease with special emphasis to the end-state syndromatology of patients, has been given little attention. This is especially surprising since there is little, if any, evidence that patients with different types of schizophrenia as classified by the Diagnostic and Statistical Manual—3rd ed., 1980 (DSM–III) or ICD–9 respond differentially to neuroleptic drugs, while there are indications for differential responsiveness in the different subtypes (end-states) described in Leonhard's (1979) classification of chronic schizophrenias. This complex classification which distinguishes 19 distinct syndromes belonging to two groups of disorders within the schizophrenias has shifted emphasis from the acute to the chronic forms of the illness. Leonhard maintains that schizophrenic disorders can best be studied after the acute manifestations common to all schizophrenias have subsided and the illness has progressed into its disease-specific final form (Ban, 1982) (Table 5).

By employing Leonhard's classification, Fish, as early as 1964, found that 117 out of 123 nonsystematic schizophrenics (95%) showed a favorable therapeutic response, while only 289 out of 351 systematic schizophrenics (69%) showed a favorable response. From both a practical and a theoretical point of view, however, the important findings were that among the nonsystematic patients, the favorable therapeutic response was rated marked to moderate in 79% of the treatment responsive patients, while among the systematic patients only 23% were so rated. Fish also noted that, among the nonsystematic patients, those suffering from periodic catatonia responded less favorably than patients with affect-laden paraphrenia and especially

TABLE 5

Leonhard's Classification of Chronic Schizophrenias

Nonsystematic			Systematic		
Cataphasia	Affect-laden Paraphrenia	Periodic Catatonia	Paraphrenias	Hebephrenias	Catatonias
			Phonemic	Autistic	Parakinetic
			Hypochondriacal	Eccentric	Proskinetic
			Confabulatory	Shallow	Speech-prompt
			Expansive	Silly	Speech-inactive
			Fantastic		Manneristic
			Incoherent		Negativistic

cataphasia; among the systematic patients, therapeutic responsiveness was not evenly distributed among the three major classes of illness. Thus, while as many as 40% of the paraphrenics showed a moderate or marked therapeutic response to neuroleptics, only 23% of the hebephrenics and 0.9% of the systematic catatonics showed a similar response.

Corresponding with these findings are our observations and results. We have reported on a patient with the diagnosis of periodic catatonia (febrile catatonia), a nonsystematic subtype, in whom an increase in neuroleptic dosage was associated with exacerbation, a decrease in dosage with amelioration, and discontinuation of medication with remission of psychopathological symptoms (Kelwala & Ban, 1981a). In another case report of two patients with diagnoses of shallow hebephrenia, a systematic subtype, discontinuation of neuroleptic medication had no detectable effect for an extended period (Kelwala & Ban, 1981b). Thus, in our two shallow hebephrenic patients, the usefulness of maintaining neuroleptic treatment was questionable; in our periodic catatonic patient, neuroleptic treatment seemed to have a negative therapeutic effect.

The notion that neuroleptic treatment in certain patients may not just be ineffective but may actually be harmful received further substantiation in our survey of 24 patients treated with lithium/neuroleptic combinations. A common characteristic of these patients was that they had previously shown insufficient therapeutic response to neuroleptic drugs alone. Analyses of data revealed that 9 of 10 patients of the nonsystematic population exhibited a favorable therapeutic response to the combination, while 9 of 14 systematic patients showed no response or an unfavorable therapeutic response. In addition, 5 of the 24 patients developed neurotoxicity during the course of treatment; 2 of the 5 patients were silly hebephrenics and 1 each belonged to the expansive, fantastic, and confabulatory subtypes of paraphrenia. While 5 out of the 14 patients with systematic schizophrenia manifested neurotoxicity, none of the 10 patients with nonsystematic schizophrenia, predominantly affect-laden paraphrenia, developed a similar undesirable response to the lithium/neuroleptic combination (Prakash et al., 1982).

Most important in this context are the findings regarding tardive dyskinesia in our multi-national survey (Ban et al., 1984a). While the overall prevalence rate for the population was 11% when determined by clinical judgment and 13% when determined by the Research Diagnostic Criteria for Tardive Dyskinesia (Schooler & Kane, 1982), within the Leonhard system, rates were found to be significantly lower in the therapeutically more responsive nonsystematic group (4.3%). Furthermore, while within the systematic catatonias, the manneristic subtype (53 patients, 32.7%) attained a prevalence rate of 28% and, within the systematic hebephrenias, the silly subtype (56 patients, 19.1%) had a prevalence rate of 53%, within the paraphrenic category, in the expansive (14 patients, 5.4%) and confabulatory (6 patients, 2.3%) subtypes, tardive dyskinesia was not encountered at all. On the basis of these findings, one may hypothesize that there is an inverse relationship between positive symptoms and adverse effects of the neuroleptic drugs at least insofar as tardive dyskinesia is concerned. Since there is no indication that the action mechanism of neuroleptics would be different in patients belonging to different diagnostic groups, one may speculate that, in the development of tardive dyskinesia, not just the administered drug but the biology of the host also plays an important role.

Concluding Remarks

One of the most important contributions for psychiatry which has resulted from psychopharmacologic progress is the recognition that schizophrenia consists of a biologically heterogeneous population. In view of this, it is rather paradoxical that identification of the role of dopaminergic structure in the action mechanism of neuroleptics and demonstration that neuroleptics produce dopamine receptor blockade led to speculations about the nature of schizophrenia in terms of dopamine excess which, in turn, provided sufficient incentive to develop a large number of "me-too" neuroleptics with similar therapeutic but somewhat different adverse effect profiles.

Ignoring the biological heterogeneity of chronic schizophrenia has created considerable difficulties for research in this population, while its recognition has provided new endpoints for preclinical research especially useful for drug development. One tangible result of this research is the introduction of a new category of psychotropic drugs, referred to as "les produits de transition" (transition compounds) in France.

Included among these substances are amoxapine, a dibenzoxazepine which combines the pharmacologic profile of a tricyclic antidepressant with a neuroleptic; carpipramine and chlorcarpipramine; tricyclic dibenzazepines with butyrophenone side chains; and carbamazepine, an anticonvulsant structurally related to the cyclic antidepressants. While the old methodology should suffice for the demonstration of therapeutic effectiveness of these drugs, the identification of the therapeutically responsive populations may require the employment of new diagnostic assessment instruments.

It is a common contention that psychopharmacology has opened unforeseen possibilities for psychiatric progress leading to a reintegration of psychiatry with other medical disciplines. Reevaluation of psychiatric concepts with consideration to psychopharmacologic contributions could open unforeseen possibilities for psychopharmacologic progress with a shift of emphasis from simple therapeutic efficacy based on statistical probabilities to the identification of therapeutically responsive chronic schizophrenic patients to specific treatment modalities.

References

Ban, T.A. Chronic schizophrenias: A guide to Leonhard's classification. *Compr. Psychiatry*, 23:155–169, 1982.

Ban, T.A., Guy, W., and Wilson, W.H. Description and distribution of the subtypes of chronic schizophrenia based on Leonhard's classification. *Psychiatr. Devel.*, 3:179–199, 1984a.

Ban, T.A., Guy, W., and Wilson, W.H. Pharmacotherapy of chronic hospitalized schizophrenics: Diagnosis and treatment. *Psychiatr. J. Univ. Ottawa*, 9:191–195, 1984b.

Ban, T.A., Guy, W., and Wilson, W.H. The AMDP-System in chronic hospitalized schizophrenics. *Compr. Psychiatry*, 26:370–374, 1985.

Fish, F. The influence of tranquilizers on the Leonhard schizophrenic syndromes. *Encephale*, 1:245–249, 1964.

Guy, W., and Ban, T.A. The AMDP-System: A Manual for the Assessment and Documentation of Psychopathology. Berlin: Springer-Verlag, 1982.

Kelwala, S., and Ban, T.A. Febrile catatonia sustained by neuroleptics. *Psychiatr. J. Univ. Ottawa*, 6:135, 1981a.

Kelwala, S., and Ban, T.A. Is maintenance neuroleptic therapy necessary in shallow hebephrenia? *J. Clin. Psychiatry*, 42:482, 1981b.

Leonhard, K. *The Classification of Endogenous Psychoses.* New York: Irvington Publishers, 1979.

Mann, S.A., and Cree, W. New long-stay psychiatric patients: A national sample survey of fifteen mental hospitals in England and Wales, 1972/3. *Psychol. Med.*, 6:603–616, 1976.

Overall, J.E., and Gorham, D.R. The brief psychiatric rating scale. *Psychol. Rep.*, 10:799–812, 1962.

Prakash, R., Kelwala, S., and Ban, T.A. Neurotoxicity with combined administration of lithium and a neuroleptic. *Compr. Psychiatry*, 23:567–571, 1982.

Schooler, N., and Kane, J.M. Research diagnoses for tardive dyskinesia (RD-TD). *Arch. Gen. Psychiatry*, 39:486–487, 1982.

Spitzer, R.I., and Endicott, J. *Schedule for Affective Disorders and Schizophrenia*. 3rd ed. New York: State Psychiatric Institute, 1978.

Todd, N.A., Bennie, E.H., and Carlisle, J.M. Some features of new long-stay male schizophrenics. *Br. J. Psychiatry*, 129:424–427, 1977.

Tsuang, M.T., and Vandermey, R. *Genes and the Mind*. New York: Oxford University Press, 1980.

Wing, J.K., Cooper, J.E., and Sartorius, N. *The Measurement and Classification of Psychiatric Symptoms*. London: Cambridge University Press, 1974.

Discussion of Dr. George Simpson's Paper on Pharmacological Treatments of Schizophrenia

Solomon C. Goldberg, Ph.D.[1]

In the earlier days of neuroleptics, there was substantial success in treating chronically hospitalized or chronic ambulatory schizophrenic patients. Unfortunately, most of the chronic patients who remain now are treatment resistant. They are a poor sample of patients on which to test new antipsychotic drugs whose mechanism is dopamine blockade. Indeed, they can lead to misunderstandings concerning the effectiveness of neuroleptics in schizophrenia if these patients are employed in a test of neuroleptic effectiveness. Paul's work (1972), in which he failed to find a drug effect in chronic schizophrenic patients, was interpreted by him to mean that antipsychotic drugs in general were not effective in chronically psychotic patients. His error was in generalizing from his results to other situations in which standard antipsychotic drugs are effective in the treatment of many schizophrenic patients. These nonresponders to dopamine blockers become prime candidates for the testing of other antipsychotic agents. We are morally obligated to try to find some treatment that will help these patients. This thought has occurred to a number of investigators, and nonresponsive patients have been tried on such agents as propranolol, alprazolam, carbamazepine, lithium, and *d*-amphetamine.

Before starting a patient on one of these agents, it may be well to confirm that the patient is indeed a nonresponder to standard neuroleptics. State hospitals are notoriously conservative in their dosing strategies because of self-protective policies which prohibit the administration of doses higher than those recommended by the *Physician's Desk Reference.* Prien and Cole (1971), for example, found a substantial number of patients who profited from very high doses of phenothiazines after not responding to standard doses.

In a nearby state hospital we are exploring lithium and carbamazepine for the treatment of neuroleptic nonresponders. There has been no difficulty in getting such patients transferred to our unit. When the patients arrive, they are almost invariably on a variety of medications, and our first step is to taper them from these while building them up on a dose of fluphenazine HCl. The fluphenazine dose is increased for 2 weeks until there is no further improvement or until side effects intervene. So far we have found a few patients who are responders to higher doses of fluphenazine, and they are no longer regarded as nonresponders. Those who do not respond become candidates for our trial drugs, but not on a double-blind clinical trial basis. We feel that this is premature until we generate some hypotheses regarding the characteristics of those who will profit from them. The formal clinical trial of any of the new drugs is postponed until a later time.

If a patient is a complete nonresponder to neuroleptics, he is first put on a trial of lithium alone. If he is a partial responder, he would be put on a combination of lithium and his neuroleptic, which in this case would be fluphenazine. If he does not respond to the first medication, he automatically is then given a trial of carbamazepine. On a case study basis, the characteristics of responders and nonresponders to the different drugs are observed.

Beyond the empirical search for new treatments for nonresponders, there is the more theoretical question of why some schizophrenic patients do not respond to neuroleptics. Here there is another line of research which proposes that the schizophrenic nonresponder shows evidence of organicity. There are now at least two studies, Weinberger et al. (1980) and Schulz et al. (1983), showing an association between enlarged ventricles on the CT scan and nonresponse to neuroleptics. These studies were partly an outgrowth of the Johnstone (1976) and Crow

---

[1] Director of Psychiatric Research, Medical College of Virginia, Richmond, VA 23298.

(1980) hypothesis to the effect that schizophrenic patients with negative symptoms have enlarged ventricles and do not respond to neuroleptics. Murray and his associates (in press–b) go a step further to indicate that the schizophrenic with organic signs has a low genetic loading by virtue of family history for schizophrenia, has a history of birth complications involving signs of asphyxia, and was born in a winter month, implying a greater likelihood of viral infection. Murray, in a recent editorial in *The Lancet* (in press–a), proposes that the time has come to recognize two major etiological types of schizophrenia, a genetically transmitted disorder, and a nongenetic disorder whose etiology is more likely environmentally induced brain damage.

What was begun as an empirical search for new treatments for nonresponders has developed a theoretical facet to try to explain the differences in the characteristics of responders and nonresponders. The heuristic value of the theoretical orientation is that it may be capable of suggesting why some of the new treatments may be effective. For example, Slater's (1963) cases of epilepsy who showed schizophrenic symptomatology might be most treatable with the anticonvulsant carbamazepine. To borrow a phrase from social science, "There is nothing so practical as a good theory."

References

Crow, T.J. Molecular pathology of schizophrenia. More than one disease process. *Br. Med. J.*, 1:66–68, 1980.

Johnstone, E.C., Crow, T.J., Frith, C.D., et al. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*, 924–926, 1976.

Murray, R.M., Lewis, S.W., and Reveley, A.M. Towards an etiological classification of schizophrenia. *Lancet*. (In press–a)

Murray, R.M., Reveley, A.M., Reveley, M.A., et al. Genetic and environmental influences in schizophrenia. In: Sakai, T., and Tsuboi, T. (eds.), *Genetic Aspects of Human Behavior*. Tokyo: Igaku-Shoin. (In press–b).

Paul, G.L., Tobias, L.L., and Holly, B.L. Maintenance psychotropic drugs in the presence of active treatment programs: A triple-blind withdrawal study with long-term mental patients. *Arch. Gen. Psychiatry*, 27:106–115, 1972.

Prien, R.F., Levine, J., and Switalski, R.W. Discontinuation of chemotherapy for chronic schizophrenics. *Hosp. Community Psychiatry*, 22:4–8, 1971.

Schulz, S.C., Sinecrop, P., Kishore, P., and Friedel, R.O. Treatment response and ventricular brain enlargement in young schizophrenic patients. *Psychopharmacol. Bull.*, 19(3):510–512, 1983.

Slater, E., Beard, A.N., and Glithero, E. The schizophrenia-like psychoses of epilepsy. *Br. J. Psychiatry*, 109:95–150, 1963.

Weinberger, D.R., Bigelow, L.B., Kleinman, J.E., et al. Cerebral ventricular enlargement in chronic schizophrenia: An association with poor response to treatment. *Arch. Gen. Psychiatry*, 37:11–13, 1980.

Multicenter International Clinical Trials

CHAIRS: Thomas Ban, M.D.
Department of Psychiatry
Vanderbilt University
Nashville, Tennessee

and

Jerome Levine, M.D.
Maryland Psychiatric Research Center
Baltimore, Maryland

Introduction

Thomas A. Ban, M.D.,[1] and Jerome Levine, M.D.[2]

The multi-center approach has been used in clinical psychopharmacology since the late 1950's. Collaborative studies coordinated by the United States National Institute of Mental Health (NIMH), United States Veterans Administration, and the United Kingdom Medical Research Council contributed to the establishment of proper usage of antidepressant and neuroleptic drugs. Without employing a multi-center approach this would have taken considerably longer, and generalization of the findings would have encountered considerably greater difficulties.

Multi-center clinical trials are particularly advantageous for studying the effect of psychotropic drugs in rare disorders. But even in common disorders such as Alzheimer's type of dementia, if one aims to study a homogeneous sample with progressive deterioration at a particular stage, only in a multi-center clinical trial can one expect to find an adequate number of suitable patients within a reasonable period of time.

International participation adds another dimension to multi-center clinical research. Such studies have at least three essential prerequisites: 1) multidimensional description of patient's condition, because of the possible differences in diagnostic practices among participating centers in different countries; 2) assessment instruments in the measurement of change which are reliable and valid across cultures; and 3) feasibility of coordination for making operational the collaboration.

In this session, findings in three multicenter international clinical trials will be presented, one carried out with an antipsychotic (fluperlapine), another with an antidepressant (fluvoxamine), and the third with an anxiolytic drug (alprazolam).

The topic of the first paper is the AMDP System in International Clinical Trials: A Report on Fluperlapine. The AMDP System stands for Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie or, in English, Association for Methodology and Documentation in Psychiatry. It was founded in 1965 by a group of psychiatrists from Germany, Switzerland, and Austria to develop a uniform system for the documentation of information which would be useful in both clinical practice and psychopharmacologic research. Since the Psychopathological Symptom Form, the instrument employed in the assessment of change in the AMDP was developed with emphasis on form, i.e., the mode by which the patient encounters contents, and as such is not contaminated by social-cultural contingents, and should be particularly suited for international collaborative psychopharmacologic research.

The first paper dealt with an international multi-center clinical trial with an antipsychotic, the second dealt with an international multi-center clinical trial with an antidepressant. Professor Cassano and his colleagues presented findings from a multi-center international trial comparing fluvoxamine, a specific serotonin reuptake inhibitor with imipramine and placebo. It should be noted that in all the different phases of this study a modification of the Biometric Laboratory Information Processing System usually referred to as BLIPS has played an important role. This system was developed at the Biometric Laboratories of George Washington University in collaboration with the Psychopharmcology Research Branch of NIMH under the leadership of one of us (J.L.). This system, which has played an important role in the development of clinical trial methodology in the United States, has been implemented in Europe, where Dr. Cassano and his colleagues have created an even more versatile system, BLIPS/BDP.

---

[1] Department of Psychiatry, Vanderbilt University, Nashville, TN 37217.

[2] Maryland Psychiatric Research Center, Baltimore, MD 21228.

The third paper by Dr. Klerman and colleagues presents, for the first time, the results of Phase I of the Upjohn worldwide panic disorder study.

In addition to the results of these studies, this session demonstrates the different ways in which multinational trials can be organized depending on the roles played by the sponsors, investigators, and the availability of computer-based data documentation and analysis systems.

The AMDP System in International Clinical Trials: A Double-Blind Comparison of Fluperlapine and Haloperidol

B. Woggon,[1] M. Linden,[2] H. Beckmann,[3] E. Krebs,[4] B. Küfferle,[5] B. Müller-Oerlinghausen,[2] B. Pflug,[6] and H.W. Schied[7]

Introduction

One important methodological problem in international collaborative studies is the selection of suitable rating scales. The translation of a psychopathological rating scale is complicated by different concepts of psychopathological symptoms and syndromes in different languages and countries. The Association for Methodology and Documentation in Psychiatry, a collaborative group of German, Swiss, and Austrian psychiatrists, was founded in 1965 and the first AMP manual was established in 1971 (Angst et al., 1969; Scharfetter, 1971). Based on broad clinical experience, many drug trials, and a number of methodological studies, a revision of the AMP system was completed in 1979, called the AMDP System (Association for Methodology and Documentation in Psychiatry) (AMDP, 1979, 1983). The AMDP System is currently available in many languages including German, Croatian, English, French, Russian, Spanish, Japanese, Portuguese, Greek, Italian, Danish, and Dutch.

This paper is composed of two parts: a) a description of the AMDP System; and b) an example of an international collaborative trial: a double-blind comparison of fluperlapine* and haloperidol in schizophrenic patients that utilizes the AMDP System.

Description of the AMDP System

AMDP consists of five integrated parts, each printed on a single sheet of paper: 1) demographic data; 2) life events; 3) psychiatric history; 4) psychopathological symptoms; and 5) somatic signs. The 100 psychopathological symptoms and 40 somatic signs are clearly arranged into groups, an aid for the rater (Tables 1 and 2). It is also possible to add write-in items of specific interest to a clinical trial.

Each symptom can be rated as "absent," "present," or "not ascertained." A symptom is rated as "not ascertained" if reliable information is not available. If a symptom is present, three degrees of severity can be rated: mild, moderate, or severe. This judgment is based on frequency, intensity, and duration of a symptom.

Each rating of psychopathological and somatic symptoms is based on a specified time period, for example 24 hours, and combines

TABLE 1

Psychopathological Symptoms (Sheet 4 of the AMDP System)

	Group	No. of Symptoms
1.	Disorders of consciousness	4
2.	Disturbances of orientation	4
3.	Disturbances of attention and memory	6
4.	Formal disorders of thought	12
5.	Phobias and compulsions	6
6.	Delusions	14
7.	Disorders of perception	6
8.	Disorders of the ego	6
9.	Disorders of affect	21
10.	Disorders of drive and psychomotility	9
11.	Circadian rhythms	3
12.	Other disturbances	9

---

[1] Department of Psychiatry of the University of Zurich, Switzerland.
[2] Department of Psychiatry of the Free University of Berlin, Federal Republic of Germany.
[3] Psychiatry Clinic of the Central Institute of Mental Health, Mannheim, Federal Republic of Germany.
[4] Psychiatric Hospital of Wil, Switzerland.
[5] Department of Psychiatry of the University of Vienna, Austria.
[6] Department of Psychiatry of the University of Frankfurt, Federal Republic of Germany.
[7] Department of Psychiatry of the University of Tübingen, Federal Republic of Germany.

*Based on recent toxicological data, the manufacturer (Sandoz AG) has suspended all clinical trials with fluperlapine.

TABLE 2

Somatic Signs
(Sheet 5 of the AMDP System)

	Group	No. of Signs
1.	Sleep	5
2.	Appetite	4
3.	Gastrointestinal	7
4.	Cardiac-respiratory	4
5.	Other autonomic	5
6.	General	6
7.	Neurological	9

both subjective (reported) and objective (observed) information.

Factor analyses of data from various patient samples have led to the development of subscales representing psychopathological syndromes. For statistical analyses of data from clinical trials, different sets of subscales can be used. A comprehensive monograph in English that describes the system includes studies of subscales, interrater reliability, validity, and sensitivity in drug trials (Bobon et al., 1983).

Double-Blind Comparison of Fluperlapine and Haloperidol

As an example of the use of the AMDP System in an international collaborative trial, we report preliminary results of a double-blind study comparing fluperlapine and haloperidol. Fluperlapine (a dibenzazepine) is very similar in structure to clozapine (Figure 1). In open trials, it showed a strong antipsychotic effect (Angst, 1984).

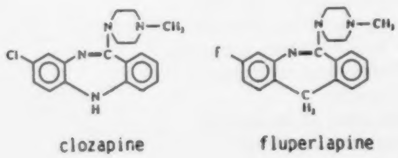


FIGURE 1. Chemical structures of clozapine and fluperlapine.

Seven psychiatric hospitals participated in the study, four in the Federal Republic of Germany, two in Switzerland, and one in Austria. These hospitals are linked to the AMDP and, therefore, the investigators and staff are familiar with and trained in the use of the AMDP System.

The following results are based on data from 120 inpatients who were randomly assigned to treatment with either fluperlapine ($N=60$) or haloperidol ($N=60$). Some patient characteristics are given in Table 3; diagnoses according to the ICD-9 (International Classification of Disease) are given in Table 4. The planned duration of treatment was 28 days. Early dropouts (before day 7) were excluded from the final analysis.

Using a flexible dose regimen, the recommended initial daily dose was 2.5 mg haloperidol or 50 mg fluperlapine, three times a day. Maximum daily dose was 60 mg haloperidol and 800 mg fluperlapine. At the end of the trial, the average daily dose was 23 mg haloperidol (s.d. = 12 mg) and 441 mg fluperlapine (s.d. = 210 mg).

Data analysis was performed at the Department of Psychiatry of the University of Zurich, Switzerland, using a set of 13 subscales (Table 5). Raw scores of the subscales are calculated by adding the included items according to the following values: absent and

TABLE 3

Description of the Patients

	Fluperlapine ($N=60$)	Haloperidol ($N=60$)
Male	30	30
Female	30	30
First manifestations	19	19
Duration of symptoms prior to hospitalization:		
Unknown	8	6
Less than 1 week	10	7
Less than 1 month	22	23
Less than 6 months	13	17
Less than 1 year	2	–
More than 1 year	5	7
Age in years:		
$\bar{x}$ (s.d.)	33.0 (9.7)	35.6 (12.3)
Range	19-59	20.63
Duration of illness (years):		
$\bar{x}$ (s.d.)	5.6 (5.9)	5.9 (8.5)
Maximum	21	39

TABLE 4

Diagnosis

ICD No.*	Diagnosis	Fluperlapine (*N* = 60)	Haloperidol (*N* = 60)
295.0	Schizophrenia simplex	3	–
295.1	Hebephrenic schizophrenia	5	3
295.2	Catatonic schizophrenia	1	3
295.3	Paranoid schizophrenia	41	45
295.4	Acute schizophrenic episode	1	1
295.5	Latent schizophrenia	1	1
295.6	Residual schizophrenia	1	1
295.7	Schizoaffective psychosis	7	5
195.8	Other schizophrenia	–	1
297.8	Other paranoid syndrome	–	1

*Degkwitz et al., 1980.

not ascertained = 0; mild = 1; moderate = 2; and severe = 3. In order to normalize the distributions, logarithmic transformations were performed for the scores of subscales 1 to 12. The scores of subscales 13 and 14 are nearly normally distributed and do not require transformation. Because the number of items in each syndrome is different (range 7 to 27), all scores are further transformed ($\bar{x}$ = 50, s.d. = 10, range 20-80).

The analysis of the Hallucinatory-Disintegrative syndrome clarifies the antipsychotic efficacy of fluperlapine and haloperidol. The symptoms are listed in Table 6. Table 7 shows mean values and s.d. for the syndrome on each rating day. Significant reduction during treatment occurred in both treatment groups [Friedman's analysis of variance (ANOVA)]. The comparisons between day 0 and subsequent rating days in each group separately indicated a significant improvement beginning on day 3. Because of multiplicity of significance, *t* tests were done; and alpha was adjusted from 5% to 1% (Figure 2).

TABLE 5

AMDP Syndromes (Zurich version)

Primary

1. Apathetic
2. Hallucinatory-Disintegrative
3. Hostility
4. Manic
5. Somatic-Depressive
6. Paranoid
7. Catatonic
8. Retarded-Depressive
9. Hypochondriac
10. Psycho-organic
11. Autonomic
12. Neurological

Second Order

13. Manic-Depressive
14. Schizophrenic

Construction of subscales:
1-9: Baumann, 1974.
10 : Monbour et al., 1975.
11 and 12: Without factor analysis
13 and 14: Woggon & Dittrich, 1979.

TABLE 6

Items of the Hallucinatory-Disintegrative AMDP-Syndrome

(57)*	Thought insertion
(58)	Other feelings of alien influence
(38)	Delusional dynamics
(48)	Verbal hallucinations
(50)	Visual hallucinations
(55)	Thought broadcasting
(37)	Systematized delusions
(49)	Other auditory hallucinations
(51)	Bodily hallucinations
(54)	Depersonalization

*Item No. on AMDP sheet 4.

T tests between the two treatment groups on each rating day revealed no significant differences. An analysis of covariance (ANCOVA) following the model for factorial experiments with repeated measurements, and constant covariates (unequal cell frequencies) was calculated using the scores at day 0 as a covariate (Winer, 1962). No significant differences between the two groups were found.

We predicted a difference in extrapyramidal side effects between the two treatments. The subscale that includes extrapyramidal symptoms is the Neurological Syn-

TABLE 7

Hallucinatory-Disintegrative Syndrome

Day	Fluperlapine (*N* = 60)		Haloperidol (*N* = 60)	
	$\bar{x}$	s.d.	$\bar{x}$	s.d.
0	61.4	7.4	60.4	7.7
3	57.2	8.7	56.4	8.9
5	55.1	9.4	52.7	8.5
7	52.6	8.6	50.7	8.6
14	49.4	8.0	49.4	8.6
21	48.4	8.3	48.1	7.8
28	47.8	8.2	46.4	6.9

Mean Values ($\bar{x}$) and Standard Deviations (s.d.)

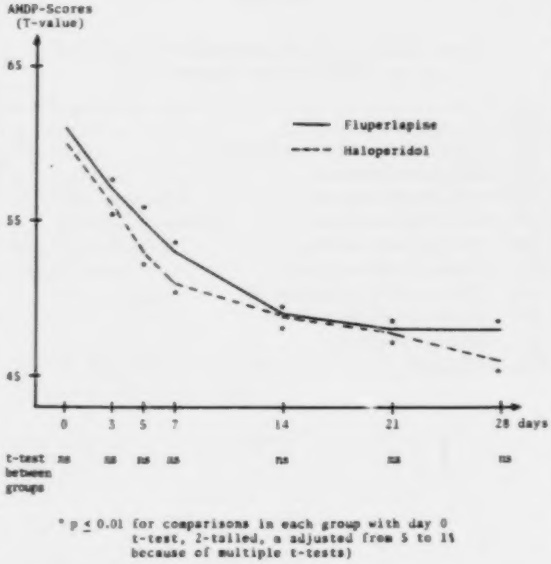


FIGURE 2. Course of the Hallucinatory-Desintegrative AMDP-Syndrome (mean values).

drome (Table 8). Mean values and s.d. of this syndrome in both treatment groups are listed in Table 9. A significant change over time in the group treated with haloperidol was found (Friedman's ANOVA). Comparison between day 0 and the following rating days demonstrated a significant increase in the haloperidol-treated patients from day 3 onward (Figure 3). *T*-test comparisons at each rating day showed no difference between the groups at pretreatment. From day 3 on, the haloperidol-treated patients had significantly higher values than the fluperlapine-treated group in this syndrome. The ANCOVA showed a significant difference between the two groups.

TABLE 8

Items of the Neurological Syndrome

(132)*	Rigor
(133)	Hypotonia
(R5)**	Tremor
(134)	Moderate to gross tremor
(139)	Nystagmus
(135)	Dyskinesia (acute)
(R6)	Persistent hyperkinesia
(136)	Hypokinesis
(R7)	Pareses
(R8)	Signs of the pyramidal tract
(138)	Ataxia
(R9)	Other neurological symptoms
(137)	Akathisia
(R10)	Primitive reflexes

*Item No. on AMDP sheet 5.
**Write-in items are marked with R.

TABLE 9

Neurological Syndrome

Day	Fluperlapine ($N = 60$)		Haloperidol ($N = 60$)	
	$\bar{x}$	s.d.	$\bar{x}$	s.d.
0	48.2	8.4	47.4	8.1
3	48.7	8.8	60.1	15.2
5	50.8	10.7	59.6	16.7
7	49.7	10.5	63.0	15.7
14	50.4	10.3	65.7	16.6
21	49.4	9.0	65.4	14.8
28	49.5	9.6	66.1	14.2

Mean Values ($\bar{x}$) and Standard Deviations (s.d.)

Summary

Analysis of the Hallucinatory-Disintegrative AMDP Syndrome demonstrates an

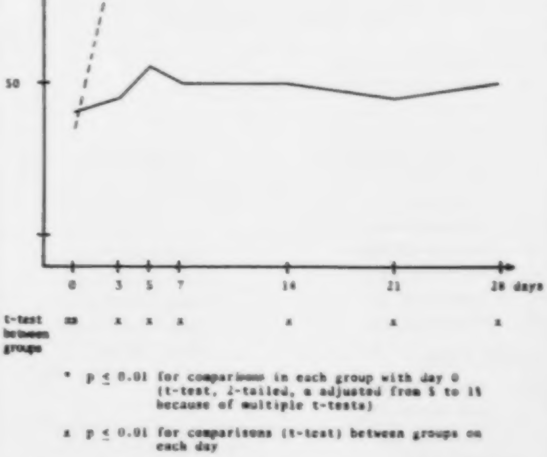


FIGURE 3. Course of the Neurological AMDP Syndrome (mean values).

equally strong antipsychotic effect of fluperlapine and haloperidol with an early onset (day 3). Analysis of the Neurological AMDP Syndrome indicates that haloperidol, in contrast to fluperlapine, causes frequent and strong extrapyramidal side effects.

References

AMDP, Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (Hrsg.). Das AMDP-System. Manual zur Dokumentation psychiatrischer Befunde. Berlin: Springer-Verlag, 1979.

AMDP, Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (Hrsg.). Testmanual zum AMDP-System. Empirische Studien zur Psychopathologie. Berlin: Springer-Verlag, 1983.

Angst, J. (ed.) Fluperlapine (NB 106-689): A new non-classical neuroleptic. *Drug Res.*, (special issue) 34(1): 109-137, 1984.

Angst, J., Battegay, R., Bente, D., et al. Das Dokumentationssystem der Arbeitsgemeinschaft fur Methodik und Dokumentation in der Psychiatrie. *Arzneimittel-Forschung*, 19: 339-405, 1969.

Baumann, U. Diagnostische Differenzierungsfähigkeit von Psychopathologie-Skalen. *Arch. Psychiatr. Nervenkr.*, 219: 89-103, 1974.

Bobon, D., Baumann, U., Angst, J., et al. *AMDP-System in Pharmacopsychiatry.* Basel: S. Karger, 1983.

Degkwitz, R., Helmchen, H., Kockott, G., and Mombour, W. ICD-Diagnoseschlüssel und Glossar psychiatrischer Krankheiten. Deutsche Ausgabe der internat. Klassifikation der WHO: ICD, 9. Rev., 5. Auflage. Berlin: Springer-Verlag, 1980. .

Mombour, W., Gammel, G., Von Zerssen, D., and Heyse, M. Die Objektivierung psychiatrischer Syndrome durch multifaktorielle Analyse des psychopathologischen Befundes. *Nervenarzt*, 44: 352-358, 1973.

Scharfetter, Ch. Das AMP-System. Manual zur Dokumentation psychiatrischer Befunde. Berlin: Springer-Verlag, 1971.

Winter, D.J. *Statistical Principles in Experimental Design.* London: McGraw Hill, 1962.

Woggon, B., and Dittrich, A. Konstruktion übergeordneter AMP-Skalen: "Manisch-depressives" und "schizophrenes" Syndrom. *Int. Pharmacopsychiatry*, 14: 325-337, 1979.

Use of a Standardized Documentation System (BLIPS/BDP) in the Conduct of a Multicenter International Trial Comparing Fluvoxamine, Imipramine, and Placebo

Giovanni B. Cassano, M.D.,[1] Luciano Conti, M.D.,[1] Gabriele Massimetti, M.D.,[1] Francesco Mengali, M.D.,[1] Jenifer S. Waekelin, M.D.,[2] and Jerome Levine, M.D.[3]

Introduction

When in 1978 Duphar BV, Holland, decided to organize a multicenter international clinical trial with the aim of assessing efficacy and safety of a new selective serotoninergic antidepressant compound, fluvoxamine maleate (FUVOX), the BLIPS/BDP system (Biometric Laboratory Information Processing System/Data Bank for Psychopharmacology), used at the Center for Clinical Psychopharmacology Data Documentation (CCPDD) of the Institute of Clinical Psychiatry of the University of Pisa, appeared to provide the necessary underlying structure for the study by offering an efficient standard data documentation system.

The organizational model that was used for the study provided that the company would maintain their usual role in the selection of sites, monitoring and collecting data, and supplying drugs to the sites. The role of the Pisa center included consultation on the design of the study, choice of the rating scales, and provision of a standardized documentation and analysis system, namely the BLIPS/BDP.

The company provided the raw original data collected from the investigators to the CCPDD. They organized several meetings with principal investigators in which the Pisa center participated, but the Pisa center had no additional contacts with the participating investigators.

The advantages of this organizational model include: a) open choice of sites and investigators (investigators do not need to belong to a previously organized group); b) the company plays its usual role with regard to site selection and monitoring; and c) the BLIPS/BDP documentation and analysis system does not require the use of special purpose (trial specific) rating scales but only the use of a standardized identification block. Therefore, widely used rating scales can be utilized by investigators without the necessity of special training, only checks of interrater reliability. This results in a very cost-effective flexible model which, as we will show, is sufficiently sensitive to establish efficacy and safety.

Material and Methods

The planned "Duphar" trial was an international multicenter, double-blind, prospectively randomized clinical trial aimed at comparing the antidepressant activity and safety of FLUVOX with that of imipramine (IMI) and placebo (PBO) in in- or outpatients aged over 18 years and suffering from a major depressive illness (according to the DSM-III definition).

Initially, there were 12 participating centers, 7 in North America and 5 in Europe (Table 1). FLUVOX and IMI, in unit doses of 50 mg, and PBO, in indistinguishable capsules, were administered according to a fixed-flexible dosage schedule: one capsule the first day, two capsules the second day, and three capsules from the third to the seventh day. After the first week the dosage could be adjusted, according to clinical judgment, from a minimum of one to a maximum of six capsules per day and administered, where possi-

---

[1] Institute of Clinical Psychiatry, University of Pisa, Pisa, Italy.

[2] Department of Clinical Research, Duphar BV, Weesp, The Netherlands.

[3] Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD 21228.

TABLE 1

Participating Centers and Data Available for Analyses

		Patients Enrolled	Patients for the Intent to Treat Analysis[a]		Patients for the Efficacy Analysis[b]	
Locations	Principal Investigators	No.	No.	%	(No.)	%
Miami, USA	Goldstein[c]	101	87	86.1	59	58.4
New York, USA	Farkas[c]	52	44	84.6	28	53.9
Ottawa, Canada	Lapierre[d]	63	60	95.2	45	71.4
Montreal, Canada	Ananth[d]	31	29	93.6	24	77.4
London, England	Paykel/Sirelig[c]	46				
London, England	Paykel/Norton[c]	45	91	100.0	83	91.2
Montreal, Canada	Amin[c]	91	89	97.8	75	82.4
Nice, France	Darcourt[d]	52	48	92.3	43	82.7
	Totals	481	448	93.1	357	74.2
Jackson, USA	Caranza[e]	3				
Houston, USA	Caranza[e]	16				
Turin, Italy	Ravizza[e]	3				
Pisa, Italy	Cassano/Conti[f]	45				

[a] Patients with at least two evaluations on drug.

[b] Patients with at least 14 days' medication and not dropped out after the 14th day because of possible study drug-related concurrent signs and symptoms or for reasons unrelated to study group.

[c] Outpatients.

[d] Inpatients.

[e] Study stopped after only a few patients enrolled; data not included in the analysis.

[f] Placebo-controlled study conducted under the same protocol; data not included in the analysis.

ble, three times a day. No other psychotropic medications were allowed with the exception of chloral hydrate or flurazepam, as hypnotics, only when this was unavoidable.

Patients with an established diagnosis of major depressive illness and with a score of at least 15 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D) at the end of the pretreatment period, and not precluded by the exclusion criteria (childbearing potential or pregnant women; antidepressant therapy in the past 2 weeks; electroconvulsive therapy within the last month; depressive symptoms secondary to other psychiatric illness; dependence upon licit or illicit drugs; serious organic diseases; need for concurrent medications which could interact with the study drugs or obscure their effects; and patients unwilling or unable to cooperate in the study) were included in the trial.

After a pretreatment period of 3 to 7 days, during which one capsule of PBO indistinguishable from the treatment capsules was given, patients received drugs for up to 28 days. For the North American centers, the treatment period was extended to 42 days. Analyses presented here are focused on 28-day data in order to utilize both European and North American data.

Assessment instruments were mostly the standard rating instruments of the BLIPS/BDP and the assessments were done on entry, at the last pretreatment day, and weekly thereafter (Table 2).

The main aim of this paper is to demonstrate the utility of the organizational model for this kind of study. Because of that, we will consider only the Adult Personal Data Inventory (APDI) for the demographic data, the Patient Termination Record (PTR) for the trial data, the HAM-D and the Clinical Global Impression Scale (CGI) for efficacy data, and the Dosage and Treatment Emergent Symptoms Scale (DOTES) and Treatment Write-in Scale (TWIS) for safety data.

Results

Of the 12 participating centers, only 8 furnished sufficient data for analyses (Table 2). Three centers (Nos. 3, 4, and 7) studied inpatients; all the others studied outpatients. Two North American centers (Nos. 8a and 8b) and one European center (No. 9) have been excluded from the analyses because of the small number of patients enrolled. Due to a delay in obtaining permission to conduct the trial

TABLE 2

Assessment Instruments and Schedule

	On Entry	Past Pretreatment Day	Day 7	Day 14	Day 21	Day 28[a]
Adult Personal Data Inventory (APDI)[b]	X					
Prior Medication Record (PMR)	X					
Clinical Examination	X					
Clinical Global Impression (CGI)[b]	X	X	X	X	X	X
Brief Psychiatric Rating Scale (BPRS)	X	X	X	X	X	X
Hamilton Rating Scale for Depression (HAM-D)[b]	X	X	X	X	X	X
Self-Report Symptom Inventory (SCL-90)		X	X	X	X	X
Self-Rating Depression Scale (SDS)		X	X	X	X	X
Dosage Record and Treatment Emergent Symptom Scale (DOTES)[b,c]	X	X	X	X	X	X
TESS Write-in (TWIS)[b,c]	X	X	X	X	X	X
Concurrent Medication		X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Hematology/Biochemistry		X		X		X
Drug Level		X		X		X
Electrocardiograph	X			X		X
Patient Termination Record (PTR)[b]						X
Investigator Summary						X

[a] Or if the patient leaves the study before day 28.

[b] Assessment instruments utilized in the present analysis.

[c] And at each change of dosage or if new important symptoms should emerge.

from the Italian authorities, the Pisa center (No. 10) conducted a separate PBO-controlled trial under the same protocol; the Pisa data are not included in these analyses.

Of the 481 enrolled patients, 448 had at least two evaluations during the drug intake period (Table 1) and have been included in the APDI, PTR, and DOTES analyses.

The distribution of the patients according to their major demographic characteristics (APDI)—age, sex, marital status, prior treatments, significant medical conditions, and previous hospitalizations—is approximately the same in the three treatment groups. The less-than-1-year duration of the actual episode is less (but not significantly so) in the PBO group (Table 3).

Data from the PTR (Table 4) provide significant differences among the three groups. The duration of treatment is approximately the same, but the reasons for premature termination differ significantly between active drugs and PBO. As can be expected, in the PBO group premature interruptions for ineffectiveness are relatively more frequent than in the two active drug groups, whereas the opposite is true for the adverse reactions. There were no differences among the groups in the number of patients requiring hypnotics, but a trend in suggesting mainly that patients on active drugs required more gastro-

TABLE 3

Demographic Summary (APDI)

Variables	FLUVOX	IMI	PBO
Total Number of Patients:	161	153	149
Age: Mean (± SD)	42.7 (± 13.7)	41.3 (± 13.8)	42.1 (± 11.8)
Min. - Max.	19 – 70	10 – 70	21 – 68
Sex: Female	99 (61.5%)	92 (60.1%)	95 (63.8%)
Marital Status: Ever Married	131 (81.4%)	104 (68.0%)	119 (79.9%)
Prior Treatments: Any Prior Treatment	102 (63.4%)	107 (70.0%)	99 (66.4%)
Duration of Present Episode: Less than 1 year	108 (67.1%)	103 (67.3%)	111 (74.5%)
Significant Medical Conditions: Any Condition	20 (12.4%)	11 (7.7%)	21 (14.1%)
Previous Hospitalization: None	117 (72.7%)	108 (70.6%)	104 (69.8%)

TABLE 4

Patient Termination Summary (PTR) — 4 Weeks' Treatment

Variables	FLUVOX	IMI	PBO
Total Days in Study: Mean (± SD)	23.3 (±7.6)	23.9 (±7.3)	24.5 (±6.4)
Premature Termination*			
Ineffectiveness	12	10	26
Improvement	2	3	1
Adverse Reactions	19	17	5
Unrelated to Treatment	21	17	17
Completed 28 Days of Treatment:	102 (63.4%)	104 (63.0%)	100 (67.1%)
Ancillary Medications:			
Gastrointestinal Preparations	24 (14.9%)	21 (13.7%)	9 (6.0%)
Hypnotics	77 (47.8%)	72 (47.1%)	63 (42.3%)
Given the choice, would you continue on this study medication (1) Mean (± SD)**	2.24 (±1.4)	2.11 (±1.5)	1.74 (±1.5)

* Chi-square = 19.08, $p < 0.05$

** Analysis of variance regular: $p < 0.05$

(1) Scale Points:
0 = Definitely No
1 = Inclined to Say No
2 = Undecided
3 = Inclined to Say Yes
4 = Definitely Yes

intestinal preparation. To the question: "Given the choice, would you continue on this study medication?" the investigators' answer is significantly in favor of the two active drugs.

The mean daily dosage of the three treatments is similar in both the week-by-week analysis and in the overall treatment period. Maximum dosage is reached in the third week (Table 5). The most frequent side effect (rated at least moderate) observed in the FLUVOX group is "nausea." "Dry mouth," "sweating," and "dizziness" are more frequent in the IMI group (Table 6).

These preliminary findings allow us to discriminate between the two active compounds and PBO and, on the basis of side effects, to differentiate FLUVOX from IMI.

TABLE 5

Mean Daily Dosage

	Fluvoxamine		Imipramine		Placebo	
	Mg	(No. of Capsules)	Mg	(No. of Capsules)	Mg	(No. of Capsules)
Week 1	115.03	2.3	118.09	2.4	124.83	2.5
Week 2	157.16	3.1	161.48	3.2	184.17	3.7
Week 3	177.47	3.5	176.56	3.5	203.70	4.1
Week 4	134.55	2.7	144.20	2.9	153.52	3.1
All Periods	144.95	2.9	149.06	3.0	166.02	3.3

At this point, rather than describe further the standard output of the BLIPS/BDP system, we would rather emphasize the flexibility and potential for rapidly and easily looking at the data in different ways. We will demonstrate the possibilities offered by the BLIPS/BDP system in handling and analyzing the pooled data of a large multicenter trial.

The major statistical procedure employed in the following analyses was a two-way analy-

TABLE 6

Emergent Signs and Symptoms (Moderate and Severe)

	FLUVOXAMINE	IMI	PBO
No. of Patients	161	153	149
Dry mouth	8	31	10
Nausea	29	9	6
Somnolence	17	15	2
Insomnia	15	10	6
Constipation	13	11	5
Headache	14	6	10
Sweating	7	13	4
Dizziness	2	15	4
Agitation	8	8	3
Anorexia	6	4	4
Tremor	4	7	2
Hyperkinesia	4	4	4
Hypokinesia	8	2	1
Hypotension	1	6	3
Manic reaction	1	4	2

TABLE 7

CGI — Severity of Illness: Results of Two-Way Covariance Analysis

	Intent-to-Treat Analysis			Efficacy Analysis		
	Score[*] Initial	Score[*] Final	Percent of Improvement	Score[*] Initial	Score[*] Final	Percent of Improvement
Fluvoxamine	4.41	3.26	26.1	4.46	2.99	33.0
Imipramine	4.47	3.29	26.4	4.47	3.08	31.1
Placebo	4.51	3.62	19.7	4.54	3.53	22.3[**]

[*] Standardized scores.

[**] Analysis of covariance: FLUVOX PBO > $p < 0.05$
IMI PBO > $p < 0.05$

TABLE 8

CGI — Global Improvement and Efficacy Index[*]: Final Scores

	Intent-to-Treat Analysis		Efficacy Analysis	
	Global Improvement Score	Efficacy Index Score	Global Improvement Score	Efficacy Index Score
Fluvoxamine	2.67	1.95[a]	2.30[b]	2.23[c]
Imipramine	2.74	1.72	2.49	1.73
Placebo	3.01	1.80	2.85	1.90

[a] Analysis of variance: FLUVOX > IMI $p < 0.05$

[b] Analysis of variance: FLUVOX > IMI $p < 0.05$

[c] Analysis of variance: FLUVOX > IMI $p < 0.05$
FLUVOX > PBO $p < 0.05$

[*] The Efficacy Index from the CGI combines a global rating of improvement and side effects.

sis of covariance ANCOVA where drug conditions and centers were the two factors in the design. For the efficacy data we performed two types of analyses "in parallel": the first includes all patients with at least two evaluations on drug (the so-called "intent-to-treat analysis"); the second method, which we call "efficacy analysis," is limited only to cases with at least 14 days' medication and not withdrawn after the 14th day because of possible study drug-related concurrent signs and symptoms, or for reasons unrelated to study drug (Table 1). With the BLIPS/BDP system, it is possible to perform the two types of analysis, one immediately after the other, by simply giving the computer the different selection criteria.

The score on the CGI item "severity of illness" is approximately the same in the three treatment groups (intermediate between "moderately" and "markedly ill") at the beginning of the treatment; the final score is close to "mildly ill" for FLUVOX and IMI and close to "moderately ill" for PBO in the intent-to-treat analysis. In the efficacy analysis, these differences are more marked and they reach the statistical significance in favor of the two active compounds (Table 7). Although significant differences were found between centers (Centers 2 and 3 in both analyses, Centers 3 and 6 in the efficacy analysis), no interactions between centers and drugs emerged.

For the CGI item "global improvement" the improvement is greater with FLUVOX and IMI than with PBO, but the statistical significance is reached only in the "efficacy analysis" where the FLUVOX- and IMI-treated patients are rated approximately "much improved" and the PBO-treated patients rated "minimally improved" (Table 8). The results of Center 2 are significantly different from all other centers except for Center 7, but no significant interactions between centers and drugs exist.

At the end of treatment, the number and percentage of patients judged as "much" or "very much improved" are greater in the FLUVOX and IMI groups than in the PBO group. These differences are greater (chi-square analysis) in the efficacy analysis (Table 9). The analysis of the CGI item "efficacy index" seems to favor FLUVOX over PBO and especially over IMI (Table 8).

TABLE 9

CGI — Global Improvement: Number and Percentage of Improved Patients

		Intent-to-Treat Analysis				Efficacy Analysis			
		FLUVOX	IMI	PBO	Total	FLUVOX	IMI	PBO	Total
Much or Very Much	No.	84	72	53	209	79	65	51	195
Improved	%	52.2	48.3	37.1	46.1	65.8	54.6	41.5	53.9
Minimally	No.	31	32	38	101	20	22	34	76
Improved	%	19.3	21.5	26.6	22.3	16.7	18.5	27.6	21.0
No Change	No.	46	45	52	143	21	32	38	91
or Worse	%	28.6	30.2	36.4	31.6	17.5	26.9	30.9	25.1
Total		161	149	143	453	120	119	123	362

The above examples give an idea of the utility of the BLIPS/BDP system in analyzing data derived from clinical trials of psychotherapeutic agents. However, the flexibility of this system enables us to perform many other analyses with very few additional simple external commands.

If, for instance, we want to study how the initial severity influences the results of treatment, we can stratify patients according to the initial severity on a selected assessment instrument and analyze the resulting groups as new cohorts. In this example, we used the initial HAM-D total score as an index of severity. In this study, 25.75 is the mean initial total score of the HAM-D and 5.72 the standard deviation (SD). We therefore consider "mildly" severe patients to be those with a score less than or equal to 20 (mean minus SD), "severe" patients with scores equal to or more than 31, and "moderately" severe patients with scores between 21 and 30. The ANCOVA (in this case drug conditions and level of severity are the two factors in the design) demonstrates that the pattern of improvement is almost the same for all analyzed items and factors (CGI and HAM-D). The improvement, however, is greater for the FLUVOX- and IMI-treated patients than for the PBO-treated patients. As is clearly seen in Table 10, the greater the initial severity, the greater is the improvement.

TABLE 10

Stratification by Initial Severity of HAM-D Total

		Total HAM-D Score* Initial	Final	Percent of Improvement
Total Sample	F	25.61	13.41	47.6
	I	25.92	13.74	47.0
	P	25.60	17.34	32.3**
Mild 20	F	17.86	13.42	24.9
	I	18.43	15.63	15.2
	P	17.18	17.62	–
Moderate 21≤30	F	25.62	14.18	44.6
	I	25.08	13.52	46.1
	P	24.66	16.87	31.6
Severe 31	F	34.53	10.24	70.3
	I	34.96	12.74	63.6
	P	34.05	19.20	43.6

F = Fluvoxamine; I = Imipramine; P = Placebo

*Adjusted scores.

**Analysis of covariance: F>P - $p<0.05$
I>P - $p<0.05$

TABLE 11

Stratification by Treatment Setting: HAM-D Retardation Factor

		Score* Initial	Final	Improvement
Total Sample	F	2.38	1.23	48.3
	I	2.20	1.26	42.7
	P	2.29	1.62	29.3**
Inpatients	F	2.77	1.18	57.4
	I	2.54	.98	61.4
	P	2.63	1.44	45.2
Outpatients	F	2.18	1.26	42.2
	I	2.05	1.38	32.7
	P	2.14	1.69	21.0
Total Sample:				
Inpatients		2.65	1.20	54.7
Outpatients		2.12	1.45	31.7***

F = Fluvoxamine; I = Imipramine; P = Placebo

*Adjusted scores.

**Covariance analysis: F>P - $p<0.05$
I>P - $p<0.05$

***Covariance analysis: Inpatients>Outpatients - $p<0.05$

As both inpatients and outpatients are included in this trial, one of the obvious analyses would be the comparison of results between the inpatients and the outpatients. With very few instructions, we stratified patients according to the treatment setting and again ran the two-way ANCOVA. The results demonstrate that the initial severity of the analyzed items and factors on CGI and HAM-D is higher in the inpatients than in the outpatients. This is shown in Table 11. For the HAM-D "retardation" factor, these differences are statistically significant.

Conclusions

In this paper, data from a multicenter international clinical study on FLUVOX have been presented to exemplify both the problems raised and the potential information that can be obtained using a comprehensive and standardized system of analyses.

The BLIPS/BDP standardized output provides a clear profile of FLUVOX from its efficacy to its safety through the comparison with IMI and PBO. Drug and center interactions, when present, are immediately in evidence, as well as possible limitations and inadequacies of the design or of the conduct of the study.

Once the cleaned data are stored in the computer data bank and processed, the first standard analyses can be presented to the principal investigators. This will stimulate suggestions for specific analyses. Multicenter trials, because of the number of subjects and centers, offer the possibility of a more complete study of a drug's profile as well as of the population in the study, and of the instruments employed in the ratings. In this way, there can be a complete exploration of the data which provides not only psychopharmacological information but also information on clinical, psychopathological, epidemiological, and transcultural aspects of the population under study. The BLIPS/BDP accomplishes this by a completely automated procedure, capable of answering a wide array of questions. Moreover, the standard outputs can be interpreted with great facility because they are in a uniform format.

Frequently, investigators collect data which are grossly underused in terms of the clinical information being analyzed. For this reason, we strongly recommend that multicenter clinical studies should be planned with a view to using an established proven data handling, processing, and documenting system.

In conclusion, we have shown that a multicenter international study can be successfully accomplished using customary pharmaceutical industry procedures and monitoring linked to an established standardized documentation system.

The Design and Conduct of the Upjohn Cross-National Collaborative Panic Study

Gerald L. Klerman, M.D.,[1] James H. Coleman,[2] and Robert P. Purpura, M.D.[3]

The decision by the Upjohn Company in the early 1980's to initiate a large and complex study came from two scientific developments: 1) new developments in understanding the psychopathology, diagnosis, and classification of anxiety disorders, and 2) the early experience with alprazolam, a new triazolobenzodiazepine.

New Developments in Psychopathology, Diagnosis, and Classification of Anxiety Disorders

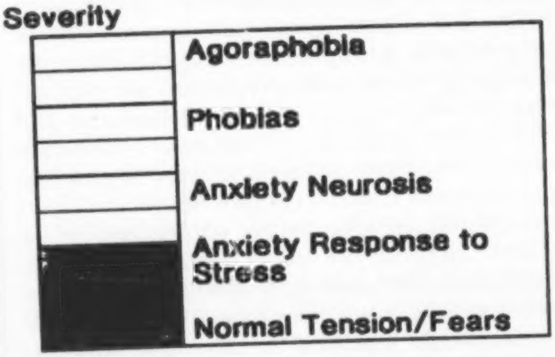
The continuum model of anxiety (as shown in Figure 1) had been the dominant view of anxiety states for many decades. This model proposed a continuum from normal fears and tension through intermediate stages of stress reactions, to full-blown anxiety neurosis (whose most severe form was agoraphobia). From World War I through the 1970's, most clinicians, whether of biological, behavioral, or psychoanalytic persuasion, accepted this continuum model of anxiety. This model emphasized the gradients of severity and was built upon the experience of anxiety and fear in everyday situations and in adaptation, and evolution.

This model drew upon the psychological research of Cannon (1936) on "fight or flight" and his demonstration of the role played by the autonomic sympathetic nervous system. Later, biological research was extended by Selye to include the hypothalamic-pituitary-adrenal-cortical system as a mediator of "stress."

In the 1960's, a number of observers challenged this continuum view. Roth and associates (1960) in England described the "phobic-depersonalization syndrome," sometimes called the "calamity syndrome." West and Dally (1959) and Sargant (1960) described a group of atypical depressives with predominant anxiety symptoms who appeared responsive to monoamine oxidase inhibitors (MAOIs). In the United States, Klein and his associates (1964) described the failure of chlorpromazine to influence severe phobic anxiety and reported that imipramine, tricyclics, and antidepressants improved panic episodes and agoraphobia.

Further research demonstrated the value of two classes of antidepressant drugs: MAOIs and tricyclic antidepressants, in contrast to the limited efficacy of conventional benzodiazepines (Sheehan, et al., 1980).

As a result of these observations, the proposal was made (*see* Figure 2) to separate agoraphobia and panic disorder from other forms of anxiety disorders and to group these conditions together. These proposals were partially embodied in the Diagnostic and Statistical Manual—3rd ed., 1980 (DSM-III) classification of Anxiety Disorders, which represented a significant departure from previous U.S. classifications as in the DSM-I, DSM-II, ICD-8, and ICD-9.



---

[1] George Harrington Professor of Psychiatry, Harvard Medical School and Director, Stanley Cobb Research Laboratories, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114. (Now at Department of Psychiatry, Cornell University Medical Center, New York, NY 10021.)

[2] Coordinator, Worldwide Panic Disorder Program, The Upjohn Company, Kalamazoo, MI 49001.

[3] Medical Manager, Psychopharmacology Research Unit, The Upjohn Company, Kalamazoo, MI 49001.

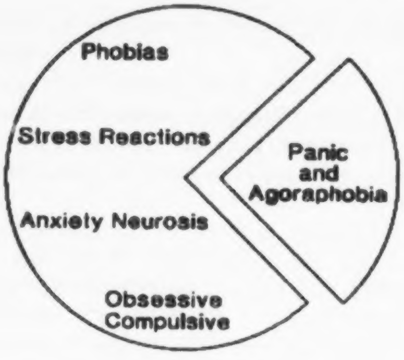


FIGURE 2. Panic and agoraphobia—separated.

In this new view, the central feature of the clinical psychopathology is the panic attack. The panic attack involves not just greater intensity of anticipatory anxiety, fears, and tension, but is a discrete time-limited episode with sudden onset of intense dread, accompanied by bodily symptoms suggestive of automonic arousal such as sweating, palpitations, tremor, and fear of losing control, going crazy, fainting, or dying.

There has been considerable controversy around the nosologic status of panic attacks, but also a continuing disagreement over the relative roles of drug treatment, MAOIs, tricyclics, beta-blocking agents, benzodiazepines, and also the efficacy and role of behavior therapy, particularly desensitization and exposure in vivo and flooding.

Alprazolam: A New Triazolobenzodiazepine

The chemical structure of alprazolam represents a modification of the conventional benzodiazepine ring structure by the addition of a triazolo group to the ring. The Upjohn Company developed a number of triazolo compounds, notably triazolam (Halcion) and alprazolam (Xanax). Trazadone (Desyrel), which has demonstrated antidepressant action, is also a triazolo compound.

Preliminary reports by Chouinard et al. (1982) suggest the value of alprazolam in panic disorder and agoraphobia, and these observations were confirmed in two controlled trials reported by Carr and Sheehan (1984).

The evidence presented by Ballenger at this meeting indicates the efficacy of alprazolam over placebo in the acute treatment of panic attacks and agoraphobia. Still unresolved is the question of the relative efficacy of alprazolam against other benzodiazepines, particularly diazepam. Experienced clinicians who have worked with patients with panic and agoraphobia are of the opinion that the efficacy of alprazolam is far superior to that of other benzodiazepines. Most patients entering recent trials with MAOIs, alprazolam, and tricyclics have had extensive prior treatment with benzodiazepines with limited success.

Should further studies demonstrate the superiority of alprazolam to other benzodiazepines, in what way can we account for this action of alprazolam? The efficacy of alprazolam in panic disorder could be due to pharmacokinetic or pharmacodynamic mechanisms.

There are suggestions that alprazolam has pharmacodynamic effects on the down-regulation of beta-blocking receptors. If substantiated, this pharmacologic profile of alprazolam would share certain similarities with antidepressant drugs such as tricyclics. Alprazolam has been effective in mild to moderate forms of depression, but not in severe endogenous, melancholic, or psychotic forms (Laakmann, in press).

The differences between alprazolam and other benzodiazepines may be pharmacokinetic. Assuming a ten-to-one equivalence between diazepam and alprazolam, 6 to 8 mg of alprazolam, the dose used in studies of panic disorder, would be the equivalent of 60 to 80 mg per day of diazepam, a dose which is seldom tolerated by most ambulatory patients.

TABLE 1

Upjohn Cross-National Project Centers

United States	New York City, New York
	Iowa City, Iowa
	Torrance, California
	Rockville, Maryland
	Charleston, South Carolina
Canada	Montreal
	Toronto
Australia	Melbourne

Studies comparing alprazolam with diazepam at equivalent doses are underway and should help resolve this question.

Goals of the Upjohn Cross-National Panic Project

In 1982, the Upjohn Company initiated a worldwide panic program (Purpura, in press) which includes a number of interrelated pharmacologic, biologic, and clinical studies. Within the large program, the Cross-National Collaborative Panic Study focuses on clinical efficacy and safety.

The major goal of the Cross-National Panic Study is to assess the efficacy and safety of alprazolam in the treatment of panic disorder and agoraphobia. Subsidiary goals include: 1) better understanding of the psychopathology and diagnosis, and 2) improved means of diagnostic assessment and of evaluation of change in clinical trials of anxiety disorders.

Another subsidiary goal is to develop improved collaboration between industry, academic medical centers and universities, and governmental agencies in the U.S. and other countries.

To achieve these goals, the Cross-National Project is being conducted in two phases.

The *First Phase*, eight centers collaborating on the common design, which involves a comparison of alprazolam versus placebo, has been completed and results are being reported today. The eight centers are shown in Table 1 and include five in the U.S. (New York City, N.Y.; Iowa City, Iowa; Torrance, California; Rockville, Md.; and Charleston, S. Carolina), two in Canada (Montreal and Toronto), and one in Melbourne, Australia. Over 500 patients have been studied for an 8-week period in these eight centers. The dose schedule was a fixed, flexible dose with the attempt that all patients receive 6 mg per day of alprazolam, a dose considerably higher than previously used in studies of anxiety and depression. Diagnostic consistency is accomplished by the use of the Structured Clinical Interview for DSM-III Diagnosis (SCID), developed by Spitzer and Williams (unpublished).

In the *Second Phase*, alprazolam is being compared against placebo and against a standard drug, imipramine. The choice of imipramine as a standard drug was a difficult one, inasmuch as no drug treatment has been approved by the FDA for this condition. In the case of depressions, the tricyclic drug is the standard drug. In the case of beta-blocking agents for cardiovascular illness, propranolol is the standard drug. However, in the case of panic disorder and agoraphobia, no drug had been approved by the FDA, and there was no consensus in the field as to what should be the standard drug; conventional benzodiazepines, such as diazepam (Valium), a tricyclic, or an MAOI. Imipramine was chosen because of the extensive evidence for its efficacy (Liebowitz, in press).

This Second Phase of the study is now underway in 12 countries, and by the spring of 1986, approximately 1,000 patients will have been entered into treatment.

The First Phase and Second Phase studies utilize the same diagnostic criteria (modified from DSM-III), the same structured interview (SCID-up), and the same battery of scales and ratings for the assessment of clinical improvement and adverse effects. All data are encoded on upscan forms and sent to a central data processing facility in Kalamazoo, Michigan.

Assurance of Diagnostic Standardization and Quality Control

In any clinical trial, attention must be given to standardization of procedures for the selection of patients, randomization, assessment of change, control of concurrent medication, etc. In multicentered trials, particularly those which involve more than one nation, these considerations become all the more paramount. In addition, in this trial, since there was some degree of controversy over the validity of the diagnostic concept of panic disorder and its relationship to agoraphobia, considerable attention had to be given to the techniques to assure standardization of diagnostic assessment.

Among the techniques utilized, the following are noteworthy:

1) A very detailed protocol and procedures manual was prepared. The attempt was made to anticipate as many contingencies as possible, so as to provide explicit instructions to

the investigators, and to increase the likelihood that the study would be conducted in a similar way at all eight sites.

2) To ensure diagnostic consistency, a modification of the DSM-III criteria for panic attack, panic disorder, and agoraphobia were developed as part of an ongoing consensus project among the investigators at the eight sites, and involve a large group of consultants who have been active in the field.

3) A structured interview, the SCID-up, was commissioned for the explicit purpose of standardizing the interview procedure, so as to reduce information variance and criterion variance. Drs. Spitzer and Williams at the New York State Psychiatric Institute and Columbia University, College of Physicians and Surgeons, developed the SCID-up to operationalize the criteria for the study, including inclusion and exclusion criteria. The SCID-up has been translated into a number of languages for the participating countries in phase two, and extensive training and reliability exercises have been conducted.

4) A 1-week training workshop was held in Boston in 1983 for the first-phase investigators, and in Pisa, Italy, in November of 1983 for the second-phase investigators. During this training exercise, the protocol was reviewed in great detail, the concept and criteria for panic attack and agoraphobia were discussed extensively, video tapes were viewed, the SCID-up was explained, and experience was gained in the use of the SCID-up in interviews with patients from local clinical settings.

5) Special attention was given to provide operational definition and systematic assessment of panic attacks. Since the reduction of panic attacks was the major outcome of the study, it was necessary to devise a new instrument. Based upon Dr. Sheehan's previous experience, with assistance from consultants (particularly Drs. Spitzer and Williams), a detailed assessment of panic attack was devised which incorporated distinctions between spontaneous and unexpected panic attacks and situationally provoked panic attacks and limited symptom attacks, and these were further distinguished from anticipatory anxiety. In addition to the physician-guided ratings, each patient completed a weekly log in which daily records were kept of the number, intensity, and duration of attacks, medication taken, and activities outside of the home.

6) As a further assurance of systematic standardization in quality, a quality assurance program was instituted in which teams of two consultants not directly involved in any of the clinical sites were recruited and trained and then made on-site visits to each of the sites at least twice during the conduct of the trial. During these visits, the records were reviewed for diagnostic consistency, and interviews with patients were observed and assessed.

Organization of the Study

The overall project, including the two phases, is coordinated by Mr. Coleman and Dr. Purpura of the Upjohn Company. I serve as a consultant.

In addition, there is a *Study Review Committee* chaired by Dr. Daniel X. Freedman which operates similarly to operations committees in VA cooperative studies, namely, it is unblinded and periodically reviews the progress of the study and evidence as to indices of safety and efficacy, in order to terminate a study for ethical reasons either because of the adverse effects which pose risks to the patient or the evidence of overwhelming efficacy which would lead to compromising the needs of patients exposed to placebo. This group also advises informally on matters of research design, statistics, and interpretation of findings.

For each two phases of the study, a *steering committee* composed of the senior investigators and co-chaired by Mr. Coleman and Dr. Klerman meets periodically to review decisions and protocol, to plan data analyses, and to monitor progress. In addition to the meetings two or three times a year, monthly teleconference calls provide for ongoing discussion of issues in the conduct of the trial, management of possible complications, and to ensure data processing and data analysis.

Training sessions have been held for each phase. The phase-one investigators met in Boston, Massachusetts in February 1983, for 1 week to review the protocol and to obtain training and experience in the use of a structured interview, the SCID.

Similar training sessions for the second phase of investigators were held in Pisa, Italy, in November 1983.

Data Processing and Data Analysis

This study has generated considerable amounts of data. Data processing is facilitated by the use of upscan forms for primary entry of data. Manual editing is conducted by the Upjohn Company and the data is entered into a computer in Kalamazoo, Michigan. Once the data processing has been completed and an edited tape is prepared, analyses are conducted at two sites — Kalamazoo, Michigan, and Massachusetts General Hospital, Boston, Massachusetts. The primary responsibility of the group at the Upjohn Company in Kalamazoo is the conduct of analyses to ensure proper information for the NDA submission to the FDA for the expected indication of treatment of panic attacks. Analyses primarily for scientific value for research undertaken by the investigators is conducted at the Massachusetts General Hospital under the leadership of Philip Lavori, Ph.D., and myself. Decisions as to scientific publications are made by the principal investigators at their respective steering committees. The Upjohn Company does not assume responsibility for scientific presentation or publication, although it has underwritten a considerable amount of the cost required for statistical analyses, preparation of graphic material, and secretarial assistance.

Conclusions

The findings to be reported here indicate the success of the overall design and the procedures utilized to ensure standardization of diagnosis and maintenance of the protocol across multiple sites in three different countries. It is expected that these procedures and techniques will prove useful in the second-phase study. Inasmuch as the second-phase study involves at least 12 different countries with multiple languages, cultural, and professional traditions, the attention given to diagnostic specification and careful assessment should prove helpful.

Preliminary experience indicates that over the course of the 2 1/2 years since this project was initiated, there have been greater acceptance and diffusion of the concept of panic attacks and panic disorder in relation to agoraphobia, and that participants in this study have increasingly accepted these diagnostic concepts as well as the importance of structured interviews and diagnostic algorithms for the selection of subjects, particularly in an area where there is controversy as to the validity of the diagnostic concept.

A clinical trial such as this one can serve as a partial validation of diagnostic concepts, in this case, panic disorder. The capacity to generate large numbers of cases in multiple sites and to demonstrate consistency of diagnosis and similarity of symptom pattern and of treatment response serves as an indirect validation of the concept of separating panic attacks from other forms of anxiety and linking panic attacks with agoraphobia as a diagnostic complex.

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder (DSM-III)*, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

Cannon, W.B. *The Wisdom of the Body*. New York: W.W. Norton, 1936.

Carr, D.B., and Sheehan, D.V. Panic anxiety: A new biological model. *J. Clin. Psychiatry*, 45:323–330, 1984.

Chouinard, G., Annable, L., Fontaine, R., and Solyom, L. Alprazolam in the treatment of generalized anxiety and panic disorders: A double-blind placebo controlled study. *Psychopharmacology*, 77:229–233, 1982.

Klein, D.F. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia*, 5:397, 1964.

Laakmann, G. Alprazolam vs. amitriptyline in the treatment of depressed outpatients: A randomized double blind trial. In: *Current Concepts in the Drug Treatment of Neurotic Disorders: Focus on Alprazolam*. New York: Churchill Livingstone, Inc. (In press)

Liebowitz, M.R. Alprazolam in the treatment of panic disorders. In: *Current Concepts in the Drug Treatment of Neurotic Disorders: Focus on Alprazolam*. New York: Churchill Livingstone, Inc. (In press)

Purpura, R.P. Controlled clinical trials. Paper presented at the Collegium Internatiónale Neuropsychopharmacologícum. (In press)

Roth, M. The phobic anxiety-depersonalization syndrome and some general aetiological problems in psychiatry. *J. Neuropsychiatry*, 1:293–306, 1960.

Sargant, W. Some newer drugs in the treatment of depression and their relation to other somatic treatments. *Psychosomatics*, 1:14–17, 1960.

Sheehan, D.V., Ballenger, J., and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch. Gen. Psychiatry*, 37:51–59, 1980.

Spitzer, R.L., and Williams, J.B. *Structured Clinical Interview for DSM-III (SCID-10/1/84).* (Unpublished)

West, E.D., and Dally, P.J. Effect of iproniazid in depressive syndromes. *Br. Med. J.*, 1:1491–1494, 1959.

Microcomputers in Clinical Psychopharmacology

CHAIRS: John E. Overall, Ph.D.
Department of Psychiatry
University of Texas Medical School
Houston, Texas

and

Joanne B. Severe, M.S.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Why a Statistical Package on a Micro?

MaryAnn Hill, Ph.D.[1]

The explosion in microcomputer sales promises to alter our society in fundamental way, changing the way we work, plan, and organize our lives. But without effective software, the microcomputer remains an engaging toy. Many researchers are currently evaluating the role of the micro in their research environment and are asking, "What kind of statistical software do we need?", "Will we have to give up familiar mainframe options?", etc.

There are several advantages in using a microcomputer to do the statistical analysis in research. Locating a micro close to the research team and its original data sheets facilitates data screening and also communication between the technical support staff and the research team. The technical support staff find it easier to focus on the data analysis, because on a micro the interface with the system is more "user-friendly"—allocation and naming of files is greatly simplified and there is no mainframe job control language (JCL). Even if the project is part of a large multicenter trial, much of the data monitoring and screening can be done on the micro and the clean data shipped or networked to the mainframe for final analyses with data from all centers. Finally, most project managers are happy to reduce mainframe computer bills.

Regardless of machine size, it pays to use a statistical package. Advantages include:

- *Correct computations.* The well-known packages have been "debugged" over a broad range of applications, and they use appropriate algorithms—they do *not* simply code textbook formulas.
- *More time for research,* because less time is spent programming.
- It is easier to do *"good" data analysis* because many data screening features appear automatically—e.g., histograms for each group in a two-sample t test.
- *One-time specification of data description instructions.* Variable names, formats, acceptable range limits, flags for missing data, transformations, etc. do not need to be tailored for each individual analysis.
- *Documentation and help facilities.* The major package distributors provide extensive manuals, short courses in data analysis, and help via telephone. You are not stuck because your programmer disappears to Tahiti.

---

[1] Department of Psychiatry, UCLA School of Medicine, West Los Angeles VA Medical Center (Brentwood Division), and BMDP Statistical Software, Inc., Los Angeles, CA 90025.

— The use of packaged software *facilitates communication of results* when submitting grant proposals and papers to refereed journals, since the methods are well known and documented.

Unfortunately, much of the statistical software for the micro is woefully inadequate. A data analyst needs a wide spectrum of techniques that can be applied easily to a collection of data. If I were called in to consult with your research team, I would need access to a number of features, all of which are currently available on an IBM PC XT or AT (and compatibles). I do not intend to present a detailed explanation of the statistics, but hope to impart a flavor of the breadth of supports required for proper data analysis. From these examples, I hope that you will understand my concern when a research group shows me preliminary results consisting of nothing but means, standard deviations, *F* statistics, and *p* values.

In addition to statistical supports for data analysis, packages often have data manipulation features that merge files and functions that extract information from nonrectangular files. Without such features on a micro, a longitudinal study would be seriously hampered.

Software Features for Data Analysis

Many of the features I would hope to find on your micro are needed for data screening. The term "screening" indicates not only finding errors and inconsistencies in the data, but also ensuring that the data conform to assumptions necessary for subsequent analyses. Screening is not one set of procedures carried out prior to the analysis—each stage of the data analysis uncovers information that affects later steps. In sizable studies, the primary analysis of interest may consume 5% of the staff time and computer costs, while data screening takes 95%. The data analyst will want to check for recording errors and compliance to protocol, as well as assess the influ-

```
   TREATMENT                   CONTROL
     x                           x
    xx                           xx
   xxxx                          xxx x
   xxxxx x                       xxxx x      x
MIN---------------MAX       MIN---------------MAX
                                      case no
                                              =
                                         max      24

HO:  μT = μC             t tests
                         p        = .0048
                         p(trim)  = .0007
```

FIGURE 1. Does the presence of an extreme value change our conclusions about differences in group means?

```
                         *************
     HISTOGRAMS FOR * HAMILTON *
                         *************

     DOCTOR A        DOCTOR B        DOCTOR C
48
45
42
39   *
36
33   *                               **
30   ***             *               ***
27   M*                              **
24   *               ***             M*
21   **              **              **
18   *               M*              ***
15                   ***
12                   **
 9                   *
 6
 3
```

FIGURE 2. After weeks of training, why did one doctor's ratings differ? The midpoints of histogram intervals for Hamilton depression scores are printed along the left. Each asterisk represents an observation.

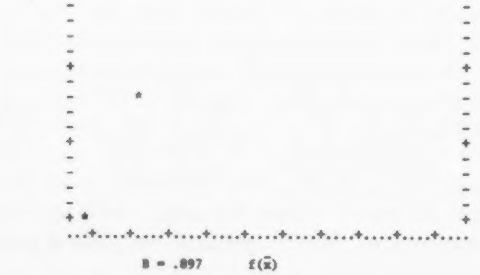


FIGURE 3. Box-Cox diagnostic plot for selecting power transformations to stabilize cell variances in an analysis of variance.

ence of outliers, distributional shape, subpopulations, patterns of missing observations, etc. Having a good statistical package at the research site makes it possible to check the data soon after they are captured—while it may still be possible to make corrections.

Testing group differences

The data analyst needs graphical displays, diagnostics, and alternative tests to help estimate the impact of problems encountered. In comparing responses for a treatment group and a control group, recording errors and other anomalies pop out when you scan small histograms for each group (high resolution graphics are not needed). In Figure 1, case 24, a control subject has a very high response. Does this real, but unusual response change our conclusions about group differences? Compare the results for the usual two-sample *t* test with those for the trimmed *t* test (note the trimmed test does not simply delete the smallest and largest values from each group—an adjustment is made to the standard deviations used in the denominator of the test statistic). Here both tests are significant.

The data analyst wants to study the distribution of values within each cell: scanning a printout of means and standard deviations may be far from adequate. In a recent project, one criterion for study entry was a Hamilton depression score of 18 or above. In a screening run of baseline scores, by doctor, (*see* Figure 2), 6 subjects appear unacceptable for study entry. This was distressing since the admitting psychiatrists had just spent weeks being trained on the anchor points for each individual scale item. So why did one doctor's rating differ? From a quick telephone call we learned that he made his evaluation using the previous 12 hours instead of the patient's history for the past week. Seeing a printout of means would not have had the same impact (the mean for doctor B was over 19).

As structure is added to the design—e.g., we study differences between treated and untreated subjects who are males and females, smokers and nonsmokers, etc.—the data analyst still wants to scan distributions within each cell for outliers and other anomalies. He also needs tests to assess the equality of cell variances, diagnostics to identify the appropriate power transformation, and extensions for the two-sample trimmed *t* test to analysis of variance (ANOVA). In an ANOVA, there should be no relation between the size of the cell standard deviation and the size of the cell mean—i.e., the cell variances should be equal. From information printed with the BOX-COX diagnostic plot (Figure 3), the data analyst would determine that the equal variance assumption is best satisfied if the data are analyzed in log units.

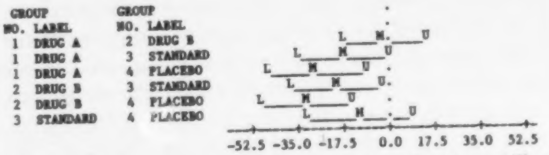


FIGURE 4. **95% confidence intervals for differences in group means with Bonferroni adjustment (means differ significantly when 0.0 is not in the interval).**

If an effect in an ANOVA is significant, the analysis is still not complete—the researcher wants to report which group means differ from one another. Probabilities from the usual two-sample *t* test cannot be used to find significant differences (since this test assumes that only one pair of means is compared). When many comparisons are made

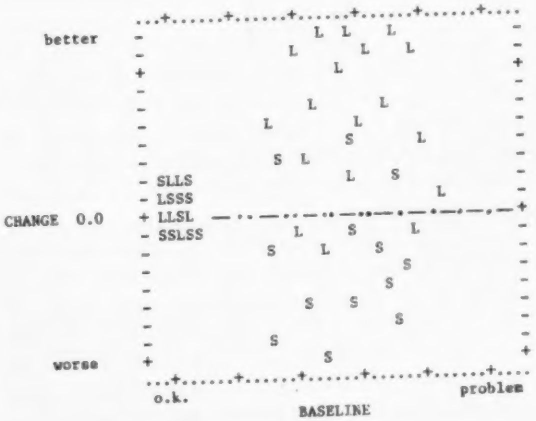


FIGURE 5. **A bivariate scatterplot with symbols S and L denoting subjects on DRUG S and DRUG L, respectively, highlights the fact that the CHANGE in cardiovascular status after drug therapy becomes worse for a small subset of DRUG S patients; while several DRUG L patients improved.**

simultaneously, the Bonferroni procedure can be used to protect against interpreting too many differences as significant. In Figure 4, confidence intervals (with Bonferroni adjustments) are displayed for differences among four means (DRUG A, DRUG B, STANDARD drug, and PLACEBO)—there is one line in the display for each pair. If zero is not in the interval (draw a vertical line down through the dots to 0.0), the pair has a significant difference in means. The difference between DRUG A and the STANDARD drug is questionable—the upper end of the confidence interval (U) touches the zero line, while the differences between both DRUG A and DRUG B versus PLACEBO are highly significant.

Relating two or more variables

When studying the relation among two or more variables, linear models (e.g., regression models and analyses based on correlations) may not be enough. By scanning a printout of correlations and regression coefficients, the researcher may not be able to see that a small subset of the subjects responds differently from the others. Bivariate scatterplots are useful in such situations, especially when symbols are used to identify subpopulations. In Figure 5, CHANGE in cardiovascular status after drug treatment is plotted against baseline values. Holter monitors were used to obtain the measurements. The majority of the subjects (more than 85% of the sample) exhibited no problems at baseline and no change after being on a drug. However, among those subjects with problems on baseline, several DRUG L subjects improved, while the status of several DRUG S subjects became worse.

Labeling subpopulations in scatterplots is also useful for identifying situations where the presence of subpopulations may mask or falsely enhance the relation between two measures. Two pairs of measures from the Fisher Iris data (Fisher) illustrate this point well. Pooling data for three types of iris flowers into one sample in Figure 6a, masks the relationship between sepal length and width—there is no relationship or at most a slight *negative* correlation. The points labeled "S" in the lower right are Setosa flowers—note how the relation for them appears to be *positive* (for the Setosa flowers alone, the correlation is +.74). In Figure 6b, when data are pooled for a plot of petal length versus width the correlation is .96; for Setosa alone, the correlation drops to .33.

When studying the intercorrelations of many variables—e.g., in the development of a questionnaire or a rating instrument—it is helpful to use a factor analysis to sort the rows and columns of a correlation matrix into blocks of similar values, and then to use a single character space to represent each correlation (*see* Figure 7, for a shaded correlation matrix for a 43-item questionnaire about smoking habits and emotional stress). The 13 smoking items appear highly intercorrelated, with the possible exception of the last item in the list, SMOKING 3. The question about

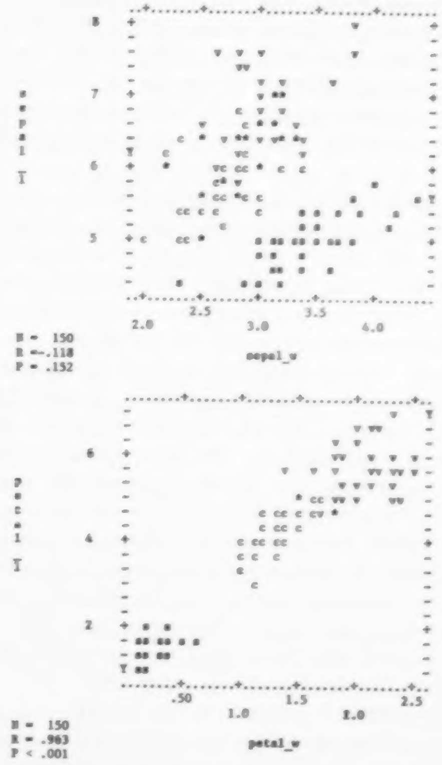
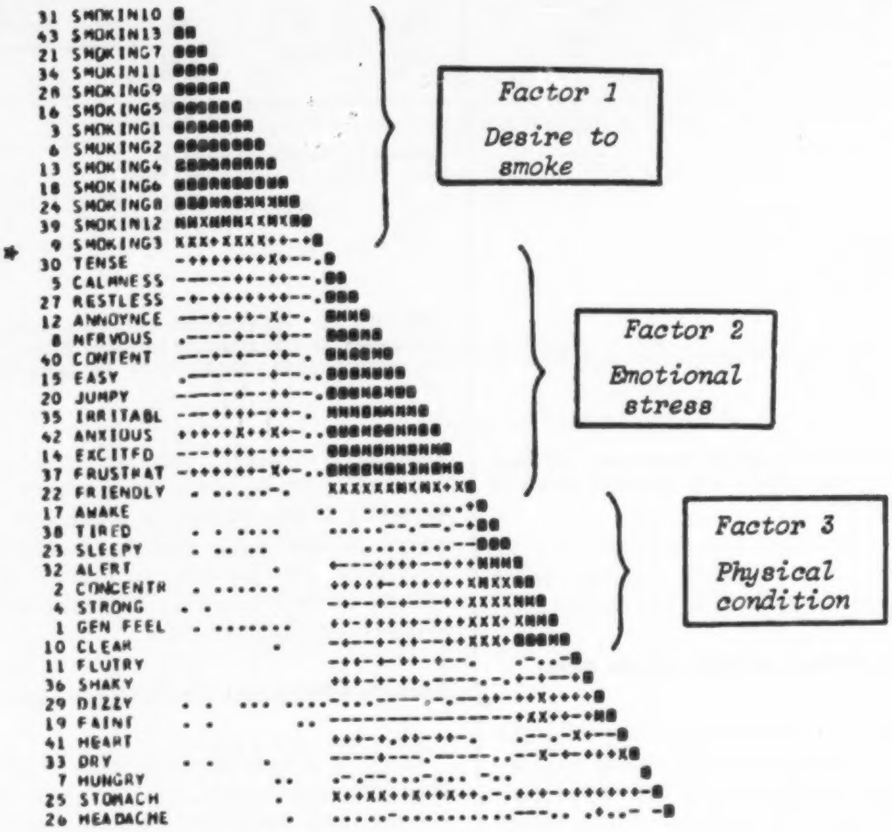


FIGURE 6. a) The presence of subpopulations can mask a relationship: sepal length versus sepal width. b) For petal length and width, the presence of subpopulations gives a false impression of the strength of the relationship.



```
THE ABSOLUTE VALUES OF
THE MATRIX ENTRIES HAVE BEEN PRINTED ABOVE IN SHADED FORM
ACCORDING TO THE FOLLOWING SCHEME
                 LESS THAN OR EQUAL TO         0.109
   .       0.109  TO AND INCLUDING             0.217
   -       0.217  TO AND INCLUDING             0.326
   +       0.326  TO AND INCLUDING             0.434
   X       0.434  TO AND INCLUDING             0.543
   M       0.543  TO AND INCLUDING             0.651
   ▨       0.651  TO AND INCLUDING             0.760
   ■                    GREATER THAN           0.760
```

FIGURE 7. A shaded correlation matrix is used to display the interrelations among items on a questionnaire. A factor analysis was used to cluster the rows and columns of the matrix.

hunger (HUNGRY—the third up from the bottom of the display) appears to have little relation to any of the other items.

When there are only two variables of interest, much can be gleaned from studying a scatterplot. However, as the number of variables in a multivariate analysis increases, additional diagnostics are needed to identify outliers and cases that exert unusual influence on the analysis. In the plot of Andrews-Pregibon statistics in Figure 8, unusual values of the statistic plotted on the AP1 axis indicate outliers in the dependent variable. One value at the top right stands apart from the others and should be checked. Unusual values on the AP2 axis are "leverage" points—cases that exert the greatest influence on the regression coefficients. Here two cases are separated from the others and identified as

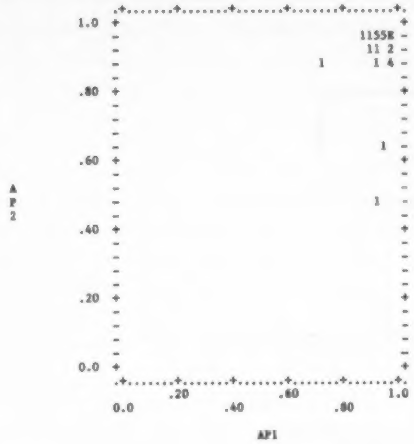


FIGURE 8. Andrews-Pregibon diagnostics AP1 and AP2 for identifying outliers and leverage points in multiple regression.

unusual. The case numbers for the three cases identified are printed in the output.

Studying the pattern of incomplete data

Missing data are often a nightmare for the data analyst. Procedures for dealing with incomplete data usually assume that values are missing randomly. The pattern of how values are missing should be investigated, since nonrandomly incomplete data can bias results. One of the first things the data analyst does when searching for patterns is to print a display of the data with one character per variable: a blank if an observation is present; a letter "M" if missing. In Figure 9, the LAB chemistry measures tend to be missing as a set. In Figure 10, a multiway table is used for deciding if this pattern is related to the outcome, SURVIVAL. Over two-thirds of the survivors (68.5%) are missing all three lab values, while fewer than 10% of the non-survivors have data missing.

```
          AS  D         LLL      S
          GE..R....Y....AAA......M.....
          EX  U         BBB      O
              G         ---      K
                        123      E
Subject   -----------------------------
   1                    MMM
   3                    MMM
   6                             M
  12                    MMM
  13                    MMM
  15                    MMM
  18                    MMM
  20       M
  23                    MMM
  24                    MMM
  25                    MMM
  28      M
  31                    MMM
   .                     .
   .                     .
   .                     .
```

FIGURE 9. A graphical display of the data matrix (using one character per variable) highlights the pattern of incomplete data.

```
                                        SURVIVAL
LAB_1       LAB_2       LAB_3           no    yes
--------------------------------------------------
miss        miss        miss            9.7   68.5
                        present          .0     .0
                        --------------------------
            present     miss             .0     .0
                        present          .0     .0
            --------------------------------------
present     miss        miss             .0     .0
                        present          .0     .0
                        --------------------------
            present     miss             .0     .0
                        present         90.3   31.5
--------------------------------------------------
                                       100.0  100.0
```

FIGURE 10. Column percents in a multiway table for assessing the relation between SURVIVAL and the pattern of incomplete data for three lab chemistries.

Software Features for Managing the Data

Data in longitudinal studies often fail to conform to the nice tidy rectangle required for analyses based on classical statistics. Patients may have varying numbers of visits and different patterns of return across time. For example, it may be necessary to extract from a series of records the number of visits, total time on study, percent improvement for the clinical rating score, worst side effect score, drug dose for week prior to worst score, etc., for each patient. For analysis, the summary of the patient's clinical experience will need to be merged with laboratory results and patient history data.

The entry of patients into the study may be staggered over time, making it hard to visualize the pattern of return visits and the total time on study for members within each treatment group. In order to plan analyses, the data analyst needs this information. In Figure 11, a record map is displayed for a study where patients are asked to return weekly for evaluation (one computer record is generated for each return visit). Week-on-study is recorded on the horizontal axis, and each row represents the pattern of returns for a single patient over time. The drug code is used as a

```
ID                     WEEK
         5        15        25        35        45
    0        10        20        30        40        50
    +----+----+----+----+----+----+----+----+----+----+----+
 1  3333 333333444 44 44 4 42222222222222 22222222 22   2
 2   22222222222  2    2 2 2  2   2   24
 7   222222222222  222222222222 22 2 2 2222 2 2  2  2 2
 8   *2222 2   2   2     2  2 4 44
10  11111 1 1   1   1   1
12  11111111111111   1         1     1  1
14  33422222
16  111111111111
18  33333333 333  3333   3  33
19  11111111111111111442222222 22 22222 2 222 22 2222 22
20  11111111111111 1   1    1   1   1   1
21  333222222222 2 2   2 2   2 2   2     22 2 2  2
22  3333334111111111111 4  4 444 44 444222222222 222 222
23   2222222    2   2    2   2    2
26  222222222222  41111111111 11 11 111   1   1 1 1   1
27   1111111.
28  22222222 2 22   2   2   2   2 2     .
29  3333 33333 3411 11 11111111111 1 1 .111 111111 1 11 1
30  1 111111
31  111 11111 11
33  3333 33333 3   3   3    .
36  33332222222222  2 2 222222  222 2 2 22  2 2 .
37  33 3
38  344411111111 1 1111111 1111.
46  1.
49  222444111 111 1111 1111
54  2222222 2 2222  22  2   2    2  2   2  2
56  11142222222222 22  2 2    22   2   2   2   2   2 2 22
57  1111111111111111 1111 1   1   1 1 1 1    1
59  222222 2222222 2   .
61  111111  1    1  1   1     .
63  22
68  222   2 2 2 2 2 2 2 2 2 2    2  2  2    2   2   2   2
69  11111111111 111111 11 1 1 1 1   1    1  1  1 1 1  1
71  22  22222 2 222 2 2 2 2 2 2 2 2 2 2 2  2  2 2   2 2
72  111111 111 1111 1 1 1 1 1 1 1 1  1  1   1 1  1 1
    +----+----+----+----+----+----+----+----+----+----+----+
    0        10        20        30        40        50
         5        15        25        35        45
```

plot symbol; blanks mark missed visits. Subject 19 (*see* underlined row) was randomly assigned to drug 1 (the plot character is 1) and continued on it for 17 weeks; had 2 weeks of wash-out (code 4); and then was randomized to drug 2. It is immediately apparent that, as time on study increases, many patients drop out and the frequency of returns decreases.

With such a distribution of values across time it is hard to use a classic repeated measures design to test for differences among the drug groups. Instead, our strategy might be to extract information from each patient's set of records (the number of records varies by patient). This summary information would then form a rectangular file and be available for plots, histograms, analysis of variance, logistic regression, etc. The data for each patient might include clinical ratings (at baseline, 4 weeks, 8 weeks, and so on.), proportion of visits with side effects present, maximum dose, drug dose for week prior to worst side effects score, and within-subject correlation between dose and side effects.

Conclusion

A microcomputer can be an effective tool for data analysis, but only if adequate software is available. A statistical package for a micro must go far beyond the simple computations of commonly used statistics. Indeed, it must encompass most of the power of the standard mainframe packages.

Reference

Fisher, R.A. The use of multiple measurements in taxonomic problems. *Ann. Eugen.*, 7:179–188, 1936.

Microcomputerized Testing of Drug Effects on Divided Attention[1]

Joe E. Thornton, M.D.,[2] Joy L. Taylor, Ph.D.,[2] Elizabeth L. Gibson, M.A.,[2] Terry P. Miller, M.D.,[2] and Jared R. Tinklenberg, M.D.[2]

In this paper we describe the use of a microcomputerized, dual-task methodology to test drug effects on divided attention. This dual-task methodology is designed to be sensitive to psychoactive drugs and to be useful in research that entails repeated assessments of the same individual. The theoretical rationale for this approach is that drug effects may be especially discernible on pervasive, non-specific processes such as attention and may be most amenable to quantification on performance tasks that are attention demanding. Certain additional psychometric and technical features of these microcomputerized tasks which make them suitable for psychopharmacologic studies will also be discussed.

Methods

The essential feature of the dual-task method is that the subject must perform two activities simultaneously. In one version of this method, which is described below, the subject also performs each task individually to provide comparisons for the dual-task condition. The decrement in performance observed when the two tasks are done simultaneously, relative to the performance observed when they are done separately, provides a measure of the extent to which the available attentional capacity is exceeded.

In our basic dual-task procedure, the first task involves manipulating an x-y joystick to pursuit track a randomly moving target, which is displayed on a video screen. The subject manipulates this control stick up/right and left/right with the preferred hand. The target is a 1.5 cm horizontal line and the joystick position is displayed as a 1.5 cm vertical cursor line. The task is to maintain a "crosshair" configuration by keeping the middle of the vertical cursor line as close as possible to the middle of the randomly moving horizontal target line. The target moves at a maximal rate of about 6.6 cm/sec throughout an unmarked 12 × 18 cm rectangle, positioned at the center of a standard 42 cm diagonal video screen. The screen is approximately 50 cm from the subject's eyes.

The second task involves the continuous monitoring of visual probe stimuli embedded in the horizontal tracking target line. The stimuli are a pair of boxes, about 4 mm long × 5 mm high, at each end of the target line. They both blink in synchrony at a baseline rate of about 1 blink/sec. The subject presses the reaction button, which is held in the non-preferred hand, as soon as he or she notices an increase in blink frequency of the boxes (to 1.8 blinks/sec). This change occurs at quasi-random intervals, approximately 4 times per minute. The button press restores the blink frequency to baseline. The temporal perceptions required in this task and the relatively high rate at which the visual stimuli must be processed combine to enhance drug sensitivity. Both tasks are designed to be intrinsically uninteresting and subtle in their measurement of performance changes. Most subjects perceive these tasks as undemanding commercial videogames, which are meant to arouse and stimulate.

The basic procedure involves three test conditions: a) a single-task only is performed, the other is ignored; b) the other single-task only is performed, the first is ignored; and c) then both tasks are performed concurrently. In the dual-task condition the subjects are

---

[1] This study was supported in part by the Medical Research Service of the Veterans Administration.

[2] Gero-Psychiatric Rehabilitation Unit, Veterans Administration Medical Center, Palo Alto, CA 94304 and Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305.

instructed to do the tracking task as well as possible and do the visual probe monitoring with whatever abilities remain. In experiments where we focus on attentional capacity, each task condition lasts 5 minutes. The order of tasks is first tracking only, then reaction task only, and then both tasks simultaneously (dual-task). Any decrement in the dual-task condition relative to the single task conditions indicates the extent to which the available attentional capacity is exceeded. In experiments where we are most interested in drug effects on general performance, we use only the dual-task condition and measure time-on-task changes during 15 or 20 minutes of continuous performance. Continuous performance obviates the confounding effects of any task interruption. The subjects receive no feedback about their performance in either paradigm.

We use Apple II and Apple IIe hardware with programming done in UCSD-Pascal. The tasks are run on an Apple II (or IIe) microcomputer using the UCSD Pascal Operating System. It requires a) an x-y joystick; b) a California Computer Systems programmable timer module (PTM) card, appropriately modified, in slot seven of the Apple II; c) a press button switch connected to the PTM; and d) dual floppy disk drives for data storage. The software for the pursuit tracking and visual monitoring procedure (PTRAK), described above, is written in UCSD Pascal and 6502 machine code. The Pascal portion of PTRAK controls the presentation of the secondary visual probe and records performance; the 6502 routine draws the positions of the target and cursor. Every 75 msec tracking accuracy is measured as the radial distance in pixels between target and control stick cursor. A pixel in this system is about a 1.0 mm horizontal and 0.6 mm vertical dot. Reaction time to the probe (to 1 msec accuracy) or a "miss" (i.e., no response within 1500 msec) are recorded. Additional technical and theoretical considerations are described elsewhere (Tinklenberg & Taylor, 1984; Tinklenberg et al., 1984, 1985).

Results

In repeated measures research designs such as those usually used in clinical psychopharmacology, an essential requirement for any performance assessment procedure is adequate test-retest reliability. We determined the test-retest reliability of PTRAK on five normal volunteers in the basic divided attention paradigm. When testing was done 1 day apart the Pearson correlation coefficients were greater than 0.80 on both tracking and reaction time performance. Testing after 1 week, the Pearson coefficients were greater than 0.69 for both tasks. One subject was tested 20 times over a 6-month period. Examination of his performance indicates an immediate improvement or practice effect in the 5-minute paradigms if testing is done on the same day or on consecutive days. This practice effect is not evident if testing sessions are more than a week apart. When the subject was tested for 10 consecutive days, performance stabilized by the fifth testing day. In the 20-minute time-on-task paradigm, practice effects are less evident.

Another obvious requirement for any psychopharmacological assessment procedure is appropriate drug sensitivity. Initial studies with dual-task procedures are promising. In a single-blind study with normal subjects, single doses of diphenhydramine 50 mg orally significantly impaired performance; 100 mg of caffeine 3 hours after diphenhydramine ingestion restored most of the performance deficit. When diphenhydramine followed caffeine, performance did not improve. We have also shown PTRAK to be sensitive to drug effects in abstinent alcoholics (Miller et al., in press). There was consistent impairment of dual-task performance with diphenhydramine: 50 mg, diazepam: 10 mg and 20 mg, and secobarbital: 100 mg.

Discussion

These preliminary results suggest to us that microcomputerized dual-tasks have adequate reliability and drug sensitivity for use in research. They also have many practical advantages in psychopharmacological studies relative to traditional tasks. Patient acceptance is generally good, and they often enjoy the game-like quality of the task. Since specific feedback is not given and level of performance is not apparent, performance anxiety is minimized. Also, the equipment is portable, relatively inexpensive, and can be adapted to obtain concurrent physiological measures of arousal such as heart rate. Personnel requirements are minimal. A tester requires little training and once the task instructions are given to the subject, the tester does not have to be present. The testing conditions are standardized and exactly replicable, even among different research groups. This is especially important with the repeated measures designs often required in testing for effects of drugs on cognitive performance.

There are also psychometric characteristics of these dual-task procedures that make them attractive for pharmacological studies. A common problem in psychopharmacology is the wide range in the performance abilities of patients. Tests that are too easy for some subjects are too difficult for others. With dual tasks these "ceiling" and "floor" restrictions are circumvented to some degree. The tracking task can be performed at widely varying levels of proficiency—ranging from continuous close contact with the target to distances on the order of 4 to 5 cm—and still be statistically and psychometrically meaningful. This feature of the tracking task is in contrast to our experience with, for example, verbal learning tasks. A second psychometric advantage is the tests' suitability for repeated assessments. Unlike some standard intelligence and memory tests, which have only a single form of the test, each session of this computerized performance test consists of randomized presentation of stimuli.

There are more potential advantages with microcomputerized dual tasks. Adaptive logic can be used so that task difficulty varies during a single test session, e.g., the performance of subjects with different abilities can be kept within specified error limits. The priority assigned to each task can be systematically manipulated so additional inferences can be made about attentional capacitites and control. Dual-task results can be interpreted on the basis of extensive theoretical and experimental work in human factors research.

There are some problems with the microcomputerized testing. Our experience indicates the need for experimental designs which can control for practice effects and performance variability due to factors such as time of day, smoking, diet, exercise, emotional state, etc. Also, some subjects change performance strategies, so that testers occasionally have to monitor the subjects performance throughout a session. With the procedure described above there is a lack of face validity, i.e., a more meaningful task might require the same perceptual and motor skills but use a graphics and hardware system that resembles an automobile. But even at this simple level the technical demands of initial development and modification are formidable and require professional engineers and computer programmers.

In summary, we believe the special psychometric characteristics and sensitivity to experimental interventions make microcomputerized dual tasks a potentially important tool in clinical psychopharmacology.

References

Miller, T.P., Taylor, J.L., and Tinklenberg, J.R. A comparison of assessment techniques measuring the effects of methylphenidate, secobarbital, diazepam, and diphenhydramine in abstinent alcoholics. (In review)

Tinklenberg, J.R., and Taylor, J.L. Assessments of drug effects on human memory functions. In: Squire, L.R., and Butters, N. (eds.), *The Neuropsychology of Memory.* New York: Guilford Press, 1984, pp. 213–223.

Tinklenberg, J.R., Taylor, J.L., Peabody, C.A., et al. Dual task peformance measures in geriatric studies. *Psychopharmacol. Bull.*, 20:441–444, 1984.

Tinklenberg, J.R., Taylor, J.L., Miller, T.P., and Redington, D. Dual-task assessment of attentional capacities in aging and dementia. In: Gaitz, C.M., Niederehe, G., and Rabinowitz, H. (eds.), *Aging 2000: Our Health Care Destiny, Volume II.* New York: Springer-Verlag, 1985, pp. 135–144.

Benzodiazepines—New Indications

CHAIRS: David J. Greenblatt, M.D.
Division of Clinical Pharmacology
Tufts University
Boston, Massachusetts

and

Allen Raskin, Ph.D.
Lafayette Clinic
Detroit, Michigan

The Use of Benzodiazepines for Psychotic Disorders: A Literature Review and Preliminary Clinical Findings[1]

George W. Arana, M.D.,[2] Marjorie L. Ornsteen,[2] Fred Kanter, M.D.,[2] H. L. Friedman, M.D.,[2] David J. Greenblatt, M.D.,[2] and Richard I. Shader, M.D.[2]

Introduction

Although antipsychotic agents (neuroleptics) have been shown to be effective for the treatment of various psychotic disorders including schizophrenia and the affective psychoses, limiting factors such as latency for onset of action (10 to 14 days) and short- (acute dystonias, neuroleptic malignant syndrome), medium- (parkinsonism, akathisia), and long-term side effects (tardive dyskinesia [TD]) have necessitated the search for other compounds that may be effective for psychotic symptoms (Baldessarini, 1980). Recent findings suggest that certain subgroups of psychotic patients may be at increased risk for TD depending on age, diagnosis, and duration of treatment (Mukherjee et al., 1982; Toenniessen et al., 1985), although much controversy still exists about these associations (Kane & Smith, 1982). Benzodiazepines, because of their low toxicity, have been studied both as potential non-neuroleptic antipsychotic agents and as adjunctive treatments for psychotic disorders, to increase sedation and possibly to allow for a significant reduction of neuroleptic dose.

We will review briefly the available literature on the use of benzodiazepines for psychotic disorders, present data from a retrospective chart review on the utility of combined use of neuroleptics and lorazepam, and review preliminary findings of an ongoing study assessing the use of lorazepam alone and lorazepam combined with haloperidol in two groups of psychotic inpatients.

In the literature review we included only those publications containing the actual number of patients responding to a specific regimen. This allowed us to construct efficacy and toxicity data about those who either responded or developed toxicity as a function of the total number treated across studies. Because the efficacy criteria were not uniform among the individual publications, it was not possible to clearly specify whether improvement was in core psychotic symptoms or in such associated symptoms as anxiety and agitation.

---

[1] This study was supported in part by USPHS Grant MH-34223 by the National Institute of Mental Health.

[2] Departments of Psychiatry at the Boston Veterans Administration Medical Center and Tufts University School of Medicine, Boston, MA 02130.

Efficacy of Benzodiazepines for Psychotic Illnesses

Diazepam

Although a variety of benzodiazepines have been employed in the treatment of psychotic disorders, diazepam is the most frequently studied compound. Table 1 presents the selected literature on the use of diazepam for schizophrenic disorders (Beckman & Haas, 1980; Hollister et al., 1963; Jimerson et al., 1982; Jos et al., 1985; Maculans, 1964; Nestoros et al., 1982, 1983; Ruskin et al., 1979; Weizman et al., 1984).

Early uncontrolled studies using relatively lower doses of diazepam were conflicting, some reporting dramatic reductions in hallucinations mand delusions in schizophrenics (Irvine & Schaechter, 1969; Kramer, 1967; Sussex et al., 1961) and others reporting that diazepam had little effect. As is evident from Table 1, few patients were studied in well-controlled clinical trials with fixed-dose regimens.

When double-blind trials are assessed separately, only 14 of 47 subjects (29%) were found to have responded, an efficacy rate equal to what is generally regarded as placebo response rate. Factors which could contribute to response rate such as clinical presentation, response to other medications, or the utility of combined therapies are inconsistent when reviewing this literature. One double-blind study described the use of diazepam for schizophrenic patients who previously were poor neuroleptic responders (Maculans, 1964); another reported a response rate to diazepam comparable to the neuroleptic response rate (Jimerson et al., 1982). Two groups, in double-blind crossover studies using diazepam, found no antipsychotic effect as compared with placebo in doses from 40 to 80 mg/day in one (Ruskin et al., 1979) and 300 mg/day in the other (Jimerson et al., 1982). In contrast to these negative findings, another group reported a dramatic reduction in both positive and negative psychotic symptoms, a broad range of diazepam doses were employed (70 to 400 mg/day) (Nestoros et al., 1982). Finally, in a double-blind randomized trial of haloperidol and diazepam (not shown in Table 2), both compounds were equally effective for the treatment of psychotic symptoms in the first 24 hours, with a trend in favor of diazepam in the first 4 hours (Lerner et al., 1979). The authors speculate that some components of psychosis may be secondary to arousal or anxiety, thus leading to the apparent efficacy of a benzodiazepine compound for psychotic symptoms (Lerner et al., 1979).

TABLE 1

The Use of Diazepam for Psychotic Disorders: A Literature Review

Author	Year	N	Dose*	Design+	Antipsychotic# Effect
Hollister et al.	1963	25	40	Open	9/25
Maculans	1964	35	20–60	DB	8/35
Ruskin et al.	1979	8	40–80	DB-CO**	0/8
Beckman & Haas	1980	15	200–400	Open	10/15
Jimerson et al.	1982	6	300	DB-CO	1/6
Nestoros et al.	1982	6	70–400	DB-PC	5/6
Nestoros et al.	1983	10	35–200	Open	7/10
Weizman et al.	1984	13	100–400	Open	0/13
Jos et al.	1985	2	15,40	Open	2/2
Totals		120			42/120 (34%)
Double-Blind Trials		47			14/47 (29%)

*Dose range of diazepam/24 hrs.

+Open = open trial; DB-CO = double-blind, crossover; DB-PC = double-blind, placebo-controlled.

#(Patients with antipsychotic response)/(Total patients studied).

**Patients concomitantly treated with haloperidol, 15 mg/day.

When all cases (double-blind and others; Table 1) are totalled, response rate is 34% (42/120). The studies reporting the use of diazepam at doses below 40 mg ($N = 60$; 51%) yielded a response rate of 28% (17/60); the three reports using over 100 mg of diazepam had an overall response rate of 33% (11/34). There does not appear to be a dose-related response pattern for diazepam in psychotic illnesses. An overall response rate of approximately 30% emerges regardless of dose used or the design of the studies.

In addition to diazepam, other benzodiazepines have been used for the treatment of psychosis (*see* Table 2). Although these reports are brief and preliminary, they offer some data on the efficacy of this class of drugs for psychotic and bipolar disorders (Astrup & Vatten, 1984; Chouinard et al., 1983; Csernansky et al., 1984; Deberdt et al., 1973; Freinhar & Alvarez, 1985; Guz et al., 1972; Hekimian & Friedhoff, 1967; Holden et al., 1968; Karson et al., 1982; Kellner et al., 1975; Lingjaerde, 1982; Modell et al., 1985; Monroe & Wise, 1965; Victor et al., 1984).

Clonazepam

Recently, interest has developed in the use of clonazepam, a benzodiazepine usually employed for its anticonvulsant properties (Browne, 1976). A number of papers have appeared exploring its value for the treatment of psychotic illnesses, particularly mania (*see* Table 2). Unlike neuroleptics, there is little risk of extrapyramidal or anticholinergic side effects, although drowsiness and ataxia, apparently dose-related symptoms occurring early in treatment, appear to be problematic (Browne, 1976).

Few controlled clinical trials of clonazepam have been conducted to assess its efficacy in the treatment of mania and psychosis. In a double-blind crossover study of 12 acutely manic patients, one group has reported that clonazepam was as effective as lithium for manic symptoms and superior to lithium for motor activity and logarrhea (excessive speech) (Chouinard et al., 1983). Two reports describing 5 patients found that clonazepam ameliorated anxiety and agitation and a limited number of manic symptoms, but psychotic symptoms (delusions, hallucinations) were refractory (Freinhar & Alvarez, 1985; Victor et al., 1984). Two reports suggest that clonazepam may precipitate aggressiveness and irritability (Browne, 1976; Karson et al., 1982). One group, in a double-blind study of 9 schizophrenic patients concomitantly treated with neuroleptics, found clonazepam to be ineffective for target symptoms of psychosis. In addition, 4 patients developed aggressive, violent outbursts, 3 of whom had no prior history of violence. The assaultive episodes occurred when the dose was being adjusted (Karson et al., 1982). These investigators concluded that clonazepam was not effective in the treatment of exacerbations of psychosis in chronic schizophrenics receiving neuro-

TABLE 2

The Use of Selected Benzodiazepines for Psychotic Disorders: A Literature Review

Author	Year	*N*	Dose[*]	Design[†]	Diagnosis	Response Rate#
			Clonazepam			
Karson et al.	1982	13	1–5	DB	C Schizophrenia	0/13
Chouinard et al.	1983	12	4–10	DB-CO	Mania	Decreased activity
Victor et al.	1984	3	0.5–4	Open	Affect Psych[a]	3/3
Freinhar and Alvarez	1985	2	16	Open	Mania	2/2
			Lorazepam			
Guz et al.	1972	–	6	—	—	—
Deberdt	1973	2	15,40	Open	Schizophrenia	0/2
Modell et al.	1985	4	5–30	Open	Mania[b]	4/4
			Estazolam			
Lingjaerde	1982	58	6	DB	C Schizophrenia[a]	Decreased hallucin.
Astrup and Vatten	1984	53	4–6	Open	Schizophrenia[a]	15/53
			Alprazolam			
Csernansky et al.	1984	8	5–7	Open	Schizophrenia[a]	4/8
			Chlordiazepoxide			
Monroe and Weiss	1965	37	40–200	Open	Schizophrenia[a]	17/37
Hekimian and Friedhoff	1967	10	200+	Open	Schizophrenia	4/10
Holden et al.	1968	22	60–100	DB-CO	Schizophrenia	6/22
Kellner et al.	1975	6	200–225	DB	Schizophrenia[a]	3/6
Totals						(36.2%) 58/160

[*] Dose range of benzodiazepine/24 hrs.

[†] Open = open trial; DB-CO = double-blind, crossover; DB-PC = double blind, placebo-controlled.

#(Patients with antipsychotic response) / (Total patients studied).

[a] Patients treated concomitantly with neuroleptics.

[b] Patients treated concomitantly with lithium.

leptics, and that it had the potential for inducing aggressive behavior. Finally, another report has indicated that psychotic symptoms, including irritability and aggression, may worsen in adolescents treated with clonazepam (Browne, 1976).

Lorazepam

Lorazepam is well established in psychiatry as an anxiolytic. Its efficacy in psychotic disorders is less well studied and confounded by secondary anxiety and arousal that may coexist in many psychotic patients. One investigator suggests that lorazepam is an effective adjuvant for the anxiety which accompanies psychosis but has no effect on the target symptoms of psychosis (Deberdt, 1973). A recent open clinical trial found lorazepam effective in the control of manic agitation and in promoting compliance and cooperation during the institution of lithium therapy, concluding that manic as well as other psychotic symptoms resolved within 10 days when both lithium and lorazepam were used (Modell et al., 1985). However, the course of recovery from the manic episode left it unclear as to which drug was more effective (Modell et al., 1985).

Estazolam

The effects of estazolam, a benzodiazepine not currently marketed in the United States, have been tested in psychotic illnesses. In a double-blind study of estazolam in 58 chronic schizophrenics, it was found that estazolam in combination with a neuroleptic was better than neuroleptic alone for the treatment of hallucinations and compulsive thoughts as evident in global clinical improvement (Lingjaerde, 1982). Another group reported the use of 4 to 6 mg of estazolam in an open trial for 53 chronic schizophrenics, concluding that this drug decreased delusional and paranoid symptoms in 15/53 patients (Astrup & Vatten, 1984). In both studies, patients were characterized as poor neuroleptic responders and were maintained on neuroleptics during the treatment with estazolam. Although encouraging, further placebo-controlled studies are needed to assess the specific efficacy of estazolam in these patients.

Alprazolam

In an open trial of alprazolam evaluating its therapeutic effect on the negative symptoms in 8 chronic schizophrenics, partial reversal of negative symptoms was observed in 6 patients, and an anxiolytic effect in all 8 (Csernansky et al., 1984). Conclusions that can be drawn from this particular study are limited, as all patients were concomitantly treated with neuroleptics. Fifty percent of the patients had a moderate overall clinical response to alprazolam. Because alprazolam is known to be effective for anxiety, panic, and depressive disorders, this improvement may have been secondary to other possible effects of this drug.

Chlordiazepoxide

Seven reports on the use of chlordiazepoxide reveal generally inconsistent findings on its efficacy in psychosis. In particular, the question of increased efficacy for psychosis if both chlordiazepoxide and neuroleptics are employed is unanswered. Three studies between 1966 and 1970 compared the combination of an antipsychotic and chlordiazepoxide with an antipsychotic alone in newly hospitalized acutely psychotic patients at Spring Grove State Hospital in Maryland and found that the combination drug treatment was less effective than the antipsychotic alone (Hanlon et al., 1969, 1970; Michaux et al., 1966). In an open trial comparing chlorpromazine, chlordiazepoxide, and placebo in 30 schizophrenic patients, 4/10 treated with chlordiazepoxide alone improved with regard to psychotic symptoms; also, chlordiazepoxide in combination with an antipsychotic was more effective than the antipsychotic alone in regard to thought disorder and motor behavior (Hekimian & Friedhoff, 1967). Consistent with these observations is a report showing that the addition of chlordiazepoxide to an antipsychotic regimen was effective in controlling acutely psychotic, episodically dyscontrolled patients (Monroe & Wise, 1965). Another group of investigators reported that chlordiazepoxide was not effective in the treatment of psychosis and that most changes in global ratings were due to the sedative and calming effects of chlordiazepoxide (Holden et al., 1968). Finally, a report on 6 schizophrenic patients concomitantly treated with neuroleptics found that 3/6 patients demonstrated an adequate response. Overall, the response rate with chlordiazepoxide in psychotic illnesses among 75 patients is just over 50%, but over half of these patients also were treated with neuroleptics. Therefore, conclusions regarding efficacy of chlordiazepoxide alone must be tentative.

Benzodiazepine Toxicity in Psychotic Illnesses

A review of seven publications (Beckman & Haas, 1980; Haas et al., 1982; Hollister et al., 1963; Jimerson et al., 1982; Karson et al., 1982; Lerner et al., 1979; Maculans, 1964) revealed a variety of side effects reported with both diazepam and clonazepam in a total of 114 patients (Table 3). Except for the final study cited which reported on manic patients (Chouinard et al., 1983), all patients were reportedly schizophrenic. However, the diagnostic criteria employed varied and many of these may have fallen in the affective spectrum if DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) were being used. In this group of patients, it was evident that the two general types of side effects seen in these reports included sedation/quieting and arousal/stimulation. This preliminary literature review would suggest that certain benzodiazepines may have a significant likelihood of producing sedation or stimulation in certain psychotic patients. The particular pattern of behavioral toxicity in an individual may be idiosyncratic, or may be mediated via other poorly understood factors not readily apparent in the limited sample reviewed.

It is of note that the arousal/stimulation pattern of toxicity seen in a number of schizophrenic patients is reminiscent of manic symptoms, i.e., hypersexuality, hyperkinesis, excitation, euphoria, and impulsive behavior. This would suggest that caution must be exercised in interpreting these symptoms in diagnostically complicated cases who are treated with benzodiazepines during the clinical evaluation period. This arousal pattern seen with the use of certain benzodiazepines in chronically psychotic individuals may confound the diagnostic process, as is mentioned in the Discussion section.

Preliminary Clinical Results With the Use of Lorazepam in Psychotic Illnesses

Retrospective Chart Review of Patients Treated With Neuroleptics and Lorazepam Over a 6-Month Period

Between January 1984 and July 1984 a total of 380 patients were admitted to one of three 22-bed acute inpatient units in the Department of Psychiatry at the Boston Veterans Administration Medical Center. When clinically indicated, patients were treated

TABLE 3

Toxicity Reported With Benzodiazepines in Psychotic Disorders

Author	Year	Benzodiazepine	Toxicity Rate	Description
Hollister et al.	1963	Diazepam	9/25	"Worsening of psychosis"
Maculans	1964	Diazepam	7/35	Sedation
Beckman and Haas	1980	Diazepam	5/15	Hypersexuality; hyperkinesis; excitation.
Haas et al.	1982	Diazepam	4/8	Euphoria; hyperkinesis.
Jimerson et al.	1982	Diazepam	3/6	Ataxia; sedation
Karson et al.	1982	Clonazepam	3/13	Violent behavior
Chouinard et al.	1983	Clonazepam	7/12	Sedation
Totals	Sedation		17/53 (32%)	
	Arousal/Stimulation		21/61 (34%)	

NOTE: All patients were diagnosed as schizophrenic except in the Chouinard study in which patients were diagnosed as bipolar disorder, manic type.

TABLE 4

Neuroleptic Dose Requirements in Psychotic Disorders: Neuroleptics With and Without Lorazepam (LZP)

Treatments	*N* (Total = 30)	CPZ-EQ (mg)* (mean ± SEM)
A Neuroleptics	22	560 ± 85
B Neuroleptics + LPZ [a]	8	265 ± 50

*Chlorpromazine-equivalents/24 hrs./patient; doses were at discharge and were determined to be lowest dose for effective control of psychotic target symptoms.
[a] Mean lorazepam dose = 2.75 mg/24 hrs.
Statistical Data:
B vs. A: $t = 2.99$; df = 28; $p < .01$

with doctor's choice of neuroleptic, doses being tapered continuously during hospitalization to achieve the lowest effective dose. Of the 380 admissions, it was found that 30 patients were discharged with either neuroleptic or neuroleptic with lorazepam at the lowest doses clinically possible without an exacerbation of symptoms. Mean discharge dose of neuroleptic was comparable for the three units as was average length-of-stay. Patients with a significant degree of agitation initially were treated with lorazepam and were discharged with the lowest effective dose of this compound.

Table 4 presents the neuroleptic dosages employed, converted to chlorpromazine-equivalents (CPZ-EQ) (Baldessarini, 1980), on these 30 patients separated into treatment groups: 1) neuroleptics, and 2) neuroleptics with lorazepam. In 22 patients discharged on neuroleptics alone, mean CPZ-EQ/day was 560 mg whereas in 8 patients treated with both neuroleptics and lorazepam (mean lorazepam dose = 2.75 mg/day), the mean CPZ-EQ/day on discharge was 265 mg, a difference found to be statistically significant ($t = 2.99$; df = 28; $p < .01$). Data on 32 patients not shown were separated into two other treatment subgroups: 1) neuroleptics and benztropines, and 2) neuroleptics, lorazepam, and benztropine. The group of patients treated with both neuroleptics and benztropines ($N = 18$; mean dose benztropine = 2.2 mg) had a mean CPZ-EQ dose of 771 mg/day (SEM ± 164). The group of 14 patients treated with neuroleptics, lorazepam, and benztropine had a mean CPZ-EQ dose of 933 mg (SEM ± 227) (*see* Table 4).

Although patients were tapered to lowest effective dose for treatment of psychotic symptoms, the heterogeneity of the population made it difficult to separate dose requirement of neuroleptic from severity of illness. Because lorazepam was initiated for agitation and irritability, it is unlikely that this cohort represented less severe forms of psychosis although, without controlling for severity, this assumption remains untested. The dose of neuroleptics in the group receiving concomitant lorazepam therapy was clearly lower than the other group shown. This lower dose of neuroleptics also may have led to a lower incidence of extrapyramidal side effects and/or akathisia, therefore not requiring the use of benztropine. This reduced requirement for neuroleptics may have reduced the incidence of neuroleptic-induced toxicity which may have reflected itself as an overall improved clinical picture at relatively lower doses of antipsychotics. Further research with carefully controlled groups of psychotic patients with uniform symptom profiles on fixed doses of neuroleptics is needed to assess whether there is a significant interaction between these two medications which allows for use of lower doses of neuroleptics. Also, it remains to be assessed whether the reduced neuroleptic dose lowered the incidence of neuroleptic-induced side effects, i.e., akathisia, hence leading to apparent efficacy which, in fact, was reduced toxicity.

Preliminary Results of the Efficacy and Toxicity of Lorazepam in 14 Psychotic Patients

Preliminary results from an ongoing study on the efficacy of lorazepam vs. lorazepam with haloperidol for psychotic disorders were reviewed. Acutely psychotic patients between the ages of 18 and 65 were admitted to a research inpatient service at the Boston Veterans Administration Medical Center, underwent a complete battery of clinical and laboratory tests to exclude active medical conditions, and were stabilized with regard to diet and fluid intake. Subjects able and willing to sign informed consent were observed clinically for 48 hours following admission and rated daily with the Brief Psychiatric Rating Scale (BPRS) to determine the nature and intensity of psychotic symptoms. Those patients who demonstrated a clear improvement in psychotic symptomatology in this time period were excluded from study and the remaining patients were treated either with lorazepam or lorazepam with haloperidol. Blood samples for analysis of lorazepam and haloperidol were drawn into heparin-containing tubes, centrifuged, separated, and kept frozen at −20° C until assay. Lorazepam was measured by gas liquid chromatography with electron-capture detection (Greenblatt et al., 1978); haloperidol was measured by gas liquid chromatography with a nitrogen-phosphorus detector (Abernethy et al., 1984).

Table 5 presents data on the 14 patients studied including basic demographics, diagnostic data, doses of lorazepam and haloperidol employed, and specific items on the BPRS showing significant improvement over the 48-hour period of treatment. Diagnostic evaluations were performed by a research psychiatrist and a research assistant employing DSM-III criteria with the aid of the Structured Clinical Interview for DSM-III (SCID). Eight patients with diagnoses of mania ($N=4$), schizophrenia ($N=3$), and atypical psychosis ($N=1$) were treated with a mean dose of 20.9 mg/day of lorazepam alone and demonstrated a mean drop in BPRS scores of 20; BPRS items showing significant improvement ($p<.05$) were tension, hostility, suspiciousness, hallucinations, unusual thoughts, conceptual disorganization, excitement, and emotional withdrawal. Six patients divided equally between mania, schizophrenia, and atypical psychosis were treated with both lorazepam and haloperidol. The mean lorazepam dose was 16.5 mg/day and mean haloperidol dose was 14.2 mg/day. The items on the BPRS which showed significant improvement were grandiosity, unusual thoughts, conceptual disorganization, blunted affect, and emotional withdrawal ($p<.05$).

In order to assess the differences between high-dose (>30 mg/day; $N=3$) vs. low-dose (<10 mg/day; $N=5$) lorazepam among the lorazepam-treated group ($N=8$), and to assess the differences between low-dose lorazepam ($N=5$) vs. low-dose lorazepam with low-dose haloperidol ($N=4$), clinical response data were analyzed in this same cohort of patients (*see* Table 6; N.B. Two patients treated with lorazepam and haloperidol who were included in Table 5 were treated with >20 mg/

TABLE 5

Lorazepam for Acutely Psychotic Patients With and Without Haloperidol: Clinical Characteristics and 48-Hour Response Data

	Treatment Groups	
Characteristics	Lorazepam	Lorazepam + Haloperidol
	$N=8$	$N=6$
Sex (M/F)	8/0	6/0
Median Age (Range)	31 (22–63)	29 (22–47)
Race (Black/White)	4/4	3/3
Diagnosis (DSM-III)		
Manic (N)	4	2
Schizophrenic (N)	3	2
Atypical Psychotic (N)	1	2
Lorazepam Dose (mg/Day)*	20.9	16.5
Haloperidol Dose (mg/Day)*	—	14.2
Baseline BPRS Score*	60.3	47.5
48 Hr BPRS Score*	40.3	32.3
BPRS Items Improved ($p<.05$)	Tension Hostility Suspiciousness Hallucinations Unusual Thoughts Conceptual Disorganization Excitement Emotional Withdrawal	Grandiosity Unusual Thoughts Conceptual Disorganization Blunted Affect Emotional Withdrawal

*Means

TABLE 6

48-Hour Clinical Change in Psychotic Patients in Three Treatment Groups: High- and Low-Dose Lorazepam and Low-Dose Lorazepam With Haloperidol

	Lorazepam		
	High-Dose ($N=3$)	Low-Dose ($N=5$)	Lorazepam + Haloperidol ($N=4$)
Lorazepam Dose[*] (mg/24 hrs)	45	6.2	5
Haloperidol Dose[*] (mg/24 hrs)	—	—	15
Plasma Lorazepam[*] (ng/ml)	688	29.5	—
Clinical Improvement[a]			
BPRS Items[b]:			
Anxiety	—	—	—
Tension	$p<.05$	—	—
Hostility	$p<.01$	—	—
Suspiciousness	$p<.05$	—	—
Excitement	$p<.05$	$p<.05$	—
Conceptual Disorganization	$p<.05$	—	$p<.01$
Unusual Thoughts	—	$p<.01$	$p<.01$
Emotional Withdrawal	—	$p<.01$	$p<.05$
Clinical Worsening[a]			
BPRS Items:			
Motor Retardation	$p<.05$	—	—
Blunted Affect	$p<.05$	—	—

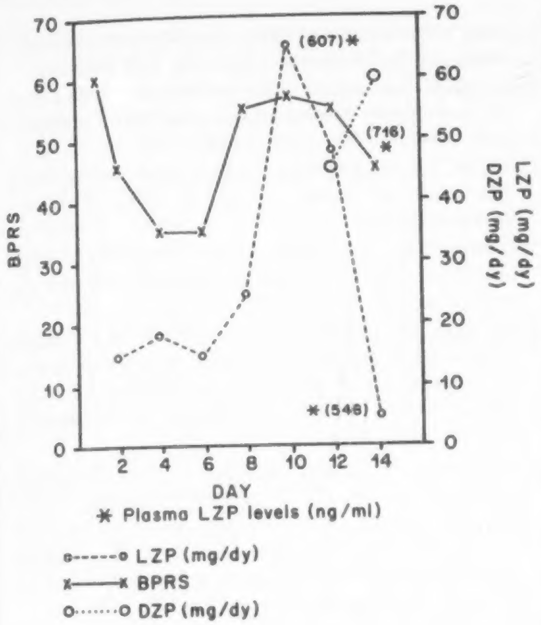
[*] Means
[a] Paired Student's *t*-test; baseline vs. 48 hours of treatment.
[b] BPRS items ≥3.5 at baseline in all three treatment groups.

day of lorazepam and were not included in the data analysis in Table 6). Mean daily lorazepam dose in the high-dose lorazepam group was 45 mg with a mean plasma level of 688 ng/ml. Nonpsychotic symptoms that were significantly improved included tension, hostility, and excitement; psychotic symptoms showing improvement were suspiciousness and conceptual disorganization. In the group receiving high-dose lorazepam, significant worsening in motor retardation and blunted affect was noted. The low-dose lorazepam group ($N=5$) received a mean daily dose of 6.2 mg/day with mean plasma levels of 29.5 ng/ml. Clinical improvement was noted with excitement, unusual thoughts, and emotional withdrawal. The 4 patients treated with both lorazepam and haloperidol were treated with mean doses of 5 mg/day and 15 mg/day, respectively. Improvement was noted in conceptual disorganization, unusual thoughts, and emotional withdrawal.

Time Course of Treatment Response of a Manic Patient

The Figure (p. 85) outlines the 2-week course of a 42-year-old white male, bipolar manic patient treated only with lorazepam and diazepam over a 14-day period. Presenting symptoms on admission included paranoia, grandiosity, insomnia, loss of appetite, restlessness, agitation, labile affect, pressured speech, racing thoughts, and poor judgment. The total BPRS score on admission was 60. By history, this episode began 4 months prior to admission.

The patient was begun on 8 mg oral lorazepam daily with 2 mg doses administered as needed for agitation. A BPRS to assess severity of psychosis and response to treatment was completed daily by a research psychiatrist. Within the first 24 hours of treatment, he received 15 mg of lorazepam and showed moderate improvement in symptoms such as



uncooperativeness, excitement, and suspiciousness as defined by a 2-point decrease on BPRS subscales. After 48 hours of treatment, total BPRS score had dropped to 33. There continued to be marked improvement in grandiosity, tension, unusual thought content, and conceptual disorganization through day 6. Unexpectedly, between day 6 and day 8, with little change in daily lorazepam dose (between 16 to 24 mg) he demonstrated a clear worsening in his clinical state as reflected in increasing BPRS scores with manic symptoms similar to those evident on admission (*see* Figure). The lorazepam dose was increased to 65 mg daily with a plasma lorazepam level of 607 ng/ml with no improvement in psychotic symptoms. Because of his failure to respond, lorazepam was rapidly tapered and on day 12, diazepam was started in order to avoid possible withdrawal symptoms from the high-dose lorazepam regimen. On day 15, haloperidol treatment was initiated with marked improvement in 3 days and remission in 2 weeks.

This case characterizes the time course observed with other psychotic patients treated with lorazepam in whom rapid improvement is not sustained beyond 4 to 6 days, with little benefit attained by increasing lorazepam dosage. This was evaluated with lorazepam levels which confirmed that drug levels increased with increasing dosage. Because antipsychotic effect was not attained with increased levels of lorazepam, this would not suggest that tolerance was developing to the antipsychotic effect of lorazepam. Further clinical and preclinical work is needed to better understand this pattern of clinical effect in psychotic illnesses.

Discussion

It is evident from this literature review that benzodiazepines are not as effective in the treatment of psychotic disorders as neuroleptics or lithium salts. The efficacy rate of benzodiazepines for the treatment of psychosis, usually reported as schizophrenia (not necessarily DSM-III), is approximately what would generally be expected from placebo rates of response (Tables 1 and 2; 98/278 = 35.2%). Because many of these reports were retrospective and/or included patients concomitantly treated with neuroleptics or lithium, the actual response rate may be lower than the apparent 35.2%.

Toxicity seen when psychotic disorders were treated with benzodiazepines included the expected sedation and drowsiness characteristic of this class of medication (32%), but also included arousal and excitation (34%) manifesting as manic symptoms in some cases and, more seriously, as assaultive behavior in others. Clinicians employing benzodiazepines for behavioral management of psychotic patients need to be alerted to this potentially confounding effect of these drugs. The literature would suggest that schizophrenia mistakenly may be seen as an affective psychosis if the clinician is not aware of these patterns of toxicity. An alternate view would hold that benzodiazepines, like tricyclic antidepressants or monoamine oxidase inhibitors, may produce a "switch" phenomenon (Goodwin, 1983) and what may have appeared initially as schizophrenia may be affective illness "unmasked" by the benzodiazepine. Because there is little evidence presently to support this hypothesis, more research is needed to delineate the meaning of the arousal evident in psychotic disorders treated with benzodiazepines.

The preliminary findings in 14 psychotic patients treated with lorazepam alone would suggest that this compound may be helpful initially (48 hours) for the treatment of acutely psychotic individuals. This effect was seen both with high- and low-dose lorazepam, the high-dose regimen apparently quite effective for a range of behavioral, affective, and cognitive symptoms of psychosis, but also more likely to cause motor retardation and blunted affect. The pattern seen in the Figure is representative of many patients we have observed in which the rapid initial improvement in psychotic symptoms is short-lived and does not respond to increasing the dose of lorazepam.

Our retrospective chart review revealed that combined neuroleptic and lorazepam treatment required significantly lower doses of neuroleptic (CPZ-EQ = 265 mg) as compared to neuroleptics alone (CPZ-EQ = 560 mg). This finding would suggest that further work is needed to assess whether combined neuroleptic and lorazepam regimens would allow for the use of lower doses of neuroleptics to achieve comparable clinical effects, i.e., a shift to the left of the dose-response curve for neuroleptics in psychosis.

References

Abernethy, D.R., Greenblatt, D.J., Ochs, H.R., et al. Haloperidol determination in serum and cerebrospinal fluid using gas-liquid chromatography with nitrogen-phosphorus detection: Application to pharmacokinetic studies. *J. Chromatogr.*, 307:194–199, 1984.

Astrup, C., and Vatten, L. Effect of the benzodiazepine derivative estazolam in schizophrenia. *Biol. Psychiatry*, 19(1):85–88, 1984.

Baldessarini, R.J. Drugs and the treatment of psychiatric disorders. In: Gilman, A.G., Goodman, L.S., and Gilman, A. (eds.), *The Pharmacological Basis of Therapeutics*. New York: Macmillan Publishing Co., Inc., 1980, pp. 391–447.

Beckman, H., and Haas, S. High dose diazepam in schizophrenia. *Psychopharmacology*, 71:79–82, 1980.

Browne, T.R. Clonazepam: A review of a new anticonvulsant drug. *Arch. Neurol.*, 133:326–332, 1976.

Chouinard, G., Young, S.N., and Annable, L. Antimanic effect of clonazepam. *Biol. Psychiatry*, 18(4):451–467, 1983.

Csernansky, J.G., Lombrozo, L., Gulevich, G.D., and Hollister, L.E. Treatment of negative schizophrenic symptoms with alprazolam: A preliminary open-label study. *J. Clin. Pharmacol.*, 4(6):349–352, 1984.

Deberdt, R. Lorazepam in the treatment of severe anxiety and anxiety associated with psychotic conditions. *Curr. Med. Res. Opin.*, 1:296–300, 1973.

Freinhar, J.P., and Alvarez, W.H. Use of clonazepam in two cases of acute mania. *J. Clin. Psychiatry*, 46:29–30, 1985.

Goodwin, F.K. The impact of tricyclic antidepressants and lithium on the course of recurrent affective disorders. *McLean Hosp. J.*, 8:1–16, 1983.

Greenblatt, D.J., Franke, K., and Shader, R.I. Analysis of lorazepam and its glucuronide metabolite by electroncapture gas-liquid chromatography: Use in pharmacokinetic studies of lorazepam. *J. Chromatogr.*, 146:311–320, 1978.

Guz, I., Morales, R., and Sartoretto, J. The therapeutic effects of lorazepam in psychotic patients treated with haloperidol. *Curr. Ther. Res.*, 14:767–774, 1972.

Haas, S., Emrich, H.M., and Beckman, H. Analgesic and euphoric effects of high dose diazepam in schizophrenia. *Neuropsychobiology*, 8:123–129, 1982.

Hanlon, T., Ota, K., Agallianos, D., et al. Combined drug treatment of newly hospitalized acutely ill psychiatric patients. *Dis. Nerv. Syst.*, 30:104–116, 1969.

Hanlon, T., Ota, K., and Kurland, A. Comparative effects of fluphenazine, fluphenazine-chlordiazepoxide, and fluphenazine-imipramine. *Dis. Nerv. Syst.*, 31:171–177, 1970.

Hekimian, L., and Friedhoff, A. A controlled study of placebo, chlordiazepoxide, and chlorpromazine in 30 male schizophrenic patients. *Dis. Nerv. Syst.*, 28:675–678, 1967.

Holden, J., Itil, T., Keskiner, A., and Fink, M. Thioridazine and chlordiazepoxide, alone and combined in the treatment of acute schizophrenia. *Compr. Psychiatry*, 9:633–693, 1968.

Hollister, L.E., Bennett, J.L., Kimbell, I., et al. Diazepam in newly admitted schizophrenics. *Dis. Nerv. Syst.*, 24:746–750, 1963.

Irvine, B.M., and Schaechter, F. "Valium" in the treatment of schizophrenia. *Med. J. Aust.*, 1:1387, 1969.

Jimerson, D.C., Van Kammen, D.P., Post, R.M., et al. Diazepam in schizophrenia: A preliminary double-blind trial. *Am. J. Psychiatry*, 139(4):489–491, 1982.

Jos, C.J., Schneider, R., and Gannon, P. Diazepam in the treatment of hallucinations. *Am. J. Psychiatry*, 142:1130–1131, 1985.

Kane, J.M., and Smith, J.M. Tardive dyskinesia: Prevalence and risk factors, 1959-1979. *Arch. Gen. Psychiatry*, 39:473–481, 1982.

Karson, C.N., Weinberger, D.R., Bigelow, L., and Wyatt, R.J. Clonazepam treatment of chronic schizophrenia: Negative results in a double-blind, placebo-controlled trial. *Am. J. Psychiatry*, 139(12):1627–1628, 1982.

Kellner, R., Wilson, R.M., Muldawer, M.D., and Pathok, D. Anxiety in schizophrenia: The responses to chlordiazepoxide in an intensive design study. *Arch. Gen. Psychiatry*, 32:1246–1254, 1975.

Kramer, J.C. Treatment of chronic hallucinations with diazepam and phenothiazines. *Dis. Nerv. Syst.*, 28:593–594, 1967.

Lerner, Y., Lwow, E., Levitan, A., and Belmaker, R.H. Acute high-dose parenteral haloperidol treatment of psychosis. *Am. J. Psychiatry*, 136(8): 1061 – 1064, 1979.

Lingjaerde, O. Effect of the benzodiazepine derivative estazolam in patients with auditory hallucinations. *Acta Psychiatr. Scand.*, 65:339–354, 1982.

Maculans, G.A. Comparison of diazepam, chlorprothixene, and chlorpromazine in chronic schizophrenic patients. *Dis. Nerv. Syst.*, 25:164–168, 1964.

Michaux, M., Kurland, A., and Agallianos, D. Chlorpromazine-chlordiazepoxide, and chlorpromazine-imipramine treatment of newly hospitalized, acutely ill patients. *Curr. Ther. Res.*, 8:117–152, 1966.

Modell, J.G., Lennox, R.H., and Weiner, S. Inpatient clinical trial of lorazepam for the management of manic agitation. *J. Clin. Psychopharmacol.*, 5(2):109–113, 1985.

Monroe, R., and Wise, S. Combined phenothiazine, chlordiazepoxide, and primidone therapy for uncontrolled psychotic patients. *Am. J. Psychiatry*, 122:694–698, 1965.

Mukherjee, S., Rosen, R.M., Cardenas, C., et al. Tardive dyskinesia in psychiatric outpatients: A study of prevalence and association with demographic, clinical, and drug history variables. *Arch. Gen. Psychiatry*, 39:466–469, 1982.

Nestoros, J.N., Suranyi-Cadotte, B.E., Spees, R.C., et al. Diazepam in high doses is effective in schizophrenia *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:513–516, 1982.

Nestoros, J.N., Nair, N.P.V., Pulman, J.R., et al. High doses of diazepam improve neuroleptic-resistant chronic schizophrenic patients. *Psychopharmacology*, 81:42–47, 1983.

Ruskin, P., Averbuch, I., Belmaker, R.H., and Dasberg, H. Benzodiazepines in chronic schizophrenia. *Biol. Psychiatry*, 14(3):557–558, 1979.

Sussex, J.N., Linton, P.A., and Herlihy, C.E. Anxiety and depression in "borderline" schizophrenic states—Treatment with Valium, a librium analog. *Psychosomatics*, 2:256–265, 1961.

Toenniessen, L.M., Casey, D.E., and McFarland, B.H. Tardive dyskinesia in the aged: Duration of treatment relationships. *Arch. Gen. Psychiatry*, 42:278–284, 1985.

Victor, B.S., Link, N.A., Binder, R.L., and Bell, I.R. Use of clonazepam in mania and schizoaffective disorders. *Am. J. Psychiatry*, 141(9):1111–1112, 1984.

Weizman, A., Tyano, S., Wijsenbeck, H., and Ben David, M. High dose diazepam treatment and its effect on prolactin secretion in adolescent schizophrenic patients. *Psychopharmacology*, 82:382–385, 1984.

New Strategies for the Treatment of Alcohol Withdrawal

E.M. Sellers, Ph.D.,[1] and C.A. Naranjo, Ph.D.[1]

Introduction

The goals in the treatment of alcohol withdrawal are the relief of subjective symptoms, the prevention or treatment of the serious complications (e.g., seizures, hallucinations, arrhythmias, and delirium), and preparation for long-term rehabilitation. Such treatment should be standardized, humane, as simple and economic as possible, and it should have a pharmacokinetic and pharmacodynamic rationale.

Over the past 10 years we have conducted studies directed toward the development of trial methodology and diagnostic and tracking criteria of the withdrawal syndrome, the determination of the natural history of the withdrawal syndrome, the assessment of the importance of nonpharmacologic treatment measures, the simplification of drug therapy, and the determination of the role of adjunctive drugs, such as phenytoin. Recently, we have been testing the hypothesis that the pharmacotherapy of alcohol withdrawal can be improved by the use of selective, nonsedating drugs.

Diagnostic Criteria and Scales to Track the Clinical Syndrome

In an effort to develop an instrument for assessing the alcohol withdrawal syndrome, Gross et al. (1973, 1974) identified disturbances in 30 clinical variables during experimental alcohol withdrawal studies. Two instruments were developed: a research battery (total severity assessment, TSA) and a clinical instrument (selected severity scale, SSA). The TSA contained all of the original 30 clinical variables, while the SSA consisted of a short list of 11 items. The SSA correlated highly with the TSA (Gross et al., 1973, 1974); however, full prospective validation of the SSA was not done. We modified this scoring system for rapid repeated use (Shaw et al., 1981). Our 15-item scale, Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) includes tremor; nausea and vomiting; paroxysmal sweating; tactile, auditory, and visual disturbances; hallucinations; quality of contact; anxiety; agitation; thought disturbances; seizures; headache; and flushing of face (Shaw et al., 1981). Heart rate, temperature, and blood pressure are also recorded, but not included in the scoring.

Several prospective studies show that the CIWA-A scale is valid, reliable, and sensitive (Naranjo et al., 1983; Sellers et al., 1983; Shaw et al., 1981). CIWA-A scores correlate with physician global ratings of withdrawal severity. Nine items in particular contribute most weight to the total score (nausea; tremor; sweating; tactile, auditory, and visual disturbances; hallucinations; anxiety; and agitation) and correlate highly with the total score ($r = 0.95$). Inter-rater and intra-rater reliability has been determined ($r = 0.8$–0.92). The scale has been successfully used in assessing the therapeutic response in clinical trials in ambulatory and hospitalized patients in withdrawal (Naranjo et al., 1983; Sellers et al., 1983; Shaw et al., 1981). Several other advantages of this standardized procedure are that medical and other health workers become aware of the symptoms that make up the alcohol withdrawal syndrome, and staff training is facilitated. Because of its brevity, this procedure can be incorporated into "routine" patient care. We are currently testing whether validity and reliability can be retained with a further simplification of the scale (i.e., reduction of number of items) and change in the scoring ranges (Sullivan et al., 1985).

---

[1] Departments of Pharmacology and Medicine, University of Toronto and Clinical Pharmacology Program, Addiction Research Foundation, Toronto, Ontario, Canada.

Nonpharmacologic Interventions

Uncontrolled studies showed that reassurance, reality orientation, frequent monitoring of signs and symptoms, personal attention, and general nursing care can be effective in over two-thirds of patients in a mild alcohol withdrawal reaction (Toshney, 1978; Whitfield et al., 1978).

Recent controlled studies using a standardized form of "supportive care" have confirmed the potency of such nonpharmacologic interventions (Naranjo et al., 1983; Sellers et al., 1983; Shaw et al., 1981). Eighty-five percent of emergency room patients (Naranjo et al., 1983) and 75% of inpatients without, and 56% with, medical complications respond to supportive care in less than 6 to 8 hours (Sellers et al., 1983).

The effectiveness of nonpharmacologic interventions has important implications for design and interpretation of studies assessing drug therapies in alcohol withdrawal. In this context, it is notable that the frequency of placebo-controlled studies of alcohol withdrawal has declined markedly. Placebos were used in 11 of the 19 controlled studies published during the 1960's but in only 4 of the 19 in the 1970's (Gessner, 1979). Since our data indicate that, to a substantial extent, the apparent efficacy of a drug can be due to the influence of nonpharmacologic interventions, it is essential to use a placebo control group (Naranjo et al., 1983).

Even though supportive care decreases the general symptoms of withdrawal, it does not appear to completely prevent hallucinations, seizures, or arrhythmias; hence, drugs are still required by patients. Since patient characteristics do not predict the occurrence of such complications, patients in moderate to severe withdrawal should receive drugs such as diazepam in addition to supportive care (Sellers et al., 1983).

Dosage Strategies and Pharmacotherapy

Benzodiazepines are currently the drugs of choice (Linnoila, 1983; Sellers & Kalant, 1976, 1982; Sellers et al., 1983). They combine at least equal efficacy as other agents with superior anticonvulsant activity and less toxicity than phenothiazines, barbiturates, and paraldehyde (Sellers & Kalant, 1982). Numerous benzodiazepines including alprazolam, bromazepam, chlordiazepoxide, chlorazepate, clobazam, diazepam, flurazepam, lorazepam, and oxazepam, have been studied and all can be effective (Linnoila, 1983; Moskowitz et al., 1983; Sellers & Kalant, 1976, 1982). Approximate equivalent doses relative to chlordiazepoxide 100 mg are diazepam 20 mg, oxazepam 120 mg, and lorazepam 5 mg.

Both chlordiazepoxide and diazepam are long-acting drugs with pharmacologically active metabolites (Greenblatt et al., 1983). Repeated daily administration at a constant dosage would result in cumulation of the parent compound and/or metabolites in the body (Sellers & Kalant, 1976; Sellers et al., 1983). Such a dosing regimen could delay the onset of maximum therapeutic and unwanted toxic effects for several days. Similar cumulation would occur with prazepam or chlorazepate which are biotransformed to desmethyldiazepam, the pharmacologically active long half-life metabolite formed after diazepam administration (Sellers & Kalant, 1976; Victor, 1966). If dosages are not adjusted carefully, excessive drowsiness, lethargy, ataxia, diplopia, and confusion may occur.

The usual strategy to avoid such side effects is to give larger doses on the first day and progressively lower the dose on subsequent days (Sellers & Kalant, 1976). Typically, multiple doses of diazepam (20 to 40 mg) or chlordiazepoxide (100 to 400 mg) are given on the first day (Sellers & Kalant, 1976, 1982). Lower doses were given daily thereafter and dose-tapering decreased by about 25% to 50% of the initial daily dose (Sellers & Kalant, 1976; Sellers et al., 1983). However, because of variability in the severity of withdrawal symptoms and in the metabolic disposition of the drugs, strict adherence to such dosage schedules may cause toxicity or ineffective treatment in some patients (Sellers et al., 1983). Recently, the dose-tapering approach to treating alcohol withdrawal has been further simplified (Sellers et al., 1983).

The procedure consists of a rapid oral loading-dose strategy using diazepam. Patients are assessed clinically or with the CIWA-A scale and unit doses of 20 mg of

TABLE

Diazepam Loading Trial*
Complications-Placebo Group Only

Subject Trial #	Complication	Time (Hour)
245	Seizure	3
213	Supraventricular tachycardia	2
222	Seizure	7.5
211	Hallucinations	7.5
201	Severe vomiting/anxiety	6
240	Seizure × 3	6

*Sellers et al., 1983.

diazepam, orally, are administered every 1 to 2 hours until the patient shows clinical improvement (CIWA-A<10) or becomes mildly sedated. The rationale of this approach is to take advantage of rapid and complete absorption of diazepam and the pharmacokinetic tapering afforded by diazepam's and N-desmethyldiazepam's long half-lives, i.e., 30 and 40 hours, respectively (Sellers et al., 1983). This pharmacokinetic "umbrella" of active drug is eliminated at about the same rate as the resolution of the withdrawal syndrome.

In a recent double-blind controlled study, patients treated with diazepam using the loading-dose approach had a faster and greater improvement than those receiving placebo (Sellers et al., 1983). Fifty percent of the patients responded to 60 mg of diazepam orally within 7.6 hours, and only an occasional patient required treatment for more than 24 hours. More importantly, complications (seizures, hallucinations, arrhythmias) occurred exclusively in those treated with placebo, indicating that delay in therapy may be responsible for the appearance of complications in withdrawal (Sellers et al., 1983) (*see* Table). We recommend that all hospitalized patients in moderate to severe withdrawal should be loaded with at least 60 mg of diazepam.

Treatment of Alcohol Withdrawal Seizures

The optimal treatment of alcohol withdrawal seizures remains controversial (Gessner, 1974; Naranjo, 1983; Sellers & Kalant, 1982; Thompson, 1978). In particular, the therapeutic and prophylactic value of phenytoin in alcohol withdrawal seizures is uncertain. The contradictory findings in the reported clinical studies possibly arise from the indiscriminate inclusion of patients with pre-existing seizure disorder and those with a previous history of withdrawal seizures only, as well as the failure to standardize and give sufficient benzodiazepine or other drugs as "baseline therapy" (Rothstein, 1973; Sampliner & Iber, 1974; Sandor et al., 1981).

To further investigate this, we have conducted studies in laboratory animals (Solorzano et al., 1985). To determine if phenytoin exhibits pharmacologic selectivity or augments the activity of diazepam in alcohol withdrawal syndrome, male Long-Evans rats were made physically dependent by the administration of intragastric ethanol (3 to 5 g/kg) twice daily for 6 days (Rothstein, 1973). In animal models of alcohol withdrawal, diazepam and phenytoin can be protective against audiogenic seizures; however, the two drugs differ in potency and intrinsic activity. For example, diazepam (3.0 mg/kg) will decrease seizures by up to 50% whereas phenytoin (100 mg/kg) can completely abolish seizures. For phenytoin, a 50% reduction in seizures occurs at 35 mg/kg.

With respect to combinations of diazepam and phenytoin, lower doses of phenytoin (25 mg/kg) plus diazepam (1.0 mg/kg) are more effective than diazepam alone and approximately equal to phenytoin (100 mg/kg) (Rothstein, 1973).

From these studies, one can suspect that diazepam's anticonvulsant action will be sufficient when seizure risk is low, but that phenytoin could increase diazepam's anticonvulsant action in a clinically important way. This will be true, however, only as long as full therapeutic doses of phenytoin are given. However, about 30% of dosing in chronic alcoholics is not straightforward, because chronic alcoholics have clearances of phenytoin that are two- to three-fold greater than normal (Sandor et al., 1981). Hence, daily maintenance doses must be increased to 600 to 900 mg/day to maintain adequate steady-state concentrations. Since some chronic alcoholics may have impaired clearance, daily measurement of phenytoin concentrations is imperative to use this drug properly (Sandor et al., 1981).

In our clinical studies, we have been impressed that patients who have received an adequate diazepam load (i.e., 60 mg or more) do not have seizures even though they may have a relatively strong history of withdrawal seizures (Sellers et al., 1983). In most patients without a previous history of seizures, benzodiazepines alone probably have sufficient anticonvulsant activity to prevent withdrawal seizures (Sellers et al., 1983). Phenytoin is reserved for patients with epilepsy or a history of recurrent or severe withdrawal seizures. A recent uncontrolled open study in 20 "high-risk" seizure patients is consistent with this approach and reiterates our previous advice (Devenyi & Harrison, 1985).

Future Treatment Strategies

Past studies that have attempted to use drugs with greater selectivity in the treatment of alcohol withdrawal have not been terribly encouraging. Lithium decreased only a few subjective symptoms (Sellers et al., 1976). Propranolol decreased tremor, heart rate, and anxiety; however, it caused an increased frequency of hallucinations (Jacob et al., 1983; Sellers et al., 1977). Clonidine appeared to be minimally effective or to actually increase the frequency of clinical seizures (Bjorkqvist, 1975; Blum et al., 1983). If drugs could be developed that were anxiolytic and anticonvulsant and at the same time had a decreased risk of sedation, interaction with ethanol or other central nervous system depressants, and dependence liability, some advances in therapy could occur. A number of newer anxiolytics of the benzodiazepine type and non-benzodiazepine type appear to demonstrate some selective anxiolytic properties (Lippa et al., 1982; Solorzano et al., 1985).

Irrespective of whether more selective drugs will prove to have therapeutic advantages, the methodologic standards for clinical trials in this area have been established. Clinical scales such as the CIWA-A should be used to quantitate drug effects (Shaw et al., 1981). There must be a clear specification of the supportive care given. The importance of such care can be estimated by the inclusion of a placebo-control group. Such a group is necessary because of the potential magnitude of the supportive care effect. In light of the simplification achieved through the diazepam loading-dose technique, it seems likely that other optimal drug therapy strategies for alcohol withdrawal should employ a similar type of titration technique. For this to be clinically feasible, a new drug should be rapidly absorbed and have an intermediate to long half-life in order to avoid withdrawal rebound.

Acknowledgments: We thank our students and other collaborators for their contribution to our studies: Drs. L. Solorzano, H. Kaplan, J. Schneiderman, P. Devenyi, D. Donat, and Ms. J. Shaw, Ms. M. Harrison, and Ms. C. Hamilton. In addition, we thank Ms. D. Campbell and Ms. Karen Cauch-Bontje for their typing and editorial assistance.

References

Bjorkqvist, S.E. Clonidine in alcohol withdrawal. *Acta Psychiatr. Scand.*, 52:256–263, 1975.

Blum, K., Briggs, A.H., and DeLallo, L. Clonidine enhancement of ethanol withdrawal in mice. *Subst. Alcohol Act/Misuse*, 4:59–63, 1983.

Devenyi, P., and Harrison, M.L. Prevention of alcohol withdrawal seizures with oral diazepam loading. *Can. Med. Assoc. J.*, 132:798–800, 1985.

Gessner, P.K. Failure of diphenylhydantoin to prevent alcohol withdrawal convulsions in mice. *Eur. J. Pharmacol.*, 27:120–129, 1974.

Gessner, P.K. Drug therapy of the alcohol withdrawal syndrome. In: Majchrowicz, E., and Noble, E. (eds.), *Biochemistry and Pharmacology of Ethanol*, Vol. 2. New York: Plenum Press, 1979, pp. 374–435.

Greenblatt, D.J., Shader, R.I., and Abernethy, D.R. Drug therapy: Current status of benzodiazepines. *N. Engl. J. Med.*, 309:354–358, 1983.

Gross, M.M., Lewis E., and Hastey, J. Acute alcohol withdrawal syndrome. In: Kissin, B., and Begleiter, H. (eds.), *The Biology of Alcoholism, Clinical Pathology*, Vol. 3. New York: Plenum Press, 1974, pp. 191–263.

Gross, M.M., Lewis, E., and Nagarajan, M. An improved quantitative system for assessing the acute alcohol psychoses and related states (TSA and SSA). In: Gross, M.M. (ed.), *Alcohol Intoxication and Withdrawal: Experimental Studies, Advances in Experimental Medicine and Biology*, Vol. 35. New York: Plenum Press, 1973, pp. 365–376.

Jacob, M.S., Zilm, D.H., MacLeod, S.M., and Sellers, E.M. Propranolol-associated confused states during

best copy available

alcohol withdrawal. *J. Clin. Psychopharmacol.*, 3:185–187, 1983.

Linnoila, M. Benzodiazepines and alcoholism. In: Trimble, R. (ed.). ***Benzodiazepines Divided***. New York: John Wiley & Sons, Ltd., 1983, pp. 291–308.

Lippa, A.S., Meyerson, L.R., and Beer, B. Molecular substrates of anxiety: Clues from the heterogeneity and benzodiazepine receptors. *Life Sci.*, 31: 1409–1417, 1982.

Moskowitz, G., Chalmers, T.C., Sacks, H.S., et al. Deficiencies of clinical trials of alcohol withdrawal. *Alcoholism: Clin. Exp. Res.*, 7:42–46, 1983.

Naranjo, C.A. Recent advances in the pharmacotherapy of alcoholism. In: Velasco, M. (ed.), ***Clinical Pharmacology and Therapeutics***. Amsterdam: Excerpta Medica, 1983, pp. 132–139

Naranjo, C.A., Sellers, E.M., Chater, K., et al. Nonpharmacologic interventions in the treatment of acute alcohol withdrawal. *Clin. Pharmacol. Ther.*, 34:214–219, 1983.

Rothstein, E. Prevention of alcohol withdrawal seizures: The role of diphenylhydantoin and chlordiazepoxide. *Am. J. Psychiatry*, 130:1381–1382, 1973.

Sampliner, R., and Iber, F.L. Diphenylhydantoin control of alcohol withdrawal seizures: Results of a controlled study. *JAMA*, 230:1430–1432, 1974.

Sandor, P., Sellers, E.M., Dumbrell, M., and Khouw, V. Effect of short- and long-term alcohol use on phenytoin kinetics in chronic alcoholics. *Clin. Pharmacol. Ther.*, 30:390–397, 1981.

Sellers, E.M., and Kalant, H. Drug therapy: Alcohol intoxication and withdrawal. *N. Engl. J. Med.*, 294:757–762, 1976.

Sellers, E.M., and Kalant, H. Alcohol withdrawal and delirium tremens. In: Pattison, E.M., and Kaufman, E. (eds.), ***The Encyclopedic Handbook of Alcoholism***. New York: Gardner Press, 1982, pp. 147–166.

Sellers, E.M., Cooper, S.D., Zilm, D.H., and Shanks, C. Lithium treatment during alcohol withdrawal. *Clin. Pharmacol. Ther.*, 20:199–206, 1976.

Sellers, E.M., Zilm, D.H., and Degani, N. Comparative efficacy of propranolol and chlordiazepoxide in alcohol withdrawal. *J. Stud. Alcohol.*, 38:2096–2108, 1977.

Sellers, E.M., Naranjo, C.A., Harrison, M., et al. Oral diazepam loading: Simplified treatment of alcohol withdrawal. *Clin. Pharmacol. Ther.*, 34:822–826, 1983.

Shaw, J.M., Kolesar, G.S., Sellers, E.M., et al. Development of optimal treatment tactics for alcohol withdrawal: I. Assessment and effectiveness of supportive care. *J. Clin. Psychopharmacol.*, 1:382–383, 1981.

Solorzano, L., Keller, J., Kaplan, H.L., et al. Selectivity of drug action in ethanol withdrawal. Proceedings of the Canadian Federation of Biological Societies 28th Annual Meeting, Toronto, June 1985, p. 143.

Sullivan, J., Schneiderman, J., Sykora, K., et al. Alcohol withdrawal (AW): Diagnostic criteria and clinical course. Abstract presented at the Royal College of Physicians and Surgeons Annual Meeting, Vancouver, September 1985.

Thompson, W.L. Management of alcohol withdrawal syndrome. *Arch. Intern. Med.*, 138:278–283, 1978.

Toshney, J. An alcoholism and detoxification centre. *Nurs. Times*, 74:573–576, 1978.

Victor, M. Treatment of alcoholic intoxication and the withdrawal syndrome. *Psychosom. Med.*, 28:636–650, 1966.

Whitfield, E.L., Thompson, G., Lamb, A., et al. Detoxification of 1,024 alcoholic patients without psychoactive drugs. *JAMA*, 293:1409–1410, 1978.

Benzodiazepines for Treatment of Panic Attacks: A New Look[1]

Karl Rickels, M.D.,[2] and Edward E. Schweizer, M.D.[2]

Introduction and Recent Literature

Panic disorder (PD) has only recently emerged as a distinct psychiatric diagnosis with the advent of DSM-III (American Psychiatric Association, 1980). Its separate status is largely an American nosological refinement, not yet officially sanctioned in Europe (Editorial, 1983). Under DSM-II (American Psychiatric Association, 1952), patients with panic presentations had been categorized under a diagnosis of either Anxiety Neurosis or Phobic Neurosis, depending on the degree of concurrent phobic avoidance behavior or agoraphobia.

The impetus for this new subtyping of anxiety stemmed from Klein (1964) and his associates (Zitrin et al., 1978, 1983) who first observed a preferential treatment response to the tricyclic antidepressant imipramine over benzodiazepines in a subset of anxious patients with crescendo anxiety associated with agoraphobia. Other researchers confirmed the utility of antidepressants in panic patients with agoraphobia and extended it to include monoamine oxidase (MAO) inhibitors such as phenelzine (Liebowitz et al., in press; Sheehan et al., 1984b). Various behavior therapies (Marks, 1976; Mavissakalian & Michelson, 1982) also proved beneficial in the treatment of such patients.

We thus have a new anxiety diagnosis—PD, with or without complicating agoraphobia—that owes its existence, in no small measure, to research suggesting the relative *ineffectiveness* of traditional benzodiazepine anxiolytics and the relative superiority of certain antidepressants in its treatment.

With the exception of alprazolam, the lack of specific effectiveness of other benzodiazepines in panic states has, in recent years, become an almost unquestioned assumption in much of clinical practice. It is a rather sweeping generalization, though, based on slim scientific evidence indeed. We are aware of only two well-controlled studies assessing the efficacy of non-triazolobenzodiazepines in PD: one is a negative, and one a positive study.

McNair and Kahn (1981) reported that chlordiazepoxide (60 mg/day) was significantly less effective in alleviating symptoms of PD than was imipramine. In contrast, Noyes et al. (1984) compared, in a 2-week, double-blind crossover study, diazepam with propranolol in patients suffering from panic disorder accompanied by various degrees of phobic avoidance behavior. They reported a significant reduction in number and intensity of panic symptoms, phobic symptoms, and social impairment in patients being treated with diazepam in the usual therapeutic daily dosage, but not in patients treated with the beta blocker propranolol (Table 1).

The question that arises is: what is the role of the benzodiazepines in PD, if any? Is it merely as a minor adjunct to antidepressant

TABLE 1

Mean (± SE) Number and Severity of Panic Attacks and Severity of Phobic Symptoms and Social Impairment During Drug Therapy

	Baseline	Propranolol Week 2	Diazepam Week 2
Panic Attacks ($N = 17$)			
Number	8.5 ± 2.79	6.4 ± 1.26	2.9 ± 0.84
Severity	2.2 ± 0.20	2.0 ± 0.19	1.2 ± 0.26
Phobic Symptoms ($N = 19$)			
Severity	2.2 ± 0.21	1.6 ± 0.27	1.0 ± 0.19
Social Impairment ($N = 21$)			
Severity	2.2 ± 0.18	1.9 ± 0.18	1.0 ± 0.26

From Noyes et al., *Arch. Gen. Psychiatry*, 41:287, 1984 treatment? Do triazolo compounds such as alprazolam have a unique treatment specificity? Do associated features such as degree of phobic avoidance behaviors or degree of generalized or anticipatory anxiety have a bearing on drug choice or treatment response? From most literature reporting on the treatment of panic attacks and agoraphobia, it is quite difficult to determine whether patients included in these studies suffered primarily from PD *without* agoraphobia or from PD *with* agoraphobia. Thus, no answer presently exists to the important clinical question of whether benzodiazepines, prescribed in therapeutic dosages, are effective agents in the treatment of patients suffering from PD without marked agoraphobia. In the succeeding sections the authors will comment on some of these issues.

---

[1] This study was supported in part by USPHS Research Grant MH-08957 from the National Institute of Mental Health.

[2] Department of Psychiatry, University of Pennsylvania, University Hospital, Philadelphia, PA 19104.

Alprazolam in Panic Disorder

Sheehan (1984a) conducted the first study of alprazolam in PD and agoraphobia. It was an uncontrolled, single-blind, crossover study comparing ibuprofen (Motrin) versus alprazolam which indicated that alprazolam was more effective in reducing PD symptoms than ibuprofen. In another larger and double-blind controlled study, Sheehan then compared alprazolam with imipramine, phenelzine, and placebo in patients suffering from PD and/or agoraphobia (Sheehan et al., 1984b) and observed that all three active agents produced significantly more improvement than placebo. Again, patients suffering only from PD were not differentiated from those suffering from both PD and agoraphobia. Chouinard et al. (1982) compared alprazolam with placebo under double-blind conditions in two groups of patients, those suffering from PD and those suffering from generalized anxiety disorder (GAD). Using the Hamilton Anxiety Scale (HAM-A) as outcome criterion, Chouinard et al. (1982) observed that alprazolam was equally effective in PD and in GAD but that placebo appeared slightly more effective in GAD than in PD patients. Medications were prescribed within Food and Drug Administration (FDA) recommended dosages.

Several years ago the Upjohn Company instituted a large controlled trial comparing the effects of alprazolam prescribed in dosages up to 10 mg/day versus placebo in PD patients with and without secondary phobic avoidance behavior or agoraphobia. The Upjohn study was conducted in a multinational, multicenter fashion and its preliminary results have recently been reported (Ballenger et al., 1985). Alprazolam, when prescribed in higher than recommended therapeutic dosages for the treatment of GAD, produced significantly more improvement than placebo in all aspects of behavior assessed, be it anxiety, number and intensity of panic attacks, phobic avoidance behavior, or work and family adjustment. However, no evidence as to whether or not alprazolam's effectiveness depended on the intensity of the agoraphobic condition present was presented.

The effective dosage range of alprazolam for panic appears, from these studies, to be 6 to 8 mg/day (though doses up to 10 mg or higher have not infrequently been required). On an equipotent basis, this translates into a diazepam dose of 60 to 100 mg/day or higher. Controlled studies of benzodiazepines in panic using equipotent dosages have, to our knowledge, not yet been conducted.

Non-Triazolobenzodiazepines and Panic Disorder: Some New Data

Recently, one of the present authors (Schweizer) treated 5 patients diagnosed by SCID-UP (Structured Clinical Interview for DSM-III Diagnosis—Upjohn) as suffering from PD with lorazepam in an open-label trial. Patients with moderate to severe degrees of agoraphobia were excluded, as were patients suffering from concomitant depression. Dosing was begun with lorazepam 0.5 mg three times a day (t.i.d.) and then gradually increased to a daily dose of 3 to 8 mg, i.e., the same dosage range as recommended for the treatment of GAD. Improvement was monitored by both the HAM-A and a Panic Attack Diary. Four of five patients obtained more than 80% control of panic attacks associated with a reduction in Hamilton scores to <8. Some well-controlled double-blind stud-

TABLE 2

Intake Criteria for Studies A and B

1) HAM-A $\geq$ 18
2) Covi-Anxiety $\geq$ 8
3) Raskin Depression < Covi-Anxiety
4) 17-item Anxiety Entry Checklist (FDA): $\geq$5 items
5) Duration of symptoms:
    Study A: >3 months
    Study B: >1 month
6) DSM-II anxiety diagnosis (patient later reclassified according to DSM-III)
7) Excluded:
    a) Phobic disorders including marked agoraphobia
    b) Depressive disorders
8) Considered by psychiatrist to be in need of anxiolytic treatment
9) Diazepam dosage (~25 mg/day)

ies presently under way at several clinical research centers should be able to confirm or refute the antipanic effects of such non-triazolobenzodiazepines as diazepam and lorazepam.

Since patients suffering from panic disorder without marked agoraphobia were diagnosed prior to the introduction of the DSM-III in 1980 as belonging to the large group of patients suffering from anxiety neurosis, the authors felt it important to review two studies conducted by their research group prior to 1980, and to divide all anxious patients into those with and those without panic symptoms. It should be stressed, however, that patients who received a DSM-II diagnosis of phobic neurosis, which would have included agoraphobia, were excluded from these studies.

Hopkins Symptom Checklist (HSCL) (Derogatis et al., 1974) data were available for both studies. Entry criteria employed in these studies are given in Table 2, and the items which make up the HSCL anxiety and panic factors are given in Table 3. The HSCL anxiety factor was further divided into a GAD subfactor and a PD subfactor, as only one of the two studies included the HSCL panic factor as a criterion measure.

Table 4 reports 6 weeks' improvement results obtained in the first of the two reviewed studies (Rickels et al., 1983). Diazepam was the treatment agent and the HSCL anxiety factor, its two subfactors, and the HSCL panic factor were used as outcome criteria. Patients improved highly significantly in all measures. When analyzing only the subgroup of patients scoring high on the HSCL panic factor ($\geq$1.60) (Table 5), even more significant improvement was observed in both general anxiety and panic anxiety symptoms.

Table 6 presents results obtained in the second study (Rickels et al., 1982). Diazepam and placebo treatment outcome was compared as a function of initial level of panic symptoms as assessed with the HSCL panic subfactor. (A score of $\geq$1.60 was considered high panic level.) Table 6 clearly indicates no evidence for a drug X panic level interaction, only highly significant main drug effects, with anxious patients improving significantly more on diazepam than on placebo, irrespective of their initial level of panic symptomatology.

Some additional evidence of the usefulness of benzodiazepines in the treatment of PD

TABLE 3

Hopkins Symptom Checklist (HSCL) Anxiety and Panic Factors

HSCL-Anxiety Factor	HSCL-Panic Factor
GAD Subfactor:	
1. Nervousness or shakiness inside	1. Feeling afraid in open spaces or on the streets
2. Trembling	2. Feeling afraid to go out of the house alone
3. Feeling fearful	3. Feeling uneasy in crowds, such as shopping or at a movie
4. Feeling tense or keyed up	4. Feeling afraid of fainting in public
	5. Feeling afraid to travel on buses, subways, or trains
Panic Subfactor:	6. Feeling nervous when left alone
1. Suddenly scared for no reason	
2. Heart pounding or racing	
3. Having to avoid certain things, places, activities because they frighten me	

TABLE 4

Six Weeks' Improvement on Diazepam of Anxious Outpatients ($N = 236$) (Study A)

	Treatment		
	Pre	Post	Δ*
HSCL-Anxiety Factor	2.21	1.70	.51
GAD Subfactor	2.43	1.87	.56
Panic Subfactor	1.92	1.48	.44
HSCL-Panic Factor	1.55	1.28	.27

*Student *t* test: $p < .001$

TABLE 5

Six Weeks' Improvement on Diazepam in a Subgroup of Anxious Outpatients Scoring High (>1.60) on HSCL Panic Factor ($N = 78$) (Study A)

	Treatment		
	Pre	Post	Δ*
HSCL-Anxiety Factor	2.83	2.06	.77
GAD Subfactor	2.96	2.19	.77
PD Subfactor	2.66	1.89	.77
HSCL-Panic Factor	2.41	1.67	.74

*Student's *t* test: $p < .001$

TABLE 6

Diazepam and Placebo Response of Anxious Neurotic Outpatients as a Function of Initial Level of Panic Symptoms (HSCL Panic Subfactor) ($N = 138$) (Study B)

HSCL Anxiety Factor	Adjusted Post-treatment Means (4-week endpoint)		F	F
	Diazepam ($N = 67$)	Placebo ($N = 71$)	Drug X Panic Effect	Mean Drug Effect
High Panic	1.79	2.11	.30	8.45
Low Panic	1.89	2.07		
HSCL GAD Subfactor:				
High Panic	1.93	2.30	.46	9.22*
Low Panic	1.94	2.14		
HSCL-Panic Subfactor:				
High Panic	1.59	1.77	.12	5.32**
Low Panic	1.85	1.95		

*$p < .005$
**$p < .025$

TABLE 7

Psychiatric Diagnosis of Chronic Benzodiazepine Users When Initiating Anxiolytic Therapy

Diagnosis	Percent
Anxiety	40
Panic	31
Depression	20
Other	3
No Diagnosis	6

comes from a study of 117 long-term chronic benzodiazepine users (in preparation). Preliminary results obtained for the first 31 of these 117 patients were recently reported (Rickels et al., 1984). An intensive psychiatric history, including an administration of the SADS-L, indicated that 31% of 117 patients who initiated benzodiazepine therapy many years ago started their treatment because of symptoms closely resembling panic attacks (Table 7). When these 117 patients were asked prior to benzodiazepine withdrawal whether they were deriving any benefit from their benzodiazepine medication, about 80% of those originally diagnosed as suffering from GAD and 72% of those originally diagnosed as suffering from PD, but only 40% of those originally diagnosed as suffering from depressive states, claimed that they had derived significant benefit from treatment with various long as well as short half-life benzodiazepines.

These data seem to indicate to the authors that the recent "discovery" of the beneficial effect of the benzodiazepine alprazolam in the treatment of PD does not seem to be unique for alprazolam, but may also be true for some of the older benzodiazepines.

Comments

Several points of clinical interest may be deduced from the data presented.

1. Klein's (1964) earlier observation that "anticipatory anxiety" of agoraphobic patients is beneficially influenced by benzodiazepine supports the benzodiazepines' efficacy in GAD, as Klein's anticipatory anxiety would probably be diagnosed within the framework of DSM-III as GAD.

2. Whether or not other benzodiazepines besides alprazolam, particularly if prescribed in higher than FDA-approved therapeutic dosages, will be helpful in patients suffering from PD with and without marked agoraphobia cannot be determined at this time. PD patients suffering from marked agoraphobia have so far not responded as well to older benzodiazepines prescribed in the usual ther-

apeutic dosages than to imipramine, phenelzine, or alprazolam. However, since studies frequently do not separate patients suffering from pure PD from those suffering from panic disorder with agoraphobia, the question is left unanswered whether the improvement registered in these studies was largely contributed by patients suffering from pure PD or patients suffering from more severe agoraphobia. It is hoped that the completed, as well as ongoing, multicenter Upjohn trials will provide important answers to this question.

3. If differences in antipanic/antiagoraphobic efficacy between alprazolam and other benzodiazepines should indeed exist, one may ask: Are these differences related to the fact that patients are better able to adjust to the sedative effects of alprazolam than to those of other benzodiazepines, or are they related to the triazolo-ring structure unique to alprazolam? Similar speculations may also be made to explain alprazolam's "antidepressive" properties (Feighner et al., 1983; Rickels et al., 1985). In fact, in a recently completed study by this research group (in preparation) alprazolam and imipramine produced equal degrees of improvement and significantly more improvement than placebo or diazepam in patients suffering from major depressive disorders.

4. If the original experience of the alprazolam research program, namely that alprazolam has to be given in relatively high daily dosages (6 to 10 mg in the Upjohn-supported studies and up to 15 mg in the authors' own experience in selected patients), should be confirmed, one certainly has cause for concern regarding treatment discontinuation, treatment which for PD with agoraphobia may last for at least 6 to 12 months. In fact, if abruptly stopped, seizures (Breier et al., 1984) or other severe withdrawal symptoms (Noyes et al., 1985) can be expected. Fortunately, at least in the authors' experience, most PD patients are not in need of such excessive daily dosages but respond well to only 2 to 4 mg/day of alprazolam. Higher daily dosages may be required, however, for patients suffering from marked agoraphobia. Research is presently under way by our research group to determine the safest and most convenient management of discontinuation from alprazolam treatment after prolonged use.

Among the many potential problems, just one should be mentioned here. Patients frequently experience panic attacks during alprazolam discontinuation which then is interpreted by patient and physician as a return of the original panic symptoms, while indeed they may represent for many patients a rebound phenomenon or withdrawal reaction. Needless to say, if other benzodiazepines are used in equipotent dosages for prolonged periods of time in the treatment of PD, similar problems to those possibly caused by alprazolam discontinuation can be expected.

5. The authors suggest that one may be dealing with several subgroups of PD patients. One group of patients either outlasts their initial panic attacks without treatment or will adjust to them in such a way that they cease to be a hindrance, such as, for example, sitting on the aisles in movie theaters or having to stand close to a door in a subway. A second group of patients suffering from panic attacks obtain relief with the usual dosages of various benzodiazepines and their panic attacks are aborted or prevented and thus little chance exists to develop secondary phobic avoidance behavior. For these two patient groups, GAD might be in many cases as appropriate a diagnosis as PD. Finally, there are those patients whose panic attacks do not go away on their own or do not respond to benzodiazepine treatment; these patients will with time either develop secondary avoidance behavior (agoraphobia) or hysterical and somatization behavior (Katon, 1984). It is probably this subgroup of PD patients, who also suffer from marked agoraphobia, who are in need of pharmacological intervention with such agents as imipramine, phenelzine, or alprazolam prescribed alone or in conjunction with various methods of behavior modification.

Conclusion

The authors suggest that the role of benzodiazepines for the treatment of panic disorder needs yet to be clarified. Good clinical evidence indicates that many patients who suffer from PD with or without agoraphobia respond to alprazolam therapy, particularly if alprazolam is prescribed in higher than FDA-approved therapeutic daily dosages. It has further been shown that patients suffering from agoraphobia and panic attacks do respond to imipramine and phenelzine. Evidence also exists, albeit based on less than the most rigorous research, that PD patients without marked agoraphobia respond well to nontriazolo benzodiazepines, such as diazepam, for example.

No answer has yet been provided to the question of whether or not benzodiazepines differ among each other in their potential to help patients suffering from PD with or without agoraphobia, when prescribed in equipotent dosages. And if differences should be found, are they related, for example, simply to the patients' ability to tolerate alprazolam's side effects, or are they related to its unique triazolo ring structure?

Much more research needs to be carried out to clarify the role of benzodiazepines for the treatment of panic disorder *with* and *without* agoraphobia. Various benzodiazepines have to be compared in equipotent dosages over similar periods of time in well-controlled studies. What is the minimum daily dosage necessary to produce desired results? Could it be that most PD patients respond to FDA-recommended therapeutic dosages and that only a limited group of severe agoraphobics may require excessive dosages not yet approved by the FDA?

Since some research has recently reported that imipramine also may possess antianxiety effects (Lipman et al., 1981), it may well be that the effect of phenelzine, a monoamine oxidase inhibitor (MAOI), and imipramine, a tricyclic, in PD may be similar to their effects in GAD when prescribed in appropriate dosages and for adequate periods of time (i.e., if patients could be persuaded not to drop out of treatment because of side effects). Thus we might learn in time that there are more similarities than dissimilarities between antidepressant, antianxiety, and antipanic agents.

In the meantime, it behooves the psychiatrist treating patients suffering from PD with or without agoraphobia to use the lowest daily medication dose which will produce desired clinical results and to treat the patients for the shortest time possible. A general guide might be that the more chronic and the more severe the panic disorder and the more intense the presence of secondary avoidance behavior and/or agoraphobia, the longer should be the duration of treatment and the higher the daily dosage. If patients have been on therapeutic or certainly if on higher than recommended therapeutic dosages of benzodiazepines for 6 to 12 months, drug discontinuation has to be conducted slowly and carefully, and physician and patient should be reminded that only a drug-free period of at least several weeks will allow for determining with some certainty whether the "reoccurrence of panic attacks" represents a return of original symptoms or a rebound phenomenon. Best results may well be obtained with a treatment regimen which combines the use of medication with some method of behavior modification.

References

American Psychiatric Association, Taskforce on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

American Psychiatric Association, Taskforce on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders (DSM-II)*, 2nd ed. Washington, D.C.: American Psychiatric Association, 1952.

Ballenger, J.C., Burrows, G.D., Noyes, R., et al. Alprazolam treatment of agoraphobia/panic disorder. Presented at the 138th Annual Meeting of the American Psychiatric Association, Dallas, May, 1985.

Breier, A., Charney, D.S., and Nelson, J.C. Seizures induced by abrupt discontinuation of alprazolam. *Am. J. Psychiatry*, 141(12):1606-1607, 1984.

Chouinard, G., Annable, L., Fontaine, R., and Solyom, L. Alprazolam in the treatment of generalized anxiety and panic disorders: A double-blind placebo-controlled study. *Psychopharmacology*, 77:229-233, 1982.

Derogatis, L.R., Lipman, R.S., Rickels, K., et al. The Hopkins symptom checklist (HSCL): A self-report inventory. *Behav. Sci.*, 19 (1):1-15, 1974.

Editorial. Panic-symptom or disorder? *Lancet*, I:1418-1419, June 25, 1983.

Feighner, J.P., Aden, G.C., Fabre, L.F., et al. Comparison of alprazolam, imipramine, and placebo in the treatment of depression. *JAMA*, 249 (22):3057-3064, 1983.

Katon, W. Panic disorder and somatization. *Am. J. Med.*, 77:101-112, 1984.

Klein, D.F. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia (Berlin)*, 5:397-408, 1964.

Liebowitz, M.R., Quitkin, F.M., Stewart, J.W., et al. Phenelzine versus imipramine in atypical depression: A preliminary report. *Arch. Gen. Psychiatry* (In press).

Lipman, R.S., Covi, L, Downing, R.W., et al. Pharmacotherapy of anxiety and depression. *Psychopharmacol. Bull.*, 17 (3):91-94, 1981.

Marks, I.M. The current status of behavioral psychotherapy: Theory and practice. *Am. J. Psychiatry*, 133:253-261, 1976.

Mavissakalian, M., and Michelson, L. Agoraphobia: Behavioral and pharmacological treatments, preliminary outcome, and process findings. *Psychopharmacol. Bull.*, 18 (4):91-103, 1982.

McNair, D.M., and Kahn, R.J. Imipramine compared with a benzodiazepine for agoraphobia. In: Klein, D.F., and Rabkin, J. (eds.), *Anxiety: New Research and Changing Concepts.* New York: Raven Press, 1981, pp. 69-79.

Noyes, R., Clancy, J., Coryell, W.H., et al. A withdrawal syndrome after abrupt discontinuation of alprazolam. *Am. J. Psychiatry*, 142 (1):114–116, 1985.

Noyes, R., Anderson, D.J., Clancy, J., et al. Diazepam and propanolol in panic disorder and agoraphobia. *Arch. Gen. Psychiatry*, 41:287–292, 1984.

Rickels, K., Case, W.G., Downing, R.W., and Winokur, A. Long-term diazepam therapy and clinical outcome. *JAMA*, 250 (6):767–771, 1983.

Rickels, K., Case, W.G., Winokur, A., and Swenson, C. Long-term benzodiazepine therapy: Benefits and risks. *Psychopharmacol. Bull.*, 20 (4):608–615, 1984.

Rickels, K., Feighner, J.P., and Smith, W.T. Alprazolam, amitriptyline, doxepin, and placebo in the treatment of depression. *Arch. Gen. Psychiatry*, 42:134–141, 1985.

Rickels, K., Wiseman, K., Norstad, N., et al. Buspirone and diazepam in anxiety: A controlled study. *J. Clin. Psychiatry*, 43(12):81–86, 1982.

Sheehan, D.V., Coleman, J.H., Greenblatt, D.J., et al. Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J. Clin. Psychopharmacol.*, 4(2):66–75, 1984.

Sheehan, D.V., Claycomb, J.B., Surman, O.S., et al. The relative efficacy of alprazolam, phenelzine, and imipramine in treating panic attacks and phobias. Read before the 137th Annual Meeting, American Psychiatric Association, Los Angeles, May 6, 1984.

Zitrin, C.M., Klein, D.F., and Woerner, M.G. Behavior therapy, supportive psychotherapy, imipramine, and phobias. *Arch. Gen. Psychiatry*, 35:307–316, 1978.

Zitrin, C.M., Klein, D.F., Woerner, M.G., and Ross, D.C. Treatment of phobias: I. Comparison of imipramine hydrochloride and placebo. *Arch. Gen. Psychiatry*, 40:125–138, 1983.

Cholinergic Mechanisms in the Treatment of Geriatric Disorders

CHAIR: Allen Raskin, Ph.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Physostigmine in Patients With Alzheimer's Disease

Michael Davidson, M.D.,[1] Richard C. Mohs, Ph.D.,[1] Eric Hollander, M.D.,[1] Bonnie M. Davis, M.D.,[1] Theresa Ryan, M.S.,[1] Thomas B. Horvath, M.D.,[1] and Kenneth L. Davis, M.D.[1]

Postmortem examination of brain specimens from patients with clinical diagnosis of Alzheimer's disease (AD) repeatedly demonstrated neurotransmitter deficiencies in the neocortex. The most consistent evidence point towards a reduction in markers reflecting cholinergic activity (Davies, 1979; Perry et al., 1977, 1978). While other neurotransmitters like norepinephrine and somatostatin were found deficient, this was in addition to, and not instead of, the cholinergic deficiency (Adolfsson et al., 1979; Rossor et al., 1980). Furthermore, reduction in choline acetyltransferase (CAT) activity was reported in brain areas related to memory and learning and the deficit quantitatively correlates with severity of dementia (Perry et al., 1978). Additional support for the role of acetylcholine (ACh) in learning and memory, and implicitly in AD, comes from pharmacological studies.

Administration of cholinomimetics to young normal subjects was found to enhance encoding of new information beyond immediate memory (Davis et al., 1978). Conversely, administration of scopolamine, a centrally active anticholinergic, resulted in transient cognitive improvements phenomenologically similar to age-related memory dysfunctions (Drachman & Levitt, 1974). For all those reasons, enhancement of cholinergic neurotransmission in patients with AD would be expected to ameliorate some cognitive dysfunction.

Pharmacologic strategies employed in this attempt included administration of direct cholinergic receptor agonists; increasing ACh synthesis by precursor loading; and limiting ACh breakdown by inhibiting acetylcholinesterase (AChE). Clinical trials of cholinergic agonists have produced very mild improvements in symptoms of AD; however, these studies were seriously hampered by adverse effects. In spite of encouraging results in laboratory animals, the precursor loading strategy using lecithin and choline produced minimal or no improvements in patients with AD (Etienne, 1983).

Physostigmine, a competitive AChE inhibitor, has been used in at least nine clinical studies of patients with a clinical diagnosis of AD (Ashford et al., 1981; Caine, 1980; Caltagiorne et al., 1982; Kaye et al., 1982; Muramato et al., 1984; Peters & Levin, 1979; Smith & Swash, 1979; Sullivan et al., 1982; Thal et al., 1983). In contrast to the tonic effect of muscarinic agonist, physostigmine administration may better mimic the more phasic effect of endogenous ACh. Furthermore, physostigmine can be administered relatively safely, an important consideration in a target population with an often compromised cardiovascular system. This paper discusses our results of clinical trials with physostigmine in AD patients together with methodological implications relevant to this pharmacologic strategy.

---

[1] Department of Psychiatry, Bronx VA Medical Center, Bronx, NY 10468.

Patients meeting National Institute for Neurological and Communicative Disorders and Stroke (NINCDS) criteria for "probable AD" were included in the study (McKhann et al., 1984). The diagnosis of AD was supported by a clinical history demonstrating at least 1 year of progressive deterioration in cognition and other higher cortical functions; Dementia Rating Scale scores higher than 4; and a Memory and Information Test score of less than 10. Other tests used in the diagnostic process were the CAT scan, biochemical screening tests, thyroid function tests, serum B_{12} and folate levels, and neurological and psychiatric examinations. Particular care was taken to rule out patients whose dementia might be due to alcoholism, depression, or other neurological or medical conditions. To rule out patients with multi-infarct dementia, all patients were assigned a Hachinski Ischemic Score (Hachinski et al., 1975) and any patient with a score over 4 was excluded. All patients were free of psychoactive medications except those administered as part of these investigations, during and for at least 2 weeks prior to any study.

In order to establish the effect of physostigmine on cognitive symptoms of AD patients, the drug was initially administered intravenously. Previous animal and human studies demonstrated that intravenous physostigmine has a narrow therapeutic window. Doses slightly below this window produced no cognitive improvement while doses slightly exceeding the therapeutic window may in fact worsen performance on cognitive testing (Bartus, 1979; Davis et al., 1976). Therefore, an adequate test of physostigmine's efficacy requires a dose-finding phase in which a best dose is assigned to individual patients. Such a study design involves several testing sessions on the drug condition and only one testing session on placebo, thus increasing the likelihood of a drug effect to occur by chance.

In order to avoid this methodological flaw at the end of the dose-finding phase, a trial of the best physostigmine dose and a trial of placebo were repeated. Physostigmine (0.125 mg, 0.25 mg, and 0.5 mg) or saline placebo was randomly infused over 30 minutes. Starting 15 minutes into the infusion and ending 5 minutes after the end of the infusion, patients were given three trials on a visual recognition memory task. On each trial the patient was first presented with 12 words or pictures which were subsequently mixed with 12 additional items not previously shown to the patient. The 24 items were then presented, one at a time, and the patient was asked for each item whether or not it was one of the previously presented. Thirteen of the 16 patients included in the study showed a moderate transient improvement while receiving a dose of physostigmine and 3 patients performed best on placebo. A significant effect was demonstrated for the 13 "responders" included in the replication phase (F 1,11) $= 8.00$, $p<.02$), indicating that patients gave more correct responses while receiving physostigmine.

In spite of the theoretical importance of this finding, confirmed by others (Christie et al., 1981), its clinical applicability is limited by the short action of intravenous physostigmine. A meaningful evaluation of the drug's therapeutic potential in AD required a better and safer delivery route which would enable a comprehensive evaluation of this drug over an extended period of time. Such a comprehensive evaluation needs to assess cognitive and non-cognitive symptoms and possess the flexibility to include AD patients in different stages of this progressive disease. Alzheimer's Disease Rating Scale (ADRS) (Rosen et al., 1984) is such an assessment instrument and its reliability and validity are established. It is specifically designed to evaluate severity of symptoms in pharmacological studies. Cognition and language are assessed by task such as object naming, following commands, orientation, and constructional and ideational praxis. Non-cognitive behaviors are assessed by item such as depression, cooperation, psychotic symptoms, motor activity, and vegetative signs. The scale includes a broad range of tasks so that both very severe and mildly symptomatic patients can be evaluated. A higher score on the scale represents a more severe form of illness. Using this scale in conjunction with repeated oral administration of physostigmine provides a framework to study the more chronic effects of this treatment.

When this oral physostigmine trial was conceived, it was predicted that not all patients would benefit from the drug. The ability of oral physostigmine to improve AD systems depends on the drug's absorption, central penetrance, and the number of functioning cholinergic neurons still intact. It should be anticipated that in patients with extensive cholinergic cell loss or major abnormalities in other neurotransmitter systems, physostigmine would be unlikely to either increase neurotransmission or improve symptoms. Consequently, it is necessary to obtain a measure of physostigmine's biological effect in the central nervous system along with measures of drug-induced behavioral change. Cortisol secretion may be a potential indicator of physostigmine effect on cholinergic activity, as suggested by human and animal studies, demonstrating that cholinergic drugs increase and anticholinergics suppress cortisol nocturnal secretion (Davis et al., 1982; Hillhouse et al., 1975; Krieger & Krieger, 1967). Therefore, the effect of physostigmine on plasma cortisol levels was measured in concomitance with the cognitive effect of the drug.

Twelve AD patients were given oral physostigmine in a dose-finding/replication study. Physostigmine (0.5 mg, 1 mg, 1.5 mg, and 2 mg) or placebo was given every 2 hours for 3 to 4 days between 7 a.m. and 11 p.m. The ADRS was administered on the last day of each drug condition between 1:30 p.m. and 3:30 p.m. On the last night of drug and placebo condition in the replication phase, blood was drawn each half hour between 11 p.m. and noon the next day and assayed for cortisol. To ensure the drug effect on the early morning cortisol secretion, physostigmine or placebo were continued until 11 a.m. on the next morning following the sleep study. Eleven of 12 patients studied had lower (better) ADRS scores on a dose of physostigmine which were maintained in 7 patients during the replication phase. Only about one-third of patients showed a consistent and clinically evident improvement on physostigmine. However, it is encouraging to note that patients who improved during the replication phase also tended to show the greatest improvement during the dose-finding phase, and this improvement was generally achieved on the highest dose of physostigmine. Examination of plasma cortisol values revealed a strong linear relationship between percent increase in cortisol and symptoms improvement ($r\ (6) = .88,\ p < .02$), suggesting that physostigmine improved AD symptoms only to the extent that the drug has a central cholinomimetic activity. Similarly, a study by Thal et al. (1983) suggests that AD patients are benefitted by physostigmine only to the extent that this drug had a significant inhibitory effect on cerebrospinal fluid AChE.

Physostigmine-induced improvement in some AD patients reported here is in agreement with most (Muramoto et al., 1984; Sullivan et al., 1982; Thal et al., 1983), but not all reported studies (Ashford et al., 1981), with consistently more robust effect being noted. These heterogeneous results have to be interpreted in light of the problems inherent in pharmacological studies of AD and, in particular, pharmacological studies with putative cholinomimetics. The diagnosis of AD is inherently problematic without tissue verification. Misdiagnosed patients have other neurologic disorders or lack the characteristic histopathologic findings required for postmortem validation of AD (Liston & Rue, 1983; Nott & Fleminger, 1975; Ron et al., 1979). Even rigorous diagnostic criteria as described in this study have a 10% error rate. Hence, typical pharmacological trials with relatively small sample sizes are less likely to find statistically significant group means if they include an inevitable misdiagnosed patient. Nevertheless, a recent study reported a mean effect of physostigmine for the entire group (Beller et al., 1985).

In addition to the uncertainty of the antemortem diagnosis of AD and suggesting a complex pathophysiology for this disorder are postmortem biochemical findings of other neurotransmitter deficiencies along with the well-established cholinergic differences. Noradrenergic, serotonergic, and occasionally dopaminergic deficiencies were reported in patients with a clinical diagnosis of AD and postmortem presence of plaques, tangles, and reduced cholinergic activity (Adolfsson et al., 1979; Bondareff et al., 1982; Bowen et al., 1983; Rossor et al., 1984). If these neurotransmitters have a functional role in symptoms of AD, a pharmacological strategy restricted to cholinergic enhancement may not benefit AD patients with multiple neurotransmitter deficiencies. Future studies should include combined neurotransmitter replacement.

Obviously any pharmacological intervention that will aid AD patients must ultimately address the cholinergic deficit. However, the ability of physostigmine to enhance cholinergic activity is dependent on the amount of ACh made available to the synaptic cleft by viable cholinergic neurons. The presumed retrograde neuronal distinction occurring in the course of this disease and the limited overlapping innervation of cholinergic receptors may decrease the efficacy of physostigmine as the disease progresses (Coyle et al., 1983). This may also explain the heterogeneous effects produced by physostigmine in AD patients in different stages of this disease.

However imperfect the theoretical background for the use of physostigmine in AD is, issues related to this drug delivery must be addressed. Little is known about physostigmine pharmacokinetics or central nervous system (CNS) penetrance; nevertheless it is presumed that a constant and stable drug presence in the CNS would be desirable. Also, experience derived from pharmacological trials of physostigmine suggest that most AD patients benefit from higher doses of this drug. This has to be reconciled with the peripheral adverse effects of physostigmine and the difficulties involved in chronic administration of multiple drug doses to a demented population. Slow oral capsules, and subcutaneous and intrathecal devices are some of the alternatives presently under consideration.

References

Adolfsson, R., Gottfries, C.G., Roos, B.E., and Winblad, B. Changes in the brain catecholamines in patients with dementia of Alzheimer type. *Br. J. Psychiatry*, 135:216–223, 1979.

Ashford, J.W., Soldinger, S., Schaeffer, J., et al. Physostigmine and its effect on six patients with dementia. *Am. J. Psychiatry*, 138:829–830, 1981.

Bartus, R.T. Physostigmine and recent memory effects in young and aged nonhuman primates. *Science*, 206:1087-1089, 1979.

Beller, S.A., Overall, J.E., and Swann, A.C. Efficacy of oral physostigmine in primary degenerative dementia. *Psychopharmacology*, 87:147-151, 1985.

Bondareff, W., Mountjoy, C.Q., and Roth, M. Loss of neurons of origin of the adrenergic projections to cerebral cortex (nucleus locus coeruleus) in senile dementia. *Neurology*, 32:164, 1982.

Bowen, D.M., Allen, S.J., and Benton, J.S. Behavioral assessment of serotonergic and cholinergic dysfunction and cerebral atrophy in Alzheimer's disease. *J. Neurochemistry*, 41:266-272, 1983.

Caine, E.D. Cholinomimetic treatment fails to improve memory disorders. *N. Engl. J. Med.*, 303:585–586, 1980.

Caltagirone, C., Gainotti, G., and Masullo, C. Oral administration of chronic physostigmine does not improve cognitive or amnesic performances in Alzheimer's presenile dementia. *Int. J. Neurosci.*, 16:247–249, 1982.

Christie, J.E., Shering, A., and Ferguson, J. Physostigmine and arecoline: Effects of intravenous infusions in Alzheimer's presenile dementia. *Br. J. Psychiatry*, 138:46–50, 1981.

Coyle, J.T., Price, D.L., and DeLong, M.R. Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science*, 219:1184–1190, 1983.

Davies, P. Neurotransmitter-related enzymes in senile dementia of the Alzheimer type. *Brain Res.*, 171:319–327, 1979.

Davis, B.M., Brown, G.M., Miller, M., et al. Effects of cholinergic stimulation of pituitary hormonal release. *Psychoneuroendocrinology*, 7:347–354, 1982.

Davis, K.L., Hollister, L.E., and Overall, J. Physostigmine: Effects on cognition and affect in normal subjects. *Psychopharmacology (Berlin)*, 51:22–27, 1976.

Davis, K.L., Mohs, R.C., Tinklenberg, J.R., et al. Physostigmine treatment of long term memory processes in normal humans. *Science*, 201:272–274, 1978.

Drachman, D.A., and Levitt, J. Human memory and the cholinergic system. *Arch. Neurol.*, 30:113–121, 1974.

Etienne, P. Treatment of Alzheimer's disease with lecithin. In: Reisberg, B. (ed.), *Alzheimer's Disease: The Standard Reference*. New York: Free Press, 1983, pp. 353–354.

Hachinski, V.E., Iliff, L.D., and Zicha, E. *Arch. Neurol.*, 32:632–637, 1975.

Hillhouse, E.W., Burden, J., and Jones, M.T. The effect of various putative neurotransmitters on the release of corticotrophin releasing hormones from the hypothalamus of the rat in vitro, I: The effect of acetylcholine and noradrenaline. *Neuroendocrinology*, 17:1–11, 1975.

Kaye, W.H., Sitaram, N., Weingartner, H., et al. Modest facilitation of memory in dementia with combined lecithin and anticholinesterase therapy. *Biol. Psychiatry*, 17:271–274, 1982.

Krieger, D.T., and Krieger, H.P. Circadian pattern of plasma 17-hydroxycorticosteroid: alteration by anticholinergic agents. *Science*, 155:1421–1422, 1967.

Liston, E.H., and Rue, A.L. Clinical differentiation of primary degenerative dementia: A critical review of the evidence. *Biol. Psychiatry*, 18:1451–1484, 1983.

McKhann, G., Drachman, D., Folstein, M., et al. Clinical diagnosis of Alzheimer's disease: Report of NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services. Task force of Alzheimer's disease, *Neurology*, 34:939–944, 1984.

Muramoto, O., Sugishita, M., Kazuya, A., et al. Cholinergic system and constructional praxis: a further study of physostigmine in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry*, 47:485–491, 1984.

Nott, P.N., and Fleminger, J.J. Presenile dementia: The difficulties of early diagnosis. *Acta Psychiatr. Scand.*, 51:210–217, 1975.

Perry, E.K., Perry, R.H., Blessed, G., and Tomlinson, B.E. Necropsy evidence of central cholinergic deficits in senile dementia. *Lancet*, i: 189, 1977.

Perry, E.K., Perry, R.H., Blessed, G., and Tomlinson, B.E. Changes in brain cholinesterases in senile dementia of Alzheimer disease. *Neuropathol. Appl. Neurobiol.*, 4:273–277, 1978.

Perry, E.K., Tomlinson, B.E., Blessed, G., et al. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Br. Med. J.*, 2:1457–1459, 1978.

Peters, B.H., and Levin, H.S. Effects of physostigmine and lecithin on memory in Alzheimer's disease. *Ann. Neurol.*, 6:219–221, 1979.

Ron, M.A., Toone, B.K., Garralda, M.E., and Lishman, W.A. Diagnostic accuracy in presenile dementia. *Br. J. Psychiatry*, 134:161–168, 1979.

Rosen, W.G., Mohs, R.C., and Davis, K.L. A new rating scale for Alzheimer's disease. *Am. J. Psychiatry*, 141:11, 1356–1361, 1984.

Rossor, M.N., Emerson, P.C., and Mountjoy, C.Q. Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of the Alzheimer type. *Neurosci. Lett.*, 20:373, 1980.

Rossor, M.N., Iversen, L.L., and Reynolds, G.P. Neurochemical characteristics of early and late onset types of Alzheimer's disease. *Br. Med. J.*, 288:961–964, 1984.

Smith, C.M., and Swash, M. Physostigmine in Alzheimer's disease (letter). *Lancet*, 1:42, 1979.

Sullivan, E.V., Shedlack, K.H., Corkin, S., et al Physostigmine and lecithin in Alzheimer's disease. In: Corkin, S., Davis, K.L., Growdin, J.H., et al. (eds.), *Alzheimer's Disease: A Report of Progress in Research*. New York: Raven Press, 1982.

Thal, L.J., Fuld, P.A., and Masur, D.M. Oral physostigmine and lecithin improve memory in Alzheimer's disease. *Ann. Neurol.*, 13:491–496, 1983.

Intracranial Drug Administration in Alzheimer's Disease

Robert E. Harbaugh, M.D.[1]

Introduction

During the last decade there has been an explosion of information regarding the neurochemical activity of the central nervous system (CNS). The identification of numerous neurotransmitter, neuromodulator, and neurohormone candidates, and the elucidation of their roles in normal and pathological brain function, have vastly expanded the possibilities for pharmacologic manipulation in the treatment of neurologic disease.

Clinical application of this neurochemical information has, however, been plagued by difficulties with drug delivery to the CNS. Long-standing problems in clinical neuropharmacology include adverse systemic effects of neuroactive drugs, peripheral metabolism or inactivation of drugs, difficulties with blood-brain barrier penetration, erratic drug absorption and binding by serum proteins, adverse effects at one level of the neuraxis to achieve therapeutic effects at another (e.g., sedation with narcotic analgesics), and problems with patient compliance. One can think of few neuroactive drugs where at least one of these problems is not clinically significant. In addition, a number of potentially therapeutic compounds may never reach clinical trials because of these problems.

With implantable drug infusion devices and stereotactic neurosurgical techniques, the technology is available today to circumvent all of the above difficulties. Direct infusion of drugs into the cerebrospinal fluid (CSF) bypasses the problems of systemic side effects, peripheral drug inactivation, poor drug absorption, serum protein binding, and blood-brain barrier penetration. Continuous or programmable drug infusion devices ensure patient compliance. Regional drug infusions can obviate adverse effects at other levels of the neuraxis and it may, in time, be possible to infuse minute quantities of drugs directly into circumscribed areas of the brain parenchyma, thereby achieving neuroanatomically precise pharmacologic manipulations of brain function.

The rationale behind drug delivery to the CNS by central infusion and selection criteria for drugs for infusion will be briefly discussed. Experience here with central drug infusion for patients with Alzheimer's disease (Harbaugh et al., 1984) will be used to illustrate the application of this technology in a clinical setting. Potential complications of this treatment approach will also be discussed.

Rationale Of Central Drug Infusion

By and large, intrathecal drug administration has not proven to be effective (Aird, 1984). Therefore, the first question to be addressed regarding central drug infusion is whether these drugs achieve adequate brain penetration. The answer to this question depends not only on the drug involved but also on the method of central drug administration.

Most clinical trials of central drug administration have employed single or intermittent bolus injections into the subarachnoid space or ventricular system. Of all the ways to deliver drugs to the CNS, this is probably the worst. Single bolus injections result in very high CSF drug concentrations and relatively limited parenchymal penetration (Blasberg et al., 1977; Lee et al., 1960). In addition, a single large bolus of drug is likely to be more toxic and less effective than more frequent, smaller doses (Bleyer et al., 1978). However, even with bolus administration, drugs will penetrate the parenchyma and, as CSF is cleared by bulk flow, diffuse back into the subarachnoid space (Blasberg et al., 1977). In situations where high drug concentrations in the CSF or immediately adjacent parenchyma

---

[1] Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756.

are desired (carcinomatous meningitis, spinal anesthesia/analgesia, chemical rhizotomy), bolus injections are effective. However, if deeper diffusion into parenchyma is necessary, longer term infusion is preferable.

Intravascular administration of drugs which cross the blood-brain barrier shows a rapid onset of action due to the short circulation time and extensive vascular-CNS interface (Aird, 1984). However, drugs administered into the CSF require much longer for adequate diffusion into the parenchyma (Lee et al., 1960). As the duration of central drug administration increases, the depth of parenchymal penetration, even of large protein molecules, also increases (Brightman et al., 1969). Therefore, to adequately evaluate the effectiveness of central drug administration, infusions must be carried out over a prolonged time.

In addition to the duration of central drug infusion, the rate of infusion may be important. Rates of infusion rapid enough to elevate CSF pressure will result in increased CSF absorption and therefore increase drug elimination by bulk flow (Katzman et al., 1970).

The site of infusion within the central compartment may also be of significance. Drug penetration into the parenchyma appears to occur more readily through the ependymal than the pial surface (Rall, 1968), and drugs administered into the subarachnoid space may not enter the ventricular system (Yen et al., 1978). Therefore, intraventricular drug infusion is a more reasonable approach for achieving diffuse brain penetration than is lumbar intrathecal administration. Conversely, if one wishes to confine drug effects to the spinal cord with minimal effects at higher levels of the neuraxis, then intraspinal infusion may be beneficial (Coombs et al., 1983; Harbaugh et al., 1982). Thus, some relatively restricted neuropharmacologic effects can be achieved. Theoretically, with stereotactic cannula placement and very low flow-rate infusion devices, delivery of minute quantities of drugs to very circumscribed regions of brain parenchyma is possible.

When evaluating the effectiveness of central drug administration, the choice of drug is at least as important as the method of delivery. The ability of a drug to cross the blood-brain barrier is more likely to be detrimental than beneficial if the drug is given as a continuous central infusion. Drugs which readily cross brain capillaries can be rapidly cleared from the CNS when infused into the CSF (Blasberg et al., 1975). The use of such drugs may be valuable if high local concentrations in tissue adjacent to the subarachnoid space or ependyma are desired. However, if deeper parenchymal penetration is the goal, then lipid insoluble, polar molecules are better candidates for infusion (Blasberg et al., 1975).

When considering drugs for long-term central infusion, chemical and biological stability become important criteria. For continuous infusion via an implantable pump, the infused drug must be stable at body temperature for at least as long as the cycle time of the infusion pump. In addition, if widespread diffusion of active drug into parenchyma is desired, then the drug infused cannot be rapidly metabolized within the CNS or CSF. This last consideration may not apply to local intraparenchymal infusion where a steep concentration gradient of active drug could be beneficial.

Clinical Experience

Our clinical experience at Dartmouth (Coombs et al., 1983; Harbaugh et al., 1982, 1984) with implantable infusion devices for central drug administration may serve to illustrate some of the points raised above. The clinical studies referred to were approved by our institution's committee for the protection of human subjects and informed consent was obtained before instituting any experimental treatment trials.

The evidence for the cholinergic hypothesis of Alzheimer's disease has been extensively reviewed (Coyle et al., 1983) and need not be repeated here. If this cholinergic hypothesis is correct, then augmentation of brain cholinergic activity may ameliorate some of the symptoms in these patients. Previous attempts at increasing brain cholinergic activity by administration of acetylcholine precursors, cholinesterase inhibitors, or systemic cholinergic agonists had been attended by some of the difficulties with drug delivery to the brain which have previously been discussed. Intracranial cholinergic drug infusion in patients with Alzheimer's disease was started as a means of testing the validity of the cholinergic hypothesis and as an attempt at therapy for a devastating neurologic disease with no known treatment.

By delivering a muscarinic agonist into the ventricular system or cisterna magna, the problems of systemic drug inactivation, serum protein binding, and drug absorption are avoided. The use of an implantable continuous infusion pump permits long-term intracranial infusion of drug or placebo on an outpatient basis and avoids any problems of patient compliance. Pump flow rates range from 1 to 2 ml/day, an insignificant amount compared to normal daily CSF production. Because of small daily drug doses (0.05 to 0.7 mg), systemic side effects are not encountered.

Bethanechol chloride, a pure muscarinic agonist, was chosen for infusion. The drug is a polar, water-soluble molecule which is not degraded by cholinesterases and is stable in solution.

For patients with Alzheimer's disease, drug distribution to the hippocampi, locus ceruleus, reticular nucleus of the thalamus, and cerebral cortex was desired and, for the reasons described above, a drug which does not cross the blood-brain barrier when infused into the ventricular system was chosen.

Potential Complications of Central Drug Infusion

The potential advantages of central drug infusion have been discussed. There are, however, some potential disadvantages which require equal consideration. These include the operative risks of catheter placement and pump implantation, and the risk of increased neurotoxicity.

As for any neurosurgical procedure, the risks of catheter placement and pump implantation include anesthetic complications, hemorrhage, and infection. Although all these risks are low, there is probably an irreducible minimum, and some complications must be anticipated. Our personal experience here with pump implantation now includes about 40 patients who have had pumps implanted for various indications. We have encountered no significant anesthetic complications but have had one infectious and one hemorrhagic complication.

The risk of neurotoxicity with intracranial drug infusions must also be considered. Certainly, toxicity studies in animals are mandatory before considering intracranial or intraspinal infusion of drugs in patients. Although such toxicity studies decrease the risk of human neurotoxicity, some unexpected reactions to drug infusions in patients are likely to occur. We have now been infusing bethanechol chloride intracranially in patients with Alzheimer's disease for up to 20 months. One patient developed a reversible parkinsonian syndrome of rigidity and bradykinesia and another developed a reversible CSF inflammatory response which may or may not have been related to drug infusion (Harbaugh et al., 1984). Certainly, experience with more patients infused for longer periods of time will be necessary before any accurate figures on the risk of neurotoxicity are available. However, to date, drug infusions appear to be well tolerated.

The feasibility of intracranial and intraspinal administration of neurotransmitter analogues has been demonstrated (Coombs et al., 1983; Harbaugh et al., 1982, 1984). However, the value of these therapeutic endeavors over presently available therapy remains to be proven. We are conducting studies of the effect of intracranial bethanechol infusion on activities of daily living and neuropsychologic test scores in a double-blind, placebo-controlled crossover design. Preliminary studies showed family reports of decreased confusion, increased initiative, and improvements in activities of daily living during drug infusion but no subjective improvement in short-term memory was reported. A battery of short-term memory tests has also not shown a statistically significant difference between drug and placebo scores.

Almost certainly, the technique of central drug infusion for neurologic disease is more important than the outcome of any single therapeutic trial. Neurologic disorders in which abnormalities of neurotransmitter activity or availability are pathogenetically implicated and structural damage to the CNS is minimal, may prove to be the most fruitful areas for the application of this technique. Movement disorders, epilepsy, and functional and psychiatric disease are obvious possibilities. Only time and further investigation will tell if this new approach for drug delivery to the brain will come to naught or herald a new era in neuropharmacology and functional neurosurgery.

Acknowledgments: David W. Roberts, M.D., Charles M. Culver, M.D., Ph.D., Mark C. Johnson, Ph.D., and Teddi M. Reeder, B.S., R.N., have been instrumental in developing and carrying out the Alzheimer's disease studies.

References

Aird, R.B. A study of intrathecal, cerebrospinal fluid-to-brain exchange. *Exp. Neurol.*, 86:342–358, 1984.

Blasberg, R.G., Patlak, C.S., and Fenstermacher, J.D. Intrathecal chemotherapy: Brain tissue profiles after ventriculocisternal perfusion. *J. Pharm. Exp. Ther.*, 194:73–83, 1975.

Blasberg, R.G., Patlak, C.S., and Shapiro, W.R. Distribution of methotrexate in cerebrospinal fluid and brain after intraventricular administration. *Cancer Treat. Report*, 61:633–641, 1977.

Bleyer, W.A., Poplack, D.R., Simon, R.M., et al. Concentration X time methotrexate via a subcutaneous reservoir: A less toxic regimen for intraventricular chemotherapy of central nervous system neoplasms. *Blood*, 51:835–842, 1978.

Brightman, M.W., and Reese, T.S. Junctions between intimately apposed cell membranes in the vertebrate brain. *J. Cell Biol.*, 40:648–677, 1969.

Coombs, D.W., Saunders, R.L., Gaylor, H.S., et al. Relief of continuous chronic pain by intraspinal narcotics infusion via an implanted reservoir. *JAMA*, 250:2336–2339, 1983.

Coyle, J.T., Price, D.L., and DeLong, M.R. Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science*, 219:1184–1190, 1983.

Harbaugh, R.E., Coombs, D.W., Saunders, R.L., et al. Implanted continuous epidural morphine infusion system. Preliminary report. *J. Neurosurg.*, 56:803–806, 1982.

Harbaugh, R.E., Roberts, D.W., Coombs, D.W., et al. Preliminary report: Intracranial cholinergic drug infusion in patients with Alzheimer's disease. *Neurosurgery*, 15:514–518, 1984.

Katzman, R., and Hussey, F. A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. *Neurology*, 20:534–544, 1970.

Lee, J.C., and Olszewski, J. Penetration of radioactive bovine albumin from cerebrospinal fluid into brain tissue. *Neurology*, 10:814–822, 1960.

Rall, D.P. Transport through the ependymal linings. *Prog. Brain Res.*, 29:159–167, 1968.

Yen, J., Reis, F.L., Kimelberg, H.K., et al. Direct administration of methotrexate into the CNS of primates. Part 2. Distribution of H3 methotrexate after intrathecal lumbar injection. *J. Neurosurg.*, 48:895–902, 1978.

The Cholinergic Hypothesis of Memory Dysfunction in Alzheimer's Disease—Revisited

Nunzio Pomara, M.D.,[1] and Michael Stanley, Ph.D.[2]

Of all the neurotransmitter deficits which have been reported in Alzheimer's disease (AD), by far the most extensive and consistent changes have involved the cholinergic system (Bartus et al., 1982; Davies & Maloney, 1976; Price et al., 1982; Rossor, 1982). Correlations between the severity of dementia before death, the density of senile plaques, and the reduction in the activity of choline acetyltransferase (CAT), a marker of presynaptic cholinergic neurons, strongly support the role of these cholinergic deficits in the pathophysiology of memory dysfunction (Perry et al., 1978). To date, no such relationships have been established between severity of dementia and any of the other neurotransmitter abnormalities which have also been described in this illness (Greenwald & Davis, 1983).

Another finding which has lent further support to the possible involvement of the cholinergic dysfunction in the pathophysiology of memory deficits observed in patients with AD has been the observation that the administration of agents such as scopolamine, which interfere with cholinergic transmission, produces memory deficits in normals. These deficits are qualitatively similar to those found in early AD (Drachman, 1977).

All of the foregoing observations, together with the precedent of alleviating motoric dysfunction in Parkinson's disease (PD) by means of dopaminergic agents, have provided a rationale for several AD treatments, i.e., cholinergic precursors (choline, lecithin) and indirect and direct muscarinic agonists (physostigmine, bethanechol chloride, RS-86).

In contrast to the successful therapeutic interventions that have been developed for the treatment of PD, by and large none of these cholinergically based therapeutic strategies has led to clinically useful improvements in AD (Mohs et al., 1985; Wettstein & Spiegel, 1984).

Several explanations have been offered for the poor therapeutic outcome which has been observed in these clinical trials. It has been suggested that:

1. CAT needs two substrates for acetylcholine synthesis, i.e., choline and acetyl coenzyme A. Therefore, if both substrates are depleted in AD, simply increasing choline by means of cholinergic precursors would not be sufficient to increase acetylcholine synthesis.
2. High-affinity uptake system for choline, acetylcholine synthesis, and release are all dependent on neuronal activity and, therefore, simply increasing choline would not be sufficient to effect these parameters.
3. The therapeutic action of physostigmine and other cholinesterase inhibitors might be limited by the failure of enough acetylcholine to be released pre-synaptically, by their narrow therapeutic window, by poor penetration into the central nervous system, and possibly by their action to cause a "feedback" inhibition of acetylcholine synthesis and release.
4. The use of exogenous direct muscarinic agonists also might have a very narrow therapeutic window which may be difficult to overcome.
5. Misdiagnosis of patients has diluted treatment effects.
6. Deficits in other neurotransmitters, e.g., somatostatin, serotonin, dopamine, or noradrenaline, also might contribute to the pathophysiology of cognitive dysfunction in patients with AD.

Even when dose has been carefully titrated to optimize response, or when problems of entry into the brain have been circumvented by direct administration of a cholinergic agonist into the cerebral ventricles, the therapeutic outcome remains poor (Harbaugh et al. 1984; Mohs et al., 1985).

---

[1] Lafayette Clinic and Wayne State University School of Medicine, Detroit, MI 48207.

[2] New York State Psychiatric Institute and Columbia University, New York, NY 10032.

The failure of cholinergic agonists in the treatment of AD is in marked contrast to the clinically relevant improvements in PD patients following treatment with dopaminergic agents, and calls into question some of the underlying assumptions regarding our understanding of the cholinergic system in AD.

Two tacit assumptions underlying treatments with cholinomimetics have been that the function of muscarinic receptors remains normal in AD and that a hypoactivity of the central cholinergic system is invariably associated with this disorder. It is our contention that the currently available data do not allow any definitive statement either about the status of muscarinic receptor function or about central cholinergic activity in AD.

Muscarinic Receptor Responsivity in AD

A specific aspect of cholinergic function that has been overlooked is that the presynaptic cholinergic deficits may account only in part for the cholinergic dysfunction seen in AD, and that alterations in the functional responsivity of the remaining muscarinic receptors (M_1 and M_2) also may contribute to the pathophysiology of AD. To the extent that cholinergic transmission is reliant on the functional integrity of both pre- and postsynaptic components, the elucidation of muscarinic response in AD is of particular importance.

Although no significant reductions in the number of muscarinic receptors have been noted in AD (Bowen, 1983; Davies & Verth, 1978), the failure of these studies to observe a difference may by itself reflect some atypical characteristics of the cholinergic system. In contrast to lesions of the noradrenergic, dopaminergic, and serotonergic neuronal systems, which have been shown to be associated with receptor and behavioral supersensitivity (Creese et al., 1978; DeMontigny et al., 1980), lesions of the cholinergic system have not been shown consistently to produce either an upregulation of muscarinic receptors or denervation supersensitivity (Bracco et al., 1982; London et al., 1984; McKinney & Coyle, 1982). The failure to observe evidence for denervation supersensitivity in these animal experiments does not exclude the possibility that muscarinic denervation supersensitivity could occur in AD.

The results of these animal experiments do not permit definitive statements to be made on the impact of presynaptic cholinergic neuronal loss on the functional status of postsynaptic muscarinic receptors. Although most studies do not report a significant reduction in the number of muscarinic receptors in AD, the failure of these studies to find changes merely may reflect the inability of quinuclidinyl benzylate (QNB) binding, as it has been commonly applied, to distinguish pre- and postsynaptic receptors. Thus in AD, the loss of presynaptic receptors might not result in net decreases in QNB as a result of concomitant increases in postsynaptic muscarinic receptors. As far back as 1978, Davies and Verth speculated on the possibility of denervation supersensitivity to reconcile their findings of normal muscarinic receptor concentrations in the context of some loss of muscarinic cholinoceptive receptors in AD.

Recently, more direct proof for compensatory increases in postsynaptic muscarinic receptors was provided by Nordberg and colleagues (1983). These investigators noted that the number of muscarinic receptors, as measured by QNB binding in the hippocampus of Alzheimer brains, was significantly and inversely correlated with CAT activity. This suggests that, as the ascending cholinergic input to the hippocampus was lost, there was a compensatory increase in the number of postsynaptic muscarinic receptors.

In a more recent study, Mash et al. (1985) reported a selective decrease of presynaptic, M_2, muscarinic receptors in the cerebral cortex of AD brains which was positively correlated with the reduction in CAT activity. They reported no change in the M_1 postsynaptic receptors. However, this group of investigators, unlike Nordberg et al. (1983), did not report on the relationship between CAT activity and M_1 receptors. Without data on the relationship between CAT activity and M_1 postsynaptic receptors, compensatory changes in the M_1 receptors might not be detected.

Recently developed techniques for measuring receptor number are believed to be more selective and capable of distinguishing pre-

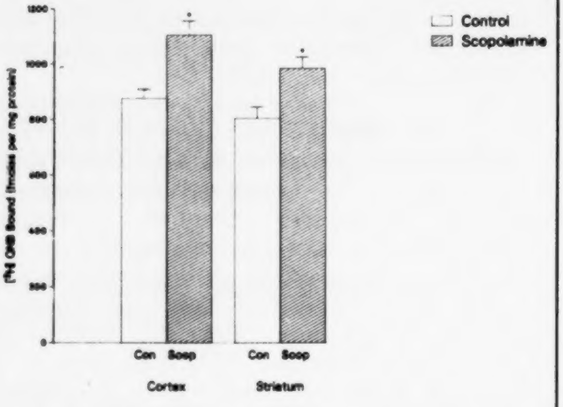


FIGURE 1. Chronic scopolamine increased the number of muscarinic receptors in rat brain as measured by QNB binding.

and postsynaptic muscarinic receptors. Nevertheless, these approaches may still not be adequate to differentiate receptors on more selectively damaged cholinergic pathways, i.e., those projecting from the nucleus basalis of Meynert, from receptors on intrinsic cortical cholinergic neurons and other non-cholinergic neuronal systems. Furthermore, the report of Mash and colleagues (1985) on the absence of upregulation of postsynaptic M_1 muscarinic receptors in AD does not address the larger question which concerns the functional status of the remaining muscarinic receptors.

Dissociations Between Muscarinic Receptor Number and Response

Changes in the functional response of muscarinic receptors are not necessarily reflected by alterations in static measures of receptor binding, i.e., number and affinity. This is illustrated in a number of animal experiments which have attempted to address this question directly.

Some studies report changes in the responsivity of muscarinic receptors that are in the direction anticipated from the change in number of muscarinic receptors as measured by QNB binding. For example, in a series of experiments conducted with rats by Lerer and colleagues (Lerer, 1985; Lerer & Sitaram, 1983), treatment with the muscarinic antagonist, scopolamine, led to an increase in the number of muscarinic receptors (Figure 1) which was accompanied by behavioral supersensitivity as measured by pilocarpine-induced catalepsy (Figure 2).

The same investigators (Lerer et al., 1983, 1984; Stanley & Lerer, 1985) found that the decrease in the number of muscarinic receptors that was produced by chronic electroconvulsive shock (ECS) (Figure 3) was accompanied by the anticipated decrease in responsivity (Figure 4).

However, this relationship between functional sensitivity and up- or down-regulation of corresponding receptors need not always be present. The same group of investigators demonstrated that while a single ECS caused no significant change in the number of QNB binding sites (Figure 5), it nevertheless induced a blunted cataleptic response to pilocarpine (Figure 6).

Data from a number of other investigators using a variety of experimental paradigms can be used to demonstrate similar dissociations between changes in receptor number and functional response (Lippa & Bartus, 1982; Marks et al., 1984; Pedigo et al., 1984).

Based on these animal data, the absence of a significant change in the number of muscarinic receptors in AD does not exclude the possibility of functional alterations in response. Both increases and decreases in functional response can occur in the absence of any change in the number of muscarinic receptors.

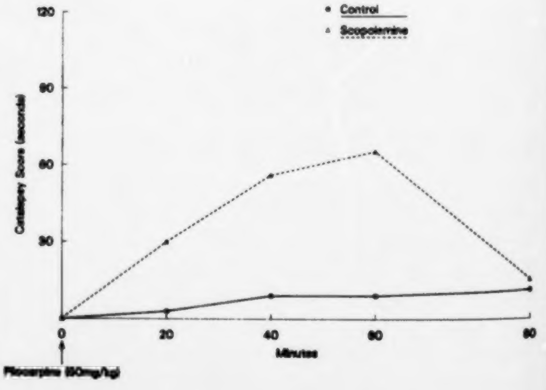


FIGURE 2. Chronic scopolamine increased pilocarpine induced catalepsy in accord with the increase in the number of muscarinic receptors.

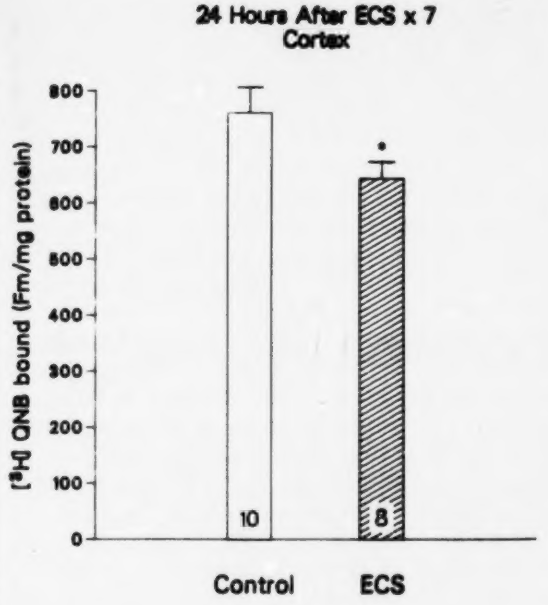


FIGURE 3. Chronic ECS decreased the number of muscarinic receptors in rat brain as measured by QNB binding.

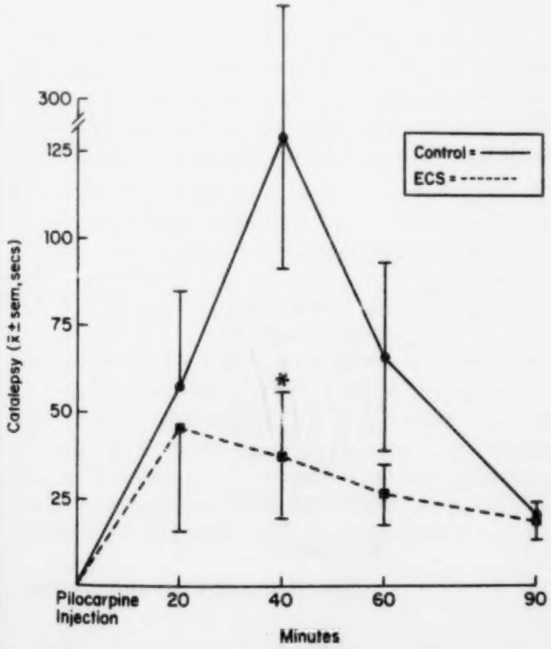


FIGURE 4. Chronic ECS decreased pilocarpine induced catalepsy in accord with the decrease in the number of muscarinic receptors.

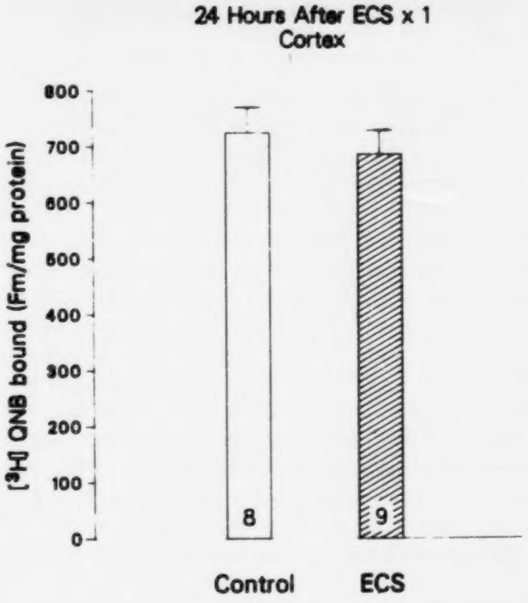


FIGURE 5. Acute ECS produced no significant change in the number of QNB binding sites.

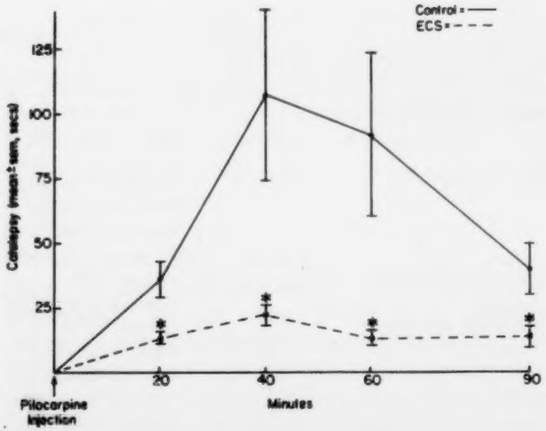


FIGURE 6. Acute ECS decreased pilocarpine induced catalepsy in rats even though muscarinic receptors, as measured by QNB binding, were not significantly altered.

Evidence for Cholinergic Hyperactivity in AD

In addition to a possible dissociation between changes in receptor number and function, there are a number of empirical findings in patients with AD which are more consistent with regional hyperactivity, rather than generalized hypoactivity of the cholinergic system. Patients with AD exhibit many abnormalities, e.g., hypercortisolemia, abnormal dexamethasone tests, depressive symptoms, and motor and memory dysfunction which also have been observed in major depression—a disorder for which a relative increase in cholinergic activity has been postulated (Janowsky et al., 1972, 1973). The Table presents some research findings which are consistent with cholinergic hyperactivity in AD.

Cortisol Hypersecretion

Cortisol hypersecretion, which has been reported in a significant number of patients with endogenous depression (Carroll et al., 1976, 1981; Fang et al., 1981; Sachar et al., 1973), also is found in a significant number of patients with Alzheimer-type dementia. There are at least three groups of investigators (Davis et al., 1983; Pomara et al., 1984; Raskind et al., 1982) that have reported high concentrations of plasma cortisol in individuals with AD. Davis et al. (1983) reported that the severity of dementia, as assessed by a number of rating scales, was correlated significantly with plasma cortisol concentration.

While a direct proof for the involvement of the cholinergic system in the development of hypothalamic-pituitary-adrenal axis hyperactivity in both depression and in AD is lacking, there are a number of observations that support such a role. Hypercortisolemia can be produced in both animals and man by administration of centrally acting cholinomimetics (Nurnberger et al., 1983; Pepper & Krieger, 1984). The administration of physostigmine, a centrally acting cholinesterase inhibitor, to normal individuals leads to the development of symptoms which mimic those found in depression. Additionally, physostigmine causes a reduction of manic symptoms in manic-depressive illness and an exacerbation of depressive symptoms in depressives (Davis et al., 1978; Janowsky et al., 1973; Risch et al., 1981). These findings suggest that central cholinergic activity may be increased in depression and may provide the basis for hypercortisolemia.

The only consistent neurochemical abnormality in AD which has been correlated with the clinical and neuropathological features of the disease has been the reduction in CAT activity. This has been interpreted as indica-

TABLE

Findings Consistent With Cholinergic Hyperactivity

	Alzheimer's Disease	Major Depression Study
Hypercortisolemia	Raskind et al., 1982 Davis et al., 1982 Pomara et al., 1984	Sachar et al., 1973 Carroll et al., 1976 Fang et al., 1981
Abnormal DSTs	Raskind et al., 1982 Davis et al., 1982 McKeith, 1984 Pomara et al., 1984	Carroll et al., 1976 Brown et al.,1979 Fang et al., 1981
Motoric Dysfunction	Pearce, 1974 Pomara et al., 1981	Wolff et al., 1985
Depressive Symptoms	Ziegler, 1954 Gustavson, 1975 Kendel, 1976 Roth, 1975 Epstein, 1976 Cawley, 1973	By definition
Cognitive and Memory Deficits	Reisberg, 1983	Weingartner et al., 1981
Dementia Syndrome	Reisberg, 1983	Folstein & McHugh, 1978 McAllister & Price, 1982

tive of a postulated decrease in central cholinergic activity. The finding of hypercortisolemia in AD patients is incompatible with the previously described animal and human studies in which more cortisol was released when central cholinergic activity increased. One would have predicted that the cholinergic deficiency in AD would have led to low cortisol levels. This contrasts with the increased incidence of hypercortisolemia reported in the AD patient population.

Abnormal Dexamethasone Suppression in AD Patients

Additional data that would be consistent with cholinergic hyperfunction are the numerous reports of abnormal dexamethasone suppression tests (DST) in individuals with Alzheimer-type dementia. At least four studies have reported significant increases in nonsuppression in patients with AD (Davis et al., 1983; McKeith, 1984; Pomara et al., 1984; Raskind et al., 1982). Further support for cholinergic hyperfunction as an underlying mechanism for dexamethasone non-suppression was provided by an experiment in which we induced an up-regulation of muscarinic receptors. This led to a significant degree of non-suppression which was not present in animals in whom muscarinic receptors were not up-regulated (Gershon et al., 1985).

A similar mechanism for abnormal dexamethasone responses in AD was suggested by the findings reported by Nordberg et al. (1983). They found a significant inverse correlation between CAT activity and the number of muscarinic receptors which suggested compensatory changes. Consistent with the interpretation of the findings of Nordberg et al.'s study, are the reports by Carroll et al. (1978) and Doerr and Berger (1983). These studies demonstrated that the usual suppression of cortisol after dexamethasone administration in normal subjects could be reversed by the administration of physostigmine.

Depressive Symptoms in AD

Also consistent with the hypothesis that major depression and AD may share some common pathophysiologic features which may be related to regional cholinergic hyperactivity, is the observation that a significant percentage of individuals with AD present with a depressive syndrome (Gustavson, 1975; Kendel, 1976; Ziegler, 1954). Similarly, many individuals with AD very often develop depressive symptoms in the course of their illness (Cawley, 1973; Epstein, 1976; Roth & Myers, 1975).

A primary depressive illness in the elderly can also lead to a dementia syndrome or to pseudodementia, a term which indicates its potential reversibility (Folstein & McHugh, 1978; McAllister & Price, 1982). These clinical entities are linked further by reports of cognitive and memory deficits in young depressives which are not qualitatively different from those found in early AD (Weingartner et al., 1981).

Motoric Dysfunction in AD and Depression

Motor activity is believed to be regulated in part by an interaction of dopaminergic and cholinergic neurons in the striatum. Extrapyramidal symptoms (EPS) in PD, a disorder associated with marked motor retardation, are believed to arise from an imbalance between dopaminergic and cholinergic tone in the striatum, i.e., the loss of dopaminergic function is believed to give rise to a relative increase in cholinergic tone. Supporting this hypothesis is the well-known observation that the administration of cholinergic antagonists leads to a diminution, whereas cholinomimetics cause an increase, in EPS.

A number of studies have reported EPS to be present in patients with AD (Pearce, 1974; Pomara et al., 1981). These observations support cholinergic hyperactivity in AD.

To our knowledge, there are no reports of EPS in depressive illness and there are no studies that have systematically evaluated the sensitivity of these patients to develop EPS in response to cholinomimetics. However, it is interesting to note that Wolff et al. (1985) recently found a significantly greater motor retardation in these patients during the depressive phase of their illness than during the euthymic or manic phases. Additionally, even during remission, individuals with affective illness showed lower motor activity than a control group.

Sleep EEG in Affective Illness and in AD

There are numerous studies that have implicated a role for the cholinergic system in the regulation of various components of sleep. Of particular interest is the finding that the induction of rapid-eye-movement (REM) sleep may be under partial cholinergic control (Sitaram & Gillin, 1979; Sitaram et al., 1984). This technique has been applied to study changes in muscarinic receptor sensitivity in individuals with affective illness. These individuals have been found to exhibit a shorter REM latency as compared to control subjects and a more rapid induction of REM sleep after administration of arecoline, a centrally acting muscarinic agonist (Jones et al., 1985; Sitaram et al., 1980, 1982).

Patients with Alzheimer-type dementia, as well as individuals with affective illness, also exhibit abnormalities in sleep architecture. On the other hand, when comparisons between the two disorders are made, they appear to be dissimilar with respect to baseline REM latency (Prinz et al., 1982). However, the important challenge tests using cholinergic agents such as arecoline will be needed to fully elucidate the extent to which these two illnesses are related.

Conclusion

The presynaptic cholinergic deficits that consistently have been observed in AD have been interpreted as indicative of a generalized cholinergic hypoactivity. However, there are a number of empirical data which have been reported in patients with AD which are best explained by regional cholinergic hyperactivity. The therapeutic strategies which have been applied in the treatment of AD, however, have been based exclusively on the underlying assumption of generalized cholinergic hypoactivity.

As we have pointed out in this review, there are a number of empirical findings about AD which may be better explained by cholinergic hyper- not hypoactivity. With this in mind, it may be useful to design treatment strategies that may explore the possibility of cholinergic hyperactivity as having a role in some of the behavioral symptoms observed in this illness.

However, one of the more basic but untested assumptions is that the remaining muscarinic receptors in AD when appropriately stimulated would result in a restoration of normal cholinergic function. To date, direct evidence in support of this contention is not available.

As we have recently reviewed elsewhere (Pomara & Stanley, in press), a presentation of receptor number in AD does not always serve as a reliable index of receptor response.

References

Bartus, R.T., Dean, R.L., Beer, B., and Lippa, A.S. The cholinergic hypothesis of geriatric memory dysfunction. *Science*, 217:408–417, 1982.

Bowen, D.M. Biochemical assessment of neurotransmitter and metabolic dysfunction and cerebral atrophy in Alzheimer's disease. In: Katzman, R. (ed.), *Biological Aspects of Alzheimer's Disease*. Cold Spring Harbor, N.Y.: Cold Spring Laboratory, 1983, pp. 219–31.

Bracco, L., Corradetti, R., and Amaducci, L. Acute subcortical lesions modify cortical muscarinic receptors in human brain. *Neurosci. Lett.*, 34:227–231, 1982.

Brown, W.A., Johnston, R., and Mayfield, D. The 24-hour dexamethasone suppression test in a clinical setting: Relationship to diagnosis, symptoms, and response to treatment. *Am. J. Psychiatry*, 136:543–547, 1979.

Carroll, B.J., Curtis, G.C., and Mendels, J. Neuroendocrine regulation in depression: II. Discrimination of depressed from non-depressed patients. *Arch. Gen. Psychiatry*, 33:1051–1058, 1976.

Carroll, B.J., Feinberg, M., Greden, J.F., et al. A specific laboratory test for the diagnosis of melancholia. *Arch. Gen. Psychiatry*, 38:15–22, 1981.

Carroll, B.J., Greden, J.F., Rubin, R.T., et al. Neurotransmitter mechanism of a neuroendocrine disturbance in depression. *Acta Endocrinol.*, (Suppl.) (KBH)220:14, 1978.

Cawley, R.H., and Whitehead, A. Barbiturate tolerance and psychological functioning in elderly depressed patients. *Psychol. Med.*, 3:39–52, 1973.

Creese, I., Burt, D.R., and Snyder, S.H. Dopamine receptor binding enhancement correlates with lesion-induced behavioral supersensitivity. *Science*, 197:596–598, 1978.

Davies, P., and Maloney, A.J.F. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet*, 2:1403, 1976.

Davies, P., and Verth, A.H. Regional distribution of muscarinic acetylcholine receptor in normal and Alzheimer's type dementia brains. *Brain Res.*, 138:385–392, 1978.

Davis, K.L., Berger, P.A., Hollister, L.E., and Defraites, E. Physostigmine in mania. *Arch. Gen. Psychiatry*, 35(1):119–122, 1978.

Davis, K.L., Davis, B., Greenwald, B.S., et al. Hypercortisolemia in Alzheimer's disease. APA Annual Meeting - New Research, New York, 1983.

DeMontigny, C.D., Wang, R.Y., Reader, T.A., and Aghajanian, G.K. Monoaminergic denervation of the rat hippocampus: Microiontophoretic studies on pre- and postsynaptic supersensitivity to norepinephrine and serotonin. *Brain Res.*, 200:363–376, 1980.

Doerr, P., and Berger, M. Physostigmine-induced escape from dexamethasone suppression in normal adults. *Biol. Psychiatry*, 18:261–268, 1983.

Drachman, D.A. Memory and cognitive function in man: Does the cholinergic system have a specific role? *Neurology*, 27:783–790, 1977.

Epstein, L.J. Depression in the elderly. *J. Gerontol.*, 3:278–287, 1976.

Fang, V.S., Tricou, J.B., Robertson, A., and Meltzer, H.Y. Plasma ACTH and cortisol levels in depressed patients. Relation to dexamethasone suppression test. *Life Sci.*, 29:931–938, 1981.

Folstein, M.F., and McHugh, P.R. Dementia syndrome of depression. In: Katzman, R., Terry, R.D., and Bick, K.L. (eds.), *Alzheimer's Disease: Senile Dementia and Related Disorders* (Series: *Aging*, Vol. 7). New York: Raven Press, 1978, pp. 87–93.

Gershon, S., McIntyre, I.M., Pomara, N., et al. Alterations in cholinergic receptors mediate the effects of dexamethasone on corticosterone. *Biol. Psychiatry*, 20:451–460, 1985.

Greenwald, B.S., and Davis, K.L. Experimental pharmacology of Alzheimer Disease. In: Mayeux, R., and Rosen, W.G. (eds.), *The Dementias*. New York: Raven Press, 1983, pp. 87–102.

Gustafson, L. Psychiatric symptoms in dementia with onset in the presenile period. *Acta Psychiatr. Scand.*, 257:9–35, 1975.

Harbaugh, R.E., Roberts, D.W., Coombs, D.W., et al. Preliminary report: intracranial cholinergic drug infusion in patients with Alzheimer's disease. *Neurosurgery*, 15(4):514–518, 1984.

Janowsky, D.S., Davis, J.M., El-Yousef, M.K., and Sekerke, H.J. A cholinergic adrenergic hypothesis of mania and depression. *Lancet*, 2:632, 1972.

Janowsky, D.S., Davis, J.M., El-Yousef, M.K., and Sekerke, H.J. Acetylcholine and depression. *Psychosom. Med.*, 35(5):459, 1973.

Janowsky, D.S., El-Yousef, M.K., Davis, J.M., and Sekerke, H.J. Parasympathetic suppression of manic symptoms by physostigmine. *Arch. Gen. Psychiatry*, 28:542–547, 1973.

Jones, D., Kelwala, S., Bell, J., et al. Cholinergic REM sleep induction response correlation with endogenous major depressive subtype. *Psychiatry Res.*, 14:99–110, 1985.

Kendel, R. The stability of psychiatric diagnosis. *Br. J. Psychiatry*, 124:352–356, 1976.

Lerer, B. Studies on the role of brain cholinergic systems in the therapeutic mechanisms and adverse effects of ECT and lithium. *Biol. Psychiatry*, 20:20–40, 1985.

Lerer, B., and Sitaram, N. Clinical strategies for evaluating ECT mechanisms: Pharmacological, biochemical and psychophysiological approaches. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 7:309–333, 1983.

Lerer, B., Stanley, M., Demetriou, S., and Gershon, S. Effect of electroconvulsive shock on muscarinic cholinergic receptors in rat cerebral cortex and hippocampus. *J. Neurochem.*, 41:1680–1683, 1983.

Lerer, B., Stanley, M., McIntyre, I., and Altman, H. Electroconvulsive shock and brain muscarinic receptors: Relationship to anterograde amnesia. *Life Sci.*, 35:2659–2664, 1984.

Lippa, A.S., and Bartus, R. Neurobiological aspects of geriatric cognitive dysfunction. In: Corkin, S., Davis, K.L., Growdon, J.H., and Wurtman, R.J. (eds.), *Alzheimer's Disease: A Report of Progress in Research.* (Series: *Aging*, Vol. 19). New York: Raven Press, 1982, pp. 223–233.

London, E.D., McKinney, M., Dam, M., et al. Decreased cortical glucose utilization after ibotenate lesion of the rat ventromedial globus pallidus. *J. Cereb. Blood Flow Metab.*, 4:381–390, 1984.

Marks, M.J., O'Connor, M.F., Artman, L.D., et al. Chronic scopolamine treatment and brain cholinergic function. *Pharmacol. Biochem. Behav.*, 20:771–777, 1984.

Mash, D.C., Flynn, D.D., and Potter, L.T. Loss of M2 muscarine receptors in the cerebral cortex in Alzheimer's disease and experimental cholinergic denervation. *Science*, 228(4703):1115–1117, 1985.

McAllister, T.W., and Price, T.R.P. Severe depressive pseudodementia with and without dementia. *Am. J. Psychiatry*, 139:626–629, 1982.

McKeith, I.G. Clinical use of the DST in a psychogeriatric population. *Br. J. Psychiatry*, 145:389–393, 1984.

McKinney, M., and Coyle, J.T. Regulation of neocortical muscarinic receptors: effects of drug treatment and lesions. *J. Neurosci.*, 2:97–105.

Mohs, R.C., Davis, B.M., Johns, C.A., et al. Oral physostigmine treatment of patients with Alzheimer's disease. *Am. J. Psychiatry*, 142:28–33, 1985.

Nordberg, A., Larsson, C., Adolfsson, R., et al. Muscarinic receptor compensation in hippocampus of Alzheimer patients. *J. Neural Transm.*, 56:13–19, 1983.

Nurnberger, J.I., Jimerson, D.C., Simmons-Alling, S., et al. Behavioral, physiological, and neuroendocrine responses to arecoline in normal twins and "well state" bipolar patients. *Psychiatry Res.*, 9:191–200, 1983.

Pearce, J. The extrapyramidal disorder of Alzheimer's disease. *Eur. J. Neurol.*, 12:94–103, 1974.

Pedigo, N.W., Minor, L.D., and Krumrei, T.N. Cholinergic drug effects and brain muscarinic receptor binding in aged rats. *Neurobiol. Aging*, 5:227–333, 1984.

Pepper, G.M., and Krieger, D.T. Hypothalamic-pituitary-adrenal abnormalities in depression: Their possible relation to central mechanisms regulating ACTH release. In: Post, R.M., and Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders.* Baltimore/London: Williams & Wilkins, 1984, pp. 245–270.

Perry, E.K., Tomlinson, B.E., Blessed, G., et al. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Br. Med. J.*, 2:1457–1459, 1978.

Pomara, N., and Stanley, M. The functional status of central muscarinic receptors in Alzheimer's disease: Assessment and therapeutic implications. In: Crook, T., Ferris, S., Bartus, R., and Gershon, S. (eds.), *Treatment Development Strategies for Alzheimer's Disease.* New Canaan, Conn.: Mark Powley Associates, Inc. (In press)

Pomara, N., Oxenkrug, G.F., McIntyre, I.M., et al. Does severity of dementia modulate response to dexamethasone in individuals with primary degenerative dementia? *Biol. Psychiatry*, 19(10):1481–1487, 1984.

Pomara, N., Reisberg, B., Albers, S., et al. Extrapyramidal symptoms in patients with primary degenerative dementia. *J. Clin. Psychopharmacol.*, 1:398–400, 1981.

Price, D.L., Whitehouse, P.J., Struble, R.G., et al. Basal forebrain cholinergic systems in Alzheimer's disease and related dementias. *Neurosci. Comment.*, 1(2):84–92, 1982.

Prinz, P.N., Vitaliano, P.P., Vitaliano, M.V., et al. Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. *Neurobiol. Aging*, 3:361–370, 1982.

Raskind, M., Peskind, E., Rivard, M.F., et al. Dexamethasone suppression test and cortisol circadian rhythm in primary degenerative dementia. *Am. J. Psychiatry*, 139:1468–1471, 1982.

Reisberg, B. Clinical diagnosis and differential diagnosis of Alzheimer's disease and related disorders. In: Reisberg, B. (ed.), *Alzheimer's Disease—The Standard Reference.* New York: The Free Press, 1983, pp. 173–187.

Risch, S.C., Cohen, P.M., Janowsky, D.S., et al. Physostigmine induction of depressive symptomatology in normal volunteer subjects. *J. Psychiatr. Res.*, 4:89–94, 1981.

Rossor, M.N. Neurotransmitters and CNS disease: dementia. *Lancet*, 2:1200–1204, 1982.

Roth, M., and Myers, D.H. The diagnosis of dementia. *Br. J. Psychiatry*, (Suppl. 9):87–89, 1975.

Sachar, E.J., Hellman, L., Roffwarg, H.P., et al. Disrupted 24 hour patterns of cortisol secretion in psychotic depression. *Arch. Gen. Psychiatry*, 28:19–24, 1973.

Sitaram, N., and Gillin, J.C. Acetylcholine: Possible involvement in sleep and analgesia. In: Berger, P., and Davis, K. (eds.), *Brain Acetylcholine and Neuropsychiatric Disease.* New York: Plenum Press, 1979, pp. 311–343.

Sitaram, N., Nurnberger, J.I., Gershon, E., and Gillin, J.C. Faster cholinergic REM sleep induction in euthymic patients with primary affective illness. *Science*, 208:200–202, 1980.

Sitaram, N., Nurnberger, J., Gershon, E., and Gillin, J.C. Cholinergic regulation of mood and REM sleep: A potential model and marker for vulnerability to depression. *Am. J. Psychiatry*, 139:571–576, 1982.

Sitaram, N., Gillin, J.C., and Bunney, W.E. Cholinergic and catecholaminergic receptor sensitivity in affective illness: Strategy and theory. In: Post, R.M., and Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders,* Baltimore/London: Williams & Wilkins, 1984, pp. 629–651.

Stanley, M., and Lerer, B. Electroconvulsive shock and brain cholinergic function: Role of striatal muscarinic receptors. *Convulsive Therapy*, 1:158–166, 1985.

Weingartner, H., Cohen, R.M., Murphy, D.L., et al. Cognitive processes in depression. *Arch. Gen. Psychiatry*, 38:42-47, 1981.

Wettstein, A., and Spiegel, R. Clinical trials with the cholinergic drug RS-86 in Alzheimer's disease and senile dementia of the Alzheimer type (SDAT). *Psychopharmacology*, 84:572–573, 1984.

Wolff, E.A., Putnam, F.W., and Post, R.M. Motor activity and affective illness. *Arch. Gen. Psychiatry*, 42:288–294, 1985.

Ziegler, D.K. Cerebral atrophy in psychiatric patients. *Am. J. Psychiatry*, 111:454–455, 1954.

Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia

CHAIRS: Carol Tamminga, M.D.
Maryland Psychiatric Research Center
Baltimore, Maryland

and Nina R. Schooler, Ph.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Ceruletide for Schizophrenia: A Review

Jeffrey A. Mattes, M.D.,[1] William Hom, M.D.,[1] and Joseph M. Rochford, M.D.

The majority of schizophrenics have residual symptoms, with functional and social impairment, despite an optimal regimen of neuroleptic medication. Additional treatment approaches, therefore, are needed. A compound recently reported to improve schizophrenics already on neuroleptics is ceruletide. Ceruletide, found in amphibians, is a decapeptide structurally nearly identical to the C-terminal amino acid sequence of cholecystokinin (CCK), a 33-amino acid polypeptide secreted by the duodenum to initiate contraction of the gall bladder during digestion (Morley, 1982).

As with other polypeptides (e.g., ACTH, vasopressin), CCK has been found to have central nervous system (CNS) effects apparently unrelated to its originally discovered hormonal effect. There is evidence that CCK is present in the brain (Beinfeld & Palkovits, 1981; Morley, 1982), acting as a neurotransmitter or neuromodulator (Snyder, 1980). Receptors for CCK have been found (Hays et al., 1982; Itoh et al., 1982; Saito et al., 1980). CCK in fact seems to be one of the most highly concentrated of the putative regulatory peptides in the brain (Noyer et al., 1980).

Relevant to schizophrenia, Hökfelt et al. (1980) discovered the coexistence of CCK and dopamine in mesolimbic, but not nigrostriatal, dopamine neurons. In addition, CCK has been reported to reduce dopamine turnover in the caudate nucleus and nucleus accumbens (Fuxe et al., 1980), to increase striatal dopamine release (Kovacs et al., 1981), to increase dopamine cell firing (Skirboll et al., 1981), to affect dopamine binding (Fuxe et al., 1981; Murphy & Schuster, 1982), and to modify dopamine receptor sensitivity (Hommer & Skirboll, 1983). Zetler (1983) found ceruletide to have neuroleptic-like activity in mice, Cohen et al. (1982) found that combining CCK-8 with haloperidol reduced signaled-avoidance behavior significantly more than either drug did alone, and van Ree et al. (1984) found ceruletide and other CCK analogues to be active in a number of behavioral test procedures in rats which predict antipsychotic activity; not all of these findings, however, have been consistently confirmed (Widerlov et al., 1983). Verbanck et al. (1984) recently reported reduced levels of CCK-8S in the cerebrospinal fluid of schizophrenics.

Moroji et al. (1982), in an open study, evaluated ceruletide in 20 schizophrenic patients refractory to neuroleptics. Results indicated

---

[1] Carrier Foundation, Belle Mead, NJ 08502.

improvement in both positive (e.g., hallucinations, delusions) and negative (e.g., withdrawal, blunted affect) symptoms after a single intramuscular (i.m.) injection of 0.3 or 0.6 mcg/kg to patients who were on stable dosages of neuroleptics for 3 weeks prior to the injection. The improvement was evident 2 hours after the dose, but peaked 1 week later. Moroji et al. found the higher dose, 0.6 mcg/kg, to be more beneficial than the lower. Side effects, slight abdominal pains, and borborygmus were minimal. Itoh et al. (1982), using a similar open design and comparable dosage, also reported benefit in 23 of 58 chronic schizophrenics; improvement was primarily in mood and spontaneity rather than in psychotic symptoms.

Nair and associates conducted two open trials of cholecystokinin (Nair et al., 1982, 1983a) and one open trial of the octapeptide CCK-8 (Bloom et al., 1983) in a total of 35 chronic schizophrenics, and also reported generally positive results. Nair et al. (1983b) subsequently conducted a placebo-controlled study of CCK in 17 schizophrenic inpatients, and reported positive effects on Brief Psychiatric Rating Scale (BPRS)-rated Anxiety-depression and Thought-disturbance 7 days after a single infusion, but the authors noted that the study was not truly double-blind since patients fairly consistently noted epigastric discomfort from the dose of CCK used. Peselow et al. (1983), in the second double-blind trial, using the octapeptide CCK-8, reported generally negative results. Nair et al. (1983b), however, found CCK-8 to show less striking results than CCK itself. Hommer et al. (1984), in a double-blind crossover study, found no benefit from ceruletide in 8 chronic schizophrenics, and no benefit from CCK-8 in 4 patients; however, the *N*s were small, and the use of a crossover design may have obscured drug-placebo differences, since the drug has been reported to act for up to 3 weeks (Moroji et al., 1982). Lostra et al. (1984), in another crossover study involving 9 drug-free schizophrenics (most other work has involved schizophrenics with residual symptoms stabilized on neuroleptics), also found no effect of ceruletide. In an additional double-blind study (Mattes et al., 1985), we administered two injections of ceruletide 0.6 mcg/kg or placebo to 17 chronic refractory schizophrenics and found no evidence of benefit.

Discussion

Five of six double-blind evaluations have not found beneficial effects of ceruletide in chronic schizophrenics. Given the previous positive reports from open studies, the samples, dosages, and evaluations used would appear to be more than adequate to demonstrate a positive effect; the most likely explanation for the discrepant results, therefore, is that positive reports reflected placebo responses.

There is still a question as to whether ceruletide crosses the blood-brain barrier (Cornford et al., 1978; Itoh et al., 1982). Analogues do affect sleep and appetite, but this may be through a peripheral mechanism, as some of these effects have been eliminated by vagotomy (Smith et al., 1981). The mechanisms of an apparent analgesic effect (Piazza et al., 1981) and of effects on dopamine receptors (Hommer & Skirboll, 1983) are unknown.

One would not expect that CCK analogues other than ceruletide would be more effective in schizophrenics; the CCK analogue found most in mammalian brains is the octapeptide CCK-8 (Cornford et al., 1978), but ceruletide has been found to be far more potent than CCK-8 in respect to CNS effects (Itoh et al., 1982). Also, ceruletide and CCK bind to the same receptors in all known receptor systems (Piazza et al., 1981).

Given the wide distribution and high concentration of CCK in the CNS, and its apparent interaction with dopamine and other neurotransmitters, it can be expected that CCK analogues and eventually CCK agonists and antagonists will continue to be of interest to psychiatrists. However, clinical relevance may depend on the development of analogues which more easily cross the blood brain barrier, or drugs structurally unrelated to CCK which nevertheless affect CCK receptors, synthesis, or release.

Acknowledgment: The authors wish to thank Sarah Robin, Mary Anne Hinz, and

Marie Magee Brown for their administrative assistance.

References

Beinfeld, M.C., and Palkovits, M. Distribution of cholecystokinin (CCK) in the hypothalamus and limbic system of the rat. *Neuropeptides*, 2:123–129, 1981.

Bloom, D.M., Nair, N.P.V., and Schwartz, G. CCK-8 in the treatment of chronic schizophrenia. *Psychopharmacol. Bull.*, 19(3):361–363, 1983.

Cohen, S.L., Knight, M., Tamminga, C.A., et al. Cholecystokinin-octapeptide effects on conditioned-avoidance behavior, sterotypy, and catalepsy. *Eur. J. Pharmacol.*, 83:213–222, 1982.

Cornford, E.M., Braun, L.D., Crane, P.D., et al. Blood-brain barrier restrictions of peptides and the lower uptake of enkephalin. *Endocrinology*, 103:1297–1303, 1978.

Fuxe, K., Agnati, L., Benfenati, F., et al. Modulation by cholecystokinins of $[^3H]$ spiroperidol binding in rat striatum: Evidence for increased affinity and reduction in number of binding sites. *Acta Physiol. Scand.*, 113:567–569, 1981.

Fuxe, K., Andersson, V., Locatelli, L.F., et al. Cholecystokinin peptides produce marked reduction of dopamine turnover in discrete areas in the rat brain following intraventricular injection. *Eur. J. Pharmacol.*, 67:329–331, 1980.

Hays, S.E., Beinfeld, M.C., Jensen, R.T., et al. Demonstration of a putative receptor site for cholecystokinin in rat brain. *Neuropeptides*, 1:53–62, 1982.

Hökfelt, T., Skirboll, L., Rehfeld, J.F., et al. A subpopulation of mesencephalic dopamine neurons projecting to limbic areas contains a cholecystokinin-like peptide: evidence from immunohistochemistry combined with retrograde tracing. *Neuroscience*, 5:2093–2124, 1980.

Hommer, D.W., Pickar, D., Roy, A., et al The effects of ceruletide in schizophrenia. *Arch. Gen. Psychiatry*, 41:617–619, 1984.

Hommer, D., and Skirboll, L. Cholecystokinin-like peptides potentiate opomorphine-induced inhibition of dopamine neurons. *Eur. J. Pharmacol.*, 91:151–152, 1983.

Itoh, H., Tanoue, S., Yagi, G., et al. Clinical study on the psychotropic effects of caerulein—an open clinical trial in chronic schizophrenic patients. *Keio J. Med.*, 31:71–95, 1982.

Kovacs, G.L., Szabo, G., Penke, B., et al. Effects of cholecystokinin octapeptide on the striatal dopamine metabolism and an apomorphine-induced sterotyped cageclimbing in mice. *Eur. J. Pharmacol.*, 69:313–319, 1981.

Lostra, F., Verbanck, P., and Mendlewicz, J. No evidence of antipsychotic effect of caerulein in schizophrenic patients free of neuroleptics: A double-blind cross-over study. *Biol. Psychiatry*, 19:877–882, 1984.

Mattes, J.A., Hom, W., Rochford, J.M., et al. Ceruletide for schizophrenia. *Biol. Psychiatry*, 20:533–538, 1985.

Morley, J.E. The ascent of cholecystokinin (CCK)—from gut to brain. *Life Sci.*, 30:479–493, 1982.

Moroji, T., Watanabe, N., Aoki, N., et al. Antipsychotic effects of ceruletide (caerulein) on chronic schizophrenia. *Arch. Gen. Psychiatry*, 39:485, 1982.

Murphy, R.B., and Schuster, D.I. Modulation of H^3-dopamine binding by cholecystokinin. *Peptides*, 3:539–543, 1982.

Nair, N.P.V., Bloom, D.M., and Nestoros, J.N. Cholecystokinin appears to have antipsychotic properties. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:509–512, 1982.

Nair, N.P.V., Bloom. D.M., Nestoros, J.N., et al. Therapeutic efficacy of cholecystokinin in neuroleptic resistant schizophrenic subjects. *Psychopharmacol. Bull.*, 19(1):134–136, 1983a.

Nair, N.P.V., Bloom, D.M., and Schwartz, G. Cholecystokinin and the treatment of chronic schizophrenia. Paper presented at the 36th Annual Meeting of the American Psychiatric Association, New York, May 1983b.

Noyer, M., Bui, N.D., Deschodt-Lanckman, M., et al. Postnatal development of the cholecystokinin-gastrin family of peptides in the brain and gut of rat. *Life Sci.*, 27:2197–2203, 1980.

Peselow, E.D., Angrist, B.M., Siekierski, J., et al. Cholecystokinin (CCK) in the treatment of chronic schizophrenic patients. Paper presented at NCDEU (New Clinical Drug Evaluation Unit) annual meeting, Key Biscayne, Florida, June 1983.

Piazza, E., Brambilla, M., Cattaneo, M.T., et al. Analgesic activity of ceruletide in cancer patients. In: Basso, N., Lexocke, E., Speronza, V., and Walsh, J.H. (eds.), International Symposium on Brain-Gut Axis, Abstracts. Florence, 1981.

Rehfeld, J.F. Immunochemical studies on cholecystokinin. *J. Biol. Chem.*, 253:4022–4027, 1978.

Saito, A., Sankaron, H., Goldfine, I.D., et al. Cholecystokinin receptors in the brain: Characterization and distribution. *Science*, 208:1155–1156, 1980.

Skirboll, L.R., Grace, A.A., Hommer, D.W., et al. Peptide-monoamine coexistence: Studies on the actions of cholecystokinin-like peptide on the electrical activity of midbrain dopamine neurons. *Neuroscience*, 16:2111–2124, 1981.

Smith, G.P., Jerome, C., Cushin, B.J., et al. Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. *Science*, 213:1036–1037, 1981.

Snyder, S.H. Brain peptides as neurotransmitters. *Science*, 209:976–983, 1980.

van Ree, J.M., Verhoeven, M.A., Brouwer, G.J., and de Weid, D. Ceruletide resembles antipsychotics in rats and schizophrenic patients. *Neuropsychobiology*, 12:4–8, 1984.

Verbanck, P.M.P., Lostra, F., Gilles, C., et al. Reduced cholecystokinin immuno-reactivity in the cerebrospinal fluid of patients with psychiatric disorders. *Life Sci.*, 34:67–72, 1984.

Widerlov, E., Agren, H., Wahlstrom, A., et al. Lack of interactions between cholecystokinin and dopamine in the central nervous system of rats and humans. *Psychopharmacol. Bull.*, 19(3):355–360, 1983.

Zetler, G. Behavioral pharmacology of CCK and analogs. *Psychopharmacol. Bull.*, 19(3):347–351, 1983.

Clinical Evaluation of Ceruletide in Schizophrenia: A Multi-Institutional Cooperative Double-Blind Controlled Study

Hitoshi Itoh, M.D.,[1] Yasuo Shimazono, M.D.,[2] Yukio Kawakita, M.D.,[3] Yoshio Kudo, M.D.,[4] Yorio Satoh, M.D.,[5] and Ryo Takahashi, M.D.[6]

Introduction

Since cholecystokinin (CCK) is present at high concentrations not only in the tissues of intestines but also in the cerebrum and other parts of the brain and exerts a variety of behavioral pharmacologic actions, it has been presumed that these peptides might have some important effects upon mental function. Having found in animal experiments that CCK-8 has sedative and various other central actions, S. Itoh (1980) speculated that CCK-8 or its homologues might have antipsychotic effects.

On May 2, 1981, the Japan Economic Journal carried a surprising piece of news as a scoop with the heading: "Highly effective schizophrenia drug is found by ex-Hokkaido professor." According to the article, Moroji, a psychiatrist who was a member of Dr. Itoh's study group, observed a marked improvement of such psychic symptoms as emotional disturbance, autism, auditory hallucination, and delusion in 16 of the 20 patients with chronic schizophrenia receiving a CCK-like compound (Moroji et al., 1982a).

In that clinical study, caerulein diethylamine was administered intramuscularly (i.m.) at doses of as low as 0.3 to 0.6 μg/kg and the patients became refreshed in mood 2 hours after injection. The above-mentioned various psychic symptoms abated most conspicuously 1 to 2 weeks after start of treatment and the effects remained sustained over the ensuing several weeks in some of the cases, according to the newspaper.

Caerulein diethylamine (ceruletide) is a polypeptide isolated from the skin of tree frogs, *Hyla caerulea*, in Australia. It is structurally analogous to CCK-8 and endowed with physiological effects on the gastrointestinal tract and central nervous system (CNS) similar to those of CCK-8. A synthetic preparation has been commercially available as a drug for testing the biliary tract and pancreatic function.

A synthetic product of Pharmitalia Co., Ltd., was used in early clinical studies in Japan, including the initial clinical trial by Moroji et al. (1982a). Since the development of a highly pure synthetic preparation of ceruletide at the Research Laboratories of Shionogi Pharmaceutical Co., Ltd., in Japan a few months later, the Japanese product has become clinically used in this country.

Since 1982, many investigators in various countries have reported results of evaluation of the antipsychotic effects of CCK and its CCK-like peptides chiefly in schizophrenia (Hommer et al., 1984; Lotstra et al., 1984; Nair et al., 1982).

In another study of Moroji et al. (1982b), 12 patients with schizophrenia were treated with 40 μg of ceruletide injected at 2-week intervals, and a long-sustained clinical effect for 1 year was evident in 11 of these cases. Follow-up studies to confirm their findings have been made by many psychiatrists in Japan.

Results of open trials conducted as early phase II studies were diverse. According to a report by Kudo (1983), a significant clinical improvement was observed in 36.6% of 292 cases of schizophrenia treated, as assessed by

---

[1] School of Medicine, Keio University, Tokyo, Japan. (Deceased)
[2] National Musashi Sanatorium, Tokyo, Japan.
[3] School of Medicine, Osaka City University, Osaka, Japan.
[4] Osaka Dai-ni Keisatsu Hospital, Osaka, Japan.
[5] Faculty of Medicine, University of Tokyo, Tokyo, Japan.
[6] School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan.

general improvement rating. It was inferred thereby that major indications for the drug would be chronic schizophrenics with manifest anxiety, blunted affect, and motor retardation.

Furthermore, Kudo (1983) conducted a double-blind, matched-pair, placebo-controlled study in patients with schizophrenia who were ceruletide responders, with the results reconfirming the efficacy of the drug.

In double-blind controlled trials with a crossover design performed by Y. Satoh, I. Hasue, and K. Miyakawa (personal communication, 1982) and by K. Sugano (personal communication, 1984), there was no significant difference in clinical effects between ceruletide and placebo.

Nakamura et al. (1984) performed a double-blind crossover trial in which ceruletide (0.6 µg/kg) and a placebo were administered on five consecutive occasions each without any other concomitant antipsychotic drug medication. They reported that the study yielded positive results, namely, general improvement rates of 67% on ceruletide and 33% on placebo and aggravation rates of 11 and 22%, respectively.

In an open trial of the drug conducted in 1981–1982 by Itoh, one of the present authors, clinical improvement was noted in 19 (34%) of the 58 patients with chronic schizophrenia receiving neuroleptic medications concomitantly (Itoh et al., 1982). This improvement rate is by no means high, and the numbers of patients studied were rather small in the above-described double-blind trials reported in Japan. Thus, the data obtained therein seemed to be insufficient for drawing any conclusion as to clinical usefulness of ceruletide.

In view of this, the authors set out a multi-institutional cooperative double-blind study as a nationwide organization.

Experimental Methods

Subjects

The subjects studied were 265 psychiatric inpatients at 28 hospitals with the diagnosis of schizophrenia according to DSM-III (Diagnostic and Statistical Manual—3rd. ed., 1980). Patients meeting the following two inclusion criteria were admitted to the trial preferentially, i.e., 1) those whose principal clinical picture was hallucinatory-delusional, abulic-apathetic, neurasthenic, or depressive state, and 2) the clinical course was chronic defective, periodic defective, transitional, or periodic complete abatement type.

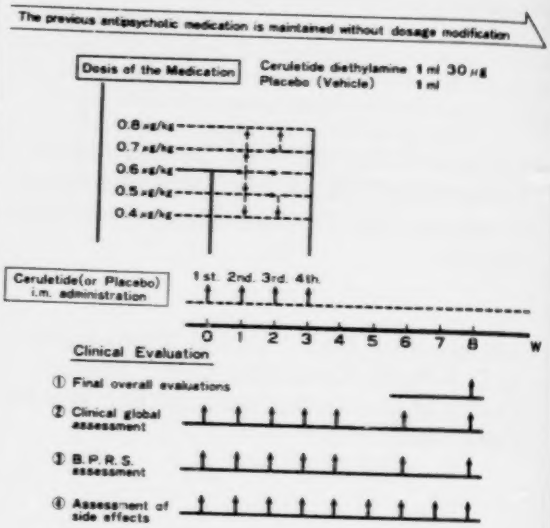

The previous antipsychotic medication is maintained without dosage modification
Dosis of the Medication
Ceruletide diethylamine 1 ml 30 µg
Placebo (Vehicle) 1 ml
0.8 µg/kg
0.7 µg/kg
0.6 µg/kg
0.5 µg/kg
0.4 µg/kg
Ceruletide(or Placebo) i.m. administration
1st. 2nd. 3rd. 4th.
0 1 2 3 4 5 6 7 8 W
Clinical Evaluation
① Final overall evaluations
② Clinical global assessment
③ B.P.R.S. assessment
④ Assessment of side effects

FIGURE 1. **Administration and evaluation schedule.**

Drugs and Administration

Patients were randomly allocated, in a double-blind manner, to ceruletide or a placebo (vehicle).

As shown in Figure 1, either drug was given at 7-day intervals on four occasions by i.m. injection. Ceruletide was administered on a fixed-flexible dosage schedule; it was begun at an initial dose of 0.6 µg/kg and the dosage was individualized thereafter at the investigator's discretion according to symptom. The maximum dose was 0.8 µg/kg.

Other antipsychotic drugs that had previously been instituted were continued without modification of dosage throughout the study treatment.

Methods of Evaluation

Clinical Global Assessment. Each patient was subjected to assessments by General Improvement Rating at Weeks 1, 2, 3, 4, 6, and 8 of treatment. The overall ratings were made by the physician on a 4-point scale, in categories of "markedly improved," "improved," "unchanged," or "deteriorated." At completion of the study treatment, Final General Improvement Rating was made on the same scale as described above.

Both the overall degree of side effects and of accompanying symptoms as a whole were assessed at the termination of study medication using a 4-point scale as the Overall Safety Rating.

Furthermore, Global Usefulness Rating for ceruletide or placebo was performed on each patient with reference to the Final General Improvement Rating and Overall Safety Rating, on a 5-point scale, i.e. "markedly useful," "moderately useful," "slightly useful," "not useful," or "undesirable."

Assessment of Symptoms. Patients were evaluated for degree of symptoms at Weeks 0, 1, 2, 3, 4, 6, and 8 of the study, using the Brief Psychiatric Rating Scale (BPRS) as a rating instrument.

Results

Background Characteristics of the Patients

A total of 265 patients received study treatment in the trial, of whom 135 received ceruletide and 130 received placebo. These two groups were remarkably comparable in practically all of the patient background characteristics. Analysis of these pretreatment data did not reveal any statistically significant difference between the two treatment groups as to any of the items.

Dosage and Trial Outcome

Inter-group comparison showed no noticeable difference with respect to mean dose per day, number of doses given, or dosing pattern.

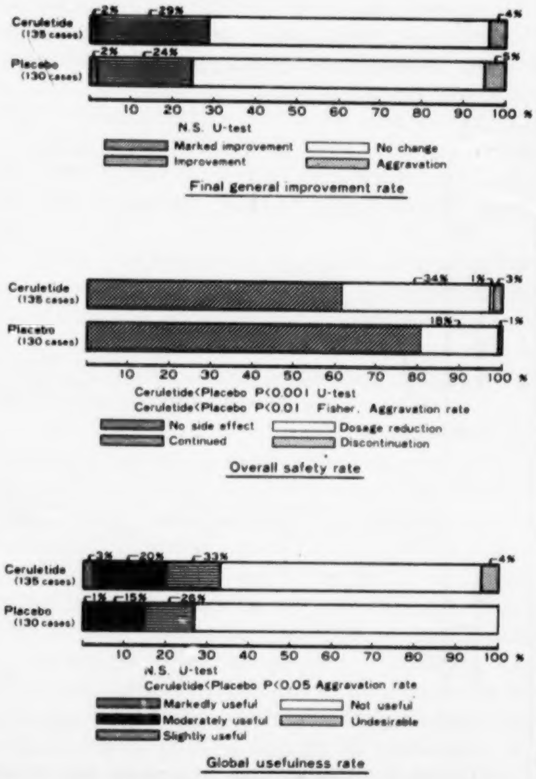
There were 7 patients who were withdrawn from the ceruletide therapy group and 1 patient from the placebo therapy group.

The Final Evaluation

The Final General Improvement Rating. As seen in Figure 2, there were only 3 markedly improved cases in each treatment group. The cumulative percentage of improved to markedly improved patients was 29% with ceruletide and 24% with placebo. Analysis of the data by Mann-Whitney U-test showed no statistically significant inter-group difference in this respect.

The Overall Safety Rating. As assessed by Overall Safety Rating, the incidence of untoward effects was 38% in the ceruletide therapy group and 19% in the placebo group. The former was significantly higher (Figure 2).

The Global Usefulness Rating. No significant inter-group difference could be seen in the overall therapeutic benefit assessment by Global Usefulness Rating by the investigator, when data were analyzed using the U-test (Figure 2).



Final general improvement rate

Overall safety rate

Global usefulness rate

FIGURE 2. Final evaluation.

The cumulative percentage of patients in whom the study medication was evaluated as "markedly useful" to "moderately useful" was 20% in the ceruletide therapy group and 15% in the placebo therapy group. Percent of cases in which the medication was "slightly useful" to "markedly useful" was 33 and 27%, respectively. Thus, there were no significant differences between the two treatment groups.

The General Improvement Rating at Each Week. The results of Weekly General Improvement Ratings during the study treatment are presented in Figure 3. No significant inter-group difference was observed at any week during the course of the 8-week treatment.

Transition of the Total Scores of the BPRS. As a method to assess the general improvement, transition of the total scores of the two drug groups was examined at each week. As shown in Figure 4, the total scores of the ceruletide therapy group were significantly improved at the end of both week 3 and 4 in comparison to the initial score ($p<0.05$, Wilcoxon test). However, there were no statistically significant differences between the two groups throughout the course of the trial by means of the total BPRS scores (Mann-Whitney U-test).

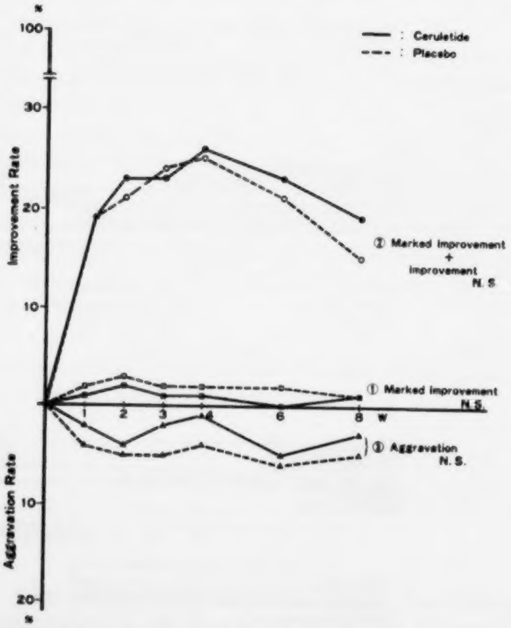


FIGURE 3. Comparison of general improvement rate (%) at each week.

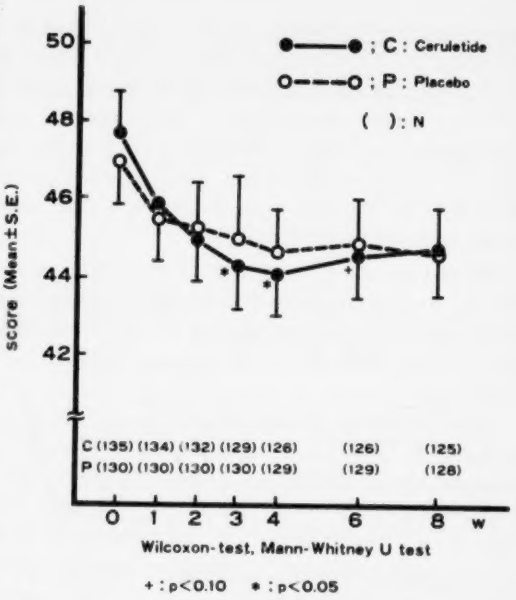


FIGURE 4. Comparison of changes of B.P.R.S. total score during the treatment.

Symptomatic Improvement Rating. From results of evaluation for degree of individual symptoms made at each week of treatment using the BPRS, improvement and aggravation rates were calculated by comparison with those at Week 0 and compared between the two treatment groups. The only symptom item for which ceruletide was significantly better was "Hostility" (Week 2, aggravation rate) whereas "Guilt feeling" was the only symptom item for which placebo was significantly superior (Week 1, aggravation rate).

Side Effects. The types and incidence of adverse effects encountered in the two treatment groups during the course of trial are shown in the Table.

Adverse reactions were significantly more frequent in the ceruletide therapy group ($p<0.001$, Fisher's test). The most common side effect was abdominal symptoms, occurring in 30 patients (41%) receiving ceruletide and in 9 patients (7%) receiving placebo; the incidence was significantly higher in the former ($p<0.001$, Fisher's test).

TABLE
Comparison of Main Side Effects

	Ceruletide (%)	Placebo (%)	Statist. analysis
Number of cases affected	49/135 (36)	21/130 (16)	$C<P^{***}$
Abdominal symptoms	41 (30)	14 (11)	$C<P^{***}$
Other symptoms	19 (14)	9 (7)	$C<P^{\dagger}$
Nausea	19 (14)	1 (1)	—
Vomiting	3 (2)	0 (0)	—
Borborygmus	5 (4)	1 (1)	—
Abdominal distension	1 (1)	2 (2)	—
Abdominal discomfort	8 (6)	2 (2)	—
Anorexia	3 (2)	2 (2)	—
Abdominal pain	10 (7)	2 (2)	$C<P^{*}$
Urgency to defecate	1 (1)	3 (2)	—
Diarrhea	6 (6)	3 (2)	—
Headache	4 (3)	0 (0)	—
Drowsiness	3 (2)	2 (2)	—
Insomnia	2 (1)	1 (1)	—
Malaise	3 (2)	0 (0)	—
Dizziness	2 (1)	0 (0)	—
Blurredvision	2 (1)	0 (0)	—

C<P : Ceruletide inferior to Placebo
*** : $P<0.001$, ** : $P<0.01$, * : $P<0.05$, † : $P<0.10$
Fisher's test

As for individual side effects, nausea and stomachache were significantly more frequent among patients receiving ceruletide.

Discussion and Conclusion

Since the first discovery by Moroji et al. (1982a), there have been some dozen clinical reports concerning the antipsychotic effect of CCK or ceruletide in the treatment of schizophrenia. According to reports with positive results, the treatment produced improvement of both positive and negative symptoms in chronic schizophrenics refractory to treatment with previously introduced drugs.

Schizophrenia is an illness which is so diverse in disease type, disease picture, and clinical course that it seems more or less difficult to deal with it as a single disease entity.

It is unclear from the data documented in the literature what particular type or types, clinical course pattern, and disease state features of schizophrenia correspond to responders to CCK or CCK-like peptides.

In the clinical trial reported herein, chronic schizophrenics with disease state features and clinical course patterns corresponding to those in the cases described to have been improved by ceruletide in the reports of Moroji et al. (1982a,b), and subsequent reports of open trials in Japan were selected as the case material, as described above.

It can be noted from the data obtained in the present series that a) there was no significant difference in percentage of improved cases between the ceruletide group and the placebo group; and b) the improvement rates were remarkably low, as assessed by Final General Improvement Rating. Only 2% of patients showed marked clinical improvements, and the cumulative rate of improved-to-marked-improved cases was as low as 29%. These are the lowest figures that have ever been found in clinical trials of antipsychotic drugs.

Gastrointestinal symptoms were encountered as side effects with significantly greater frequency in the ceruletide therapy group; 4 patients receiving the drug complained of nausea and/or abdominal pain that led to withdrawal. These manifestations were attributable to the pharmacologic actions of ceruletide. The data indicated that the incidence and severity of these side effects increased with increasing therapeutic dosage and dosing frequency of ceruletide, an undesirable condition from the therapeutic viewpoint.

Thus, the results of the present multiclinical cooperative, double-blind controlled trial conducted in 265 patients with schizophrenia failed to provide evidence for clinical effects that would qualify ceruletide as a drug for the treatment of schizophrenia.

The numerous new findings reported by investigators in various countries concerning the interrelation of the central actions of CCK and the psychic function are of profound interest and of great importance. Among them are investigations aiming at elucidation of the underlying mechanisms of action on the hypothesis that CCK or ceruletide is endowed with antipsychotic effects on schizophrenia. Furthermore, as described in the reports of Moroji et al. (1982a,b) and in several other papers, it may be probable, in fact, that some patients with chronic schizophrenia respond with some alterations in symptoms when treated with CCK or ceruletide injections.

It is concluded from the present cooperative trials that no evidence has been found to substantiate usefulness of ceruletide as a drug for the treatment of schizophrenia.

References

Hommer, D.W., Pickar, D., Roy, A., et al. The effects of ceruletide in schizophrenia. *Arch. Gen. Psychiatry*, 41:617–619, 1984.

Itoh, H., Tanoue, S., Yagi, G., et al. Clinical study on the psychotropic effects of caerulein—an open clinical trial in chronic schizophrenic patients. *Keio J. Med.*, 31:71–95, 1982.

Itoh, S. *Neuropeptides* (Japanese). Tokyo: Rikogaku-sha, 1980.

Kudo, Y. Clinical evaluation of ceruletide (883-S) on chronic schizophrenia. (Japanese) *Rinsho Seishinigaku*, 12:703–710, 1983.

Lotstra, F., Verbanck, P., Mendlewicz, J., and Vanderhaeghen, J.J. No evidence of antipsychotic effect of caerulein in schizophrenic patients free of neuroleptics: A double-blind crossover study. *Biol. Psychiatry*, 19:877–882, 1984.

Moroji, T., Watanabe, N., Aoki, N., and Itoh, S. Antipsychotic effects of ceruletide (Caerulein) on chronic schizophrenia. *Arch. Gen. Psychiatry*, 38(4):113–124, 1982a.

Moroji, T., Watanabe, N., Aoki, N., and Itoh, S. Antipsychotic effects of caerulein, a decapeptide chemically related to cholecystokinin octapeptide on schizophrenia. *Int. Pharmacopsychiatry*, 17(4):255–273, 1982b.

Nair, N.P.V., Bloom, D.M., and Nestoros, J.N. Cholecystokinin appear to have antipsychotic properties. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:509–512, 1982.

Nakamura, G., Nobuyama, M., and Kudo, Y. Antipsychotic effect of ceruletide as a sole agent. Presented at 14th C.I.N.P. Congress, Florence, June 1984.

Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia

Carol A. Tamminga, M.D.,[1] Robert L. Littman, M.D.,[1] and Larry D. Alphs, M.D.[1]

The distribution and functional activity of many peptidergic substances in the gastrointestinal system have been known for many years; more recently, a number of these have been found in the brain and are presumed to be neurally active. Cholecystokinin (CCK) is a member of this growing family of gut-brain peptides. It was first isolated from the gastrointestinal system in 1928 (Ivy & Oldberg, 1928), identified by its action on gall bladder smooth muscle, and sequenced as a 33-amino acid peptide in 1971 (Mutt & Jorpes, 1971). Not until 1975 was there evidence of a CCK-like substance in the brain (Dockray, 1976; Vanderhaeghen et al., 1975). Since that time various anatomic, biochemical, and behavioral studies have suggested a transmitter/modulator role for CCK in the brain (Beinfeld et al., 1981; Innes et al., 1979; Mueller et al., 1977; Rehfeld, 1978).

The predominant form of neuronal CCK is the carboxy-terminal octapeptide (CCK-8) (Mueller et al., 1977; Rehfeld, 1978). It derives from a polypeptide precursor synthesized in neuronal cell bodies, and modified by post-translational processing and cleavage during axonal transport down the neuraxis to form the octapeptide which remains stored in vesicles at the synapse (Eng et al., 1983; Schmitt et al., 1982). With depolarizing stimuli, CCK-8 is released from the nerve terminus to associate with specific receptors on postsynaptic neuronal surfaces. Inactivation of the peptidergic transmitter occurs by peptidase-mediated degradation rather than by reuptake into the presynaptic neuron. The initial catabolic step of CCK-8 degradation involves cleavage of the octapeptide into a C-terminal pentapeptide (Deschoht-Lanckman et al., 1981); subsequent steps produce the C-terminal di- and tri-peptide of CCK-8, which are relatively stable final products (Steardo et al., 1985). These intermediate and final catabolic products of CCK-8 are of interest because several of them show an affinity for the central CCK receptor and may have a functional interaction at the receptor (Knight et al., 1984). Thus, CCK, in addition to exerting an action itself at its receptor, may, after subsequent degeneration, continue to produce either agonist, partial agonist, or frank antagonist action at the same receptor through its peptide products.

CCK is known to produce characteristic hormonal effects in the body, which include stimulation of pancreatic enzyme secretion and gall bladder contraction. In addition, CCK has been associated with specific centrally mediated actions: appetite regulation, hyperglycemia, hypothermia, analgesia, central nervous system (CNS) depression, ptosis, catalepsy, and pituitary hormone modulation (Morley, 1982). CCK-8 produces what is described as satiety in rat, monkey, and man (Gibbs et al., 1973); it reduces conditioned avoidance responding in laboratory rodents (Cohen et al., in press), inhibits apomorphine-induced stereotypies (Zetler, 1983), and suppresses social behavior in mice (Crawley et al., 1981). These behavioral actions of CCK have been found after both central and systemic administration.

Interest in CCK for the treatment of schizophrenia was stimulated when CCK-8 was discovered to coexist with dopamine (DA) in certain mesencephalic neurons in the substantia nigra, area compacta, and in the ventral tegmental area (Hökfelt et al., 1980a). CCK-8 is found predominantly in those DA-containing neurons which project to the prefrontal and limbic cortex (Hökfelt et al., 1980b). Moreover, evidence suggests cholecystokinin may play a functional role in DA release (Markstein & Hökfelt, 1984), and in modulating neuronal metabolism in DA-dependent areas of cortex (Lucignani et al., 1984), even though this interaction remains difficult to consistently characterize

---

[1] Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, Baltimore, MD 21228.

(Widerlöv et al., 1983). Since psychotic symptoms of schizophrenia improve after a reduction in DA-mediated transmission, neurally active substances which modulate activity of DA neurons hold promise as being active in the treatment of schizophrenia. Since currently available treatments for schizophrenia have considerable limitations, without other known pharmacologic strategies being effective in modifying psychosis (Tamminga, 1982), additional, improved therapeutic strategies for the treatment of this illness are eagerly being pursued.

This theoretical rationale for the use of CCK-8 in the treatment of schizophrenia is supported by a number of open clinical studies which have reported symptomatic improvement in schizophrenia with CCK-8 administration and with the administration of its more potent analogue caerulein (Moroji et al., 1982; Nair et al., 1982). However, since these early studies were not carried out in a blind design, and because a subsequent replication study was negative (Hommer et al., 1984), we carried out a series of studies with caerulein in schizophrenia to test for potential antipsychotic activity (Tamminga et al., in press).

In the first of these studies, 5 schizophrenic subjects, who were free from all medication for at least 1 month, were given a 0.3 μg/kg dose of caerulein, intramuscularly, in a double-blind design with placebo. Patients were evaluated prior to drug administration and at 2 hours, 4 hours, and 24 hours after the drug by Brief Psychiatric Rating Scale (BPRS) assessment for evidence of a change in psychotic symptoms, in DA-mediated endocrine parameters (prolactin and growth hormone), and in visual-evoked potential pattern, after either the caerulein or placebo. This study was intended to evaluate any immediate or delayed effects of a single dose of caerulein on psychosis, endocrine function, or visual-evoked potential. The results showed no effect of caerulein on the level of psychosis in these schizophrenic patients (Table 1), or on plasma levels of prolactin or growth hormone. In addition, caerulein did not alter the brain electroencephalogram (EEG) pattern of visual-evoked response. Despite these negative clinical indices, significant increases in plasma levels of caerulein were demonstrated after drug administration; levels achieved a maximum in 20 to 30 minutes and largely disappeared by 60 minutes (Table 2). We concluded from this experiment that caerulein administration at the previously tested dose levels, despite demonstrable blood levels, has no effect on psychosis of an immediate or delayed nature.

TABLE 1

Effect of Caerulein on Psychosis

Total Score	0	4 hr	24 hr
PL	53.7±15.5	49.5±14.2	52.7±15.2
CCK	53.3±24.2	54.5±26.3	53.0±25.2
Psychosis Score			
PL	9.5±6.7	8.8±5.6	10.3±5.2
CCK	9.5±6.7	9.7±6.1	9.0±7.4

The mean±SD of scores on BPRS: total score (Total) and psychosis subscale score (Psychosis) were collected after placebo (PL) and after 0.3 μg/kg caerulein (CCK), prior to drug administration (0), and at 4 hours (4 hr) and 24 hours (24 hr) following the drug. No significant differences were found between treatments or between treatments over time.

To evaluate the possibility that the previously administered dose levels were inadequate, increasing doses of caerulein from 0.3 μg/kg to 1.5 μg/kg were administered in a double-blind, placebo-controlled design to these same patients. The five drug-free schizophrenics received a 10-day course of daily medication: 5 days of active drug, and 5 days of placebo. The active drug was given in a rising dose sequence with single doses of placebo interspersed before, during, and after the caerulein sequence. Psychosis was evaluated at 0 time (prior to drug administration), at 4 hours, and 24 hours after caerulein and placebo administration. No patients showed an antipsychotic response to the peptide at any of the dose levels tested: 0.3 μg/kg, 0.6 μg/kg, 1.2 μg/kg, or 1.5 μg/kg. The

TABLE 2

Change In CCK-Li In Plasma After Caerulein Administration

	Minutes							
	0	5	10	15	20	30	45	60
Placebo	0	−1.7	−11.3	−9.0	1.0	−18	−7	3.7
		(8.6)	(10.1)	(11.5)	(1.0)	(15.9)	(10.8)	(17.8)
Caerulein	0	50.3	48.3	66	65.8	53.7	22.8	15.5
		(47.9)	(9.3)	(30.5)	(24.5)	(47.3)	(37.3)	(12.0)

Difference from basal values (mean SD) in CCK-like immunoreactivity (CCK-LI) (pg/ml plasma) after intramuscular administration of caerulein (0.3-0.6 μg/kg) or placebo to four human volunteers. Basal level of CCK-LI prior to placebo was 38.7±18.0, and prior to caerulein was 35.3±27.8.

upper dose of 1.5 μg/kg was limited by gastrointestinal side effects, chiefly mild pain and diarrhea.

Based on the suggestion from previous studies that a CCK-like drug would be active in neuroleptic-treated schizophrenic patients with a more chronic form of the illness, 6 chronically institutionalized patients, who were concurrently treated with stable doses of neuroleptic drugs, were given single doses of 0.3 μg/kg of caerulein or equivalent volumes of placebo in a parallel-group design. Their baseline psychosis level was established before they received the medication. Then, they were followed for psychosis change with the BPRS for 28 days after the single dose of drug administration. No patients who received the caerulein demonstrated improvement in their psychosis, nor did their response differ from those who received the placebo.

These studies provide no evidence for the hypothesis that systemic administration of caerulein, a potent CCK analogue, modifies schizophrenia, either by stimulating or reducing psychotic symptoms. Moreover, despite adequate caerulein drug levels in plasma, no definitive CNS effects of caerulein could be demonstrated; neither EEG patterns of visual-evoked potential changed nor plasma levels of prolactin were modified with caerulein, despite previous demonstration that intraventricular administration of CCK-8 elevates plasma prolactin in rats (Tanimoto et al., 1985).

While drawing a cautious conclusion because of the small number of patients tested, we would suggest that insufficient quantities of caerulein actually entered the CNS to produce a CCK-like effect. Thus, we would propose that the main hypothesis, namely that CCK-8 reduces psychosis through modifying DA-mediated neural transmission in the CNS, remains untested in schizophrenia at the present time.

We are pursuing the possibility of modifying CCK-8 levels in brain using other pharmacologic strategies, one being through inhibition of its degradation. CCK-8 is initially cleaved by a Mg^{++}-dependent metalloendopeptidase at the CCK^{3}/CCK^{4} bond (Steardo et al., in press). Blockade of this enzyme would be predicted to raise CNS levels of CCK-8 by inhibiting its breakdown and thereby producing a centrally mediated CCK agonist effect. Competitive and irreversible antagonists for this degradative enzyme are being synthesized. After establishing in vitro agonist effects of these compounds in laboratory animals, in vivo evidence of CCK-8 accumulation in the brain with systemic administration, and safety in human use, clinical evaluation in schizophrenia might be indicated. These kinds of alternate pharmacologic strategies will be necessary to test the hypotheses about the functional importance of CNS CCK systems in schizophrenia.

References

Beinfeld, M.D., Meyer, D.K., Eskay, R.L., et al. The distribution of cholecystokinin immunoreactivity in the central nervous system of the rat as determined by radioimmunoassay. *Brain Res.*, 212:51–57, 1981.

Cohen, S., Knight, M., Tamminga, C.A., and Chase, T.N. A comparison of peripheral and central effects of caerulein. *Br. J. Pharmacol.* (In press)

Crawley, J.N., Hayes, S.E., O'Donohue, T.L., and Paul, S.M. Neuropeptide modulation of social and exploratory behavior in laboratory rodents. *Peptides*, 2:123–219, 1981.

Deschoht-Lanckman, M., Bui, N.D., Noyer, M., and Christophe, J. Degradation of cholecystokinin-like peptides by a crude rat brain synaptosomal fraction: A study by high pressure liquid chromatography. *Regul. Pept.*, 2:15–30, 1981.

Dockray, G.L. Immunochemical evidence of cholecystokinin-like peptides in brain. *Nature*, 264:568–570, 1976.

Eng, J., Shiina, Y., Pan, Y-CE., et al. Pig brain contains cholecystokinin octapeptide and several cholecystokinin desoctapeptides. *Proc. Natl. Acad. Sci., USA*, 80:6381–6385, 1983.

Gibbs, J., Young, R.C., and Smith, G.P. Cholecystokinin elicits satiety in rats with open gastric fistulas. *Nature*, 245:323–325, 1973.

Hökfelt, T., Rehfeld, L., Skirboll, B., et al. Evidence for co-existence of dopamine and CCK in meso-limbic neurons. *Nature*, 285:476–478, 1980a.

Hökfelt, T., Skirboll, L., Rehfeld, J.F., et al. A subpopulation of mesencephalic dopamine neurons projecting to limbic areas contains a cholecystokinin-like peptide: Evidence from immunohistochemistry combined with retrograde tracing. *Neuroscience*, 5:2093–2124, 1980b.

Hommer, D.W., Pickar, D., Roy, A., et al. The effects of ceruletide in schizophrenia. *Arch. Gen. Psychiatry,* 41:617–622, 1984.

Innis, R.B., Correa, F.M.A., Uhl, G.R., et al. Cholecystokinin octapeptide-like immunoreactivity: Histochemical localization in rat brain. *Proc. Natl. Acad. Sci., USA,* 76:521–525, 1979.

Ivy, A.C., and Oldberg, E. A hormone mechanism for gall-bladder contraction and evaluation. *Am. J. Physiol.,* 86:599–613, 1928.

Knight, M., Tamminga, C.A., Steardo, L., et al. Cholecystokinin-octapeptide fragments: Binding to brain cholecystokinin receptors. *Eur. J. Pharmacol.,* 105:49–55, 1984.

Lucignani, G., Porrino, L.J., and Tamminga, C.A. Effects of systemically administered cholecystokinin-octapeptide on local cerebral metabolism. *Eur. J. Pharmacol.,* 101:147–151, 1984.

Markstein, R., and Hökfelt, T. Effect of cholecystokinin-octapeptide on dopamine release from slices of cat caudate nucleus. *J. Neurosci.,* 4:570–575, 1984.

Morley, J.E. The ascent of cholecystokinin from gut to brain. *Life Sci.,* 30:479–493, 1982.

Moroji, T., Watanabe, N., Aoki, N., and Itoh, S. Antipsychotic effects of ceruletide (caerulein) on chronic schizophrenia. *Arch. Gen. Psychiatry,* 39:485–486, 1982.

Mueller, J.E., Straus, E., and Yalow, P.S. Cholecystokinin and its COOH-terminal octapeptide in the pig brain. *Proc. Natl. Acad. Sci., USA,* 74:3035–3041, 1977.

Mutt, V., and Jorpes, J.E. Hormonal polypeptides of the upper intestine. *Biochem. J.,* 125:57–58, 1971.

Nair, N.P., Bloom, D.M., and Nestoros, J.N. Cholecystokinin appears to have antipsychotic properties. *Biol. Psychiatry,* 6:509–512, 1982.

Rehfeld, J.F. Immunochemical studies on cholecystokinin. *J. Biol. Chem.,* 253:4022–4030, 1978.

Schmitt, F.O., Bird, S.J., and Bloom, F.E. (eds.), *Molecular Genetic Neuroscience.* New York: Raven Press, 1982, pp. 171–188.

Steardo, L., Knight, M., Tamminga, C.A., and Chase, T.N. Products of cholecystokinin octapeptide proteolysis interact with central CCK receptors. *Neurosci. Lett.,* 54:319–325, 1985.

Steardo, L., Knight, M., Tamminga, C.A., et al. CCK_{26-33} degrading activity in brain and nonneural tissue: A metalloendopeptidase. *J. Neurochem.* (In press)

Tamminga, C.A. Atypical neuroleptics and novel antipsychotic drugs. In: Coyle, J.T., and Enna, S.J. (eds.), *Neuroleptics: Neurochemical, Behavioral, and Clinical Perspectives.* New York: Raven Press, 1982, pp. 281–295.

Tamminga, C.A., Littman, R.L., Alphs, L.D., et al. Neuronal cholecystokinin and schizophrenia: Pathogenic and therapeutic studies. *Psychopharmacology.* (In press)

Tanimoto, K., Tamminga, C.A., Knight, M., and Chase, T.N. Intraventricular cholecystokinin octapeptide elevates plasma prolactin. *Neurosci. Abstr.,* 1985.

Vanderhaeghen, J.J., Signeau, J.C., and Gepts, W. New peptide in the vertebrate CNS reacting with antigastrin antibodies. *Nature,* 257:604–605, 1975.

Widerlöv, E., Kalivas, P.W., Lewish, M.H., et al. Influence of cholecystokinin on central monoamine pathways. *Regul. Pept.,* 6:99–109, 1983.

Zetler, G. Neuroleptic-like effects of ceruletide and cholecystokinin octapeptide: Interactions with apomorphine, methylphenidate, and picrotoxin. *Eur. J. Pharmacol.,* 94:261–270, 1983.

Fenfluramine Therapy for Autism: Promise and Precaution

CHAIRS: *Judith Rapoport, M.D.*
Child Psychiatry Branch
National Institute of Mental Health
Bethesda, Maryland

and

Natalie Reatig
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Fenfluramine Treatment of Autism: UCLA Collaborative Study of 81 Patients at Nine Medical Centers[1]

Edward R. Ritvo, M.D.,[2] B.J. Freeman, Ph.D.,[2] Arthur Yuwiler, Ph.D.,[2] Edward Geller, Ph.D.,[2] Phillip Schroth, M.S.,[2] Alice Yokota,[2] Anne Mason-Brothers,[2] Gerald J. August, Ph.D.,[2] William Klykylo, M.D.,[2] Bennett Leventhal, M.D.,[2] Kay Lewis, M.D.,[2] Leonard Piggott, M.D.,[2] George Realmuto, M.D.,[2] E. Gene Stubbs, M.D.,[2] and Richard Umansky, M.D.[2]

Introduction

We recently reported that fenfluramine produced significant symptomatic improvements in patients with the syndrome of autism (Ritvo et al., 1984). These included increased social awareness, eye contact and attention to school work, decreased hyperactivity and repetitive behaviors such as hand flapping and spinning, and improved sleep patterns. No serious side effects, adverse drug reactions, or disruptions in growth or weight gain occurred. Significant positive correlations were found between good clinical response and high baseline IQ ($r = 0.80$, $p = <.001$), between good clinical response and low baseline blood serotonin concentration ($r = 0.57$, $p = <.05$), and between low baseline IQ and high initial blood serotonin concentration ($r = 0.72$, $p = <.01$). However, due to the small number of subjects, these correlations were only considered suggestive. Interestingly, the onset of symptomatic improvements varied from a few days to 2 months and relapses showed similar wide variations after patients returned to placebo. Similar findings have been reported on other small groups of patients (August et al., 1985; Klykylo et al., in press; Stubbs et al., in press).

To extend these preliminary findings, we designed a two-part multicenter study to obtain data from a much larger number of autistic patients. This report contains the results of the first part of this study, an ABA design utilizing 81 patients from nine medical centers. Our results confirm the previous findings that fenfluramine is a safe and effective treatment for some autistic patients (August et al., 1985; Klykylo et al., in press; Ritvo et al., 1984; Stubbs et al., in press).

---

[1] Supported by National Institute of Mental Health Grants MCT 927 and HD 46-12, Food and Drug Administration Grant 1 R01 FD 226-83-0023, Clinical Research Center for the Study of Child Psychosis Grant MH 30897, the Max and Lottie Dresher Fund, the Bennin Fund, the A.H. Robins Company, and the Veterans Administration Medical Research Service.

[2] Division of Mental Retardation and Child Psychiatry, Department of Psychiatry, University of California at Los Angeles, and the Neurobiochemistry Laboratory, Veterans Administration, Brentwood Medical Center, Los Angeles, and eight collaborating medical centers.

Reprint requests: Edward R. Ritvo, M.D., Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024.

The A.H. Robins Company supplied fenfluramine (Pondimin®) and placebo tablets.

Methods

1. *Patient selection.* Eighty-one patients (80% boys, ages 33 months to 24 years; mean 8.8 years, mode 5.9 years) were selected at nine medical centers throughout the United States (*see* Appendix for list of multicenter participants). They represented the entire clinical spectrum of patients with the syndrome of autism, from the mute and totally dependent to those living semi-independently. Each unequivocally met the DSM-III, 299.0 (APA Diagnostic and Statistical Manual—3rd Ed., 1980), and National Society for Children and Adults with Autism (NSAC) (Ritvo & Freeman, 1978) criteria for autism according to clinicians at each medical center. Furthermore, each patient's history was reviewed with the principal investigator at UCLA (E.R.R.) who concurred that they had manifested pathognomic symptoms and delays prior to 30 months of age. All patients had been free of central nervous system active medication for at least 3 months before the study and were either attending special education classes or rehabilitation programs specifically designed for autistic persons. None had other specific diagnosable neurological or medical conditions except one girl who was subsequently identified in Portland, Oregon, as having Retts' syndrome (Stubbs et al., in press). Two had electroencephalograph abnormalities and one of these had a seizure when younger.

2. *Human subject protection procedures and FDA approval.* Each participating institution obtained Human Subject Protection Committee approval and informed consent agreements. Since fenfluramine is approved by the FDA only as an anorexia agent in adults, a new drug application (NDA) was obtained for use in children and for autism (for fenfluramine #17,085 and for the placebo #16,935).

3. *Experimental protocol.* The study began with a 2-week training period using a known placebo to accustom patients to taking tablets and to assure parental compliance (stage 1). The double-blind phase then began with all patients receiving placebo for 1 month (stage 2), followed by 4 months of drug treatment (stage 3), and 2 months of placebo (stage 4). One investigator at each center was aware of the placebo-drug schedule during the study but did not participate in dispensing medication or in clinical assessments. All patients received tablets twice a day throughout the study (0.75 mg/kg body weight for a total daily dose of 1.5 mg/kg body weight).

4. *Biomedical monitoring.* General medical histories and weights were recorded at monthly intervals throughout the study. Blood serotonin levels were obtained at the initial visits and between stages of the experiment.

5. *Parental reports.* Parental interviews were conducted monthly to monitor each child's clinical status and to detect possible side effects. Parents kept diaries documenting daily medication administration, patient behaviors, appetite changes, and weekly body weights. They were requested to weigh their children on the same scales, in similar clothing, and at the same time of the day.

6. *IQ tests.* Psychologists blind to the drug protocol administered tests selected according to each patient's baseline developmental level. Patients who initially were younger than 4 years or had IQ < 45 were given the Merrill-Palmer Preschool Performance Test (Stutsman, 1948) and the Cattell (1960) or Stanford-Binet Intelligence Scale. Patients initially older than 4 years or with IQ > 45 were given a Wechsler Intelligence Scale (1967, 1974, 1981) appropriate for their age. A verbal IQ score was assigned for each patient by using the verbal score for the Wechsler Scales, the Cattell score, or the Stanford-Binet scale. A performance scale for each patient was also assigned by using the performance score of the Wechsler Scales or the Merrill-Palmer Preschool Performance Test.

7. *Alpern-Boll Developmental Profile* (Alpern et al., 1980). This standardized parental interview scale was administered to patients for whom it was age appropriate. It consists of five developmental scales (academic, communication, physical development, self-help, and social development).

8. *Ritvo-Freeman Real-Life Rating Scale for Autism* (Freeman et al., in press). This scale consists of 47 behaviors grouped in five categories (motor, affect, language, sensory, and social). Behaviors are coded on a 4-point scale (0 = never, 1 = rarely, 2 = frequently, and

3 = almost always). It was administered by raters blind to the drug protocol, who observed the patients for 45 minutes.

9. *Principal investigators' classification of strong, moderate, and nonresponders.* One month after each center completed its protocol the principal investigator was asked to list any patients in whom "strong clinical improvements were noted by themselves and the patients' parents and teachers." These were labeled "strong responders." Two weeks later each principal investigator was again contacted and asked to list patients who "they and the patients' parents and teachers agreed showed absolutely no changes." These were labeled "nonresponders." Strong responders, nonresponders, and moderate responders (defined as those not placed in one of the other two categories by the principal investigators) were then grouped for correlation analyses.

10. *Statistical analysis.* Mean scores for all patients at each visit were used in the statistical analyses. The statistical procedures for the Alpern-Boll Developmental Profile, IQ, and Ritvo-Freeman Real-Life Rating Scale were repeated-measures analyses of variance, with individual comparison of means using the Duncan multiple-range test. Program was procedure GLM, Statistical Analysis System (Ray, 1982). Serotonin blood levels and blood platelet counts were analyzed by percent changes from baselines.

Results

1. *Patient compliance.* Three patients were withdrawn during the course of the study (in one case the parents moved; in two cases parents complained of irritability, anorexia, weight loss, and insomnia). Despite the blind nature of the study, the majority of parents observed symptomatic improvements during the medication phase and a return of pathologic behaviors after the blind crossover back to placebo. Some wished to withdraw their child from the study and obtain active medication from their personal physicians. However, all were persuaded to continue through the study before again medicating their children.

2. *Parental reports.* The beneficial effects most often reported by parents were 1) decreased restlessness and hyperactivity; 2) decreased repetitive behaviors such as hand flapping, jumping, self-injury, and spinning; 3) increased social responsiveness and eye contact ("more tuned in"); 4) increased attention span and participation in school programs; and 5) improved speech and nonverbal communication. After the blind crossover back to placebo, the order of symptom return reported was similar. Hyperactivity and repetitive behaviors reappeared first, then withdrawal and social inappropriateness and, lastly, cognitive and communication skills decreased to pretreatment levels. Great variability in the time of onset of improvements and remissions was reported.

3. *Side effects.* No serious adverse reactions occurred. Lethargy and irritability were the most frequent side effects reported. The side effects observed and their incidences at all the centers are being systematically studied and will be reported upon separately (George Realmuto, M.D., personal communication) as are those at one center (Piggott et al., in press).

4. *Blood serotonin concentrations and platelet counts.* Blood serotonin concentrations were available on 62 of the 81 patients (77%). Since assays were conducted in different laboratories (Yuwiler et al., 1970), percent changes from baselines were used for statistical analyses. Average blood serotonin concentrations fell 46% from baseline after 2 months on drug, 57% from baseline after 4 months on drug, and rebounded to 5% over baseline 2 months after drug was replaced by placebo. These changes on drug were highly significant ($p = <.0001$). Platelet counts were available on 44 patients of the 81 total (54%). Percent changes from baseline were again used for analysis. The average of all counts fell 5% from baseline after 2 and 4 months on drug. These decreases approached significance ($p = <.0867$). Inspection of the data reveals that changes in serotonin concentrations and platelet counts were quite consistent across patients. Thus it appears that the dosage selected (1.5 mg/kg body weight/day) uniformly decreases serotonin concentrations approximately 50% regardless of the initial blood levels (*see* Figure 1 and Table 1).

5. *Appetite and weight changes.* Anorexia occurred initially in 16 patients (20%) with remission in all but 2 patients after 4 weeks. In these 2 cases, food prompting and supplements were sufficient to prevent weight loss.

6. *Wechsler Intelligence, Cattell, and Stanford-Binet Scales and the Merrill-Palmer Preschool Performance Test.* Data on these are shown in Table 1. Significant differences occurred between baseline and medication periods as indicated.

7. *Ritvo-Freeman Real-Life Rating Scale for Autism.* The mean values of the overall, motor, social, and sensory scales showed significant improvements between baseline and drug periods (*see* Figure 2 and Table 1). The affect and language scales trended in the direction of improvement but mean changes did not reach significant levels.

8. *The Alpern-Boll Developmental Profile.* The mean values for the communication, self-help, and overall scales showed significant improvement between the baseline and drug periods (*see* Figure 3 and Table 1). The academic age, social, physical development, and IQ scales trended in the direction of improvement but did not reach significant levels.

9. *Principal investigators' classification of strong, moderate, and non-responders.* The distribution (number and percent) of all 81 patients by center and sex is shown in Table 2. Twice as many patients were classified strong responders as nonresponders (33% vs. 15%). The percentage of strong, moderate, and nonresponders at various centers ranged from 0% to 100%, indicating wide variability within and among centers. The combined total of strong and moderate responders was far in excess of just nonresponders (85% to 15%), indicating that a consistent overall favorable clinical impression was created. Sex is not correlated with response. The sex distribution in the 81 patients (4:1) is similar within the principal response classifications (86% of males and 81% of females classified as strong and moderate responders vs. 14% males and 19% females as nonresponders). Within the strong responder category alone there was a nonsignificant higher percentage

TABLE 1

Effect of Fenfluramine on Laboratory and Clinical Measures

	No. of Pts.	Baseline	4 Mos. on Drug	2 Mos. on Placebo
Percent Serotonin	62	100%	−57%*	+5%*
Platelets	44	100%	− 5%	+2%
Verbal I.Q.	51	49.3	51.9*	51.3
Performance I.Q.	61	59.8	63.8*	65.8
Real Life Rating Scale	78			
Overall		.66	.55*	.60
Motor		.36	.26*	.38*
Social		1.06	.88*	.93
Sensory		.52	.39*	.44
Affect		.47	.36	.43
Language		.85	.84	.85
Alpern-Boll Profile	48			
Overall		39.9	44.9*	43.4
Communication		27.8	34.7*	34.4
Self-help		48.6	55.7*	54.0
Academic		38.7	43.9	42.9
Physical		49.1	53.5	50.3
Social		33.8	36.7	35.7

*Significant differences from prior period ($p < 0.05$).

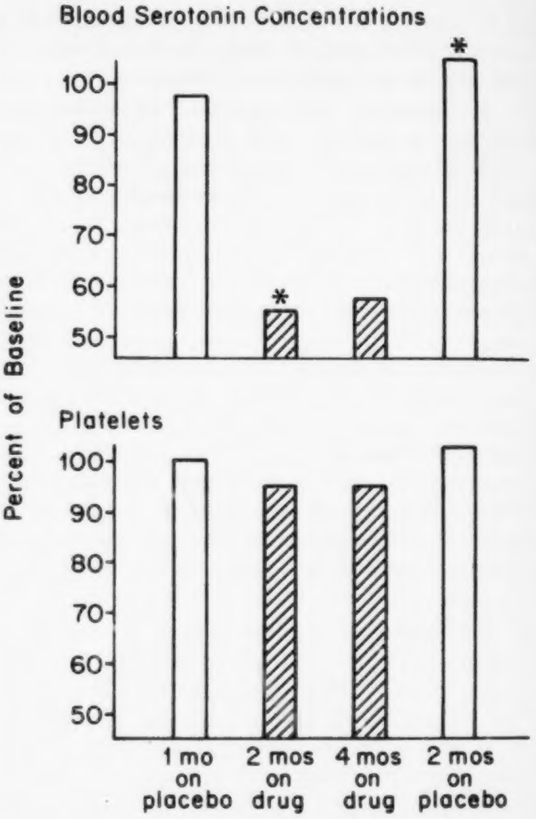


FIGURE 1. Effects of fenfluramine on blood serotonin concentrations and platelet counts (percent changes from baselines). * = significant change from prior period ($p < .0001$).

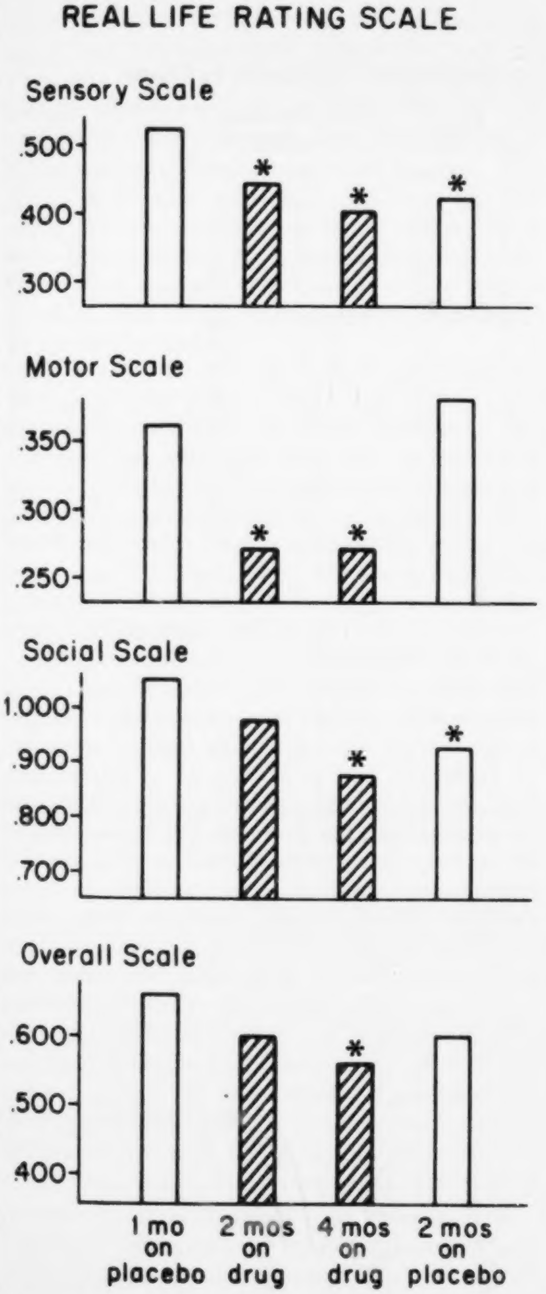


FIGURE 2. Ritvo-Freeman Real Life Rating Scale. * = significant difference from the initial placebo period (Sensory Scale $p < .0006$; Social Scale $p < .002$; Motor Scale $p < .006$; Overall Scale $p < .002$).

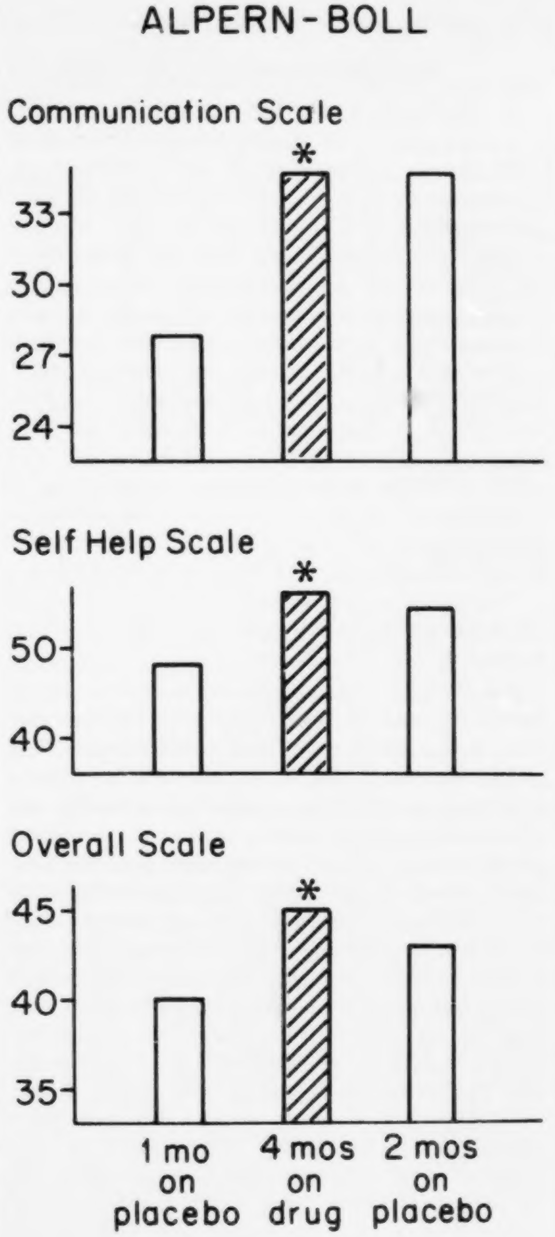


FIGURE 3. Effects of fenfluramine on the Alpern-Boll Developmental Profile. * = significant differences from the initial placebo period (Communication Scale $p < .001$; Self-help Scale $p < .01$; Overall Scale $p < .05$).

TABLE 2

Principal Investigators' Classification of Clinical Responses: Distribution by Center

I. Center			Strong Responders		Moderate Responders		Non-Responders	
	N	%[a]	N	%[b]	N	%[b]	N	%[b]
U.C.L.A.	14	17	6	43	8	57	0	0
Portland	8	10	2	25	6	75	0	0
Chicago	16	20	0	0	12	75	4	25
Oakland	7	9	2	29	2	29	3	42
Detroit	6	7	3	50	3	50	0	0
Minneapolis	3	4	0	0	3	100	0	0
Houston	13	16	10	77	3	23	0	0
Cincinnati	4	5	1	25	2	50	1	25
Galveston	10	12	3	30	3	30	4	40
Totals	81	100	27	33	42	52	12	15
II. Sex Distribution								
Males	65	80	24	37	32	49	9	14
Females	16	20	3	19	10	62	3	19

[a] Column percentage
[b] Row percentages

of males (37% of all males vs. 19% of all females).

10. *Correlations among baseline serotonin, IQ, behaviors, and clinical response.* The distribution by baseline laboratory and clinical data are shown in Table 3. Age is not correlated with response category, the means being only 13 months apart and the ranges showing great overlap. Baseline serotonin concentrations show a significant inverse correlation with clinical response categories, being lowest in the 11 strong responders measured (mean = .250), next higher in the 20 moderate responders measured (mean = .280), and highest in the 4 nonresponders measured (mean = .330) ($r = -.35$, $p < .05$). Verbal IQ and Performance IQ, Real Life Rating Scale, and Alpern-Boll Scale scores did not show significant correlations with any of the clinical response categories. Significant inverse correlations were also found between baseline serotonin concentrations and performance IQ ($r = -.57$, $p < .0025$) (*see* Table 3).

Discussion

The results indicate that fenfluramine is a safe and effective treatment for some autistic children and young adults, thus confirming earlier reports (August et al., 1985; Freeman et al., 1985; Geller et al., 1982; Klykylo et al., in press; Ritvo et al., 1983, 1984 Stubbs et al., in press). During the 4 months we administered it to children, only the same side effects observed in adults were noted. Any longer range effects will have to be studied separately. However, our prior report of administration for 12 months (Ritvo et al., 1984) and dozens of autistic patients we have learned about who have been on the medication for over 3 years indicate that at least in some children it can be well tolerated over these extended periods. Our anecdotal information also indicates that irritability, lethargy, anorexia, and other mild side effects usually last only during the first month of administration and can be eliminated by reducing the dosage. Although only a small percentage of patients experienced any side effects (Piggott et al., in press), certainly all parents should be informed of their potential appearance.

It is important to note that fenfluramine produced significant symptomatic improvements on both professionally administered scales (Ritvo-Freeman Real Life Rating Scale and the intelligence scales) as well as on the parent reported scales (Alpern-Boll). The improvements noted in the study of 81 patients were consistent with previous smaller sample studies in both the type and timing of onset after treatment began, and the return of symptoms after switching back to placebo.

This confirmation is particularly noteworthy, since the experimental design we utilized does not allow for assessing treatment order effect. However, such an effect should not confound the results of a study of autistic patients whose clinical courses are known to be stable over the span encompassed by this study (8 months) (Freeman et al., 1985). Nevertheless, a second experiment utilizing a design which mitigates treatment order effects is under way on an additional 99 patients at 14 medical centers.

IQ test scores showed slight but significant increases during the drug phase as was observed in our first two cases (Geller et al., 1982). The improvement in verbal scale scores probably reflects improved concentration and better relating to the examiner. The improved performance scale scores may have been due to these factors, combined with practice effects, as we have previously discussed (Ritvo et al., 1984).

The correlations that were found between baseline serotonin concentrations, IQ, and clinical response are consistent with earlier reports (Ritvo et al., 1984) and warrant further exploration.

TABLE 3

Principal Investigators' Classification of Clinical Responders and the Distribution of Baseline Measures

	Strong Responders	Moderate Responders	Non Responders
Number of patients	27	42	12
Percentages	33%	52%	15%
Age mean (months)	110	107	97
Range (months)	42–247	33–293	37–154
Serotonin mean*	.250	.280	.380
No. tested	11	20	4
Range	.140–.350	.090–.450	.230–.570
Real Life Rating Scale			
overall	0.60	0.69	0.68
Motor	0.29	0.40	0.36
Social	1.04	1.10	1.07
Sensory	0.46	0.59	0.51
Alpern-Boll overall	56	51	60
Communication	34	27	48
Self-help	48	48	57
IQ Verbal	51	48	45
No. tested	18	36	11
Range	20–100	15–126	24–138
IQ Performance**	58	63	60
No. tested	22	35	10
Range	9–130	16–127	36–131

*Significant correlation ($r = -.57$, $p < .0025$) between baseline serotonin and performance IQ.

**Significant correlation ($r = .35$, $p < .05$) between response and baseline serotonin.

Several principal investigators reported their impressions that the medication produced differential effects in certain patients, depending upon their baseline verbal IQs. The clinical consensus was that patients with initially high verbal IQs (70 or higher) who responded showed mainly increased appropriate social responsiveness, lengthened attention spans, better concentration to cognitive tasks, and improved social conversation. They also showed, but to a lesser degree, decreased hyperactivity and repetitive behaviors. In contrast, patients with initially low IQs (50 or less) showed primarily decreased hyperactivity, improved sleep patterns, newfound ability to interrupt repetitive behaviors with appropriate training ("We had tried to get him to stop arm flapping before but it never worked"), and were "more tuned in."

The present results shed no light on such important issues as the method of action of fenfluramine or dose-response relationships. Hopefully, these and other relevant clinical and neurobiochemical issues will become of sufficient interest to be explored now that the efficacy and safety of fenfluramine as a treatment for some autistic patients has been more firmly established. Also remaining is the fascinating task of learning how to predict responders in advance, thus obviating the need for prolonged clinical trials of up to 8 months (Ritvo et al., 1984).

Appendix

The medical centers and personnel contributing to the research are (1) University of Texas Medical Branch, Department of Psychiatry and Behavorial Sciences, Galveston, Texas: Gerald J. August, Ph.D., Principal Investigator, Teresa D. Baerd, M.D., Naftali Raz, Ph.D., Louise Hsu, Ph.D.; (2) University of Cincinnati, Department of Psychiatry, Children's Hospital Medical Center, Cincinnati, Ohio: William Klykylo, M.D., Principal Investigator, Dorothyann Feldis, Ph.D., Donald O'Grady, Ph.D., Diana L. Ross, M.D., Charlotte Halloran, M.A.; (3) University of Chicago Pritzker School of Medicine and

Wyler Children's Hospital, Chicago, Illinois: Bennett Leventhal, M.D., Principal Investigator, Marolyn Morford-Boswell, M.A., Daniel X. Freedman, M.D. (presently at U.C.L.A.); (4) Texas Research Institute of Mental Health, Houston, Texas: Kay Lewis, M.D., Principal Investigator; (5) LaFayette Clinic, Detroit, Michigan: Leonard Piggott, M.D., Principal Investigator, Charles Gdowski, Ph.D., Charles Frohman, Ph.D., David Villanueva, M.D., Joseph Fischhoff, M.D.; (6) University of Minnesota, Division of Child and Adolescent Psychiatry, Medical School, Minneapolis, Minnesota: George Realmuto, M.D., Principal Investigator; (7) The Oregon Health Sciences University, Department of Psychiatry, Crippled Children's Division, School of Medicine, Portland, Oregon: E. Gene Stubbs, M.D., Principal Investigator, Sarojini Budden, M.D., Russell Jackson, Ph.D., Leif Terdal, Ph.D.; (8) Children's Hospital Medical Center, Oakland, California: Richard Umansky, M.D., Rosamond Gardner, Ph.D., Principal Investigators; (9) University of California at Los Angeles, Division of Mental Retardation and Child Psychiatry, Los Angeles, California: Edward R. Ritvo, M.D., Principal Investigator.

References

Alpern, G.D., Boll, T.J., and Shearer, M.S. *Developmental Profile II: Manual*. Aspen, Colo.: Psychological Development Publications, 1980.

August, G.J., Raz, N., and Baird, T.D. Effects of fenfluramine on behavioral, cognitive, and affective disturbances in autistic children. *J. Autism Dev. Disord.*, 15:97, 1985.

Cattell, P. *The Measurement of Intelligence of Infants and Young Children.* New York: The Psychological Corporation, 1960.

Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

Freeman, B.J., Ritvo, E.R., Yokota, A., et al. A scale for rating symptoms of patients with the syndrome of autism in real life settings. *J. Am. Acad. Child Psychiatry*. (In press)

Freeman, B.J., Ritvo, E.R., Needleman, R., et al. Stability of cognitive and linguistic parameters in autism. *J. Am. Acad. Child Psychiatry*, 24:459, 1985.

Geller, E., Ritvo, E.R., Freeman, B.J., et al. Preliminary observations on the effect of fenfluramine on blood serotonin and symptoms in three autistic boys. *N. Engl. J. Med.*, 307:165, 1982.

Klykylo, W.M., Feldis, D., O'Grady, D., et al. Clinical effects of fenfluramine in ten autistic subjects. *J. Autism Dev. Disord.* (In press)

Piggott, L.R., Gdowski, C.L., Villenueva, D., et al. Side effects of fenfluramine in autistic children. *J. Am. Acad. Child Psychiatry*. (In press)

Ray, E. (ed.). *SAS User's Guide: Statistics 1982*. Raleigh, N.C.: SAS Institute, 1982.

Ritvo, E.R., and Freeman, B.J. The National Society for Autistic Children definition of the syndrome of autism. *J. Am. Acad. Child Psychiatry*, 17:565, 1978.

Ritvo, E.R., Freeman, B.J., Geller, E., et al. Effects of fenfluramine on 14 outpatients with the syndrome of autism. *J. Am. Acad. Child Psychiatry*, 22:549, 1983.

Ritvo, E.R., Freeman, B.J., Yuwiler, A., et al. Study of fenfluramine in outpatients with the syndrome of autism. *J. Pediatr.*, 105:823, 1984.

Stubbs, E.G., Budden, S.S., Jackson, R.H., et al. Effects of fenfluramine on 8 outpatients with the syndrome of autism. *J. Am. Acad. Child Psychiatry*. (In press)

Stutsman, R. *Merrill-Palmer Scale of Mental Tests*. New York: Harcourt, Brace, and World, 1948.

Thorndike, R.L. *Manual for Stanford-Binet Intelligence Scale*. Boston: Houghton Mifflin, 1972.

Wechsler, D. *Manual for the Wechsler Preschool and Primary Scale of Intelligence*. New York: Psychological Corporation, 1967.

Wechsler, D. *Manual for the Wechsler Intelligence Scale for Children, Revised*. New York: Psychological Corporation, 1974.

Wechsler, D. *Manual for the Wechsler Adult Intelligence Scale, Revised*. New York: Psychological Corporation, 1981.

Yuwiler, A., Plotkin, S., Geller, E., et al. A rapid accurate procedure for the determination of serotonin in whole human blood. *Biochem. Med.*, 3:426, 1970.

Short-Term Efficacy and Safety of Fenfluramine in Hospitalized Preschool-Age Autistic Children: An Open Study[1]

Magda Campbell, M.D.,[2] Stephen I. Deutsch, M.D., Ph.D.,[2] Richard Perry, M.D.,[2] Barbara B. Wolsky, C.S.W.,[2] and Michael Palij, Ph.D.[3]

Introduction

Ritvo and associates (1983) reported encouraging results associated with administration of fenfluramine over a period of 4 months in 14 autistic subjects; decreases of certain symptoms and increases in IQ scores, with only a few side effects, were rated.

Structurally, fenfluramine is similar to amphetamine, though their mechanisms of action differ. Fenfluramine is a potent antiserotonergic drug (Costa et al., 1971). Some reports suggest that fenfluramine is a mild antidopaminergic drug with sedative or tranquilizing properties (Alphin et al., 1964; Franko et al., 1964; Jori et al., 1974), while others indicate that stimulating effects are dose dependent (Riley et al., 1969).

It has been demonstrated that about one-third of autistic children show elevated serotonin levels in blood, as compared to normal controls; this elevation of serotonin was found in those autistic children who were more retarded and who showed more florid symptomatology (Campbell et al., 1975). In the studies of Ritvo and his associates (1983, 1984), there was a marked decrease of serotonin levels following treatment with fenfluramine.

New and potentially therapeutically effective drugs, which are devoid of long-term untoward effects, are sought for the treatment of autistic children. D- and L-Amphetamine, dopamine agonists, had untoward effects in this population which often outweighed therapeutic effects (Campbell et al., 1972, 1976). Haloperidol, a potent antidopaminergic drug, was found to decrease significantly behavioral symptoms and to facilitate learning in the laboratory, in two large samples of autistic children, when administered under double-blind and placebo-controlled conditions at doses ranging from 0.5 to 4.0 mg/day (Anderson et al., 1984; Campbell et al., 1978). At these doses, haloperidol was a safe drug when given over a period of up to 3 months cumulatively. However, in a prospective study, when given over a longer period of time to 58 children, 22% developed tardive or withdrawal dyskinesias (Perry et al., 1985). There is no agreement about the therapeutic efficacy of L-dopa (Campbell et al., 1976; Ritvo et al., 1971), a drug which reduces serotonin levels.

The 14 subjects who participated in the study of Ritvo et al. (1983) were all outpatients exposed to a variety of educational programs and heterogeneous in regard to chronological age (3 to 18 years).

We wished to administer fenfluramine in an open fashion under close clinical and laboratory monitoring to a small sample of carefully diagnosed inpatients, with a relatively narrow age range.

Method

Subjects

Ten children, 7 males and 3 females, ages 3 to 5.75 years (mean, 4.15), participated in this pilot study. They were all inpatients in Bellevue Hospital, Psychiatric Division, Chil-

---

[1] This work was supported in part by USPHS Grant MH-32212 from the National Institute of Mental Health.

[2] Children's Psychopharmacology Unit, Department of Psychiatry, New York University Medical Center, New York, NY 10016.

[3] Department of Psychiatry and Behavioral Sciences, Health Sciences Center, State University of New York at Stony Brook, Long Island, NY 11794.

Address reprint requests to Magda Campbell, M.D., Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, NY 10016.

dren's Inpatient Service and all met the DSM-III (1980) criteria for Infantile Autism, Full Syndrome, as determined by at least 2 board-certified child psychiatrists independently. Following admission, baseline evaluations were performed: these included complete medical diagnostic workup as well as psychiatric observation; psychological, neurological, pediatric, hearing, and speech evaluations; and laboratory studies. Children with a known cause for autism were excluded from the study. Two children had seizure disorder (grand mal).

All children were withdrawn, displayed stereotypies, and had very short attention spans. In addition, 6 children had temper tantrums; 8 were very irritable and were screaming; 8 were hyperactive and, in 3 of these 8, hyperactivity alternated with hypoactivity. One child was exclusively hypoactive. Eight children were aggressive and, in 4 of these, aggression was also directed against self. In 2 children, self-injurious behavior resulted in prominent frontal bossing due to chronic severe head banging. Four children had insomnia. The children's intellectual functioning ranged from mildly to profoundly retarded.

Procedures

All children were free of psychoactive drugs for at least 2 weeks prior to the study.*

Ratings were done at fixed intervals, twice during the placebo baseline and during treatment, independently, by two child psychiatrists. Ratings were videotaped. The following rating scales were used: the Children's Psychiatric Rating Scale (CPRS), Clinical Global Impressions (CGI), and Abnormal Involuntary Movements Scale (AIMS) (*Psychopharmacology Bulletin*, 1985); the Simpson Abbreviated Dyskinesia Rating Scale (Simpson et al., 1979); and the Fenfluramine Untoward Effects Checklist.

Electrocardiogram (ECG) and laboratory studies (urinalysis, complete blood count, differential, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase, creatine phosphokinase, alkaline phosphatase, and electrolytes) were also done during the baseline period and at the end of each 4-week treatment period. Blood pressure and heart rate were taken daily, and weight weekly, at fixed times, adhering to a protocol.

Fenfluramine and identical matching placebo tablets were supplied by A.H. Robins Company. Following a placebo baseline period,** fenfluramine was started at a dose of 10 mg/day, in two divided doses, and increments occurred gradually at fixed intervals. Dosage was regulated individually, until positive or untoward effects were observed. Dosage was reduced when untoward effects emerged.

Results

Dosage

Optimal doses for the 10 children ranged from 15 to 30 mg/day or 1.093 to 1.787 mg/kg/day (mean, 1.413). The maximum dose explored, in two children was 60 mg/day (3.625 mg/kg/day).

Untoward Effects

The untoward effects necessitating dosage reduction consisted of drowsiness and lethargy ($N=9$), including falling asleep 4 1/2 hours after the administration of an 8 a.m. dose, loss of weight ($N=7$), excessive and uncontrollable irritability ($N=6$), body "rigidity," tension, and fidgetiness ($N=1$), sadness ($N=2$), increased aggressiveness against self or others ($N=2$), insomnia ($N=1$), increased withdrawal ($N=1$), and increase of stereotypies ($N=1$). These untoward effects occurred above optimal doses or during dosage regulation, on 1.23 to 3.625 mg/kg/day of fenfluramine. There were no untoward effects at optimal doses: the exception was a 46-

---

*The exception were two children with seizure disorder: one was receiving Tegretol, and the other Dilantin, throughout the study.

**Exception were two children who were placed as an emergency without placebo baseline on fenfluramine because of their extremely severe irritability, insomnia, or self-mutilating behavior with temper tantrums.

month-old boy, who showed only slight improvement on fenfluramine (1.787 mg/kg). As indicated above, 7 of the 10 children lost weight (from 0.02 to 1.70 kg) at the end of 1 month of fenfluramine administration. At the end of the second month, all but one* gained weight (from 0.23 to 0.91 kg). One child gained weight during the first month of fenfluramine administration (1.68 kg), and lost 1.11 kg at the end of second month. During the entire period of fenfluramine administration, only two children lost weight. No child developed dystonic reactions or dyskinesias during this study.

Laboratory Studies

Blood pressure and pulse rate remained essentially the same throughout the study; there was no change in ECG and in laboratory studies.

Rating Scales

Children's Psychiatric Rating Scale (CPRS). Of the first 28 items, only 14 were analyzed because the remaining 14 are usually rated as absent in autistic children. Although CPRS ratings were taken at four different times, that is, two baseline and one at 4 weeks on drug and 8 weeks on drug, the measures taken at 8 weeks on drug are not included. This was done because only five subjects had complete data for the four occasions, in contrast to the eight subjects for the three times listed in Table 1. Obviously, the sample with the larger number provides for more powerful statistical tests as well as better representation of the population of subjects.

The values reported in the fifth column of Table 1, labeled ANOVA F represents the F statistic and significance level from a one-way repeated measure (analysis of variance) for the three occasions of measurement. Five of the items (i.e., items 3, 4, 8, 10, and 28) produced F values which were significant at the traditional .05 level. Item 16 produced an F value of marginal significance ($p<.10$). The sum of the 14 items, when treated as a separate dependent variable, also produced a significant F value. In all instances, the rated severity for the items decreased after 4 weeks on drug.

Those items with significant F values were followed up with matched *t* tests. Only comparisons between the two baselines and 4 weeks on drug are presented (no significant differences were found between the baseline measures for any of the items). All of these comparisons showed a significant decrease in rated severity between the two baselines and 4 weeks on drug except for items 3 and 28. On item 3, fidgetiness, the decrease between the second baseline and 4 weeks on drug was not significant, apparently because the mean rating for the second baseline was lower than that of the first baseline (though not significantly). On item 28, rhythmic motions, the decrease between the first baseline and 4 weeks on drug is only marginally significant. These comparisons should be interpreted with caution appropriate to the number of comparisons performed.

Clinical Global Impressions (CGI). Table 2 contains the ratings for the three items on the CGI for various combinations of times of measurement. The last column contains the F values from one-way repeated measures ANOVA. Each of the items are presented in two ways: first, analyses based on the largest sample possible for the smallest number of meaningful times of measure and, second, analyses based on a smaller sample size but representing all times of measurement.

Item 1, the rated severity of illness, indicated a significant decrease in rated severity from baseline to measures made while on drug. Row 1(a) contains values based on the same subjects represented by the CPRS ratings in Table 1. The two baseline measures did not differ from each other but both were significantly higher than the rating made at 4 weeks on drug (both $p<.05$). Row 2(a) contains the second drug measurement made at 8 weeks after drug treatment began. Here, again, the two baseline measures did not differ, nor did the two ratings made while on drug. Ratings made on baseline were both significantly higher than either rating made on drug (one $p=.07$, others $p<.05$).

Item 2, improvement in the child relative to first interview by the clinician, shows only a marginal improvement from the second

---

*One child received fenfluramine only for 31 days.

TABLE 1

Children's Psychiatric Rating Scale (CPRS) Items at First and Second Baseline and at 4 Weeks on Fenfluramine*

CPRS Items	B1 First Baseline	B2 Second Baseline	D1 Four Weeks on Drug	ANOVA *F* Value	Posthoc Comparisons *t* values B1 vs D1	Posthoc Comparisons *t* values B2 vs D1
2. Underproductive speech	5.87	5.87	5.12	ns	—	—
	(2.23)	(2.10)	(2.17)			
3. Fidgetiness	4.00	3.50	1.87	22.13	6.06	1.53
	(0.76)	(0.76)	(1.25)	($p<.001$)	($p<.01$)	ns
4. Hyperactivity	3.12	3.50	1.25	7.84	2.61	4.33
	(1.55)	(1.29)	(0.71)	($p<.01$)	($p<.05$)	($p<.01$)
5. Hypoactivity	1.87	1.62	1.37	ns	—	—
	(1.25)	(1.77)	(1.06)			
7. Abnormal object	4.75	4.50	3.50	ns	—	—
relationships	(2.19)	(2.07)	(1.60)			
8. Withdrawal	6.12	6.12	4.75	6.67	2.99	2.99
	(0.99)	(1.13)	(1.16)	($p<.01$)	($p<.05$)	($p<.05$)
10. Negative, uncooperative	4.00	4.37	1.75	6.96	3.81	2.90
	(1.31)	(1.77)	(1.49)	($p<.01$)	($p<.01$)	($p<.05$)
11. Angry affect	3.37	3.25	1.87	ns	—	—
	(1.77)	(2.37)	(1.81)			
16. Unspontaneous relation	7.00	7.00	5.75	2.97	—	—
to examiner	(0.00)	(0.00)	(2.05)	($p<.10$)		
20. Lability of affect	2.25	3.12	1.75	ns	—	—
	(1.91)	(2.29)	(2.12)			
24. Low voice	1.37	1.75	1.00	ns	—	—
	(0.74)	(1.03)	(0.00)			
25. Loud voice	1.75	2.12	1.37	ns	—	—
	(1.49)	(1.81)	(1.06)			
27. Other speech deviance	4.62	4.00	3.75	ns	—	—
	(2.56)	(2.33)	(3.01)			
28. Rhythmic motions	5.38	5.00	3.87	3.74	2.05	2.55
(Stereotypie)	(1.41)	(0.93)	(1.73)	($p<.05$)	($p<.10$)	($p<.05$)
Sum of above 14 items	55.50	56.87	40.62	9.14	3.40	3.25
	(8.50)	(11.08)	(9.30)	($p<.01$)	($p<.05$)	($p<.05$)

*Means and standard deviations (in parenthesis) are based on eight subjects. Items are rated on a 7-point scale where 1 means not present, 2 means very mild, and so on to 7 which means extremely severe. Degrees of freedom for the repeated measures ANOVA are 2 and 14 and 7 for the matched *t* test used in the posthoc comparisons.

baseline to 4 weeks on drug. When the second drug measure is included, the repeated measures ANOVA is nonsignificant even though there is a steady improvement from baseline.

Item 3, the efficacy of the drug treatment, a rating which is to reflect the relative benefit of a drug given the number of side effects that are observed, shows a significant therapeutic effect of fenfluramine at 4 weeks on drug relative to baseline measures [row 3(a)]. When the second drug measure is included, we still obtain a significant F value from the repeated measures ANOVA. Though the two ratings made on drug did not differ from each other, both were significantly higher than the baseline measure ($p = .06$ and $p = .02$).

Conclusions

In this open-label study, a variety of positive stimulating and tranquilizing effects of fenfluramine were observed: the most consistent and striking effects were increased relatedness and animated facial expression, decreases of irritability, temper tantrums, aggressiveness, self-mutilation, hyperactivity, and improved sleep pattern. Ritvo et al.

TABLE 2

Clinical Global Impressions (CGI) Ratings for Two Baselines, 4 Weeks, and 8 Weeks on Fenfluramine[1]

CGI Items	Placebo Baseline 1	Baseline 2	Fenfluramine Treatment 4 Weeks	8 Weeks	ANOVA F
1(a) Severity of Illness	5.75	6.12	4.12	—	10.62**
	(1.03)	(0.83)	(0.99)	—	
	N=8	*N*=8	*N*=8		
1(b) Severity of Illness	5.80	6.20	4.20	4.00	6.62**
	(0.84)	(0.84)	(1.09)	(1.58)	
	N=5	*N*=5	*N*=5	*N*=5	
2(a) Global Improvement	—	4.44	2.67	—	4.41+
	—	(1.94)	(1.41)	—	
		N=9	*N*=9		
2(b) Global Improvement	—	3.67	3.00	2.67	ns
	—	(1.97)	(1.55)	(1.21)	
		N=6	*N*=6	*N*=6	
3(a) Efficacy (Drug Effect)	—	0.77	2.47	—	19.28**
	—	(0.44)	(1.75)	—	
		N=9	*N*=9		
3(b) Efficacy (Drug Effect)	—	0.83	2.71	2.33	6.40*
	—	(0.41)	(1.27)	(1.21)	
		N=6	*N*=6	*N*=6	

[1] Means, standard deviations (in parentheses), and sample size.

+ = $.05 < p < .10$

* = $p < .05$

** = $p < .01$

(1983) and August et al. (1985) also reported improvements in sleep pattern, attention, and social relatedness, as well as decreases in hyperactivity and stereotypies. Marked global improvement was observed in 4 children; 2 had moderate and 4 showed minimal or no change. However, in 2 children, the level of initial improvement could not be sustained over a 2-month period of active medication. Therapeutic effects occurred as early as 2 days after medication was started.

Major untoward effects included drowsiness and lethargy, excessive and uncontrollable irritability, and a transient weight loss at the end of 1 month (followed by weight gain at the end of the second month). While Ritvo did not find weight loss a problem, August et al.'s (1985) findings are in agreement with ours. Ritvo states that weight monitoring may have been flawed in his study. We used the same scale throughout the study and adhered to a strict protocol. Untoward effects seemed to be dose-dependent as they disappeared upon dosage reduction. While in the previous reports children adapted to sedation after a few days (August et al., 1985; Ritvo et al., 1983), this was not true for our patients. Actually, no child adapted to behavioral toxicity.

In conclusion, we learned the following from this open clinical trial of fenfluramine, when administered at the specified doses over a period of up to 2 months to hospitalized preschool-age autistic children under the present conditions (100% compliance and 24-hour a day careful monitoring):

1. Flexible, and not a fixed dosage schedule should be employed since the range of optimal doses was wide: 1.1 to 1.8 mg/kg/day; mean, 1.4.

2. Onset of therapeutic effects was as early as 2nd day of treatment; one child fell asleep 4 1/2 hours after the morning dose.

3. Stimulating and calming properties of drug were reflected in both therapeutic and in untoward effects.

4. The most consistent and striking therapeutic effects were increased relatedness and animated facial expression, and decreases of irritability, temper tantrums, aggressiveness, self-mutilation, hyperactivity, and improved sleep pattern.

5. Four of the 10 children showed dramat-

ic improvement: all 4 had low IQs. All 4 failed to respond to haloperidol and to special education.

6. In some children, therapeutic effects are transient.

7. In a subsample of 7 children who received separate trials of both fenfluramine and of haloperidol, 3 responded to haloperidol and not to fenfluramine; 4 responded to fenfluramine but not to haloperidol.

8. Untoward effects with fenfluramine occurred mainly above therapeutic doses and there was a good therapeutic margin. Major untoward effects were drowsiness, uncontrollable irritability, and transient weight loss.

The observed effects in our study could be attributed to antiserotonergic or amphetamine-like, or antidopaminergic properties of fenfluramine.

However, while in our previous studies of D- and L-amphetamine the potentiating effects on stereotypies were striking in most autistic children, with fenfluramine only one child showed increases of stereotypies on 3.625 mg/kg/day, a dose which was above optimal (1.787 mg/kg/day). On therapeutic doses, there was reduction of stereotypies. This observation is consistent with the preclinical literature demonstrating that fenfluramine can antagonize apomorphine-induced stereotypies in rats (Jori et al., 1974), although in our sample the reduction of stereotypies was only mild.

While the literature (Alphin & Ward, 1969) indicates that fenfluramine has mild antidopaminergic-tranquilizing properties, in our patients calming effects were pronounced: decreases of aggressiveness, temper tantrums, hyperactivity, and insomnia were observed at therapeutic doses and, at higher doses, 9 of the 10 patients were drowsy or fell asleep.

Future well-designed, carefully planned, and placebo-controlled studies involving large samples of hospitalized autistics who are homogeneous with respect to age are needed to assess critically the efficacy and the safety of fenfluramine in this disorder.

We have recently begun such a study: in this double-blind, placebo-controlled parallel group's clinical trial we will assess the effects of fenfluramine on both behavioral symptoms and on discrimination learning.

References

Alphin, R.S., Funderburk, W.H., and Ward, J.W. Anorexigenic activity of N-ethylmethyl-3-trifluoromethylphenethylamine hydrochloride (AHR-965), a non-CNS stimulant. *Toxicol. Appl. Pharmacol.*, 6:340, 1964.

Alphin, R.S., and Ward, J.W. Anorexigenic effects of fenfluramine hydrochloride in rats, guinea pigs and dogs. *Toxicol. Appl. Pharmacol.*, 14:182–191, 1969.

Anderson, L.T., Campbell, M., Grega, D.M., et al. Haloperidol in infantile autism: Effects on learning and behavioral symptoms, *Am. J. Psychiatry*, 141 (10): 1195–1202, 1984.

August, G.J., Raz, N., and Baird, T.D. Brief report: Effects of fenfluramine on behavioral, cognitive, and affective disturbances in autistic children. *J. Autism Dev. Disord.*, 15(1):97–107, 1985.

Bowers, M.B., Jr., Swigar, M.E., Jatlow, P.I., and Goicoechea, N. Plasma catecholamine metabolites and early response to haloperidol. *J. Clin. Psychiatry*, 45:248–251, 1984.

Campbell, M., Anderson, L.T., Meier, M., et al. A comparison of haloperidol, behavior therapy and their interaction in autistic children. *J. Am. Acad. Child Psychiatry*, 17(4):640–655, 1978.

Campbell, M., Fish, B., David, R., et al. Response to triiodothyronine and dextroamphetamine: A study of preschool schizophrenic children. *J. Autism Child Schizophr.*, 2(4):343–358, 1972.

Campbell, M., Small, A.M., Collins, P.J., et al. Levodopa and levoamphetamine: a crossover study in young schizophrenic children. *Curr. Ther. Res.*, 19(1):70–86, 1976.

Costa, E., Groppetti, A., and Revuelta, A. Action of fenfluramine on monoamine stores of rat tissues. *Br. J. Pharmacol.*, 41:57–64, 1971.

Franko, B.V., Garber, J.L., and Hudson, B.H. Cardiovascular effects of N-ethylmethyl-3-trifluoromethylamine hydrochloride (AHR-965), an appetite suppressant lacking CNS-stimulating activity. *Fed. Proc.*, 23:330, 1964.

Jori, A., Cecchetti, G., Ghezzi, D., and Samanin, R. Biochemical and behavioral antagonism between fenfluramine and apomorphine in rats. *Eur. J. Pharmacol.*, 26:179–183, 1974.

Perry, R., Campbell, M., Green, W.H., et al. Neuroleptic-related dyskinesias in autistic children: A prospective study. *Psychopharmacol. Bull.*, 21(1):140–143, 1985.

Psychopharmacol. Bull. Rating scales and assessment instruments for use in pediatric psychopharmacology research. Vol. 21 (4), 1985.

Riley, I., Carson, J., Haider, I., and Oswald, I. Fenfluramine overdosage. *Lancet*, II: 1162–1163, 1969.

Ritvo, E.R., Yuwiler, A., Geller, E., et al. Effects of L-dopa in autism. *J. Autism Child Schizophr.*, 1:190–205, 1971.

Ritvo, E.R., Freeman, B.J., Geller, E., and Yuwiler, A. Effects of fenfluramine on 14 outpatients with the syndrome of autism. *J. Am. Acad. Child Psychiatry*, 22:549–558, 1983.

Ritvo, E.R., Freeman, B.J., Yuwiler, A., et al. Study of fenfluramine in outpatients with the syndrome of autism. *J. Pediatr.*, 105(5):823–828, 1984.

Simpson, G.M., Lee, J.H., Zoubok, B., and Gardos, G. A rating scale for tardive dyskinesia. *Psychopharmacology (Berlin)*, 64(2):171–179, 1979.

Fenfluramine: Neurotoxicity[1]

Charles R. Schuster, Ph.D.,[2] Marilyn Lewis,[3] and Lewis S. Seiden, Ph.D.[4]

Fenfluramine [(M-trifluoromethyl)-N-ethyl-amphetamine)], a secondary amine, is structurally similar to its analog the primary amine, amphetamine, and shares its anorectic effects but not its stimulant effects (Le Douarec & Neveu, 1970). Its anorectic actions are based upon its ability to release and block reuptake of serotonin from neurons (Fuxe et al., 1975; Trulson & Jacobs, 1976). Our interest in the neurotoxic effects of fenfluramine was generated in the course of investigating currently marketed anorectic drugs as part of a program of research conducted at the Drug Abuse Research Center at the University of Chicago. We investigated the efficacy, dependence potential, and possible neurotoxicity of structurally related anorectic drugs. We have established that methylamphetamine, as well as certain other related anorectics, produce long-term possibly irreversible damage to one or more monoaminergic systems in the brain (Ricaurte et al., 1982; Schuster & Johanson, 1984; Seiden et al., 1976; Wagner et al., 1979). We report here that fenfluramine is different from most other anorectic drugs because it produces evidence of long-term, possibly irreversible, changes in serotonergic neurons at comparatively low doses compared to those which suppress food consumption.

Several investigators have reported that brain serotonin levels in rats were significantly lowered several hours after the administration of fenfluramine (Duhault & Verhavainne, 1967; Opitz, 1967). Costa et al. (1971) showed that serotonin (5–hydroxytryptamine, 5-HT) brain concentrations were depleted at maximum between 2 and 5 hours after a low interperitoneal injection (10 μmol/kg) of fenfluramine and returned to only 80% of normal 48 hours post-injection. Subsequently, a number of investigators reported that the fenfluramine-induced depletions of brain 5-HT in rats lasted for weeks after drug administration was stopped (Clineschmidt et al., 1978; Harvey & McMaster, 1975; Harvey et al., 1975; Sanders-Bush et al., 1975). In these studies, brain levels of serotonin were found to gradually return to near-normal levels over a 30- to 60-day period. In addition to demonstrating a long-lasting effect upon serotonin brain levels, these investigators also demonstrated long-lasting decreases in the rate limiting enzymatic activity of tryptophan hydroxylase, serotonin uptake, and production of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA). These neurochemical changes are similar to those produced by 5,6-dihydroxytryptamine (5,6-DHT), a toxin known to act on 5-HT neurons. This suggests that fenfluramine also produces a degeneration of serotonergic nerve terminals. The return of serotonin levels to near-normal in most areas suggested that the terminal degeneration was not sufficient for death of the neuron and that sprouting occurred with the formation of new nerve terminals. In addition to this neurochemical evidence for toxic effects on serotonergic nerve terminals, Harvey reported in 1975 that fenfluramine produced morphologic changes in the cell bodies of serotonergic neurons located in the ventral tegmentum of the rat brain, but not in the dorsal or median raphe nuclei (Harvey & McMaster, 1975; Harvey et al., 1975). Although this morphological evidence of cytotoxic effects of fenfluramine is controversial, it suggests that fenfluramine has two types of toxic effects on

---

[1] This work was supported in part by NIDA Grant DA-00085. C.R. Schuster is the recipient of a RSA Award DA-00024. L. S. Seiden is the recipient of a RSA Award MH-10562.

[2] The University of Chicago, Drug Abuse Research Center, Department of Psychiatry, Chicago, IL 60637.

[3] The University of Chicago, Department of Behavioral Sciences, Chicago, IL 60637.

[4] The University of Chicago, Department of Pharmacological and Physiological Sciences, Chicago, IL 60637.

serotonergic neurons in the rat: 1) on the terminals of 5-HT neurons in general regions of the brain, and 2) on cell bodies in a restricted region.

Studies from our laboratory have found that the dose of fenfluramine necessary to reduce food intake by 50% in the rat is 5.0 mg/kg subcutaneous (s.c.) (Schuster & Johanson, 1984). To investigate the possible neurotoxic effects of fenfluramine, two s.c. injections per day were given for 4 days over a range of doses from 6.25 to 50 mg/kg/injection. Two weeks after the last injection, rats were killed and their brains rapidly removed, dissected, and assayed for neurochemical changes as described by Heffner et al. (1980) and Ricaurte et al. (1981). In the caudate hippocampus, and cortex-limbic system, caudate serotonin was depleted by approximately 50% by all dose levels of fenfluramine. In contrast, the levels of dopamine and norepinephrine were not significantly different than controls.

To investigate the neuronal changes responsible for the depletions, we assessed the uptake of tritiated 5-HT into synaptosomal preparations of cortical cells from rats 2, 4, or 8 weeks after the 4-day administration regimen of fenfluramine. When fenfluramine was given twice daily at a dose of 6.25 mg/kg/injection for 4 consecutive days, the number of uptake sites (V_{max}) is decreased by approximately 50% of control values at 2 weeks, but is less affected at 4 weeks and is at control levels by 8 weeks post-fenfluramine. The decrease in the number of uptake sites suggests that fenfluramine damaged the terminals of serotonergic neurons, but that there was a gradual recovery over an 8-week period.

When the effects of fenfluramine were examined at 2, 8, and 16 weeks after two 12.5 mg/kg injections per day for 4 days, it was found that 5-HT levels in the caudate and cortex-limbic system fractions showed a gradual return to control levels over the 16-week period. In contrast, hippocampal 5-HT levels continued to show 50% depletions up to and including the 16-week period. The fact that the 5-HT depletion is longer lasting in the hippocampus than that found in other brain regions confirms previous findings by Harvey et al. (1975). It should be noted that the 5-HT uptake studies cited above were done with synaptosomes from 5-HT nerve terminals from the cortex, a region in which 5-HT levels show a return to normal. We presume that 5-HT uptake into synaptosomes from the hippocampus would continue to be low since the levels of 5-HT show little trend towards returning to control levels over the 16-week period. We may conclude from these studies that at a dose approximately equal to that necessary to produce a significant decrease in food intake (50%), fenfluramine produces long-term changes in 5-HT neurons. It remains to be determined whether the changes induced by fenfluramine in hippocampal 5-HT nerve terminals are irreversible.

Guinea Pigs

Fenfluramine is metabolized in the rat to norfenfluramine which has been shown to cause the release of 5-HT from neurons and to produce long-term depletions of brain levels of 5-HT (Clineschmidt et al., 1978; Sterenka & Sanders-Bush, 1979). In the guinea pig, however, fenfluramine is not changed into an active metabolite (Beckett et al., 1973). This difference in the metabolism of fenfluramine in the guinea pig allows the determination of whether the parent compound alone can produce long-term depletions of 5-HT in the brain.

Four groups of guinea pigs were used in this investigation. Group I was given 6.25 mg/kg/injection twice daily for 8 days. Group II was given 6.25 mg/kg/injection twice daily for 4 days and then 12.5 mg/kg/injection for an additional 4 days. Group III was given 12.5 mg/kg/injection twice daily for 4 consecutive days. Group IV was given saline injections twice daily for 8 consecutive days. Fourteen days after the last injection, animals were killed and the levels of 5-HT in the hippocampus determined. Animals treated with fenfluramine showed a significant dose-related depletion of 5-HT. At the higher dosage level (Groups II and III) these depletions were approximately 50%.

This study indicates that fenfluramine does not have to be metabolized to norfenfluramine in order to produce long-term depletions of brain levels of 5-HT. A similar conclusion was reached by Garattini et al. (1975) who blocked the metabolism of fenfluramine to norfenfluramine in the rat by pretreatment with SKF 525-A.

Rhesus Monkeys

In order to strengthen the prediction of neurotoxicity from animal studies to humans, it is necessary to use a number of species. It is particularly important to determine whether neurotoxicity found in rodents can be replicated in primates. Data on the long-term neurochemical effects of fenfluramine in the rhesus monkey have begun to be collected by our laboratories.

Rhesus monkeys were administered either saline (*N* = 2) or fenfluramine (*N* = 4) at doses of 10 mg/kg/injection by a s.c. route twice daily for 14 consecutive days. Two and 8 weeks later, one of the control animals and two of the fenfluramine-treated monkeys were sacrificed for neurochemical studies. Levels of 5-HT were markedly lower in the fenfluramine-treated animals in caudate, hippocampus, and somatosensory cortex at both 2 and 8 weeks postdrug. In addition, studies of the uptake of tritiated 5-HT into synaptosomal preparations from the cortex showed that 2 weeks after the last injection of fenfluramine there was a 51% decrease in the number of uptake sites (V_{max}) but no change in the affinity (K_m). This is in accord with the results of the studies in rats and suggests that in both species fenfluramine destroys 5-HT nerve terminals.

Before any conclusions can be drawn about the degree and duration of the neurotoxicity produced by fenfluramine in rhesus monkeys, a larger number of animals must be studied. Nevertheless, the concordance in the data from the rat, guinea pig, and rhesus monkeys strengthens the prediction that fenfluramine probably produces similar long-term effects on 5-HT neurons in humans. This conclusion is given support by the findings of Chase and Shoulson (1975) who demonstrated that cerebrospinal fluid (CSF) levels of 5-HIAA were significantly decreased 24 hours after a 7-day treatment regimen with fenfluramine. It would be of great significance to determine the duration of such changes in 5-HIAA levels after fenfluramine administration is stopped. Even if 5-HIAA levels return to normal in the CSF, it does not guarantee that fenfluramine does not produce irreversible changes in 5-HT neurons in restricted brain regions. Our findings in the rat that hippocampal levels of 5-HT are still significantly lower 16 weeks after the last injection of fenfluramine is in accord with previous reports of long-term depletions by Harvey et al. (1975). This suggests that certain 5-HT neurons may be more sensitive to the neurotoxic effects of fenfluramine.

The question remains: What are the implications of this pre-clinical laboratory evidence regarding long-term changes in 5-HT neurons for clinicians? When fenfluramine is used in the treatment of obesity, one must ask whether the therapeutic benefits gained warrant even the slightest risk that long-term changes in 5-HT neurons are being produced. At the very least, clinicians should be aware of this possibility in order to make a decision as to whether the drug should be prescribed. In the case of the possible benefits of fenfluramine for the treatment of autism, the problem is somewhat different. This disease may be sufficiently devastating and intractable to warrant the possible risks of long-term changes in 5-HT neurons. It is even conceivable that such depletions might be therapeutic for some autistic patients.

Before clinicians can make an appropriate analysis of the cost/benefit ratio for fenfluramine in the treatment of autism, more research is needed. At the present time, however, the findings from animal studies strongly suggest that the therapeutic benefits produced by fenfluramine must be sizable and durable in order to outweigh the potential risk of long-term, possibly irreversible, changes in 5-HT neurons in the brain.

References

Beckett, A.H., Coutts, R.T., and Ogunbona, F.A. N-ethyl-a-methyl-a-(m-trifluoromethylbenzyl)nitrone—the major in vitro metabolic product of fenfluramine in guinea-pig liver microsomal fractions. *J. Pharm. Pharmacol.*, 24:190–192, 1973.

Chase, T.M., and Shoulson, I. Behavioral and biochemical effects of fenfluramine in patients with neurologic disease. *Postgrad. Med. J.*, 51(1):105–109, 1975.

Clineschmidt, B.V., Zacchei, A.G., Totaro, J.A., et al. Fenfluramine and brain serotonin. *Ann. NY Acad. Sci.*, 305:222–241, 1978.

Costa, E., Groppetti, A., and Revuelta, A. Action of fenfluramine on monoamine stores of rat tissue. *Br. J. Pharmacol.*, 41:57–64, 1971.

Duhault, J., and Verdavainne, C. Modification du taux de serotonine cerebrale chez le rat par le trifluoromethyl-phenyl-2-ethyl-aminopropane (Fenfluramine 768 S). *Arch. Int. Pharmacodyn. Ther.*, 170:276, 1967.

Fuxe, K., Farnebo, L.O., Hamberger, B., and Ogren, S.O. On the in vivo and in vitro actions of fenfluramine and its derivatives on central monoamine neurons, especially 5-hydroxytryptamine neurons, and their relation to the anorectic activity of fenfluramine. *Postgrad. Med. J.*, 51(1):35–45, 1975.

Garattini, S., Buczko, W., Jori, A., and Samanin, R. The mechanism of action of fenfluramine. *Postgrad. Med. J.*, 51(1):27–35, 1975.

Harvey, J.A., and McMaster, S.E. Fenfluramine: Evidence for a neurotoxic action on midbrain and a long-term depletion of serotonin. *Pharmacol. Commun.*, 1:217-228, 1975.

Harvey, J.A., McMaster, S.E., and Yunger, L.M. p-Chloroamphetamine: Selective neurotoxic action in brain. *Science*, 187:841–843, 1975.

Heffner, T.G., Hartman, J.A., and Seiden, L.S. A rapid method for the regional dissection of the rat brain. *Pharmacol. Biochem. Behav.*, 13:453–456, 1980.

Le Douarec, P., and Neveu, C. Pharmacology and biochemistry of fenfluramine. In: Costa, E., and Garattini, S., (eds.), *Amphetamine and Related Compounds.* New York: Raven Press, 1970, pp. 75–105.

Opitz, K. Anoroxigene phenylalkylamine und serotoninstoffwechsel. *Naunyn-Schmied. Arch. Exptl. Pathol. Pharmacol.*, 259:56–65, 1967.

Ricaurte, G.A., Guillery, R.W., Seiden, L.S., et al. Dopamine nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain. *Brain Res.*, 235:93–103, 1982.

Ricaurte, G.A., Schuster, C.R., and Seiden, L.S. Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: A regional study. *Brain Res.*, 193:153–163, 1980.

Sanders-Bush, E., Bushing, J.A., and Sulser, F. Long-term effects of p-chloroamphetamine and related drugs on central serotonergic mechanism. *J. Pharmacol. Exptl. Ther.*, 192(1):33–41, 1975.

Schuster, C.R., and Johanson, C.E. Efficacy, dependence potential, and neurotoxicity of anorectic drugs. In: Seiden, L.S., and Balster, R.L. (eds.), *Behavioral Pharmacology The Current Status.* Vol. 13. New York: Alan R. Liss, Inc., 1984, pp. 263–280.

Seiden, L.S., Fischman, M.W., and Schuster, C.R. Long term methamphetamine-induced changes in brain catecholamines in tolerant rhesus monkeys. *Drug Alcohol Depend.*,1(3):215–219, 1976.

Sterenka, L.R., and Sanders-Bush, E. Species differences in the rate of disappearance of fenfluramine and its effects on brain serotonin neurons. *Biochem. Pharmacol.*, 28:3103–3107, 1979.

Trulson, M.E., and Jacobs, B.L. Behavioral evidence for the rapid release of CNS serotonin by PCA and fenfluramine. *Eur. J. Pharmacol.*, 36:149–154, 1976.

Wagner, G.C., Schuster, C.R., and Seiden, L.S. Methamphetamine induced changes in brain catecholamines in rats and guinea pigs. *Drug Alcohol Depend.*, 4:435–439, 1979.

Fenfluramine Treatment of Childhood Attention Deficit Disorder With Hyperactivity: A Preliminary Report

Maureen Donnelly, M.D.,[1] Judith L. Rapoport, M.D.,[1] and Deborah R. Ismond, M.A.[1]

Attention Deficit Disorder With Hyperactivity (ADD-H) is a common childhood disorder, with significant morbidity and a chronic course (Weiss, 1985). Pharmacotherapy with stimulant medications has been the mainstay of drug treatment (Gittelman, 1980). However, limitations of stimulant therapy—such as lack of response in about 20% of individuals, inconvenience of multiple daily dosing, possible rebound effects, abuse potential, and adverse effects such as growth suppression—have led to the investigation of alternative drug treatments (Rapoport et al., 1985).

Fenfluramine is a halogen-substituted phenethylamine derivative, presumed to act in part through serotonergic mechanisms. Acutely and at low doses, it increases central nervous system (CNS) serotonin (5-HT) activity, via 5-HT release, reuptake inhibition, and weak receptor agonist action. At high doses or with chronic use, it depletes brain 5-HT (Garattini et al., 1975; Mueller et al., 1984; Reuter et al., 1975).

Clinical and preclinical studies suggest that CNS 5-HT systems might be altered in ADD-H and that serotonergic activity might mediate stimulant drug effect (Solanto, 1984). In rats, increased 5-HT activity, by various means, is associated with decreased locomotor activity (Warbritton et al., 1978) and perhaps acquisition of behavioral inhibitory responses (McElroy et al., 1982). In autistic children, fenfluramine has been reported to decrease hyperactive behaviors (Ritvo et al., 1984). Other pharmacotherapeutic agents thought to enhance CNS 5-HT activity—namely, L-tryptophan (Brown, personal communication, 1984), chlorimipramine (Garfinkel et al., 1983), and clorgyline (Zametkin et al., 1985) have shown some beneficial effects in hyperactive populations.

This study evaluates behavioral, cognitive, and motor activity response of boys with ADD-H in a randomized, double-blind, crossover trial of fenfluramine, amphetamine, and placebo.

Method

Ten boys (mean age 8 ± 2 years) with DSM-III diagnoses of ADD-H, Conners Teacher Rating Scale (Goyette et al., 1978) Factor IV baseline ratings greater than two standard deviations above age means, and Wechsler Intelligence Scale for Children–Revised (WISC-R) full scale IQ scores of 80 or above (mean 104 ± 12) participated in a 10-week, double-blind, placebo-controlled day-hospital study. Six boys also met diagnostic criteria for Conduct Disorder and four met Developmental Learning or Language Disorder criteria. All subjects were medication-free for at least 4 weeks.

After a 1-week baseline assessment period, subjects received 3 weeks of placebo, 3 weeks of D-amphetamine (0.5 mg/kg/day in two doses), and 3 weeks of fenfluramine (week 1: (low dose) 0.6 mg/kg/day; week 2: 1.3 mg/kg/day; week 3: (high dose) 2.0 mg/kg/day, in two doses) in randomized counterbalanced order.

The children also attended school and participated in a structured group activities program while at the hospital.

The classroom teacher rated behavior daily using the 10-item Conners Abbreviated Rating Scale (Conners, 1976). Sustained attention was measured at the end of weeks 1 and 3 of each drug phase with a modified version of the Continuous Performance Test (CPT) (Rosvold et al., 1956). Daytime ward motor activity was recorded daily with an acceleration sensitive activity monitor (Colburn et al.,

---

[1] Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20892.

1976). In addition, weekly weights and side effects complaints (using the Subject's Treatment Emergent Symptom Scale) (ECDEU, 1976) were obtained.

Results

Data were analyzed with three- or four-way repeated measure analysis of variance (ANOVA) for drug, time (week, hour), and treatment × time interaction. Significant effects by Greenhouse Geisser probability of .05 or less were then examined by Bonferroni *t* tests.

A significant drug effect ($F = 12.76$; df 1,7; $p = .009$) was found for motor activity, though not for drug × week interaction. Motor activity significantly decreased on amphetamine ($p<.05$) compared to fenfluramine and to placebo. The latter two conditions did not differ. Figure 1 illustrates drug effects for weeks 2 and 3 of each treatment.

Behavioral ratings improved significantly with amphetamine, as opposed to placebo, treatment ($p<.05$). Fenfluramine, however, did not differ from amphetamine or placebo, indicating perhaps a weak response. Though ANOVA showed significant drug and week effects ($F = 4.80$; *df* 2,18; $p = .03$ and $F = 3.95$; *df* 2,18; $p = .05$, respectively), there was no medication × time interaction. Therefore, behavioral response to "low-dose" and "high-dose" fenfluramine did not differ. Figure 2 illustrates mean behavioral rating scores for week 3 of each medication phase.

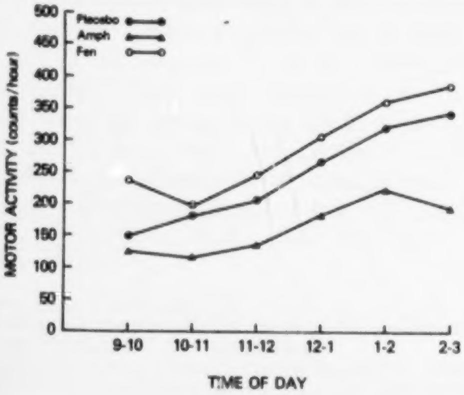
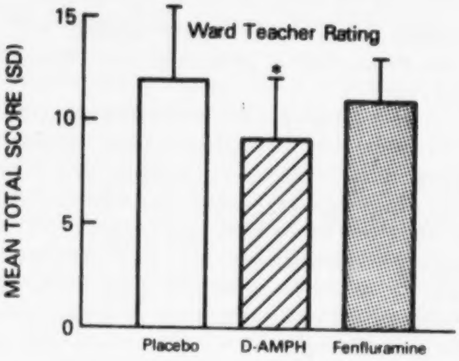


FIGURE 1. **Weeks 2 and 3: Effects of fenfluramine, D-amphetamine and placebo on Ward motor activity of hyperactive boys (*N*–*8*) (means for weeks 2 and 3 of each treatment).**



*$p< .05$ *vs.* placebo

FIGURE 2. **Ward behavioral ratings for hyperactive boys (*N*–10) on week 3 of placebo, D-amphetamine (.5 mg/kg) and fenfluramine (mean 60 mg/day).**

Performance on the CPT, a measure of vigilance, for commission errors, omission errors, and interstimulus interval did not significantly change on any drug at any time. This is an unexpected finding, as improved performance on the CPT is usually found with amphetamine treatment.

Analysis of group data for side effects showed no significant problems with either medication. One child showed clinically significant sedation for the first 3 days on fenfluramine, which disappeared thereafter.

Children's weights did not change significantly from admission to discharge from the study. Only one child had significant weight loss (2.5 kg) during the fenfluramine phase, necessitating a decrease in drug dosage. This subject's weight subsequently returned to baseline by the end of his hospitalization.

Discussion

Clinically, these results are disappointing as fenfluramine, which has less abuse potential than stimulants, does not appear to be an effective agent for the treatment of ADD-H. It had no beneficial effects on hyperactivity, classroom behavior, or attention. Though statistically there was an insignificant trend toward behavioral improvement with fenfluramine, this is probably not clinically significant.

If the assumptions of low dose and acute treatment, extrapolated from animal and adult data, have been met by the low dose (0.6 mg/kg/day) fenfluramine trial of 1 week, then these findings suggest that a serotonergic mechanism does not mediate stimulant or other drug efficacy in ADD-H. The findings also suggest that if fenfluramine is found effective in autism, then this is not secondary to a nonspecific antihyperactive action.

References

Colburn, T., Smith, B., Guarini, J., et al. An ambulatory activity monitor with solid-state memory. *ISA Trans.*, 15: 149-154, 1976.

Conners, C. Rating scales for use in drug studies with children. *Psychopharmacol. Bull.* (Special Issue), 59-60, 1976.

Early Clinical Drug Evaluation Unit Assessment Manual. Rockville, Md: National Institute of Mental Health, 383-395, 1976.

Garattini, S., Buczko, W., Jori, A., and Samanin, R. The mechanism of action of fenfluramine. *Postgrad. Med. J.*, 51 (Suppl. 1):27-35, 1975.

Garfinkel, B., Wender, P., Sloman, L., and O'Neill, I. Tricyclic antidepressant and methylphenidate treatment of attention deficit disorder in children. *J. Am. Acad. Child Psychiatry*, 22:343-348, 1983.

Gittelman, R. Childhood disorders. In: Klein, D., Gittelman, R., Quitkin, F., and Rifkin, A. (eds.), *Drug Treatment of Adult and Childhood Psychiatric Disorders.* New York: Williams & Wilkins, 1980.

Goyette, C., Conners, C., and Ulricr, R. Normative data on revised Conners Parent and Teacher Rating Scales. *J. Abnorm. Child Psychol.*, 6:221-236, 1978.

McElroy, J., DuPont, A., and Feldman, R. The effects of fenfluramine and fluoxitine on the acquisition of a conditioned avoidance response on rats. *Psychopharmacology*, 77:356-359, 1982.

Mueller, E., Siever, L., and Murphy, D. Neuroendocrine responses to serotonin agonists as possible markers of the functional state of serotonergic neurotransmission in psychiatric disorders. In: Beckmann, H., and Biederer, P. (eds.), *Pathochemical Markers of the Psychoses.* Berlin: Springer Verlag, 1984.

Rapoport, J., Zametkin, A., Donnelly, M. and Ismond, D. New drug trials in attention deficit disorder. *Psychopharmacol. Bull.*, 21(2):232-236, 1985.

Reuter, C. A review of the CNS effects of fenfluramine, 780SE and norfenfluramine on animals and man. *Postgrad. Med. J.*, 51 (Suppl.1):18-27, 1975.

Ritvo, E., Freeman, B., Yuwiler, A., et al. Study of fenfluramine in outpatients with the syndrome of autism. *J. Pediatr.*, 105:823-828, 1984.

Rosvold, H., Mirsky, A., Sarason, I., et al. A continuous performance test of brain damage. *J. Consult. Clin. Psychol.*, 20:343-350, 1956.

Solanto, M. Neuropharmacological basis of stimulant drug action in attention deficit disorder with hyperactivity: A review and synthesis. *Psychol. Bull.*, 95:387-409, 1984.

Warbritton, J., Stewart, M., and Baldessarini, R. Decreased locomotor activity with intraventricular infusion of serotonin in the rat. *Brain Res.*, 143:372-382, 1978.

Weiss, G. Followup studies on outcome of hyperactive children. *Psychopharmacol. Bull.*, 21(2):169-177, 1985.

Zametkin, A., Rapoport, J., Murphy, D., et al. Treatment of childhood attention deficit disorder with hyperactivity with monoamine oxidase inhibitors. *Arch. Gen. Psychiatry.* (In press)

The Effects of Fenfluramine on Suicidal Behavior[1]

Elaine Meyendorff, M.D.,[2] Anil Jain, M.D.,[2] Lil Träskman-Bendz, M.D., Ph.D.,[2] Barbara Stanley, Ph.D.,[2] and Michael Stanley, Ph.D.[3]

Suicidal behavior is one of the few mental health problems for which no pharmacologic treatment aimed specifically at the behavior itself has been developed. Instead, this behavior is treated as a symptom of other illnesses, usually depression. However, several reports have indicated that in addition to affective illness, attempted and completed suicide occurs in other diagnostic groups, including schizophrenia and personality disorders (Barraclough et al., 1974; Dorpat et al., 1960; Robins et al., 1959).

In addition to behavioral studies which provide evidence that suicide occurs across diagnosis, there is also evidence that there may be a common biochemical deficit associated with suicide and attempted suicide.

In a series of postmortem studies evaluating the levels of biogenic amines in various brain regions of suicide victims, it was noted that the most consistent finding was that 5-HT or 5-HIAA levels were reduced in suicides compared with non-suicide controls (Lloyd et al., 1974; Pare et al., 1969; Shaw et al., 1967). Subsequent to these reports, recent studies which have examined the status of serotonergic receptors in the brains of suicide victims have indicated changes in binding which are consistent with the above reported reductions in 5-HT and 5-HIAA (Paul et al., 1984; Perry et al., 1983; Stanley et al., 1982, 1983).

In addition to postmortem studies, there have been a large number of studies which have examined the cerebrospinal fluid (CSF) levels of 5-HIAA in individuals who have attempted suicide. In these CSF studies, 5-HIAA levels from those having a history of a suicide attempt included individuals from various diagnostic groups (e.g., schizophrenia, personality disorders, and depression) (Åsberg et al., 1976; Brown et al., 1979; Van Praag, 1983). In the majority of these studies, lower levels of 5-HIAA were reported for those with a history of a suicide attempt.

The diagnostic heterogeneity of those who attempt suicide, as well as the common biochemical deficit in 5-HT they are reported to manifest, led to our decision to investigate the effects of fenfluramine on suicidal behavior. Fenfluramine has been shown to promote the release of 5-HT and to block its reuptake. Chronic exposure to fenfluramine causes a reduction in the number of 5-HT_2 binding sites in the brain. This latter effect, the reduction of 5-HT_2 binding, is apparently a common pharmacologic property of antidepressant drugs of a variety of classes. Furthermore, the time course of 5-HT_2 binding reduction parallels clinical response, it may relate to the therapeutic mode of action of these compounds (Peroutka & Snyder, 1982).

Methods

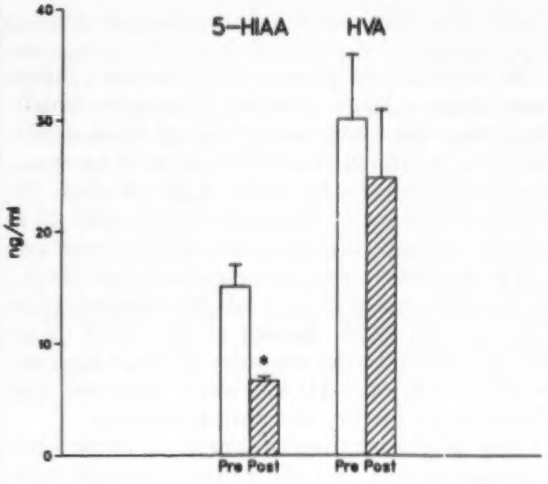
Eight suicidal patients from various diagnostic categories with a history of suicide attempts were entered into the study. All patients were free of major medical illness. Two patients had a diagnosis of bipolar disorder, depressed phase; one patient, bipolar disorder mixed; two patients, major depression with psychotic features; one patient, major depression; one patient, schizoaffective disorder; and one patient had a diagnosis of chronic undifferentiated schizophrenia. Subjects were inpatients ranging in age from 21 to 47 years, with a mean age of 35 years. Diagnosis was determined by interview performed according to the Schedule for Affective Disorders and Schizophrenia (SADS), and was established according to DSM-III criteria.

---

[1] This study was supported in part by USPHS Grant MH-40048 from the National Institute of Mental Health.

[2] Lafayette Clinic, Wayne State University, Detroit, MI 48207.
[3] New York State Psychiatric Institute, New York, NY 10032.

Address all correspondence to Michael Stanley, Ph.D., Department of Psychiatry, Columbia University, New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032.



* p<0.05

FIGURE 1. CSF levels of 5-HIAA and HVA before and after chronic fenfluramine treatment.

Supplemental information for Axis II diagnosis was obtained with the Schedule for Interviewing Borderlines, and psychological testing including a Rorschach.

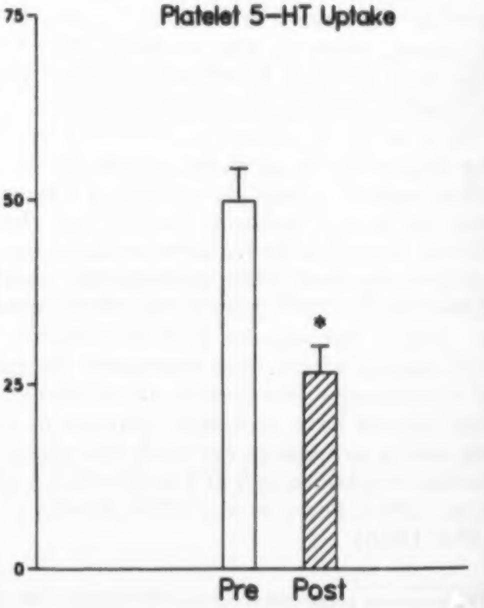
Patients were maintained free of active medication for 2 to 3 weeks. During the third week they received fenfluramine placebo. This was followed by 4 weeks of treatment with active fenfluramine. Acetominophen, diazepam, or chloral hydrate were occasionally administered for relief of anxiety, insomnia, or other acute symptoms. Fenfluramine was administered in an open-dose ranging fashion with an initial dose of 20 mg orally three times daily, up to a maximum dosage of 60 mg three times daily.

Weekly measures of psychopathology and suicidality, designed to assess treatment response, were performed. These included the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression and Anxiety Scales, the Scale for Suicide Ideation (SSI), and the Suicide Assessment Scale (SAS) (Stanley et al., 1986), a scale designed specifically to assess suicidal and related behaviors.

During the drug-free period, participants had routine chemistries performed, and blood was drawn in EDTA-treated tubes for determination of platelet tritiated imipramine binding, and platelet serotonin uptake. At the end of the final week of medication a plasma sample was drawn for determination of platelet tritiated imipramine binding and serotonin uptake. Subjects received a lumbar puncture prior to the study following a drug-free period for measures of 5-HIAA and homovanillic acid (HVA). To minimize the effects of movement and diet upon CSF 5-HIAA levels, lumbar punctures were performed between the hours of 8 to 10 a.m., after the subject had had nothing by mouth and had been resting supine for 8 hours. In several subjects enrolled in the study, a second lumbar puncture was performed 24 hours after the last dose of medication.

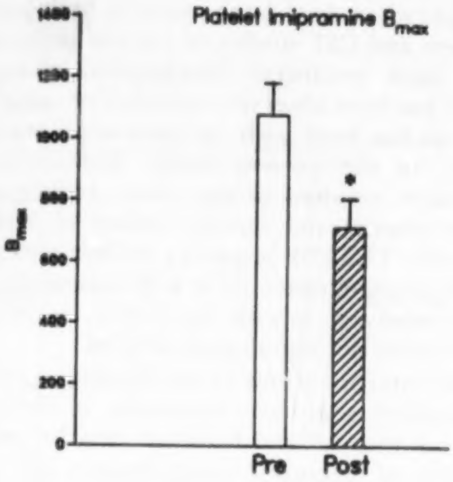
Isolation of platelets from whole blood was performed according to Briley et al. (1980). Tritiated imipramine binding was analyzed as described in Raisman et al. (1982). Serotonin uptake was determined by methods described by Tuomisto (1980). 5-HIAA and HVA were assayed in spinal fluid with high performance liquid chromatography.

Statistical analysis was done using paired *t* tests and analysis of variance.



p<0.01

FIGURE 2. Platelet serotonin uptake before and after chronic fenfluramine treatment.



p<0.1

FIGURE 3. Platelet imipramine binding before and after chronic fenfluramine treatment.

Results

Biochemical Findings

Chronic treatment with fenfluramine caused a significant reduction in the concentration of 5-HIAA in the CSF when compared with the values obtained prior to treatment. The 66% decrease in 5-HIAA is in contrast to the nonsignificant 18% decrease seen in HVA levels for the same patients (Figure 1).

Reductions in platelet 5-HT uptake and imipramine binding were also observed following treatment with fenfluramine. V_{max} values for platelet 5-HT uptake were reduced from 49.8±4.44 to 26.6±3.61 (pmol/10^8 platelets/min) ($p<0.005$) (Figure 2). Platelet imipramine binding was decreased from 1078±104 to 711±92.9 (fmol/mg protein) ($p<0.10$) (Figure 3).

Behavioral Ratings: Suicidal Behavior

Both scales used in this study to assess suicidality reflected a time-dependent decrease in the severity of this behavior. SSI scores were reduced to their lowest point after 4 weeks of fenfluramine treatment (Figure 4). Similarly, SAS scores were lowest after 4 weeks of fenfluramine (Figure 5). The downward trend observed for both of these measures was reversed immediately upon discontinuation of fenfluramine (Figures 4 and 5).

Measures of Psychopathology

In contrast to the uniform effect fenfluramine treatment exerted on the above measures of suicidality, it had a differential effect on psychotic and depressive symptoms. Hamilton depression scores showed a time-dependent reduction maximal at 5 weeks. However, psychotic symptoms, as assessed by the BPRS, reflected virtually no change over the entire treatment period (Figures 6 and 7).

Side Effects

With regard to side effects, subjects demonstrated a net weight loss of approximately 3 lbs, including one patient who lost 12 lbs, 4 patients who lost 4 to 5 lbs, one patient who lost 1 lb, one who gained 1 lb, and one patient gained 8 lbs. There were no clinically significant changes in either blood pressure or pulse rate throughout the active treatment

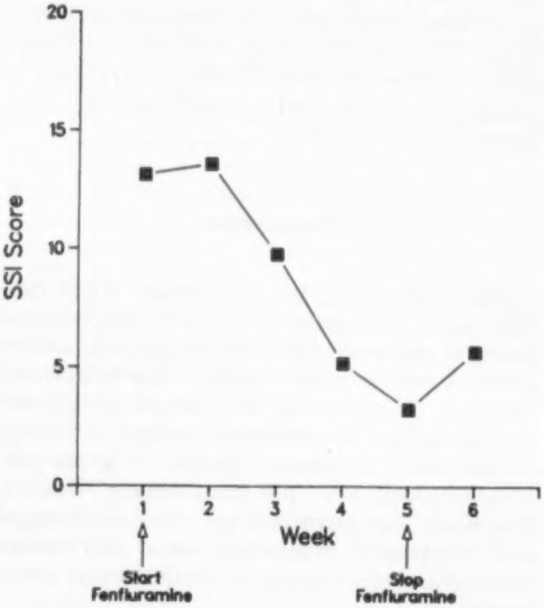


FIGURE 4. Effect of 4 weeks of fenfluramine treatment on Scale for Suicide Ideation Scores.

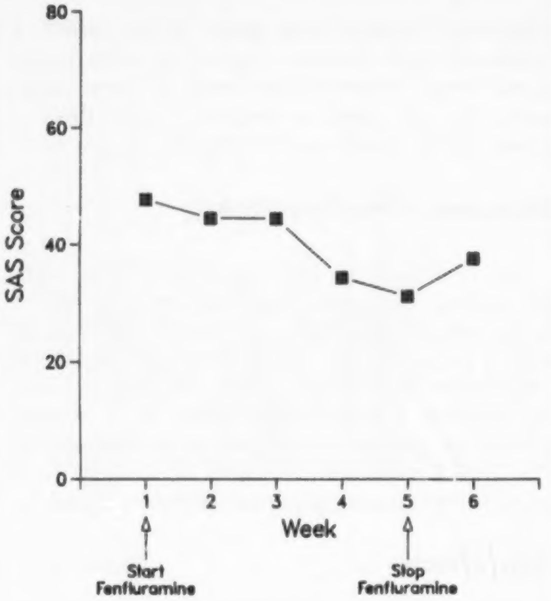


FIGURE 5. Effect of 4 weeks of fenfluramine treatment on Suicide Assessment Scale Scores.

phase of the study. No dystonia or other adverse effect was observed. Two patients with a diagnosis of bipolar disorder became manic during the treatment phase, and one patient with a diagnosis of bipolar disorder and another with a diagnosis of borderline personality became manic after discontinuation of the drug. Whether the drug induced the symptoms, or this was coincidental emergence of symptoms which were unaffected by fenfluramine, was unclear.

Discussion

The findings of this preliminary study parallel both the behavioral and biochemical findings reported for individuals who either attempt or complete suicide. The behavioral changes observed in this mixed diagnostic group indicate a consistent change in ratings of suicidality whereas changes in gross psychopathology were not consistently affected. Psychotic symptomatology was unchanged and depressive symptoms were diminished throughout the course of fenfluramine treatment.

The biochemical findings of this study were also consistent with the biochemical changes which have been noted in both postmortem and CSF studies of suicidal patients. The most consistent biochemical change which has been observed in studies of suicidal patients has been with the neurotransmitter 5-HT. In the present study, fenfluramine treatment resulted in significant reductions in peripherial and central indices of 5-HT function. The CSF measures further indicated the changes observed in 5-HT metabolism were relatively specific for 5-HT, as HVA values were not significantly altered.

The interpretations of the findings of this preliminary study are supportive of the hypothesis that suicidal behavior may be independent of diagnostic categorization and are also consistent with a serotonergic deficit. However, it must be noted that these results are of a very preliminary nature. Further, the study was conducted in a dose-ranging and open design on a relatively small patient sample. Accordingly, future studies of fenfluramine treatment of suicidal behavior should employ a larger patient sample and consider the use of a double-blind experimental design.

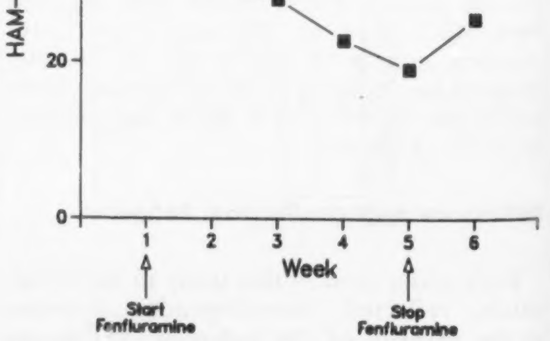


FIGURE 6. Effect of 4 weeks of fenfluramine treatment on Hamilton Depression Scale Scores.

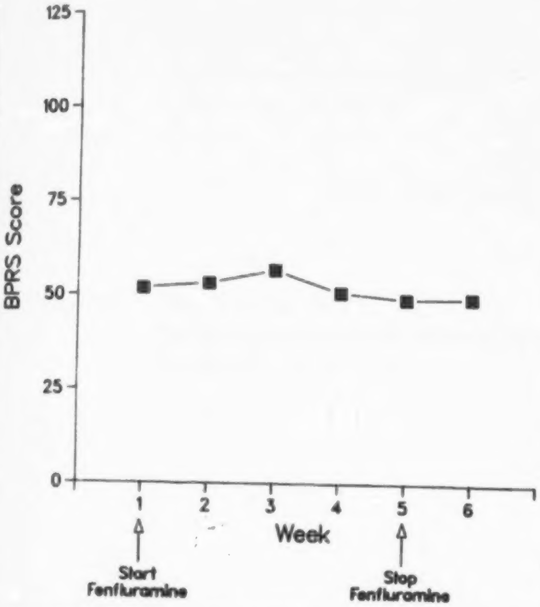


FIGURE 7. Effect of 4 weeks of fenfluramine treatment on Brief Psychiatric Rating Scale Scores.

References

Åsberg, M., Thorén, P., and Träskman, L. "Serotonin depression"—A biochemical subgroup within the affective disorders? *Science*, 191:478, 1975.

Barraclough, B., Bunch, J., Nelson, B., et al. A hundred cases of suicide: Clinical aspects. *Br. J. Psychiatry*, 125:355–373, 1974.

Briley, M., Langer, S.Z., and Raisman, R. Tritiated imipramine binding sites are decreased in platelets of untreated depressed patients. *Science*, 209:303, 1980.

Brown, G.L., Goodwin, F.K., Ballenger, J.C., et al. Aggression in human correlated with cerebrospinal fluid amine metabolites. *Psychiatry Res.*, 1:131–139, 1979.

Dorpat, T.L., and Ripley, H.S. A study of suicide in the Seattle area. *Compr. Psychiatry*, 1(6):349–359, 1960.

Lloyd, K.G., Farley, I.J., Deck, J.H.N., et al. Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brainstem of suicide victims and control patients. In: Costa, E., Gessa, G.L., and Sandler, M. (eds.), *Serotonin*. New York: Raven Press, 1974, pp. 389–397.

Pare, C.M.B., Yeung, D.P.H., Price, K., et al. 5-Hydroxytryptamine, noradrenaline, and dopamine in brainstem, hypothalamus, and caudate nucleus of controls and outpatients committing suicide by coal-gas poisoning. *Lancet*, ii:133–135, 1969.

Paul, S.M., Rehavi, M., Skolnick, P., and Goodwin, F.K. High-affinity binding of antidepressants to biogenic amine transport sites in human brain and platelet: Studies in depression. In: Post, R.M., and Ballenger, J.C. (eds), *Neurobiology of Mood Disorders*. Baltimore; Williams & Wilkins, 1984. pp. 846–853.

Peroutka, S.J., and Snyder, S.H. Different synaptic location of mianserin and imipramine binding sites. *Science*, 215:1112–1115, 1982.

Perry, E.K., Marshall, E.F., Blessed, G., et al. Decreased imipramine binding in the brains of patients with depressive illness. *Br. J. Psychiatry*, 142:188–192, 1983.

Raisman, R., Briley, M., Bouchami, F., et al. [^{3}H]-Imipramine binding and serotonin uptake in platelets from untreated depressed patients and control volunteers. *Psychopharmacology*, 77:332–335, 1982.

Robins, E., Murphy, G.E., Wilkinson, R.H., et al. Some clinical considerations in the prevention of suicide based on a study of 134 successful suicides. *Am. J. Publ. Health*, 49:888–889, 1959.

Shaw, D.M., Camps, F.E., and Eccleston, E.G. 5-Hydroxytryptamine in the hind brain of depressive suicides. *Br. J. Psychiatry*, 114:1407–1411, 1967.

Stanley, M., and Mann, J.J. Increased serotonin-2 binding sites in frontal cortex of suicide victims. *Lancet*, ii:214–216, 1983.

Stanley, M., Virgilio, J., and Gershon, S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science*, 216:1337–1339, 1982.

Stanley, B., Träskman-Bendz, L., and Stanley, M. The Suicide Assessment Scale: A scale evaluating change in suicidal behavior. *Psychopharmacol. Bull.*, 22(1): 200–205, 1986.

Tuomisto, J. Platelet uptake of serotonin in pathological conditions. In: Angrist, B., Burrows, G.D., Lader, M., et al. (eds.), *Recent Advances in Neuropsychopharmacology*. New York: Pergamon Press, 1980.

Van Praag, H. CSF-5HIAA and suicide in nondepressed schizophrenics. *Lancet*, i:977–978, 1983.

Free Communications—Session A

CHAIRS: Paul Leber, M.D.
Food and Drug Administration
Rockville, Maryland

and

Jack D. Blaine, M.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

The Relationship of Antiobsessional and Antidepressant Effects of Tricyclic Antidepressants[1]

Matig Mavissakalian, M.D.,[2] Samuel M. Turner, Ph.D.,[2] Larry Michelson, Ph.D.,[2] and Rolf Jacob, M.D.,[2]

Antidepressant medications, primarily clomipramine, have been found effective in treating obsessive-compulsive disorder (OCD) although the relationship between their well-established antidepressant action and their antiobsessional effects remains an open question (Ananth et al., 1981; Insel & Murphy, 1981; Insel et al., 1983; Marks et al., 1980; Mavissakalian, 1982, 1983; Montgomery, 1980; Thorén et al., 1980). Observations made in 8 OCD patients treated with either clomipramine or imipramine (Mavissakalian & Michelson, 1983) revealed synchronous patterns of change in depression, anxiety, and obsessive-compulsive symptoms which, coupled with the tendency for responders to have higher initial depression ratings, tentatively supported Marks' contention (Marks, 1983; Marks et al., 1980) that antidepressant drugs may not have an antiobsessional effect independent of their antidepressant properties. However, in a more recent placebo-controlled study of 12 OCD patients (Mavissakalian et al., 1985), it was found that OCD symptoms improved significantly more with clomipramine compared to placebo, while outcome of depression was equivalent in the two groups. The discrepancy between the fate of depression and obsessive-compulsive symptomatology in the placebo group was interesting and suggested that change in these symptom dimensions can occur independently from each other. The aim of this presentation is to further explore the relationship between the antidepressant and antiobsessional effects of tricyclic drugs in the combined sample of 15 primary OCD patients who were treated with clomipramine or imipramine in the aforementioned studies.

Subjects

Table 1 presents the individual characteristics of the 15 patients who were uniformly selected to be part of two consecutive mul-

---

[1] Supported by Grants M2323K and M2964K from Ciba-Geigy and Grant MH-34177 from the National Institute of Mental Health.

[2] Department of Psychiatry, University of Pittsburgh, School of Medicine, Pittsburgh, PA 15213.

Reprint requests to Matig Mavissakalian, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

TABLE 1

Patient and Treatment Characteristics of the Sample

Drug Condition	Age	Sex	Type of Ritual	Duration of Illness	Dosage	Response
Clomipramine						
1	23	M	Checking	4 years	200 mg	NR
2	51	F	Washing/Checking	8 years	200 mg	NR
3	65	M	Checking	38 years	100 mg	R
4	45	F	Washing/Checking	13 years	300 mg	R
5	43	M	Washing/Obsessional Fears	10 years	250 mg	NR
6	32	M	Compulsive Touching/ Counting/Washing	20 years	200 mg	NR
7	36	F	Washing/Obsessional Fears	13 years	150 mg	NR
8	20	F	Washing/Ruminations (Counting)	5 years	200 mg	R
9	35	F	Washing/Checking/ Obsessional Fears	10 years	200 mg	R
10	29	F	Washing	2 years	300 mg	NR
$\bar{X}$	37.9	60%		12.3 years	210 mg	40% R
(SD)	(13.54)	(F)		(10.43)	(61.46)	
Imipramine						
1	23	M	Obsessional Fears	2 years	300 mg	NR
2	26	F	Washing/Checking	16 years	200 mg	R
3	54	F	Washing/Checking	34 years	300 mg	R
4	20	F	Washing/Checking	6 years	250 mg	NR
5	39	F	Obsessional Fears/ Checking	18 years	200 mg	R
$\bar{X}$	32.4	80%		15.2 years	250 mg	60% R
(SD)	(14.08)	(F)		(12.46)	(50.0)	
Overall Sample						
N = 15	36.1	67%		13.3 years	223.3 mg	47% R
	(13.48)	(F)		(10.78)	(59.36)	

ticenter projects sponsored by Ciba-Geigy (Mavissakalian & Michelson, 1983; Mavissakalian et al., 1985). Inclusion criteria included: 1) DSM-III diagnosis of primary OCD; 2) a score of at least 56 on the Obsessive-Compulsive Neurotic Scale (*see* Assessment); and 3) a psychotropic medication-free and alcohol-free period of at least 2 weeks. Exclusionary criteria included: 1) diagnosis of primary affective disorder or major depressive episode with melancholic features, schizophrenia, and organic brain syndrome and 2) presence of physical illness precluding the use of antidepressants either because of the illness itself or because of treatment necessary for that illness.

Patients were randomly assigned to double-blind clomipramine or imipramine in the respective protocols. Initial drug dose was 50 mg/day in the first week with gradual increases to the largest tolerable level or a maximum of 300 mg/day. In order to remain in the study, patients had to be on at least a 100 mg/day regimen. Patients were seen weekly up to 6 weeks and then at 8 and 12 weeks of treatment at which time the trial ended. The tone of these sessions was supportive, and patients were encouraged to tolerate obsessions without engaging in compulsive behavior. The maximum stable dosage for the individual patients is presented in Table 1.

Major assessments included a uniform battery of tests which were administered at pretreatment, and at 4, 8, and 12 weeks posttreatment. The Obsessive-Compulsive Neurotic Scale (OCNS), a 25-item questionnaire covering commonly encountered obsessive-compulsive symptoms, was used as the patient-rated measure of change. Each item was rated on 4-point scales where 1 = none or little of the time; 2 = some of the time; 3 = a good part of the time; and 4 = most or all of the time (range 25 to 100). In addition, clinician-rated 5-point obsessive-compulsive scales were used to assess 1) frequency of obsessive thoughts (OCRS-O), 2) distress-anxiety caused by obsessive thoughts (OCRS-A), 3) frequency of compulsive behaviors (OCRS-C), and 4) interference with everyday life due to compulsive behavior (OCRS-I). On these scales, 0 = absent or none; 1 = infrequent or mild; 2 = moderate frequency or severity; 3 = very frequent or severe; and 4 = almost constant or extremely severe, incapacitating. These measures were also utilized to classify patients into responders (posttreatment ratings of ≤ 1 on at least 3 out of 4 criteria). Depression (HD-17) and anxiety (ZAS) measures consisted of the first 17 items of the Hamilton Depression Rating Scale (Hamilton, 1960) and the Zung Self-Rating Anxiety Scale (Zung, 1971), respectively.

Results

There were no significant differences on any demographic and clinical variables or pretreatment dependent measures between patients recruited from the two different studies. Nor did analysis of variance reveal significant pretreatment and improvement differences between the 5 imipramine- and the 10 clomipramine-treated patients (*see* Figure 1). For the purposes of investigating the relationship between the antidepressant and antiobsessional effects of tricyclic drugs among OCD patients, therefore, pooling of data across the two studies and the two drugs seemed justified.

Two-tailed *t* tests comparing pretreatment mean group scores and 4th week, 8th week, and posttreatment assessments, respectively, revealed significant improvement ($p < .05$) on all measures at all occasions in the samples as a whole. As shown in Table 1, 7 (47%) patients were classified as responders. Figure 2 illustrates the contrasting patterns of change between them and the nonresponders. Two-tailed *t* tests did not reveal significant differences at pretreatment. Significant differences on depression and anxiety were present only at posttreatment while differences on all obsessive-compulsive measures were significant at 4 and 8 weeks of treatment and ostensibly at posttreatment. Figure 2 also indicates an overall synchronous pattern of change between all three symptom dimensions.

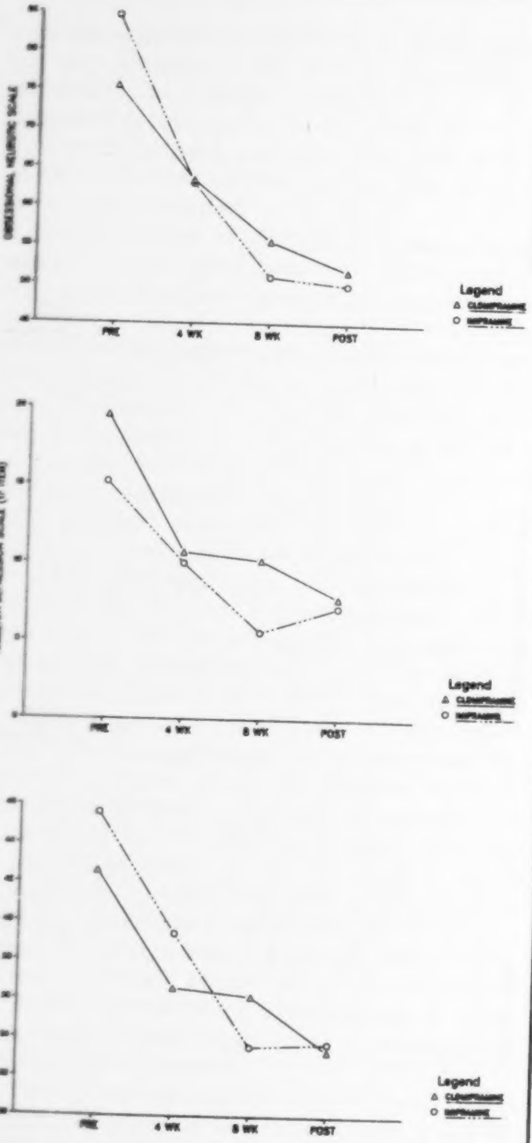


FIGURE 1. **Differential improvement of obsessive-compulsive, depressive, and anxiety symptoms with clomipramine ($N = 10$) and imipramine ($N = 5$).**

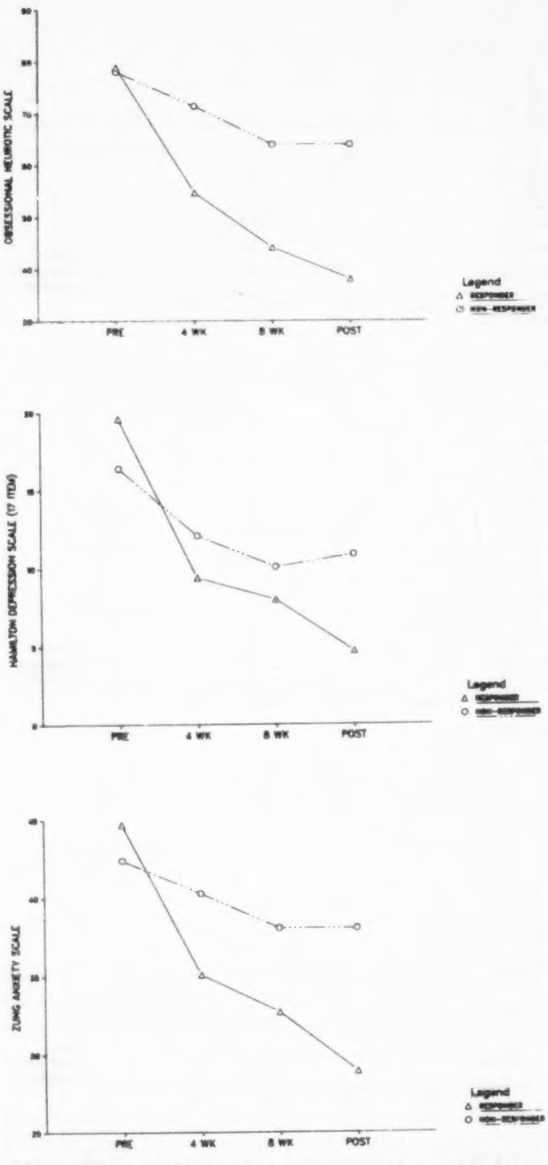


FIGURE 2. Differential improvement of obsessive-compulsive, depressive, and anxiety symptoms between responders ($N = 7$) and nonresponders ($N = 8$).

TABLE 2

Pearson Correlations Between Change in Depression and Obsessive-Compulsive Symptoms at Various Phases of Treatment

	Obsessive-Compulsive Symptoms	
Depression	OCNS	OCRS-T
4 Weeks		
HD-17	.53*	.50*
8 Weeks		
HD-17	.37	.38
12 Weeks		
HD-17	.30	.70**

*$p \leq .05$
**$p \leq .001$

To assess the degree of association between the antidepressant and antiobsessional effects, change scores in depression were correlated with change scores in obsessive-compulsive symptoms. For this purpose, the 4 clinician-rated scales were combined into a total measure (OCRS-T) to reduce the quantity of analysis required and to make its range (0 to 16) more comparable with the other scales. As shown in Table 2, there were significant correlations at Week 4, but these had decreased in strength by the 8th week and had become inconsistent at posttreatment.

Finally, the 5 patients with the lowest depression scores ($\overline{X} = 9.6$, range 4–14, s.d. $= 5.18$) were compared with the 5 patients who were most depressed ($\overline{X} = 25.6$, range 23–28, s.d. $= 2.61$). *T*-test comparisons of absolute and change scores at each assessment did not reveal significant ($p < .05$) differences on the anxiety or any of the obsessive-compulsive measures. Figure 3 illustrates the overall similarity in improvement of obsessive-compulsive symptoms in these two subgroups.

Discussion

The present findings suggest that the antiobsessive effect of tricyclic antidepressants may be at least partially independent of their antidepressant mechanisms. Although correlational analyses suggested that improvement in depression and obsessive-compulsive symptoms co-vary, most consistently in the earlier phases of treatment, and despite the overall synchronous pattern of change between these symptom dimensions, the comparison between low- and high-depressed subgroups was compelling evidence that an antidepressant effect is not a prerequisite to the antiobsessional effects of clomipramine or imipramine. Because the study was not prospectively designed to compare OCD patients with high

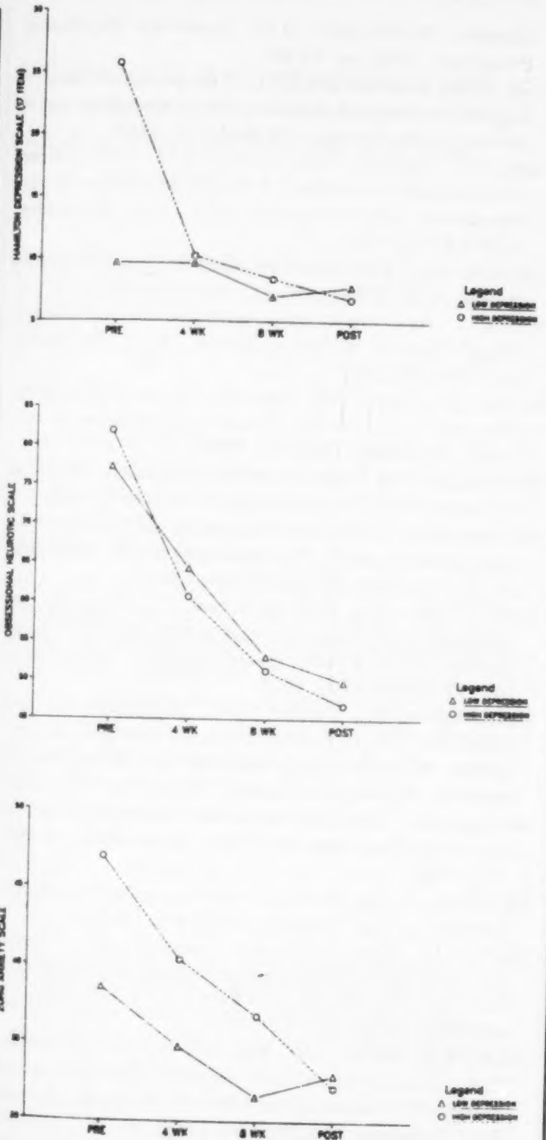


FIGURE 3. Differential improvement of obsessive-compulsive, depressive, and anxiety symptoms between high ($N = 5$) and low ($N = 5$) depressed subgroups.

and low initial depression levels, however, the findings warrant cautious interpretation. Indeed, 12 of the 15 patients had Hamilton depression scores ≥14, a level of dysphoria incurring high probability for an antidepressant effect in depressed outpatients (Stewart et al., 1983). Nevertheless, the categorization of the low depressed group appeared satisfactory not only because of the low initial levels, but also because of the very minimal and inconsequential changes in dysphoria over the course of treatment. Still, for more definitive data in this regard, placebo-controlled studies in OCD patients without appreciable dysphoria would be needed.

Several points of clinical and research interest warrant brief comment. First, and in contrast to the near maximal improvement of depression noted at 4 weeks, improvement in obsessive-compulsive symptoms continued throughout the 12 weeks suggesting that robust antiobsessional effects require long periods of treatment. Second, in this study, both obsessions and compulsions improved in a clinically significant degree with 56% and 48% pre-post reduction on their respective clinician-rated scores (details available upon request). Although it would be plausible to suggest that some of the improvement noted was due to the encouragement to apply the behavioral principles of exposure-response prevention (Foa et al., 1985), none of the 5 placebo patients treated under similar conditions (Mavissakalian et al., 1985) had improved to a level of virtual freedom from obsessive-compulsive symptoms as compared to nearly half of the sample treated with the active drugs. Thus, at the very least, it seems reasonable to conclude that clomipramine and impramine had significant facilitatory interactive effects with behavioral instructions. From a clinical vantage point, studies of the relative and combined effectiveness of pharmacological and behavioral treatments of OCD seem warranted.

Third, the equivalent improvement noted with clomipramine and imipramine is particularly interesting inasmuch as the investigation of a specific antiobsessional effect has primarily concerned clomipramine, and some studies have suggested superior clinical effects with clomipramine in comparison to other antidepressants (Ananth, 1983). The similar effects observed, on the other hand, are not entirely surprising given that, in addition to their close chemical structure, imipramine and clomipramine undergo parallel pharmacokinetic changes which control their neurobiochemical activities, i.e., they are mostly serotonergic while their active desmethyl metabolites are mostly noradrenergic (Risch et al., 1979). Although the small numbers do not permit confident generalizations, the finding has practical significance since clomipramine is still unavailable for clinical use in the United States.

Conclusion

The present data add to the literature suggesting that clomipramine, and probably imipramine, may be specific antiobsessional agents independently from their antidepressive properties. On the other hand, it is clear that a complex association exists between the antiobsessional and antidepressant effects of these drugs which may not be easily elucidated by symptom rating scales alone. A more promising approach is suggested by findings implicating clomipramine's serotonergic action in the control of obsessive-compulsive symptoms and the drug's noradrenergic action in the control of depressive symptoms (Stern et al., 1980; Thorén et al., 1980). Newer pharmacological agents with more selective action on neurotransmitter systems (Lapierre, 1983) can therefore be used to dissect the broad spectrum clinical effects of clomipramine and imipramine and to explore the neurobiological basis of OCD (Insel & Mueller, 1984; Richelson, 1983).

References

Ananth, J. Clomipramine in obsessive-compulsive disorder: A review. *Psychosomatics*, 24(8):723-727, 1983.

Ananth, J., Pecknold, J.C., van den Steen, N., and Engelsmann, F. Double-blind comparative study of clomipramine and amitriptyline in obsessive-neurosis. *Prog. Neuro-Psychopharmacol.*, 5:257-262, 1981.

Foa, E.B., Steketee, G.S., and Ozarow, B.J. Behavior therapy with obsessive-compulsives—From theory to treatment. In: Mavissakalian, M., Turner, S.M., and Michelson, L. (eds.), *Obsessive-Compulsive Disorder: Psychological and Pharmacological Treatment.* New York: Plenum Press, 1985, pp. 49-129.

Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry*, 23:56-62, 1960.

Insel, T.R., and Mueller, E.A. The psychopharmacologic treatment of obsessive-compulsive disorder. In: Insel, T.R. (ed.), *New Findings in Obsessive-Compulsive Disorder.* Washington, D.C.: American Psychiatric Press, Inc., 1984, pp. 72-88.

Insel, T.R., and Murphy, D.L. The psychopharmacological treatment of obsessive-compulsive disorder: A review. *J. Clin. Psychol.*, 1(5):304-311, 1981.

Insel, T.R., Murphy, D.L., Cohen, R.M., et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline. *Arch. Gen. Psychiatry*, 40:605-612, 1983.

Lapierre, Y.D. New antidepressant drugs. *J. Clin. Psychiatry*, 44(8):41-44, 1983.

Marks, I. Are there anticompulsive or antiphobic drugs? Review of the evidence. *Br. J. Psychiatry*, 143:338-347, 1983.

Marks, I.M., Stern, R.S., Mawson, D., et al. Clomipramine and exposure for obsessive-compulsive rituals: I. *Br. J. Psychiatry*, 136:1-25, 1980.

Mavissakalian, M. Pharmacological treatment of anxiety disorders. *J. Clin. Psychiatry*, 43:487-491, 1982.

Mavissakalian, M. Antidepressants in the treatment of agoraphobia and obsessive-compulsive disorder. *Compr. Psychiatry*, 24(3):278-284, 1983.

Mavissakalian, M., and Michelson, L. Tricyclic antidepressants in obsessive-compulsive disorder: Antiobsessional or antidepressant agents? *J. Nerv. Ment. Dis.*, 171(5):301-306, 1983.

Mavissakalian, M., Turner, S.M., Michelson, L., and Jacob, R. Tricyclic antidepressants in obsessive-compulsive disorder: Antiobsessional or antidepressant agents?—II. *Am. J. Psychiatry*, 142(5):572-576, 1985.

Montgomery, S.A. Clomipramine in obsessional neurosis: A placebo controlled trial. *Pharm. Med.*, 1:189-192, 1980.

Richelson, E. Are receptor studies useful for clinical practice? *J. Clin. Psychiatry*, 44(9):4-9, 1983.

Risch, S.C., Huey, L.Y., and Janowsky, D.S. Plasma levels of tricyclic antidepressants and clinical efficacy: Review of the literature—Part II. *J. Clin. Psychiatry*, 40:58-69, 1979.

Stern, R.S., Marks, I.M., Mawson, D., and Luscombe, D.K. Clomipramine and exposure for compulsive rituals: II. Plasma levels, side effects and outcome. *Br. J. Psychiatry*, 136:161-166, 1980.

Stewart, J.W., Quitkin, F.M., Liebowitz, M.R., et al. Efficacy of desipramine in depressed outpatients: Response according to research diagnostic criteria diagnoses and severity of illness. *Arch. Gen. Psychiatry*, 40:202-207, 1983.

Thorén, P, Åsberg, M., Bertilsson, L., et al. Clomipramine treatment of obsessive-compulsive disorder. *Arch. Gen. Psychiatry*, 37:1289-1294, 1980.

Thorén, P., Åsberg, M., Cronholm, B., et al. Clomipramine treatment of obsessive-compulsive disorder. *Arch. Gen. Psychiatry*, 37:1281-1285, 1980.

Zung, W.W.K. A rating instrument for anxiety disorders. *Psychosomatics*, 12:371-379, 1971.

A Comparison of Alprazolam and Imipramine in the Treatment of Agoraphobia and Panic Disorder

Ross Rizley, Ph.D.,[1] Richard J. Kahn, M.D.,[1] Douglas M. McNair, Ph.D.,[1] and Laura M. Frankenthaler, B.A.[1]

McNair and Kahn (1981) reported the results of a double-blind clinical trial showing greater efficacy of imipramine (IMI) over relatively high dosages of chlordiazepoxide (CDZ) in the treatment of agoraphobia, panic disorder, and mixed panic-phobic syndrome. The antipanic effects of IMI were not attributable to its antidepressant effects. However, they were somewhat late in onset (6 to 8 weeks), and the level of unpleasant early side effects was fairly substantial. The effects of IMI on the agoraphobic syndrome component were complicated. There were drug interactions with initial levels of both depression and phobia which could not be unconfounded. Differences in outcome as a function of depression and phobia were substantial on IMI but relatively small on CDZ. IMI-treated subjects who were both more depressed and more phobic at baseline showed the greatest reduction of phobic symptoms.

Recently, a class of triazolo-benzodiazepines, represented by alprazolam (APZ), have shown promise in relieving both anxiety and depression. Strong evidence shows that APZ is well tolerated and effective in the treatment of anxiety (Cohn, 1981), and considerable evidence suggests its effectiveness for depression (Feighner et al., 1983). Thus, a trial of APZ for the panic-phobic syndrome seemed warranted.

Reported here are the results from a 12-week, double-blind, independent group comparison of APZ with IMI for the treatment of panic-phobic disorder. Among the questions asked were: are there differences in their relative efficacy, speed of onset, presence of side effects, and specificity of effects?

Method

Recruitment and Screening

Subjects were symptomatic volunteers recruited through newspaper advertisements, pre-screening procedures, and intensive screening interviews and workups. To be screened, respondents had to score at least two standard deviations above normative means on the Hopkins Symptom Checklist (HSCL) anxiety factor (Lipman et al., 1979), be 18 to 60 years of age, not be in psychiatric treatment, and have no contraindicated medical condition. At screening, they had medical and psychiatric examinations and self-rating assessments to ascertain that they met selection criteria including DSM-III criteria for agoraphobia, panic disorder, or study criteria for panic attacks with mixed phobias. The last group was diagnostically similar to DSM-III agoraphobics with panic in that their phobias included situations such as elevators, tunnels, bridges, or places from which escape would be difficult, but differed in that they did not clearly include the interpersonal components such as fear of crowds and leaving home alone. Accepted subjects had a 1-week placebo (PBO) washout period followed by 12 weeks of randomly assigned, double-blind, active drug plus supportive treatment with weekly visits the first month and biweekly visits for 2 months.

Measures

At baseline and repeatedly during the trial, subjects completed the Profile of Mood States (POMS) (McNair et al., 1971), an 80-item version of the HSCL providing eight syndrome cluster scores, a 7-point Global Improvement Scale, and daily, weekly, or biweekly ratings of panic and agoraphobia on scales described below. Psychiatrists repeatedly completed the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959), the Hamilton Depression Scale (HAM-D) (Hamilton, 1967), the Treatment Emergent Signs and Symp-

---

[1] Clinical Psychopharmacology Laboratory, Boston University, Boston, MA 02114.

toms Inventory (TESS) (Guy, 1976), a doctor version of the HSCL, and a 7-point Global Improvement Scale. Vital signs were recorded at each visit.

Attrition

Of 126 patients screened, 51 (40%) were accepted and began the PBO period, 7 dropped out while on PBO, and the remaining 44 were randomly assigned to an active agent by a computer program designed to balance the two groups as closely as possible for severity of phobic and panic symptoms, severity of depression, sex, and age (in that order of priority). Six of the 44 who began the active phase continued less than 1 week, and their response after baseline could not be assessed.

Completion rates for the entire 12 weeks of active treatment were 58% for IMI and 60% for APZ. However, 90% of the APZ patients completed at least 4 weeks of active treatment compared with only 71% of the IMI group. The IMI dropouts were due to side effects more often than those on APZ (4 vs. 0), with most such attrition occurring the first month.

Completer vs. Endpoint Samples

Thirty-five of the 44 patients beginning active treatment completed 4 or more weeks. This group was designated as the Endpoint Sample ($N = 35$). The Completer Sample consisted of 26 patients treated the entire 12 weeks. Efficacy and related analyses were conducted separately on each sample. Both types of analyses yielded similar results except that there were fewer significant findings favoring APZ in the Endpoint analysis despite the larger *N*. The most likely reason for the less conclusive patterns seemed to be that APZ subjects who discontinued treatment between 4 and 8 weeks did not improve and differed from those who completed the trial, while this was far less true for IMI. Data from the Completer Sample were used for the principal comparisons reported below.

TABLE 1

Sample Characteristics
($N = 26$)

Current Age	37.9
Age First Episode	19.5
Women	62%
Education	Some college
Duration Current Episode	2 to 3 years
Prior Psychotropic Treatment	73%
Diagnosis	
Agoraphobia Without Panic	8%
Agoraphobia With Panic	42%
Mixed Phobia With Panic	38%
Panic Disorder	12%

Sample

Table 1 displays the major clinical and demographic characteristics of the Completer Sample at baseline, just prior to beginning active medication. They are very similar to the groups studied by McNair and Kahn (1981) and by Zitrin et al. (1976). Diagnostically, over 90% reported panic attacks and over 85% reported substantial phobic and avoidance behavior. Table 2 displays mean scores at screen and after PBO on the HAM-A, HAM-D, and *t*-scores on the POMS tension-anxiety and depression-dejection factors. Psychometrically and clinically, depressive symptom levels were low. Drug groups were very similar at baseline.

Medication

During the PBO period, all subjects received 1 capsule twice a day (b.i.d.). During the 12-week active phase, they received matching capsules containing either 25 mg IMI or 0.5 mg APZ. Dosage actually taken is in Table 3. Based on counts of returned med-

TABLE 2

Sample Means Pre and Post Placebo Washout

	Pre	Post
Hamilton Anxiety	14.7	12.8
Hamilton Depression	10.5	9.0
POMS Normative T Scores		
Tension-Anxiety	59.0	54.0
Depression-Dejection	53.0	49.0

TABLE 3

Dosage
(mg daily)

Week	Alprazolam	Imipramine
2	1.5	70.0
4	2.3	112.5
6	2.5	127.5
8	2.7	132.5
10	2.6	130.0
12	2.8	132.5

ication, compliance with prescribed dosage was above 95%. Maximum protocol daily dosages were 4.5 mg APZ and 225 mg IMI. The mean daily IMI dosage of 132.5 mg during the final 2 weeks was almost identical to that in the IMI versus CDZ study reported by McNair and Kahn (1981). Five IMI cases required low dose (10 mg) capsules, but no low dose APZ was required.

Efficacy Results

One-way analysis of covariance (ANCOVA) was the principal statistical procedure, with the pre-active, post-PBO score as the covariate. Because the groups were well matched for initial severity, interpretation of the ANCOVA results was straightforward.

Panic Cluster

Self-ratings on a Daily Panic measure consisting of two HSCL items ("Suddenly scared for no reason" and "Spells of terror or panic") scored on a 0 to 3 point scale were completed each evening and phoned in the next day. The results showed a trend toward lower panic levels in the APZ group by the latter half of week 1 ($p<.10$). By week 4, the APZ group was significantly lower on Daily Panic ratings than the IMI group with a trend continuing through week 5. The superiority of APZ to IMI during the early weeks suggests faster onset of action. The IMI group changed relatively little until after 5 weeks, when they appeared to catch up with the APZ-treated patients.

Weekly and biweekly Panic Cluster self-ratings included the two items from the Daily Panic measure plus three items from the POMS ("Desperate," "Terrified," and "Panicky"), scored on a 0 to 4 point scale. The results indicated comparable improvement in the two drug groups although there was a trend at week 4 in favor of APZ. This is consistent with results from the Daily Panic measure suggesting faster relief with APZ.

A slightly modified version of Klein and Zitrin's Acute Panic Inventory focused primarily on distress during the past month from signs and symptoms of panic attacks. Obtained at baseline and at 12 weeks, the Panic Distress subscale results showed that APZ subjects improved significantly more than those on IMI ($p<.05$). Thus, convergent evidence from the daily, weekly, and pre-post panic measures indicated more rapid and greater efficacy for APZ in reducing the distress from panic symptoms.

Agoraphobia

Daily and weekly Agoraphobia Distress measures were collected in the same manner as for Panic. The 5-item cluster is shown in Table 4. Except for one item (fear of fainting in public), it is identical to the HSCL phobic-anxiety factor.

On both the Daily and the Weekly Agoraphobia Distress measures, there was a trend at week 4 favoring APZ ($p<.10$). However, doctor ratings of agoraphobic symptom severity on a global 7-point scale failed to discriminate between the active agents. Overall, there was little evidence of a differential drug effect.

Anxiety

There were no significant differences between groups on self-rated anxiety on a daily measure (composed of 5 of the 12 items from the HSCL anxiety factor), on the weekly

TABLE 4

Agoraphobia Cluster (HSCL-80)

Feeling afraid in open spaces or on streets
Feeling uneasy in crowds, shops, or movies
Fear of going on buses, subways, or trains
Being afraid to go out of house alone
Feeling nervous when left alone

POMS tension-anxiety factor, or on the weekly, full HSCL anxiety factor. However, psychiatrists' ratings of anxiety on both a 7-point global HSCL anxiety scale and on the HAM-A showed early differences favoring APZ. The more striking results were from the HAM-A (Figure 1). By the first week, and continuing through the first month, the APZ group was rated as significantly less anxious.

Global Improvement

Doctors and patients independently rated Global Improvement "since beginning medication" on 7-point rating scales. In both cases, the results favored APZ, although the pattern of significant treatment effects differed. Psychiatrists saw the clear APZ advantage as early as 2 weeks ($p<.05$), and it continued during the first month. Patient Global Improvement showed APZ to be more effective at 4 weeks and during the final month (Figure 2).

Depression

The subjects were not highly depressed. Baseline POMS depression means were at the 50th percentile relative to unselected college student norms and at the 24th percentile compared with psychiatric outpatient admission norms. HAM-D means also were low relative to the minimum scores of 18 to 21 often required for outpatient antidepressant drug trials, and no patient in the Completer sample had HAM-D scores greater than 15 after washout. However, results from several measures of depressive symptomatology were of interest. At 2 weeks, psychiatrists rated the APZ group as significantly less depressed on the HAM-D ($p<.01$), although there were no further significant differences. It is well known that the HAM-D includes components of both anxiety and depression, and the result may only reflect decreased anxiety. Given the growing body of evidence suggesting APZ is effective in decreasing depression, it is also possible that there was a small but genuine decrease in subclinical depression.

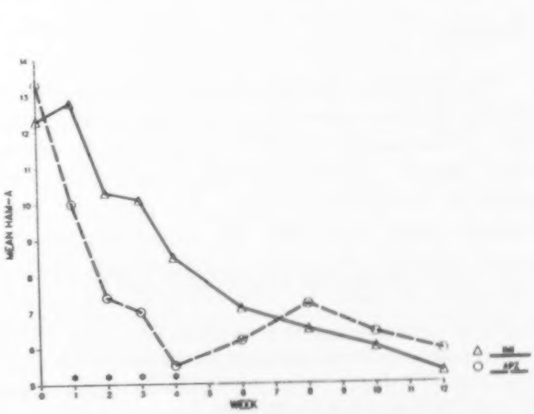


FIGURE 1. **Hamilton anxiety ratings (*$p<.05$).**

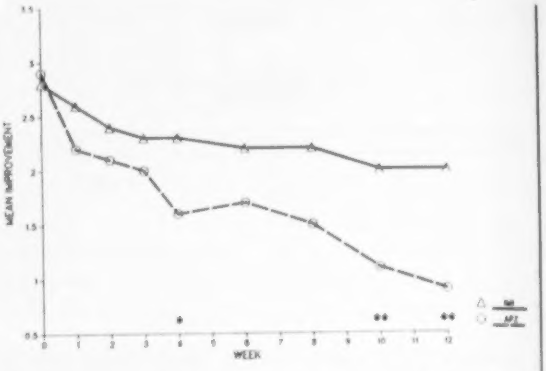


FIGURE 2. **Patient global improvement ratings (*$p<.05$; **$p<.01$).**

Self-ratings on two depression measures consistently favored APZ at every visit. Results from the POMS depression-dejection factor showed the APZ group to be significantly less depressed at week 2 ($p<.05$), but not thereafter. Stronger evidence was found in increased POMS elation scores, where significant findings favored APZ at 2, 6, and 12 weeks ($p<.05$).

Other Effects

The POMS vigor factor, a measure of general alertness and arousal, showed the APZ group to be more alert, efficient, and vigorous after 2 weeks ($p<.01$). Subsequent differences on vigor continued to favor APZ, but not significantly (although there were trends at 10 and 12 weeks).

Psychiatrists rated patients' anger-hostility using the global HSCL scale. The IMI group was less angry by week 8 ($p<.10$) and significantly less so by week 12 ($p<.05$). It is important to note that the APZ Completers did not show increased anger over the 12-week trial, but simply a smaller decrease than IMI-treated subjects.

Endpoint and Completer samples were analyzed for subjects' self-ratings of HSCL anger-hostility. There were no significant differences between the two Completer groups, but there were interesting relative differences between the Completer and Endpoint groups for each drug. Results from the Completer and Endpoint samples were virtually identical for IMI, but not for APZ. APZ patients who terminated the study between 4 and 8 weeks had increases on this measure relative both to their baseline and to the Completers. It is possible that APZ exacerbated anger-hostility in a subgroup of patients, but it is unclear whether this reaction was a reason for their premature termination.

Side Effects

A majority of patients in both groups reported drowsiness, but significantly more IMI cases reported dizziness, constipation, sweating, and dry mouth ($p<.05$). IMI significantly elevated supine diastolic blood pressure relative to APZ by the first week, and the elevation continued throughout (Figure 3). McNair and Kahn (1981) also reported that IMI elevated diastolic blood pressure relative to CDZ.

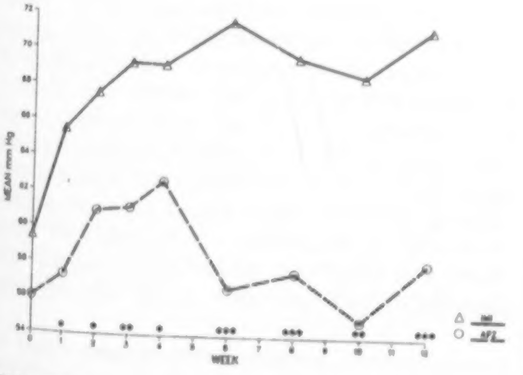


FIGURE 3. Supine diastolic blood pressure (*$p<.05$; **$p<.01$; ***$p<.001$).

Relation Between Anti-Panic and Anti-Agoraphobic Action

While there was evidence that the APZ group improved on both panic and agoraphobia, there was no indication that improvement occurred earlier in one component than the other. Actually, in neither group was there evidence of differential speed of onset of action for panic versus agoraphobia. This is also consistent with the results of the earlier IMI-CDZ trial (McNair & Kahn, 1981).

Summary

These results appear to replicate the earlier study by McNair and Kahn (1981) demonstrating the efficacy of IMI in the treatment of panic-phobic disorder. In addition, they support the efficacy of the newer benzodiazepine, APZ, in the treatment of this syndrome. Moreover, APZ showed significantly earlier onset of action and fewer side effects than IMI. In addition to the anti-panic effects, there may be a significantly greater and faster boost in feelings of well-being (elation and vigor) even when pre-treatment levels of depression are low. Finally, there may be some advantage of IMI over APZ in reducing anger. The findings also suggest a small proportion of patients fail to respond well to APZ after 4 to 8 weeks of treatment, but the number of such patients in this trial was too small to clearly characterize.

References

Aden, G.C., and Thein, S.G. Alprazolam compared to diazepam and placebo in the treatment of anxiety. *Br. J. Psychiatry*, 41:245-248, 1980.

Cohn, J.B. Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J. Clin. Psychiatry*, 42:347-351, 1981.

Feighner, J.P., Aden, G.C., Fabre, L.F., et al. Comparison of alprazolam, imipramine, and placebo in the treatment of depression. *JAMA*, 249(22):3057-3064, 1983.

Guy, W. *ECDEU Assessment Manual for Psychopharmacology*. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (ADM) 76-338, Washington, D.C.,: U.S. Government Printing Office, 1976

Hamilton, M. The assessment of anxiety states by rating. *Br. J. Med. Psychol.*, 32:50-55, 1959.

Hamilton, M. Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychol.*, 6:278-296, 1967.

Lipman, R.S., Covi, L., and Shapiro, A.K. The Hopkins Symptom Checklist (HSCL). *J. Affective Disord.*, 1:9-24, 1979.

McNair, D.M., and Kahn, R.J. Imipramine compared with a benzodiazepine for agoraphobia. In: Klein, D.F., and Rabkin, J. (eds.), *Anxiety: New Research and Changing Concepts*. New York: Raven Press, 1981, pp. 69-78.

McNair, D.M., Lorr, M., and Droppleman, L.F. *Manual for the Profile of Mood States*. Educational and Industrial Testing Service, San Diego, Calif., 1971.

Zitrin, C.M., Klein, D.F., Lindemann, C., et al. Comparison of short-term treatment regimens in phobic patients. In: Spitzer, R.L., and Klein, D.F. (eds.), *Evaluation of Psychological Therapies*. Baltimore: Johns Hopkins University Press, 1976, pp. 233-250.

Taper Withdrawal Studies With Alprazolam in Patients With Panic Disorder and Agoraphobia

John C. Pecknold, M.D.,[1] and Richard P. Swinson, M.D.[2]

Introduction

Since the introduction of chlordiazepoxide in the 1960's, the benzodiazepines have become the major therapeutic modality in the treatment of anxiety and insomnia. New work indicates that the triazolobenzodiazepine alprazolam is also effective in the treatment of panic disorder (Klerman et al., 1986). Most authors focus primarily on efficacy and patient acceptance. However, the problems of tapering and discontinuing medication have become increasingly important. Physical dependence on high doses of chlordiazepoxide has been described by Hollister et al. (1961) and later by Covi et al. (1973). Since then, withdrawal reactions have been described with virtually all current benzodiazepines (Swinson et al., in press).

Evaluation of phenomena associated with the stopping of anxiolytic medication requires careful differentiation among physical dependency, rebound phenomena, and the return of the pre-existing condition. The cessation of pharmacological treatment in chronically anxious or insomniac patients and in those for whom the existing crisis has not been resolved may result in the return of the pre-existing syndrome. A rebound phenomenon implies the recurrence of pre-existing symptoms in an exaggerated way with greater intensity than before treatment. A withdrawal syndrome implies that tolerance has developed to the drug and that the presenting symptoms are pharmacologically derived in a direction opposite to the pharmacological action of the drug. Dependence on the compound thus derives from a physiological basis. This particular syndrome has also been referred to as the onset of new symptoms (Lapierre, 1981).

The present study is a careful assessment of patients who have been on an 8-week trial of either alprazolam or placebo for the treatment of panic disorder with agoraphobia and who were followed on a 4-week taper and a 2-week post-taper weekly assessment schedule.

Methods

As part of the cross-national collaborative panic disorder study, subjects with panic disorder and agoraphobia or limited phobic avoidance were enrolled in five centers in the United States, two in Canada, and one in Australia. Those meeting the DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) criteria modified for the study were randomly assigned to either alprazolam or placebo for an 8-week period of treatment. All patients then underwent a 4-week gradual tapering of medication and a final 2 weeks in which they were assessed. During the taper period, medication was withdrawn no faster than 1 mg in every 3 days and, for the most part, 4 weeks were taken to accomplish that. During the 2 weeks post-taper, patients were permitted to take placebos on an as-needed basis. The two Canadian sites at St. Mary's Hospital in Montreal and the Toronto General Hospital in Toronto studied the taper withdrawal phenomenon according to the following protocol. In addition to the time and dosage schedule mentioned above, patients were assessed on a weekly basis with the following instruments: the Panic Attack Scale, the Disability Scale (DISS), the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D), the Sheehan Patient-Rated Anxiety Scale (SPRAS), the Sheehan Clinical Rated Anxiety Scale (SCRAS), the Patient's Global Im-

---

[1] St. Mary's Hospital, McGill University, Montreal, Quebec, Canada.

[2] University of Toronto, Toronto General Hospital, Toronto, Ontario, Canada.

provement, the Physician's Global Improvement, the Symptoms and Side Effect Checklist, the Phobia Scale, the Benzodiazepine Withdrawal Checklist (BWCL), the Merz, and the SCL-90. These assessments were done weekly during the entire 14-week period with the exception of the BWCL and Merz which were done at baseline, at week 8, and then weekly during the taper and post-taper. In addition, patients completed a diary on a weekly basis which itemized the numbers of panic attacks, whether they were situational or spontaneous, their intensity and duration, as well as their outings and the intensity of discomfort on their outings.

Population

Of the 61 evaluable patients originally placed on alprazolam after a 1-week washout, 58 patients completed the 8-week trial but only 33 completed the withdrawal study. All patients were eventually tapered off alprazolam.

Of the 58 evaluable patients who initially enrolled on placebo, 49 patients completed the drug trial but only 21 patients completed the withdrawal study. Table 1 shows the demographic variables of patients who completed not only the 8-week active treatment but also the 6 weeks of taper withdrawal. Statistical analysis was completed using analysis of variance and a regression analysis for the Panic Attack Scale.

Results

Panic Attacks: Combined situational and spontaneous panic attack data are presented as derived from the daily patient diaries and the Weekly Panic Attack Scale. The group as a whole is presented in Figure 1. In the group as a whole the problem is that we are offering data during the withdrawal period only from those patients on placebo who were able to continue on medication, and they represent only a fraction of the starting group.

TABLE 1

Demographic Data by Drug Group
(Post-Taper Week 2 Completers)

	Alprazolam	Placebo
Number of patients	32	21
Mean age (S.D.)	31.8 (10.7)	32.3 (8.5)
Female	59.4%	57.1%
Male	40.6%	42.9%

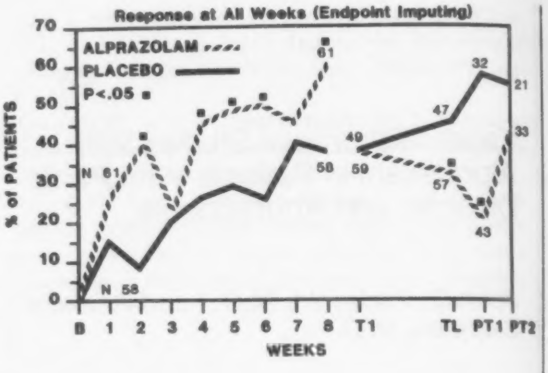


FIGURE 1. Percentage of patients with "o" panic attacks.

Rebound Panic: The criteria for rebound were set at the following: a 50% increase over baseline values and a change of at least three panic attacks. In 28% of alprazolam patients rebound is shown to occur; one patient on placebo (a nonresponder) also had a rebound.

The Figures show the response for the group as a whole with all available data (Figure 2).

Rebound Anxiety: The criteria for rebound anxiety on the HAM-A were an increase of 50% over the baseline levels and a change in score of 3. Twenty-two percent of patients on

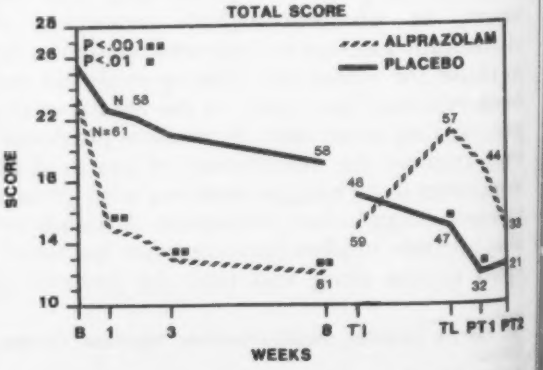


FIGURE 2. Hamilton anxiety scale.

alprazolam had rebound; 2 patients on placebo also had rebound.

Severity of phobias overall shows a similar pattern to the HAM-A with significant decrease in the alprazolam group only after 1 week of medication and thereafter, and a return of phobia during the taper with a drop to previous gains by the end of post-taper week 2. Work and Social Disability scales showed a similar pattern to the severity of phobias.

Benzodiazepine Withdrawal Checklist (BWCL): Our criteria for the emergence of new symptoms included the definition that the patients had never before had the symptoms, that they were seen to occur on the BWCL, and they had to occur during the final taper and withdrawal period. They divided into the percentage who had no new symptoms, the percentage who had mild new symptoms, and the percentage who had severe new symptoms. On the BWCL there was a significant drop in symptoms for the alprazolam versus placebo group during the 8 weeks of study representing primarily the various symptoms of anxiety. During the withdrawal period, the last week of taper and the first post-taper week, the trial score rose to above baseline level (significantly higher than placebo patient group) but returned to nonsignificant levels by the end of post-taper week 2. Table 2 shows the syndromes in four alprazolam patients.

TABLE 2

Benzodiazepine Withdrawal Checklist (New Symptoms — Last Taper/First Post-Taper Weeks: Patients With Three or More New Symptoms)

Patients	Last Taper Week	First Post-Taper Week
#203 Alprazolam	Blurred vision Clouded sensorium* Dysosmia*	Muscle cramps* Blurred vision
#38 Alprazolam	Tremor Paresthesias Dysosmia* Muscle cramps*	Tremor
#49 Alprazolam	Blurred vision Headaches Paresthesias Muscle cramps*	(nothing)
#36 Alprazolam	(nothing)	Blurred vision Heightened sensory perceptions Paraesthesias Muscle cramps*

*Patient not asked about symptom during weeks 1-7 of acute study.

Conclusion

We report that despite a 4-week taper period, many patients have a symptomatic withdrawal. Very few of the patients on alprazolam were able to continue through this period without a return of symptoms. This occurred despite the excellent therapeutic success during the 8-week active treatment. Furthermore, we document the presence in a proportion of patients of panic rebound. The measurement, namely the Panic Attack Scale, is backed up by a daily diary questionnaire which gives a behavioral measurement of the occurrence of the panic attacks. The findings on the panic are different from those observed with the HAM-A. Twenty-five of our 60 patients had rebound; of panic (50%), of anxiety (32%), and both panic and anxiety (20%). Most of the patients with panic disorder did not have panic rebound but rather had a gradual return of the original syndrome. There is, however, a peaking during the latter end of the taper and the beginning of the drug-free period that shows rebound. This is proportional in fact to the onset and dosage schedule during the efficacy period.

The behavior of the placebo responders also shows a return of symptoms after discontinuation of the medication which documents a kind of psychological worsening. However, none of these patients had the type of rebound found in the active alprazolam group.

A small minority of patients have the development of new symptoms despite the tapering. This is related to the high dosage levels of medication and may be found with most benzodiazepine withdrawal studies.

Two important clinical questions are addressed by this withdrawal data: the first is the adequacy of the length of trial. Our patients were treated for an 8-week period with a 4-week taper and then discontinued. There was a considerable relapse. This finding was also seen in the study of Solyom et al. (1981) in which phenelzine was the drug used in comparison with placebo. Perhaps panic disorders are similar in some respect to depressive disorders in terms of length of treatment required. Certainly, more detailed comparison of short-term treatment period, namely 8 weeks, and a longer-term treatment period, namely 6 months, is required. It is very likely that patients with panic disorder and agoraphobia require a minimum of 6 months' medication, and a premature discontinuation of medications may trigger a relapse.

The second question has to do with the taper. Our patients had a 4-week period in which their medication was tapered mostly at 1 mg reduction every 3 days. Furthermore, at the end of the period the medication went from 1 mg to 0. The taper schedule should perhaps be much more prolonged with decrements in the dosage but a continual division over time, inasmuch as the pharmacokinetics of alprazolam tend to require divided dosages. This taper perhaps should be accomplished over a more prolonged period, possibly a 2-month period rather than a 4-week period. Nonetheless, a proper study of taper after a prolonged 6-month trial of the drug would be informative.

Finally as to the issue of tolerance and dependency, it appears that our patients do not have a tendency to increase the dosage and this is confirmed by other withdrawal schedules (Dupont & Pecknold, 1985). My impression is that the dependency resides more in the development of new symptoms and rebound and that the gravity of those symptoms is more likely to cause a prolonged period of drug taking. Once again, it is likely that a proper therapeutic interval, namely 6 months, would result in an easier period of taper and withdrawal. Certainly further studies comparing a short-term administration period with a longer-term administration period are required. Furthermore, a more prolonged taper appears to be highly desirable.

References

Covi, L., Lipman, R.S., Pattison, J.H., et al. Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. *Acta Psychiatr. Scand.*, 49:51-64, 1973.

Dupont, R.L., and Pecknold, J.C. Symptoms after stopping alprazolam: Withdrawal or relapse? Presented at the Annual Meeting of the American Psychiatric Association, Dallas, Texas, May 18-24, 1985.

Hollister, L.E., Motzenbecker, F.P., and Degan, R.O. Withdrawal reactions from chlordiazepoxide (Librium). *Psychopharmacologia*, 2:63-68, 1961.

Klerman, G.L., Coleman, J.H., and Purpura, R.P. The design and conduct of the Upjohn cross-national collaborative panic study. *Psychopharmacol. Bull.*, 22(1):59–64, 1986.

Lapierre, Y.D. Benzodiazepine withdrawal. *Can. J. Psychiatry*, 26(2):93-95, 1981.

Solyom, C.L., Lapierre, Y., Pecknold, J.C., and Morton, L. Phenelzine and exposure in the treatment of phobias. *Biol. Psychiatry*, 16:239-247, 1981.

Swinson, R.P., Pecknold, J.C., and Kirby, M.E. Benzodiazepine dependence. (In press)

Amitriptyline and Haloperidol in Unstable and Schizotypal Borderline Disorders[1]

Paul H. Soloff, M.D.,[2] Anselm George, M.D.,[2] Swami Nathan, M.D.,[2] Patricia M. Schulz, M.S.W.,[2] Richard F. Ulrich, M.S.,[2] and James M. Perel, Ph.D.[2]

Empirical study of the borderline syndrome delineates two statistically independent but overlapping dimensions to this disorder, defining a spectrum of symptoms with affective instability at one extreme and mild thought disorder at the other. Separated in DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) into an unstable borderline personality disorder (BPD) and a schizotypal personality disorder (SPD), the two dimensions co-exist in over half of clinically defined borderline patients (Spitzer & Endicott, 1979; Spitzer et al., 1979). The heterogeneity of symptoms presented by borderline patients confounds efforts to define a single treatment of choice. The affective, schizotypal, and impulsive-behavioral symptoms characteristic of these patients are treated with a wide variety of antidepressants, major and minor tranquilizers, and even anticonvulsants, without systematic proof of efficacy or empirically defined guidelines. Treatment is further complicated by a lack of agreement on the target symptoms for chemotherapy, on the delineation of state from trait manifestations of the disorder, and on the responsiveness of each to chemotherapy. To address these issues, we are conducting a first double-blind, placebo-controlled study of antidepressant and neuroleptic medication in acutely symptomatic, criteria-defined borderline patients. Our objectives are twofold: 1) to determine the differential efficacy of an antidepressant (amitriptyline: AMI) and a neuroleptic (haloperidol: HAL) medication against the affective, schizotypal, and impulsive-behavioral presentations of acutely symptomatic borderline patients; and 2) to test the hypothesis that medication response can define clinically meaningful borderline subtypes. Following current clinical prejudice, we predicted preferential responsiveness of schizotypal borderlines (SPD) to haloperidol and unstable borderlines (BPD) to amitriptyline.

Method

Patients for this study were referred from both inpatient and outpatient divisions of the Western Psychiatric Institute and Clinic of the University of Pittsburgh. Following informed consent, and a thorough medical and psychiatric evaluation, Gunderson's Diagnostic Interview for Borderlines was used to define a study sample with a cut-off score of 7 or greater required for inclusion (Kolb & Gunderson, 1980). A DSM-III subtype diagnosis of BPD, SPD, or Mixed BPD/SPD was made on the basis of direct patient interviews. Exclusion criteria for chronicity, medical disorders, and organicity were adopted from Gunderson et al. (1975). Co-morbidity on Axis I was defined by the Schedule for Affective Disorders and Schizophrenia (SADS) interviews with exclusion for schizophrenic disorders, major depression with psychosis, and bipolar related disorders in either current (SADS) or lifetime (SADS-L) experience. Major depression without psychosis is reported in 14% to 50% of borderline patients and was not an exclusionary criterion but was coded for separate statistical analysis (Kroll et al., 1981; Pope et al., 1983). Following a medication-free period of at least 7 days, patients were required to demonstrate

---

[1] This work was supported by NIMH Grant #35392 and MHCRC #30915.

[2] Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

continuing symptom severity defined by the Global Assessment Scale (GAS≤50) and *either* the Hamilton Rating Scale for Depression-24 item (HAM-D≥17) *or* the Inpatient Multidimensional Psychiatric Rating Scale (IMPS≥66).

Patients were randomly assigned to haloperidol (HAL) (2 mg), amitriptyline (AMI) (25 mg), or placebo (PLC) (tablets) with titration in 1 week up to a daily maximum of HAL 12 mg, AMI 150 mg, and PLC 6 tablets. (Early experience prompted a reduction in the daily maximum haloperidol dose to 6 mg.) Medication trials lasted 5 weeks with weekly self- and observer-rated measures of mood [HAM-D-24, Beck Depression Inventory (BDI)], schizotypal symptoms [Inpatient Multidimensional Psychiatric Rating Scale (IMPS), Schizotypal Symptom Inventory (SSI)], and global functioning [Global Anxiety Scale (GAS), Symptom Checklist-90 (SCL-90), and Ward Scale of Impulse Action]. Two of these scales, the SSI and the Ward Scale, were adapted from other sources for this study. The SSI is a symptom checklist with an associated severity scale which incorporates all eight of Spitzer's DSM-III Schizotypal criteria (Spitzer et al., 1979), seven of Khouri's discriminating symptoms for Schizotypal disorder (Khouri et al., 1980), and three of Meehl's diagnostic criteria for schizotypy (e.g., ambivalence, anhedonia, pan-anxiety) (Meehl, 1964). The Ward Scale of Impulse Action is derived from the Impulse Action section of Gunderson's Diagnostic Interview for Borderlines (DIB) and lists 12 behavioral items (with an associated severity scale) which are characteristic of borderline patients in long hospital stays (e.g., self-mutilation, manipulation of staff, suicidal threat, etc.). The Ward Scale is scored weekly by the patient's primary nurse while all other observer measures are scored by two raters (P.H.S., P.M.S., or A.G.) during a weekly research interview. Weekly plasma levels were drawn and analyzed for HAL and for the AT+NT metabolites of AMI to allow for control for systemic exposure.

Statistical Analysis

Specific tests for medication effects and differences between groups were performed by Analysis of Covariance (ANCOVA) using Week 1 (baseline) as the covariate and the average of Weeks 5 and 6 as outcome. Our study hypothesis predicted that patients with a preponderance of affective symptoms would respond preferentially to AMI while those with more schizotypal symptoms would do better on HAL—and both would improve more on medication than on PLC. Because of the heterogeneity of affective and schizotypal symptoms presented by these patients, we felt it desirable to have a composite measure of change which reflects overall symptom severity and direction of change (i.e., between affective and schizotypal poles). To address our study hypothesis and complement the conventional ANCOVA for specific medication effects, a composite measure of overall change was constructed from a factor analysis of rating scales reflecting affective or schizotypal pathology. These included the HAM-D-17; Beck Depression Inventory; SCL-90: Hostility and Psychoticism Subscales; IMPS: Intropunitiveness, Hostility, Paranoia, and Perceptual Distortion Subscales; SSI; and GAS.

Taking the unrotated factors of these selected scores defined the first two components of variation, namely, an overall measure of severity and a subsequent bipolar factor which presumably contrasts affective and schizotypal symptoms. The existence of a severity factor and a bipolar factor is the standard result of factoring among a set of measures that are all positively correlated. The first factor provides a robust measure of severity to be used to test the multivariate hypothesis of symptom differences favoring a group. The second factor provides a bipolar measure of affective vs. schizotypal symptom pattern. Constructed as a contrast of two equally weighted extremes, the second factor will be less robust than the severity factor, owing to measurement issues. With care, it can be used to test for the hypothesized interaction of medication and symptom polarity (e.g., affective vs. schizotypal). Finally, using both the severity factor score and baseline scores as covariates, a separate ANCOVA can be performed on each of the outcome scales to "partial out" the effects of severity to see if treatment has any unique effect independent of severity.

TABLE 1

Overview of Pharmacotherapy Outcomes

Outcome Measures	Med Effects 3-Way	Hal vs PLC	AMI vs PLC	AMI vs HAL
		Analysis of Covariance[a]		
	(F)	(F)	(F)	(F)
Global Assessment Scale	1.14	2.04	0.65	0.44
Hamilton Rating Scale-17	0.81	0.54	1.76	0.18
Beck Depression Inventory	3.09†	4.69* (H>P)	3.24† (A>P)	0.49
Schizotypal Symptom Inventory	1.76	3.10† (H>P)	0.26	1.57
Ward Scale of Impulse Action Patterns	1.64	3.47† (H>P)	0.00	2.90
SCL-90 Factors				
Somatization	3.63*	5.22* (H>P)	2.83	0.76
Obsessive-Compulsive	3.00†	5.34* (H>P)	0.33	2.78
Interpersonal Sensitivity	6.40**	12.15*** (H>P)	2.22	2.90† (H>A)
Depression	1.85	3.11† (H>P)	0.50	1.56
Anxiety	4.26*	6.34* (H>P)	0.34	5.55* (H>A)
Hostility	7.75***	12.73*** (H>P)	1.83	5.65* (H>A)
Phobic Anxiety	2.79†	4.93* (H>P)	1.25	2.10
Paranoid Ideation	5.03**	8.61** (H>P)	0.59	5.78* (H>A)
Psychoticism	3.80*	5.86* (H>P)	3.00† (A>P)	0.87
Additional Items	3.03†	2.52	5.98* (A>P)	0.53
General Severity Index	5.39**	8.03** (H>P)	1.39	3.74† (H>A)
IMPS Factors				
Excitement	1.94	2.64	3.63† (A>P)	0.08
Hostile Belligerence	2.33	3.73† (H>P)	2.08	0.67
Paranoid Projection	1.68	2.79	0.28	1.66
Grandiose Expansiveness	0.04	0.19	0.13	0.00
Perceptual Distortions	1.07	1.62	0.67	0.47
Anxious Intropunitiveness	0.93	0.65	0.20	2.44
Retardation-Apathy	0.72	0.86	0.12	0.65
Disorientation	1.84	1.81	0.95	1.97
Motor Disturbances	0.99	1.26	0.07	1.23
Conceptual Disorganization	1.05	3.07† (H>P)	0.31	1.60
Total	0.87	1.54	0.80	0.12

*p<.05
**p<.01
***p<.001
†p<.1
(two-tailed tests) N: HAL = 21, AMI = 20, PLC = 20
[a]Baseline scores are covariates. Greater improvement noted as X>Y.

Factor analyses were performed each week separately for Weeks 1, 5, and 6. The results were quite similar at each. Factors were operationalized by giving equal weights to variables loading on a factor, and were standardized across all periods to have an overall mean of 50 and a standard deviation (s.d.) of 10, scoring across all data. Change on this standardized measure is in s.d. units (×10). Higher scores indicate greater severity on the first factor and an excess of affective traits on the second.

Results

Sixty-four patients have entered protocol to date, 49 women and 15 men, with an age range of 16 to 53 (median age 25 years). Among this sample were 51 inpatients recruited from consecutive acute admissions and 13 outpatients who met all inclusion, exclusion, and continuation criteria but refused or did not require hospitalization. By DSM-III criteria, 43.8% are diagnosed as "pure" borderline disorder, 50% as mixed borderline and schizotypal disorder, and 6.2% as "pure" schizotypal disorder. (The "pure" SPD patients are included in the mixed BPD/SPD sample for analysis. It should be noted that these are DIB-defined borderline patients with prominent schizotypal symptoms in the context of otherwise typical borderline affect, impulse, and interpersonal relatedness. These patients are *not* the isolated affectless schizotypes related to the schizophrenia spectrum) (Soloff & Millward, 1983).

Random assignment resulted in 23 HAL trials, 20 AMI trials, and 21 PLC trials. Average daily medication dosage by Day 42 was 7.24±3.19 mg for HAL and 147.62±13.47 mg for AMI. Analysis of plasma levels indicated a mean (±s.d.) of 11.87 (±11.68 ng/ml) for HAL and 244.74 (±73.07 ng/ml) for AT+NT by Day 35 (i.e., after 4 weeks of treatment). Assuming a minimum therapeutic range of 160 ng/ml–200 ng/ml for AT+NT, all but one inpatient achieved minimum therapeutic range by Day 35.

Three patients terminated the study before completing 2 full weeks of medication (Day 21) which was defined as the minimum duration required for inclusion of data. Two patients terminated for adverse medication effects: extrapyramidal side effects in one inpatient, unwitnessed hives in an outpatient, both on HAL. One inpatient on PLC terminated the study before Day 21 for reasons of personal convenience and left the hospital despite remaining symptomatic. These three trials are not included in end-point analyses, reducing the sample to 61. An overview of preliminary pharmacotherapy outcomes is given in Table 1.

Significant medication effects (i.e., $p<.05$) with baseline scores as covariates were found exclusively on self-rated measures: SCL-90 Somatization, Interpersonal Sensitivity, Anxiety, Hostility, Paranoid Ideation, Psychoticism factors, and the SCL-90 General Severity Index. Near significance ($p<.1$) was achieved on SCL-90 Obsessive Compulsive, Phobic Anxiety and Additional factors, and the BDI. It is noteworthy that the *observer-rated* measures of depression, psychoticism, and global functioning—i.e., the HAM-D, IMPS, SSI, and GAS—did not demonstrate significant medication effects.

Between-group comparisons produced clear differences. HAL was significantly superior to PLC (i.e., $p<.05$) on a broad spectrum of symptom patterns including SCL-90 Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism factors; the SCL-90 General Severity Index; and the BDI. (Trends were apparent on SCL-90 Depression; IMPS: Hostile Belligerence and Conceptual Disorganization; the SSI; and the Ward Scale of Impulse Action.) In contrast, AMI proved significantly superior to PLC only on one scale, the ill-named SCL-90 Additional factor, a scale defined largely by depression items (e.g., poor appetite, trouble falling asleep, early morning awakening, guilt, and thoughts of death and dying). Changes favoring AMI but short of significance were found on the BDI, SCL-90 Psychoticism, and IMPS Excitement factors. The SCL-90 Psychoticism factor contains several items common to depression (e.g., the idea that you should be punished for your sins, or feeling lonely with other people) while IMPS Excitement highlights arousal behavior (e.g., loud, overactive, hurried speech), perhaps responsive to the sedative effects of AMI.

Randomization resulted in no significant differences in severity or polarity factor scores across the three medication groups at baseline (Table 2). Following treatment, patients in the HAL group improved significantly more on the composite severity measure than those receiving AMI or PLC, with no difference between AMI and PLC. Post-treatment polarity factor scores reflect a trend toward differences among groups attributable to an increase in affective polarity in the PLC group and a decrease in affective polarity among patients treated with AMI. These effects are independent of severity.

In the comparison of severity and polarity factor scores by borderline subtype, increased severity is attributed to the mixed BPD/SPD group while increased affective polarity is associated with the pure BPD patients (Table 3). There was no significant interaction of medication group with polarity of symptom pattern (affective vs. schizotypal) on overall severity, leaving unsupported the hypothesis of significant differential efficacy

TABLE 2

Medication Effects on Severity and Polarity Scores[a]

Outcome Factor	AMI N = 18	HAL N = 20	PLC N = 17	ANCOVA F	 p
Severity, Pretreatment	54.78	58.65	56.29	1.322	n.s.
Severity, Posttreatment[b]	49.57***	44.45***	51.87†	3.993	.024
Polarity, Pretreatment	50.67	53.10	48.47	1.041	n.s.
Polarity, Posttreatment[c]	48.28	49.84	54.24†	2.768	.073

***$p < .001$ †$p < .1$ Pre- vs. Posttreatment, within group. Two-Tailed *t* test.

[a] *N* decreased by six cases with inadequate data to compute factor scores (2 AMI, 1 HAL, 3 PLC).

[b] Pretreatment Severity as Covariate

Posttreatment Severity: HAL vs. PLC (*F* 5.782, *p* .022); AMI vs. PLC (*F* 0.713, n.s.)
AMI vs. HAL (*F* 3.974, *p* .054).

[c] Pretreatment Polarity, Posttreatment Severity as Covariates

Posttreatment Polarity: HAL vs. PLC (*F* 2.547, n.s.), AMI vs. PLC (*F* 6.687, *p* .015)
AMI vs. HAL (*F* 0.481, n.s.)

of medication by affective or schizotypal dimensions. Analysis of medication effect by borderline subtype produced similar results. There was no significant interaction of medication group with subtype diagnosis (BPD vs. BPD/SPD) on overall severity. Using this statistical strategy, we were unable to demonstrate a pharmacologic behavioral dissection of medication responsive borderline subtypes. To identify unique effects of medication independent of severity, the severity scores were factored out in an ANCOVA. With composite severity "partialled out," significant medication effects remained in measures of hostility (IMPS, SCL-90) and paranoid ideation (SCL-90) suggesting a specific effect for HAL, and on the Additional Factor of the SCL-90, reflecting an antidepressant effect for AMI. The pattern of change over time was striking—with most improvement occurring by Day 21 (e.g., 7 days med-free followed by 2 weeks of medication). This is well illustrated in the Figure indicating the course of response over the study on the self-rated General Severity Index of the SCL-90.

TABLE 3

Severity and Polarity Factors
by Borderline Subtype
AMI vs. HAL vs. PLC (*N* = 55)

	DSM-III BPD (*N*-24)	DSM-III BPD/SPD (*N*-31)	*F*/*p*
Severity, Pretreatment	53.57	59.02	7.381, <.01
Severity, Posttreatment[a]	48.93	48.02	0.137, n.s.
Polarity, Pretreatment	54.41	48.13	5.797, <.05
Polarity, Posttreatment[a]	51.55	50.02	0.467, n.s.

[a] ANCOVA: Pretreatment severity, pretreatment polarity as covariates; higher score implies greater severity/more affective polarity.

Summary

Although these are preliminary results of a study in progress, several important observations arise from our data. Significant medication effects are found consistently in self-rated measures—not interview based ratings. The sensitivity and relevance of our interview based measures to specific borderline symptoms warrant further study. There is a need for measures of change more relevant to this disorder. We are unable to determine

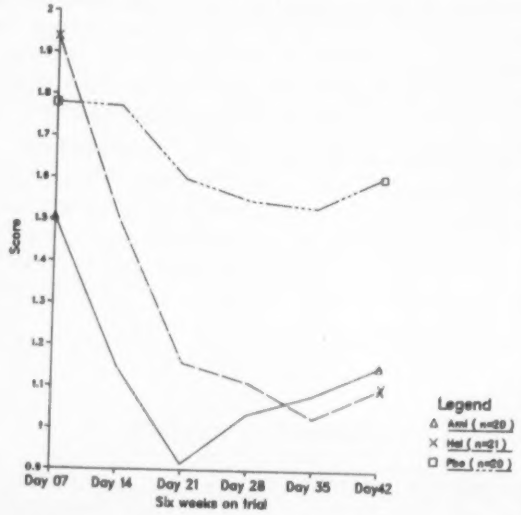


FIGURE. Comparison of SCL–GSI across three treatments.

if interviewer bias plays a role in minimizing reported effects, since expectation of clinical change is understandably modest given the degree of chronic impairment. Similarly, the interview setting may affect patients' willingness to report change.

The disappointing response to AMI in patients with strong depressive symptoms suggests that more attention be given to the atypical pattern of depressive presentations in borderline patients as a possible indication for future research with monoamine oxidase inhibitor antidepressants.

Despite these limitations, our preliminary results support the use of low-dose neuroleptics in borderline disorder and demonstrate significant efficacy against a broad range of symptoms including hostility, paranoia, anxiety, and depression. Despite the prevalence of affective symptoms in this population, AMI is no better than HAL against depression and little better than PLC against a wide range of associated borderline symptoms. Medication effects are modest in magnitude, generally attributable to decreased severity and occur early in the treatment course. Both unstable and schizotypal borderline patients demonstrate some improvement. We are unable to separate borderline subtypes by medication response or support the clinical prejudice predicting selective efficacy for HAL in schizotypal patients and AMI in unstable borderlines. Rather, we have shown that HAL is broadly effective while AMI adds little to the treatment of borderline disorder.

References

Gunderson, J.G., Carpenter, W.T., and Strauss, J.S. Borderline and schizophrenic patients: A comparative study. *Am. J. Psychiatry*, 132:1257–1264, 1975.

Khouri, P.J., Haier, R.J., Rieder, R.D., et al. A symptom schedule for the diagnosis of borderline schizophrenia: A first report. *Br. J. Psychiatry*, 137:140–147, 1980.

Kolb, J.E., and Gunderson, J.G. Diagnosing borderline patients with a semi-structured interview. *Arch. Gen. Psychiatry*, 37:37–41, 1980.

Kroll, J., Sines, L., Martin, K., et al. Borderline personality disorder: Concept validity of the concept. *Arch. Gen. Psychiatry*, 38:1021–1026, 1981.

Meehl, P.E. *Manual for Use with Checklist of Schizotypal Signs.* Psychiatric Research Unit, University of Minnesota, 1964.

Pope, H.G., Jr., Jonas, J.M., Hudson, J.I., et al. The validity of DSM-III borderline personality disorder: Phenomenologic, family history, treatment response, and long-term follow-up study. *Arch. Gen. Psychiatry*, 40:23–30, 1983.

Soloff, P.H., and Millward, J.W. Psychiatric disorders in the families of borderline patients. *Arch. Gen. Psychiatry*, 40:37–44, 1983.

Spitzer, R.L., and Endicott, J. Justification for separating schizotypal and borderline personality disorders. *Schizophr. Bull.*, 5:95–104, 1979.

Spitzer, R.L., Endicott, J., and Gibbon, M. Crossing the border into borderline personality and borderline schizophrenia: The development of criteria. *Arch. Gen. Psychiatry*, 36:17–24, 1979.

Open Trial of Buspirone in the Treatment of Major Depressive Disorder

Edward E. Schweizer, M.D.,[1] Jay Amsterdam, M.D.,[1] Karl Rickels, M.D.,[1] Myron Kaplan, D.O.,[1] and Marian Droba, M.D.[1]

The pharmacologic treatment of depression and anxiety rests on the clinical judgment, often difficult to make, as to which diagnosis is primary. Confidence in the essential therapeutic importance of this decision has been undermined recently by studies suggesting anxiolytic properties for antidepressants (Klein, 1964; Sheehan et al., 1980), and antidepressant properties for benzodiazepines (Rickels et al., 1985). Buspirone is a newer anxiolytic with a novel chemical structure and an atypical profile of pharmacologic activity (Riblet et al., 1982). It has demonstrated an anxiolytic efficacy comparable to the benzodiazepines (Goldberg & Finnerty, 1979; Rickels, 1981), despite having no apparent activity at the Bz-GABA receptor. The side-effect profile of buspirone, at doses in the anxiolytic range of 15 to 30 mg, compares favorably with benzodiazepines, with significantly less sedation (Newton et al., 1982).

Several studies (Feighner et al., 1982; Goldberg & Finnerty, 1979) using buspirone in anxious patients have noted concomitant improvement in associated depressive symptoms. This led us to undertake an open-label study of the efficacy of buspirone in major depression.

Methods

Thirty patients meeting DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) criteria for Major Depressive Disorder were entered in an open-label treatment protocol. Eligibility criteria required a score of at least 18 on the Hamilton Depression Scale (HAM-D), and at least 9 on the Raskin Depression Scale, with the Covi Anxiety Scale scoring less than the Raskin scale. Excluded from the study were patients with personality disorders, organic brain syndrome, schizophrenia, alcohol, drug abuse, or acute or unstable medical conditions. Also excluded were pregnant or lactating women, or women of child-bearing potential not taking birth control precautions. Concomitant medications were not permitted. A 1-week, single-blind placebo washout was employed prior to entry into a 4-week acute treatment phase. Initial dosing with buspirone was begun at 15 or 30 mg, given on a three-times-a-day (t.i.d.) schedule. Dosage adjustments were made every 3 to 4 days to a maximum dose of 90 mg, as tolerated by the patient and in light of clinical indications. At the end of 4 weeks' acute treatment, the patient had the option of entering a 3-month maintenance phase.

Participation in the study was voluntary and written informed consent was given. Table 1 shows the clinical characteristics of the patients. Notable are the duration of current illness, which averaged over 1 year for both melancholic and non-melancholic subtypes;

TABLE 1

Clinical Characteristics of Patients ($N = 30$)

Major Depression Subtype	No.	Sex	Age ($\bar{X}$ Yrs)	Duration of Illness ($\bar{X}$ Mos)	No. Previous Antidepressant Trials
Melancholic	10	F = 7 M = 3	48.0	17.0	3.0
Non-Melancholic	20	F = 9 M = 11	41.6	14.4	2.2

TABLE 2

Reasons for Attrition

Reasons	Melancholic	Non-Melancholic
Unimproved	6	3
Side Effects Therapy Refused	1	2

---

[1] University of Pennsylvania Hospitals, Philadelphia, PA 19104.

TABLE 3

Buspirone Side Effects
($N = 30$)

Side Effect	Mild (%)	Mod-Severe (%)
1. Lightheadedness/Dizziness	23	16
2. Restlessness/Agitation	6	26
3. "Spacey" Feeling	6	13
4. Nausea	6	10
5. Paresthesias	10	3
6. Insomnia	3	10
7. Drowsiness/Tiredness	10	3
8. Hot Flashes/Sweating	6	3

TABLE 4

Global Treatment Outcome
($N = 30$)

Major Depression	Marked-Moderate	Mild	None
Melancholia (Includes two Bipolar II)	0	1	9*
Non-Melancholic	11	4	5

Fishers Exact Test

Marked-moderate vs. mild, none = $p < .03$
Marked-moderate, mild vs. none = $p < .01$
*Includes two patients with only 1 week's data because of side effects.

also the fact that most patients had had more than one previous trial of antidepressant treatment. Ten patients met melancholic criteria while 20 were non-melancholic. At intake, the mean HAM-D score for melancholics was 28.1±3.5, and for non-melancholics, it was 20.6±3.6. Weekly HAM-D, Hopkins Symptom Checklist, and a 6-point physician- and patient-rated global improvement scale were used to assess treatment outcomes.

Results

Of the 30 patients entering treatment, 18 completed the 4-week acute phase (3 melancholic and 15 non-melancholic). As indicated in Table 2, attrition was higher for the melancholic than for the non-melancholic group. Lack of therapeutic effect was most frequently cited as the reason for drop out.

Table 3 indicates percentages of patients reporting a given side effect. Overall, 11 patients complained of none or mild side effects and 19 complained of moderate to severe side effects. These figures must be understood in light of a dosing strategy that, in the absence of a known antidepressant dose range, called for incremental increases to 90 mg, or until significant side effects developed, whichever came first. As a result, the mean maximal dose for buspirone was 78 mg, which was well above the usual anxiolytic range. In retrospect, a dose of 40 to 60 mg appeared sufficient to produce the desired antidepressant effect and was well tolerated.

Table 4 gives the results for physician rated global improvement at the end of acute treatment. Moderate to marked improvement was seen for 55% of non-melancholic depressives as opposed to none of the melancholics. This is a significant treatment effect for non-melancholics (moderate and marked improvement vs. mild, none) at $p < .05$. There was virtual identity between patients evincing moderate to marked improvement, and those deciding to continue the trial of buspirone into a maintenance phase.

Tables 5 and 6 show the HAM-D scores for melancholic vs. non-melancholic patients at each of the study weeks, presented in two different ways. Table 5 presents "endpoint" data in which final HAM-D scores of dropouts are carried forward to final Week 4. This corrects for the artifactual improvement in HAM-D scores that results from deleting dropouts, who frequently have higher scores

TABLE 5

Weekly Endpointer HAM-D Scores (Mean ±SD)
Repeated Measures Analysis

	Week				
	0	1	2	3	4
Melancholic ($N = 10$)	28.1 ± 3.54	27.1 ± 7.3	27.8 ± 7.36	28.6 ± 5.27	28.7 ± 6.18
Non-Melancholic ($N = 20$)	20.6 ± 3.65	17.7 ± 4.18	15.8 ± 6.28	14.0 ± 7.18	11.6 ± 7.59

Treatment Group × Time: F(Linear) = 13.38, df 1,28, $p < .001$

TABLE 6

Weekly Completer HAM-D Scores (Mean ± SD)
Repeated Measures Analysis

	Week 0	1	2	3	4
Melancholic (*N* = 3)	25.0 ± 3.46	23.0 ± 5.20	20.7 ± 5.51	24.7 ± 2.52	25.0 ± 7.55
Non-Melancholic (*N* = 15)	19.8 ± 3.43	17.1 ± 4.13	14.3 ± 5.31	11.5 ± 6.16	8.30 ± 5.12

Treatment Group × Time: *F* (Linear) = 8.53, df 1,16, $p < .01$.

and have failed to respond to treatment. To counterbalance this approach, Table 6 presents weekly HAM-D data on "completers" of the 4-week active treatment protocol. Repeated measures analysis of variance, conducted on endpoint and completer data, demonstrated a significant improvement in HAM-D scores over the 4 weeks of the study for the non-melancholic, but not the melancholic, subgroup.

To address the question of whether baseline levels of anxiety would predict treatment response, baseline Covi anxiety scores were examined in treatment responders vs. nonresponders. As can be seen (Table 7), baseline levels of anxiety were not significantly different for treatment responders vs. nonresponders.

Conclusion

A preliminary study of buspirone in the treatment of DSM-III Major Depression suggests a significant antidepressant effect for this novel compound for a non-melancholic subgroup. Further, antidepressant efficacy did not appear to be merely the result of an anxiolytic "halo" effect, since treatment response was not predicted by baseline levels of anxiety or its reduction. A daily dose in the range of 40 to 60 mg of buspirone appears sufficient to produce an antidepressant effect. The open-label nature of the study obviously makes any conclusions highly tentative. But given these preliminary results, and the favorable side-effect profile, a well-controlled, double-blind trial of buspirone in the treatment of non-melancholic depression would appear to be indicated.

TABLE 7

Baseline Anxiety

Depression Subtype	Treatment Response	Covi Score
Melancholic (*N* = 10)	Nonresponders	7.8
Non-Melancholic (*N* = 11)	Responders	5.9
Non-Melancholic (*N* = 9)	Nonresponders	6.0

References

Feighner, J.P., Merideth, C.H., and Hendrickson, G.A. A double-blind comparison of buspirone and diazepam in outpatients with generalized anxiety disorder. *J. Clin. Psychiatry*, 43(2):103–107, 1982.

Goldberg, H.L., and Finnerty, R.J. The comparative efficacy of buspirone and diazepam in the treatment of anxiety. *Am. J. Psychiatry*, 136:1184–1187, 1979.

Klein, D.J. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia (Berlin)*, 5:397–408, 1964.

Newton, R.E., Casten, G.P., Alms, D.R., et al. The side-effect profile of buspirone in comparison to active controls and placebo. *J. Clin. Psychiatry*, 43(2):100–102, 1982.

Riblet, L.A., Taylor, D.P., Eison, M.S., and Stanton, H.C. Pharmacology and neurochemistry of buspirone. *J. Clin. Psychiatry*, 43(2):11–16, 1982.

Rickels, K. Recent advances in anxiolytic therapy. *J. Clin. Psychiatry*, 42(2):40–44, 1981.

Rickels, K., Feighner, J.P., and Smith, W.T. Alprazolam, amitriptyline, doxepin, and placebo in the treatment of depression. *Arch. Gen. Psychiatry*, 42:134–141, 1985.

Sheehan, D.V., Ballenger, J., and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. *Arch. Gen. Psychiatry*, 37:51–59, 1980.

A Review of Controlled Studies of Adinazolam Mesylate in Patients With Major Depressive Disorder

John P. Feighner, M.D.[1]

Introduction

At the NCDEU Annual Meetings in 1982 and 1984, some results of the dose-finding studies with adinazolam mesylate (DERACYN® Tablets, The Upjohn Company) in depressed patients, and two subsequent placebo-controlled antidepressant trials using the new triazolobenzodiazepine, were presented. Since then, a total of five studies controlled with placebo have been completed, and four larger studies controlled with both placebo and an active standard have also been completed or nearly completed. The latter were 6-week trials comparing adinazolam with imipramine in depressed outpatients and with amitriptyline in depressed inpatients. The purpose of this paper is to review the clinical data obtained in these Phase II and III trials.

In animal studies using assays known to predict anxiolytic activity, e.g., pentylenetetrazol antagonism, adinazolam was effective at doses similar to those for diazepam (Hester et al., 1980). Yet, in assays known to predict antidepressant activity, e.g., yohimbine toxicity potentiation, adinazolam was effective at doses similar to those for imipramine (Hester et al., 1980). Works by others also indicate that adinazolam shows typical antidepressant-like activities in animals. For instance, in rats, adinazolam inhibited reserpine-mediated upregulation of cortical β-adrenergic receptors (Lahti et al., 1984) and sensitized forebrain hippocampal neurons to applied serotonin (Turmel & deMontigny, 1984). The apparent key to the novel dual activity was the addition of a tertiary amino group to the 1-position of the triazolobenzodiazepine ring system.

The first clinical trials with adinazolam were done in patients hospitalized for severe depression. These trials indicated antidepressant activity with little or no anticholinergic activity. Perhaps greater novelty, however, rested in the rapidity of the responses. About half those responding to adinazolam responded markedly within 2 to 7 days after starting the new drug (Pyke et al., 1983).

Methods

The five Phase II double-blind, placebo-controlled studies with adinazolam were conducted in patients with DSM-III Major Depression. The two inpatient studies required a total score of greater than 25 on the 21-item Hamilton Rating Scale for Depression (HAM-D); the three outpatient studies required HAM-D scores greater than 20. In all five studies, patients had to be more depressed than anxious on Raskin and Covi scores, respectively.

The Phase III double-blind, placebo- and tricyclic-controlled studies also treated DSM-III Major Depression. Three studies required outpatients with HAM-D total scores of greater than 19; one study required inpatients with Melancholia and HAM-D total scores greater than 25.

Patients under age 18 or over age 65 were excluded, as were women not using reliable contraceptive methods. Patients with uncontrolled physical illness or those taking concomitant psychotropics, patients with a history of substance abuse or benzodiazepine sensitivity, and patients who had been treated with electroconvulsive therapy or investigational drugs within a month of the study were excluded. Patients with DSM-III diagnoses of bipolar, dysthymic, or atypical depression were also excluded, but bipolar II subjects

---

[1] Feighner Research Institute, La Mesa, CA 92041.

(atypical bipolar major affective disorder) were allowed in one Phase II outpatient study (6310, Dunner).

Study Design

During screening, for which up to 7 days were allowed, a placebo was given three times a day while physical examinations and diagnostic workup were completed. Patients who fulfilled entrance criteria were then randomized to receive either adinazolam or placebo tablets for 6 weeks. In Phase III studies, an additional group of patients received either imipramine (outpatients) or amitriptyline (inpatients).

Follow-up evaluations were conducted on day 3 or 4 and at weeks 1, 2, 4, and 6 after medication was initiated. Efficacy judgments were made on the basis of the rating scales shown in Tables 1 and 2. These included the HAM-D total score, the Physician's Global Impressions, and, at final evaluation, a Patient's Drug Evaluation Form. Tolerance was rated through a modification of the Treatment-Emergent Symptoms and Side Effects (TESS) Form (Guy, 1980). For analyses, all medical events were added to the TESS results.

Results

Phase II Studies

A total of 172 patients were treated with adinazolam and 171 patients were treated with placebo; of these, 164 adinazolam-treated patients and 158 placebo-treated patients completed more than 5 days of study medication and were considered evaluable. An analysis of patient enrollment and results by study is given in Tables 1 and 2. Except for study 6306 (Cohn), which predominantly enrolled males, female enrollees outnumbered males in Phase II by 64% to 36%.

Adinazolam (30 to 90 mg daily) was significantly superior to placebo on most or all measures in four of the studies (6306, Smith; 6309, Cohn and Feighner; 6310, Dunner), which cumulatively treated 140 patients with adinazolam and 140 patients with placebo. Of these, more than twice as many adinazolam-treated patients (63%) completed the 6-week study as compared with placebo-treated patients (31%). The predominant reason for dropping out was inefficacy of the placebo. The combined incidence of moderate or marked therapeutic effect at final evaluation in these four studies was 61% with adinazolam and 29% with placebo. The final incidence of 50% or greater decrease in HAM-D

TABLE 1

Incidence of Success Measured by Primary Efficacy Variables
Inpatient Studies

	Protocol No. 6306			
	Cohn		Smith	
	Adinazolam	Placebo	Adinazolam	Placebo
Total Enrolled	32	31	40	40
Evaluable Patients*	28	24	40	40
Completers	14 (50%)	9 (38%)	25 (63%)**	15 (38%)
Physician's Global: Much or very much improved since admission	17 (61%)	9 (38%)	25 (63%)**	14 (35%)
Physician's Global: Moderate or marked therapeutic effect of drug	13 (48%)	9 (38%)	25 (63%)**	15 (38%)
Hamilton Depression Scale: Total score decrease ≥50% of initial	7 (26%)	8 (33%)	24 (60%)**	15 (38%)
Patient's Drug Evaluation Form: Felt drug helped moderately, much, or very much	15 (54%)**	6 (25%)	24 (60%)**	12 (30%)

*Patients were required to complete at least 5 days of study medication to be considered evaluable.
**Significant difference from placebo ($p<0.05$) using one-tailed Fisher's exact test.

TABLE 2

Incidence of Success Measured by Primary Efficacy Variables
Outpatient Studies

	Protocol No. 6309				Protocol No. 6310	
	Cohn		Feighner		Dunner	
	Adinazolam	Placebo	Adinazolam	Placebo	Adinazolam	Placebo
Total Enrolled	40	40	20	20	40	40
Evaluable Patients*	36	36	20	18	40	40
Completers	24 (67%)**	7 (19%)	12 (60%)**	5 (28%)	24 (60%)**	15 (38%)
Physician's Global: Much or very much improved since admission	28 (78%)**	7 (19%)	11 (55%)**	2 (11%)	22 (55%)	15 (38%)
Physician's Global: Moderate or marked therapeutic effect of drug	24 (67%)**	7 (19%)	12 (60%)**	4 (22%)	21 (53%)	15 (38%)
Hamilton Depression Scale: Total score decrease ≥50% of initial	22 (61%)**	6 (17%)	12 (60%)**	3 (17%)	24 (60%)**	15 (38%)
Patients Drug Evaluation Form: Felt drug helped moderately, much, or very much	26 (72%)**	6 (17%)	12 (60%)**	3 (17%)	21 (53%)**	12 (30%)

*Patient's were required to complete at least 5 days of study medication to be considered evaluable.
**Significant difference from placebo ($p<0.05$) using one-tailed Fisher's exact test.

total score was 60% with adinazolam and 28% with placebo.

The Figure shows the Physician's Global Impression of the therapeutic effect of the drug relative to length of treatment combining the two outpatient studies done under the same protocol (6309, Cohn and Feighner). Only those with a moderate or marked therapeutic effect are counted. By one-tailed Fisher's exact test, the difference between groups is already significant by day 2, the first follow-up evaluation. More than half of the eventual responders to adinazolam did so by day 4, and three-fourths, by day 7.

The only study not significantly favoring adinazolam on most measures was a study of 63 Veterans Administration Hospital patients, 32 given adinazolam and 31 given placebo (6306, Cohn). The results in this study were not significantly different for the two treatments except in response to the Patient's Drug Evaluation Form; significantly more patients (54%) who had taken adinazolam felt that the drug helped them moderately, much, or very much, as compared with patients who had taken placebo (25%).

Table 3 shows the side effects observed in 10% or more of the patients in either treatment group in the largest compilation made to date, that for studies 6306 (Cohn) and 6309 (Cohn and Feighner). The side effects reported at incidences higher with adinazolam than with placebo were mainly drowsiness, followed by lightheadedness, dizziness,

Pooled Outpatient Studies
Protocol 6309 (Cohn, Feighner)

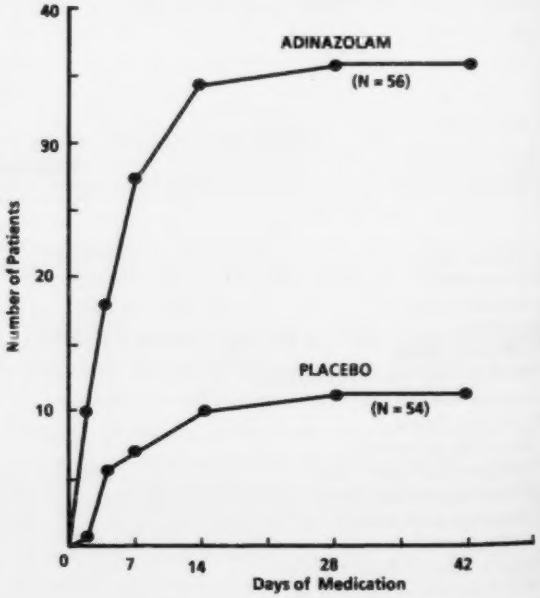


FIGURE. Number of patients with a Physician's Global Impression rating of moderate or marked therapeutic effect of the study drug.

or faintness; excessive dreaming was also more frequent with adinazolam than placebo, but only in one of the three studies. No hypomanic episodes, even in the bipolar II subjects, and no significant anticholinergic effects were observed.

Phase III Studies

Four 6-week comparisons with placebo and a tricyclic antidepressant, each with 40 subjects or more per treatment group, have been analyzed. Three single-center studies involved outpatients who were required to have DSM-III Major Depression and a HAM-D total score greater than 19; one multicenter study involved inpatients, required to have DSM-III Major Depression with Melancholia and a HAM-D total score greater than 25. The interim results from these Phase III studies are shown in Table 4.

In the outpatient studies, adinazolam (30 to 90 mg daily) was compared with imipramine (75 to 225 mg daily) and with placebo. Approximately 40 patients were enrolled per treatment per center; a majority of the patients enrolled completed the study in each treatment group at each center. Across the centers, the final incidence of moderate or marked therapeutic effect was 64% with adinazolam, 55% with imipramine, and 38% with placebo. The final incidence of 50% HAM-D total score reduction was 47% with adinazolam or imipramine and 30% with placebo.

The inpatient studies compared adinazolam (30 to 120 mg daily) with amitriptyline (75 to 300 mg daily) and with placebo in eight participating centers. Interim results with 54 patients given adinazolam, 46 given amitriptyline, and 41 given placebo, indicate that a majority of the patients completed treatment with adinazolam or amitriptyline (59% and 61%, respectively), but only 39% completed treatment with placebo. The incidence of moderate or marked therapeutic effect (50%, 56%, and 27%, respectively), that of HAM-D total score decrease to eight or less (30%, 33%, and 15%, respectively), and perhaps that of 50% symptom reduction on HAM-D (39%, 52%, and 27%, respectively), indicate that adinazolam is an effective antidepressant in severe depression, also.

The only side effects seen significantly more with adinazolam than with placebo in any Phase III study have been drowsiness and some confusion, decreased memory, etc., which were transient. Again, no significant anticholinergic effects were seen.

Discussion

In Phase II trials adinazolam was active as an antidepressant; it was superior to placebo in almost all measurements. It had a rapid onset of action, providing a significant antidepressant effect after 2 to 7 days in most eventual responders. Little dose titration was

TABLE 3

Side Effects or Medical Events in ≥ 10% of Patients Adinazolam Studies 6306 (Cohn) and 6309 (Cohn, Feighner)

	Adinazolam (*N* = 92)					Placebo (*N* = 91)
	Mild	Moderate	Severe	Total	%	%
Drowsiness***	25	31	5	61	66.3	16.5
Lightheadedness, dizziness, or faintness*	13	8	1	22	23.9	5.5
Vivid dreams or dreaming*	8	6	0	14	15.2	1.1
Dry mouth or decreased salivation	8	2	0	10	10.9	8.8
Headache	4	4	2	10	10.9	7.7

Asterisks: Incidence significantly higher with drug than with placebo in: *** = each of the three studies and * = one study.
No Asterisk: No significant differences in the incidence from placebo.

best copy available

TABLE 4

Interim Analysis of Adinazolam Phase III Antidepressant Trials
Incidence of Success

	R-6318 Outpatients[a]			R-6329 Inpatients[b]		
	Adinazolam	Imipramine	Placebo	Adinazolam	Amitriptyline	Placebo
Evaluable Patients	122	120	120	54	46	41
Completers	67%	62%	58%	59%	61%	39%
Physician's Global:						
Moderate or marked therapeutic effect of drug	64%	55%	38%	50%	56%	27%
Hamilton Total Score:						
≥50% decrease	47%	47%	30%	39%	52%	27%
Final score≤8				30%	33%	15%

[a] DSM-III diagnosis: Major depression. Interim analysis across three studies.
[b] DSM-III diagnosis: Major depression with melancholia. Interim analysis across eight centers.

needed before the onset of efficacy (an initial dose of 30 mg daily was titrated to a final dose median of 45 to 80 mg daily).

Adinazolam alleviated the core symptoms of depression in these studies, as measured using HAM-D cluster scores, and it appeared useful in severe (inpatient) or moderate (outpatient) Major Depression, in chronic or relatively acute depression, and in drug-resistant depression. In addition, in studies done by Dr. David Dunner, 21 outpatients with bipolar II depression were given adinazolam with outcomes similar to those in patients with unipolar illness; none became hypomanic or manic. Since these were 6-week studies, only limited conclusions may be drawn regarding safety in bipolar II subjects.

Adinazolam was well-tolerated; the Phase II dropout rate for side effects was 4%, compared with 3% for placebo. The typical side effects observed were moderate and usually transient. Drowsiness was the most common and dizziness was the next most common. Anticholinergic effects were absent or equal to placebo. A tapered withdrawal period served to decrease side effects reported after extended use of benzodiazepines.

In the Phase III trials, interim analysis of the studies with larger enrollment appears to support the conclusion that adinazolam is an active antidepressant that is useful in both outpatients and inpatients. The side effects seen in Phase III were similar to those seen in the Phase II trials.

The overdose profile of adinazolam has so far been completely benign. Five suicide attempts using up to 500 mg produced no cardiovascular toxicity; in these patients cognitive impairment and oversedation were the only effects observed and these were rapidly reversible without neurologic sequelae.

In conclusion, adinazolam is a new triazolobenzodiazepine that appears to be an effective antidepressant, even for hospitalized patients with Major Depression with Melancholia. The therapeutic index of this drug appears to be extremely promising and warrants further study.

Acknowledgment: While my center performed two of these studies and is currently participating in a third, the other studies reviewed herein were performed under the supervision of Drs. G.C. Aden, S.C. Bhatia, J.D. Carman, J.B. Cohn, D.L. Dunner, W.E. Fann, R.H. Gerner, B. Hubbard, M. Morphy, E. Robins, W.T. Smith, S. Thein, and C.C. Weise. The editorial assistance of M.M. Wesley is also appreciated.

References

Guy, W. *ECDEU Assessment Manual for Psychopharmacology.* Rockville, Md.: U.S. Department of Health, Education, & Welfare, 1976.

Hester, J.B., Jr., Rudzik, A.D., and VonVoigtlander, P.F. 1-(Aminoalkyl)-6-aryl-4H-s-triazolo [4,3-a] [1,4] benzodiazepines with antianxiety and antidepressant activity. *J. Med. Chem.*, 23:392–402, 1980.

Lahti, R.A., Pyke, R.E., and Sethy, V.H. Adinazolam, a triazolobenzodiazepine antidepressant. Preclinical and clinical data. In: *IUPHAR 9th International Congress of Pharmacology*, London: The Macmillan Press Ltd., 1984 (abstract 1983P).

Pyke, R.E., Cohn, J.B., Feighner, J.P., and Smith, W.T. Open-label studies of adinazolam in severe depression. *Psychopharmacol. Bull.*, 19(1):96–98, 1983.

Turmel, A., and deMontigny, C. Sensitization of rat forebrain neurons to serotonin by adinazolam, an antidepressant triazolobenzodiazepine. *Eur. J. Pharmacol.*, 99:241–244, 1984.

Chronic Depression: Demographic and Clinical Characteristics[1]

James H. Kocsis, M.D.,[2] Carlyle Voss, M.D.,[3] J. John Mann, M.D.,[2] and Allen Frances, M.D.[2]

Interest in states of chronic depression has recently been raised because of observations that these conditions may represent unrecognized and/or poorly treated forms of affective disorder (Weissman & Klerman, 1977), and do share clinical, familial, biological, and treatment response characteristics with acute or episodic affective illnesses (Akiskal et al., 1980, 1981; Kocsis et al., 1985; Rounsaville et al., 1980; Ward et al., 1979). Prior to 1980, patients having chronic depression tended to be seen as suffering primarily from personality disorders, and their chronic depression was viewed as an aspect of, or complication of, character pathology (Diagnostic and Statistical Manual—2nd ed., 1968; Schildkraut & Klein, 1975). Recently, Akiskal et al. (1980) proposed a reclassification of "chronic characterologic depressions" into two major subgroups, one which shares many features of typical affective disorders including response to antidepressant medication and a second, medication unresponsive type, with "unstable" personality disorders. An extension of this reconceptualization of chronic depressions was placement in DSM-III (1980), under the term Dysthymic Disorder, in the Affective Disorder section of that classification.

Chronic depression has been regarded variously as a complication of personality disorders, an attenuated form of affective disorder, or as a reaction to chronic stress (DSM-III, 1980). However, there have been few empirical studies which have reported data pertinent to these theories. Validation of meaningful subtypes of chronic depression along the suggested theoretical lines remains a goal of research.

The current study was undertaken for the purpose of systematic collection of data about concomitant affective and personality diagnoses, presence of psychosocial stressors, and family history of psychiatric disorders in a sample of patients with chronic depression and a comparison group of outpatients having episodes of acute depression.

Methods

Description of the Study: The study was conducted in two outpatient clinics (Department of Psychiatry, Maine Medical Center and Department of Psychiatry, New York Hospital-Cornell Medical Center) according to identical protocols and selection criteria. Patients were interviewed by research psychiatrists utilizing a semi-structured interview designed to elicit information which would allow diagnosis according to the DSM-III. Based on this interview, clinicians rated DSM Axis I, II (Personality Disorders), and IV (Psychosocial Stressors). Systematic inquiry about demographic material and family history of psychiatric disorders was also done and results were recorded at this time. Clinical symptom profile and severity were rated by use of the 24-item version of the Hamilton Scale for Depression (HAM-D; 1960). Information about prior treatments with psychotherapy or drugs was recorded and informed consent was obtained from all subjects.

Selection of Patients and Depressive Controls: Two patient groups were sampled, both drawn from the Affective Disorders clinics of the New York Hospital or Maine Medical Center. The chronic depression patients were included if they met DSM-III criteria for Dysthymic Disorders, i.e., had depressed or dysphoric mood for longer than 2 years and at least three associated symptoms of depression. Presence or absence of current Major Depression or Melancholia was systematically determined but patients were included

---

[1] This study was supported in part by USPHS Grant MH-37103 from the National Institute of Mental Health.

[2] Department of Psychiatry, New York Hospital-Cornell Medical Center, New York, NY 10021.

[3] Department of Psychiatry, Maine Medical Center, Portland, ME 04102.

The authors wish to thank Carmen Fontanes for her help in the preparation of this manuscript.

whether or not they had these associated or superimposed conditions. Patients with nonaffective DSM-III Axis I diagnosis (e.g., schizophrenia, drug or alcohol dependence, or organic brain syndromes) were excluded, as were patients with severe chronic or acute medical illness.

The sample of acute depressive controls included 26 age- and sex-matched patients who participated in one of two outpatient psychopharmacology studies of acute depression in the Affective Disorders clinic of New York Hospital. All had durations of the current episode under 1 year. They received the same battery of diagnostic and clinical evaluations at baseline with the exception of the evaluation of family psychiatric history.

Results

Comparisons of demographic and clinical characteristics between patients with chronic depression and the acute depressive control group are shown in Table 1. Age and sex did not differ significantly between the two groups. Significantly fewer acute depressives had ever married.

Thirty-seven of 39 (95%) chronic depressives fulfilled DSM-III criteria for Major Depressive Disorder in addition to their Dysthymic Disorder, and 23 (59%) also met criteria for Melancholia. Forty-seven percent of depressives were rated as having an Axis II diagnosis. Personality disorder diagnoses included: Dependent (*N* = 9), Avoidant (*N* = 4), Narcissistic (*N* = 3), Schizotypal (*N* = 3), Compulsive (*N* = 2), and five others which were given once each.

Axis I and Axis II diagnoses were similar for the acute depressive controls. All had Major Depressive Disorder by definition, 73% met criteria for Melancholia, and 40% were given an Axis II diagnosis. Moderate to severe psychosocial stress tended to be more prevalent in the acute depressives (62% vs. 47%). There was no significant difference in severity of illness in the two groups as measured by the 24-item HAM-D total score.

By definition, all patients in the chronic depressive sample had durations of illness greater than 2 years. In fact, this group reported remarkable chronicity of their depression. Fifty percent stated that depression had been continually present for more than 10 years. The chronic group showed a trend for earlier age of onset, with 65% reporting onset prior to age 25, as compared to 42% of the acute depressives.

TABLE 1

Demographic and Clinical Characteristics of Chronic Depressives and Acute Depressive Controls

Characteristic	Chronic (*N* = 39)	Acute (*N* = 26)
$\bar{X}$ Age (Years)	40.1	42
Male	11	8
Female	27	18
Never Married	10	16*
Married	18	5
Divorced, Separated, or Widowed	10	5
% Current Major Depression	95	100
% Current Melancholia	59	73
% Current DSM-III Axis II Dx	47	40
$\bar{X}$ HAM-D Total Score	26.2	28
% FH Depression	55	–
% FH Mania	11	–
% Onset Before Age 25	65	42**
% Prior Psychotherapy	76	–
% Prior Antidepressant Drug Rx	18	50*
% Prior Psychiatric Hospitalization	13	15
% Prior Suicide Attempt	19	10
% DSM-II Axis IV = 4 (Moderate)	47	62

* $p < .01$
** $p < .1$

Profiles of clinical symptoms as rated on the HAM-D in the two patient groups are compared in Table 2. Although chronic and acute depressives had similar frequencies of most items, acute depressives had significantly higher frequencies of four symptoms: loss of productivity, general somatic complaints of fatigue and body pains, diurnal variation of mood with morning worsening, and feelings of worthlessness. A history of suicide attempts was found in 19% of chronic and 10% of acute depressives. Only one patient had a history of more than one attempt.

Systematic family history data was collected in the chronic depressive sample. Fifty-five percent reported a history of depression in a first-degree relative, and 11% reported a history of mania.

A significant difference was noted in history of prior psychiatric treatment between

TABLE 2

Frequency of Occurrence of Individual HAM-D Symptoms*

Item	% Occurrence Chronic (*N* = 39)	 Acute (*N* = 26)
Depressed Mood	92	100
Guilt	41	54
Suicide	54	50
Early Insomnia	28	46
Middle Insomnia	33	46
Late Insomnia	23	31
Work and Interests	77	100**
Retardation	15	15
Agitation	0	8
Psychic Anxiety	77	88
Somatic Anxiety	54	42
GI Symptoms	15	12
General Somatic	51	81**
Genital	38	42
Hypochondrias	38	35
Weight Loss	15	27
Insight	0	0
AM Mood Worsening	21	46**
Depersonalization	13	15
Paranoia	3	4
Obsessions	0	8
Helplessness	28	50
Hopelessness	46	50
Worthlessness	51	80**
$\bar{X}$ Total Score	26.2	28.4

*Item score higher than one.
**Acute > Chronic $p < .05$

chronic depressive and controls. Fifty percent of the acute depressives had received at least one prior adequate trial of antidepressant medication, compared to only 18% of chronic patients. Seventy-six percent of chronic depressives had received prior treatment by psychotherapy. No comparison data were available for acute depressives.

Discussion

We report results of a study of clinical and demographic characteristics in 39 outpatients with Chronic Depression (DSM-III—Dysthymic Disorder). A group of 26 patients with acute Major Depressive Disorder was used as a comparison group.

Thirty-seven of the 39 chronic depressives also fulfilled DSM-III criteria for Major Depression and 59% also fulfilled criteria for Melancholia. Therefore, in this sample of patients there was clearly a good deal of symptomatic overlap between chronic depression and typical acute affective disorders as defined in DSM-III. The relationship between chronic depression and affective illness is further emphasized by the few differences seen in these two groups in other clinical and demographic characteristic and similarities in profiles of symptoms. These results and the high incidence of affective illness reported by the chronic depressives in their first-degree relatives support the notion recently advanced by Akiskal (1983) and Akiskal et al. (1980, 1983) that many states of chronic depression seen in psychiatric outpatients may represent attenuated or alternative forms of typical, acute affective disorders. Our previously reported preliminary results from a placebo-controlled trial of imipramine treatment conducted in this same chronic depression sample also supports similarity to acute forms of depression (Kocsis et al., 1985).

Another issue which has been raised by Akiskal et al. is the relationship of Dysthymic Disorders to Bipolar Illness (1981). In our sample of chronic depressives we indeed saw a larger than expected family incidence of bipolar illness, and one of our patients did develop a possible episode of drug-induced hypomania. Further data will be needed to address the relationship between these disorders, but it appears that a subgroup of dysthymic patients may be "sub-bipolar."

It has previously been suggested that some forms of chronic depression may result from the chronic presence of severe psychosocial or other kinds of stress (Schildkraut & Klein, 1975). The current study found a nonsignificant trend toward more current psychosocial stress in the acute depressives. However, prior studies have found interactions between stress, chronicity of depression, and non-response to antidepressant medications (Akiskal, 1982; Kocsis et al., 1984). We have not yet accumulated sufficient data to address such interactions in our chronic depressive sample. Some anecdotal experience suggests that chronic depression related to severe psychosocial stress may be a particular indication for psychotherapy or a combined treatment. It remains to be determined whether a meaningful subgroup of chronic depressives exists having chronic stress, a distinct clinical picture, and differential response to treatment.

Because of a long history of interest in relationships between chronic depression and personality disorder and the possibility that some forms of chronic depression may represent either a class of or complication of personality disorders, we have also examined the frequency of Personality Disorders in the two groups. Axis II diagnoses were given in 47% of chronic depressives and 40% of acute depressives, a nonsignificant difference. Because personality characteristics are known to be markedly influenced in a state-dependent fashion by depression (Akiskal et al., 1983; Liebowitz et al., 1979), evaluation of personality diagnosis in depressed patients is fraught with uncertainty. There may, in fact, not be an excess of personality disorders in chronic depressions and the apparent association may have resulted from the presence of depression itself on a chronic basis. However, further evidence that these patients have been seen previously by health professionals as being characterologic rather than affective is provided by our findings that chronic depressives have received frequent prior psychotherapy and little prior adequate antidepressant drug therapy. This has obvious important clinical implications in light of the increasing evidence that a substantial proportion of chronic depressions may respond to antidepressant drugs (Akiskal et al., 1980; Kocsis et al., 1985; Rounsaville et al., 1980; Ward et al., 1979).

References

Akiskal, H.S. Factors associated with incomplete recovery in primary depressive illness. *J. Clin. Psychiatry*, 43:266–271, 1982.

Akiskal, H.S. Dysthymic disorder: Psychopathology of proposed chronic depressive illness. *Am. J. Psychiatry*, 140:11–20, 1983.

Akiskal, H.S., Hirschfeld, R.M.A., and Yerevanian, B.I. The relationship of personality to affective disorders. *Arch. Gen. Psychiatry*, 40:801–810, 1983.

Akiskal, H.S., King, D., Rosenthal, T.L., et al. Chronic depressions. I. Clinical and familial characteristics in 137 probands. *J. Affect. Dis.*, 3:297–315, 1981.

Akiskal, H.S., Rosenthal, T.L., Haykal, R.F., et al. Characterologic depressions: Clinical and sleep EEG findings separating "subaffective dysthymias" from "character spectrum disorders." *Arch. Gen. Psychiatry*, 37:777–783, 1980.

Diagnostic and Statistical Manual of Mental Disorders, 2nd Ed. (DSM-II), American Psychiatric Association, Washington, D.C., 1968.

Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. (DSM-III), American Psychiatric Association, Washington, D.C., 1980.

Hamilton, M. A rating scale for depression. *J. Neuro. Neurosurg. Psychiatry*, 25:56–62, 1960.

Kocsis, J.H., Butler, T., and Mason, B. Psychosocial stress predicts tricyclic antidepressant response. *Am. Psychiatr. Assoc.*, New Research Abstracts, 1984.

Kocsis, J.H., Frances, A., Mann, J.J., et al. Imipramine for the treatment of chronic depression. *Psychopharmacol. Bull.*, 21(3):698–700, 1985.

Liebowitz, M.R., Stallone, F., Dunner, D.L., et al. Personality features of patients with primary affective disorders. *Acta Psychiatr. Scand.*, 60:214–224, 1979.

Rounsaville, B.J., Sholomskas, D., and Prusoff, B.A. Chronic mood disorders in depressed outpatients. *J. Affective Disord.*, 2:73–88, 1980.

Schildkraut, J.J., and Klein, D.F. The classification and treatment of depressive disorders. In: Shader, R.I. (ed.), *Manual of Psychiatric Therapeutics*, Chapt. 3. Boston: Little Brown Co., 1975.

Ward, N.G., Bloom, V.L., and Friedel, R.O. The effectiveness of tricyclic antidepressants in chronic depression. *J. Clin. Psychiatry*, 40:49–52, 1979.

Weissman, M.M., and Klerman, G.L. The chronic depressive in the community: Unrecognized and poorly treated. *Compr. Psychiatry*, 18:523–531, 1977.

Self-Rating of Personality Characteristics and Their Relationship to Treatment Response in Recurrent Unipolar Depressives: A Pilot Study[1]

Ellen Frank, Ph.D.,[2] David J. Kupfer, M.D.,[2] David B. Jarrett, M.D., Ph.D.,[2] and Miriam Jacob, ACSW[2]

Introduction

In their review of the relationship of personality to affective disorders, Akiskal et al. (1983) point out that personality variables have been hypothesized to relate to affective illness in at least four ways: 1) as predisposing factors to affective episodes, 2) as modifiers of affective episodes, 3) as a complication of affective illness, and 4) as an attenuated expression of affective illness. These authors point out that the predisposing factors hypothesis suggests that personality pathology may be etiologic with respect to affective illness. When personality variables are considered as modifiers of affective episodes there is no etiologic speculation, simply the observation that personality characteristics may have an effect on clinical presentation, course, treatment response, and outcome. Personality pathology may also be viewed as a complication of affective illness; it may be either state-dependent (i.e., present during the episode), or it may represent either a short-term or long-term complication observed following the remission of affective symptoms. Finally, personality pathology may represent an attenuated expression of affective illness. In this view, both personality features and affective episodes are considered to be expressions of the same underlying genetic or constitutional endowment.

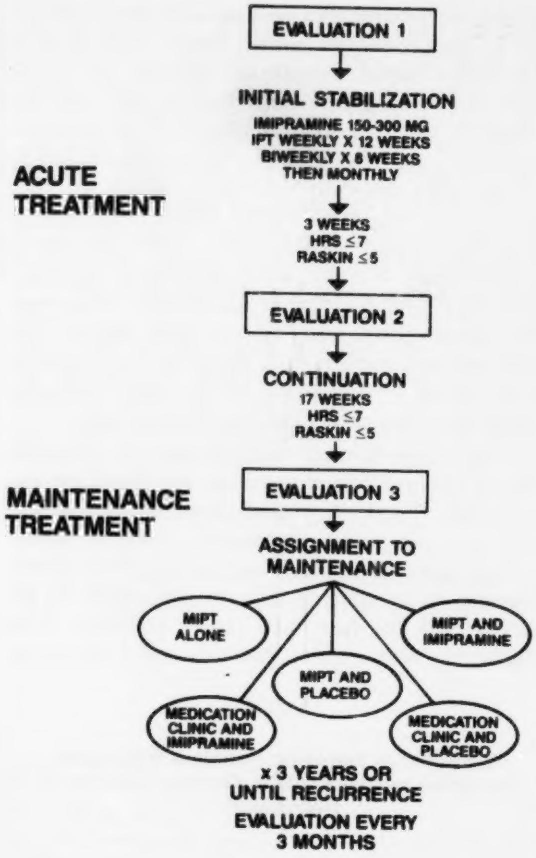
Study Design

When we began the Maintenance Therapies in Recurrent Depression Study, we had no particular bias as to which of these views might be correct. However, we thought it would indeed be important to measure characteristics of personality in the patients being studied. The design of the Maintenance Therapies in Recurrent Depression Study has been described in detail elsewhere (Frank et al., 1984). Briefly, however, the study involves acute treatment of recurrent unipolar patients who present in at least their third episode of major depressive disorder. Patients must have a single-rater Hamilton ≥15 and a Raskin of ≥7. Prior to entering the study, all patients are evaluated with respect to sleep electroencephalograph (EEG) and neuroendocrine parameters after a 2-week drug-free period. Self-report and interview measures of clinical state and social functioning are taken at that time; however, personality is not assessed at baseline. Acute treatment combines imipramine (150 to 300 mg) and Interpersonal Psychotherapy offered weekly for 12 weeks, biweekly for 8 weeks, and then monthly. Patients remain in acute treatment until they achieve a Hamilton of ≤7 and a Raskin of ≤5 for 3 consecutive weeks. At this time, sleep EEG and all night neuroendocrine studies are repeated and self-report measures of personality are administered. Patients then enter a continuation treatment phase of 17 weeks, during which their symptoms are expected to remain stable and no changes are made in the treatment regimen. Following this 17-week period, patients receive a third evaluation including sleep EEG, neuroendocrine, and personality measures. They are then assigned on a random basis to one of five maintenance treatments (*see* Figure) which are continued for 3 years or until the patient experiences a recurrence of illness.

---

[1] This work is supported by NIMH Grants MH-29618 and MH-30915 and the John D. and Catherine T. MacArthur Foundation.

[2] Western Psychiatric Institute and Clinic, Pittsburgh, PA 15213.


EVALUATION 1
INITIAL STABILIZATION
IMIPRAMINE 150-300 MG
IPT WEEKLY X 12 WEEKS
BIWEEKLY X 8 WEEKS
THEN MONTHLY
ACUTE TREATMENT
3 WEEKS
HRS ≤7
RASKIN ≤5
EVALUATION 2
CONTINUATION
17 WEEKS
HRS ≤7
RASKIN ≤5
MAINTENANCE TREATMENT
EVALUATION 3
ASSIGNMENT TO MAINTENANCE
MIPT ALONE
MIPT AND IMIPRAMINE
MIPT AND PLACEBO
MEDICATION CLINIC AND IMIPRAMINE
MEDICATION CLINIC AND PLACEBO
x 3 YEARS OR UNTIL RECURRENCE
EVALUATION EVERY 3 MONTHS

Subjects

The present report is based on the first 95 patients to finish the first 16 weeks of the Maintenance Therapies in Recurrent Depression protocol. The patient group consisted of 23 males and 72 females with a mean age of 40.6 ±10.8 years. The average length of the index episode was 23 weeks and the median was 19 weeks. Typically, age of onset was young (mean = 27.2±9.8 years; median = 24.0 years). Although the protocol requires only two previous episodes, the mean number of prior episodes was 6.1±5.8 and the median was 4.0. As we have reported elsewhere (Frank et al., 1984), a little over one third of the patients entering the Maintenance Therapies study have the expected treatment response. That is, they achieve remission within the first 7 to 8 weeks and remain well throughout the continuation period. A second third shows a more variable response, taking up to 16 weeks to achieve a stable remission. Finally, one third of the patients studied show only a partial response to the combined pharmacotherapy/psychotherapy treatment regimen. An algorithm was developed for assigning patients to these response categories on the basis of absolute Hamilton scores and percent change in Hamilton scores from baseline (Frank et al., 1984). When these three treatment response groups were examined, no differences were observed among them on age, sex, length of index episode, age at onset of illness, or number of previous episodes of affective illness. However, differences were observed in terms of baseline biological characteristics with the normal responders showing the most biological disturbance.

When we examined this larger cohort of 95 patients, we continued to observe the same kinds of differences between normal and slow responders in terms of sleep EEG and neuroendocrine changes. The present paper focuses on the differences in self-ratings of personality between the normal ($N = 35$) and the slow ($N = 32$) responders, and on the relationship between biological variables measured prior to treatment and personality variables measured once remission was achieved. The Hirschfeld-Klerman Personality Battery, a 436-item self-report inventory made up of a total of 17 scales taken from the Guilford-Zimmerman Temperament Survey, the Interpersonal Dependency Inventory, the Lazare-Klerman-Armor Personality Inventory (short version), the Maudsley Personality Inventory, and the Ego Control and Ego Resiliency Scales of the Minnesota Multiphasic Personality Inventory (MMPI), was used to assess personality.

Results

Since we had obtained personality ratings on patients at both Evaluation II (end of the 3-week stabilization period) and Evaluation III (end of continuation treatment) which, by design, are separated by 17 weeks, we examined the stability of scores on the Hirschfeld-Klerman battery over that time period.

TABLE 1

Hirschfeld-Klerman Battery:
Normal Versus Slow Responders

Scale	t
Ascendance (GZTS)	2.51*
Sociability (GZTS)	2.27*
Emotional Stability (GZTS)	3.97***
Objectivity (GZTS)	3.36***
Lack of Self-Confidence (IDI)	2.56*
Orality (LKA)	3.65***
Neuroticism (MPI)	4.24***

$^{*}p<.05$
$^{***}p<.001$

Abbreviations: GZTS = Guilford-Zimmerman Temperament Survey
IDI = Interpersonal Dependency Inventory
LKA = Lazare-Klerman-Armor Personality Inventory
MPI = Maudsley Personality Inventory

Test-retest correlation coefficients for the 17 scales ranged from .61 to .86, all $p<.001$.

When we compared normal responders with slow responders in terms of their personality characteristics, we found that on 7 of the 17 scales, normal responders showed significantly less personality pathology than did the slow responders. On no scale was the reverse true; the remaining 10 scales revealed no statistically significant differences between the two response types (*see* Table 1).

When comparisons were made between baseline biological characteristics and scores on the Hirschfeld-Klerman battery once patients had achieved remission, a complementary pattern emerged. Table 2 illustrates this pattern of relationships, indicating a dissociation between biological pathology and personality pathology.

Discussion

These pilot data suggest four preliminary conclusions. First, among outpatients with a history of recurrent unipolar illness, personality variables appear to remain relatively stable when the affective illness is in remission. Second, there appears to be a striking dissociation between biological disturbance (as measured when the patient is acutely ill) and the personality disturbance (as measured in remission). That is, the more disturbed the patient's baseline biology the less disturbed the patient's personality, and vice versa. Third, when recurrent unipolar patients are offered combined pharmacotherapy and psychotherapy as an acute treatment, those who show a relatively rapid response appear to have clear-cut biological disturbance, at least in terms of EEG sleep and neuroendocrine parameters, and little personality disturbance. Those who respond relatively slowly to this treatment regimen have little biological disturbance and considerably more personality pathology. Finally, with respect to the four hypotheses of Akiskal et al. (1983), whatever else personality may be, it does appear to function as a modifier of the affective episode in terms of the rapidity of response to combined pharmacotherapy/psychotherapy.

These preliminary studies suggest a number of interesting directions for further exploration. First, it would seem to be important to explore the personality characteristics of that group classified as partial responders, keeping in mind that this group needs to be subdivided further into those patients who ultimately went on to have a rapid response

TABLE 2

Relationship Between Baseline Biological Variables and Hirschfeld-Klerman Scores in Remission

	r
Cortisol nadir with	
Sociability (GZTS)	.37*
Emotional Stability (GZTS)	.28*
Thoughtfulness (GZTS)	−.32*
Hysterical Pattern (LKA)	−.31*
Orality (LKA)	−.30*
Neuroticism (MPI)	−.37*
Extraversion (MPI)	.34*
Cortisol latency with	
Hysterical pattern (LKA)	.31*
Ego Control (MMPI)	.29*
Sleep maintenance with	
Emotional Stability (GZTS)	−.46***
Objectivity (GZTS)	−.45***
Emotional Reliance (IDI)	.38**
Assertion of Autonomy (IDI)	.25*
Hysterical pattern (LKA)	.42***
Orality (LKA)	.36**
Neuroticism (MPI)	.46***
REM latency with	
Restraint	−.23*

$^{*}p<.05$
$^{**}p<.01$
$^{***}p<.001$

Abbreviations: GZTS = Guilford-Zimmerman Temperament Survey
LKA = Lazare-Klerman-Armor Personality Inventory
MPI = Maudsley Personality Inventory
MMPI = Minnesota Multiphasic Personality Inventory
IDI = Interpersonal Dependency Inventory

to another treatment regimen (typically monoamine oxidase inhibitors) and those patients who, after being tried on several treatment regimens, continued to show only partial remission of their symptoms. Second, it will be important to explore the clinician ratings of personality features collected using the Personality Assessment Form at the same evaluation points as those used to administer the Hirschfeld-Klerman battery. Third, since the Maintenance Therapies in Recurrent Depression protocol also includes the evaluation of significant others using von Zerssen Personality Inventory (in press), it will be possible to examine the relationship between personality characteristics as perceived by a patient's significant other and the patient's biology and response to treatment. The questions of greatest interest, however, are how these biological and personality parameters might influence the risk of recurrence in a population at high risk for another affective episode and how each of these parameters interact with each of the five maintenance treatment conditions being studied. The answers to these final questions will have to await the completion of the 3-year maintenance phase.

References

Akiskal, H.S., Hirschfeld, R.M.A., and Yerevanian, B.I. The relationship of personality to affective disorders. *Arch. Gen. Psychiatry*, 40:801–810, 1983.

Frank, E., Jarrett, D.B., Kupfer, D.J., and Grochocinski, V.J. Biological and clinical predictors of response in recurrent depression. A preliminary report. *Psychiatry Res.*, 13:315–324, 1984.

von Zerssen, D. Clinical self-rating scales (CSr-S) of the Munich psychiatric information system (Psychis Munchen). In: Sartorius, N., and Ban, T.A. (eds.), *Assessment of Depression*. (In press)

The Suicide Assessment Scale: A Scale Evaluating Change in Suicidal Behavior[1]

Barbara Stanley, Ph.D.,[2,4] Lil Träskman-Bendz, M.D., Ph.D.,[3] and Michael Stanley, Ph.D.[4]

Introduction

Evidence increasingly points to a biochemical deficit associated with suicidal behavior (Åsberg et al., 1976; Stanley et al., 1982). As this body of evidence grows, it becomes more likely that pharmacologic studies designed to alter suicidal behavior will be conducted. In order to perform these studies, adequate means of evaluating change in levels of suicidality must be utilized. However, available measures of psychopathology and suicidality are inappropriate in this regard. There are several reasons for this lack of suitability. First, existing scales (Beck et al., 1979) focus principally on suicide ideation only. For treatment studies, it is vital that evaluation be linked to more than ideation, since ideation relies solely on verbal report. Suicidal thoughts can be denied or distorted and, thus, a rating that relies only on the patient's report can be faulty. While scales measuring other forms of psychopathology may have similar problems, this problem is particularly acute in assessing suicidality where patients may have greater motivation to conceal suicidal thoughts than other forms of symptomatology.

In addition to scales which evaluate suicidal ideation, another group of scales focuses on the prediction of suicide (Zung, 1974). These scales seek to identify individuals at risk for committing suicide and often combine demographic information with an assessment of psychopathology. These measures are also unsuitable for pharmacologic treatment studies because they focus on identification of future behavior. For purposes of treatment studies, current status and fluctuations in this status over time are of prime importance.

Some of the more widely used suicide scales which, while valid in many settings, would be limited in pharmacologic studies, include the following:

1. Scale of a Suicidal Ideation (SSI) (Beck et al., 1979)—This is a 19-item rating scale designed to assess suicidal ideation and includes items such as the wish to die;
2. Suicide Intent Scale (SIS) (Beck et al., 1974a)—This is a 20-item scale designed to characterize and describe a suicide attempt;
3. Index of Potential Suicide (IPS) (Zung, 1974)—The IPS is a 50-item scale combining psychopathology ratings with an index of level of social support to predict suicide potential;
4. Hopelessness Scale (Beck, 1974b)—This is a 20-item scale designed to evaluate pessimism in outlook toward life;
5. Reasons for Living Inventory (Linehan, 1983)—This is a 48-item scale which identifies reasons that individuals have to prevent them from committing suicide. It has been shown to differentiate suicide attempters from non-attempters.

An alternative to using suicide ideation scales would be to consider suicidal behavior as a symptom of a larger diagnostic entity. In most traditional psychiatric conceptualizations of suicide, suicidal ideation is viewed as a manifestation of depression. In this case, standard scales for depression treatment studies such as the Hamilton Depression Scale (HAM-D) (Hamilton, 1976) could be used. However, since both epidemiological and biochemical studies of suicide appear to point to a deficit that cuts across diagnoses

---

[1] This study was supported in part by USPHS Grant No. 40048 from the National Institute of Mental Health.

[2] Department of Psychology, City University of New York, John Jay College, 445 West 59th Street, New York, NY 10019.

[3] Karolinska Institute, Stockholm, Sweden.

[4] New York State Psychiatric Institute, New York, NY 10032.

(Robins, et al., 1954), diagnosis-linked scales would be of only limited value.

Given that available scales were inappropriate for suicide treatment studies, the Suicide Assessment Scale, a scale assessing suicidality and related factors, was developed. Several criteria were established for this scale: 1) it was to evaluate both observable and reported symptomatology associated with suicidality; 2) the scale would not be linked to a specific diagnosis or weighted more heavily toward one diagnosis; and 3) the scale would be designed to evaluate current levels of suicidality and would be sensitive to change in suicide-related symptoms.

Method and Results

Scale Description

The Suicide Assessment Scale (SAS) contains 20 items each rated on a 5-point Likert-type scale. The ratings are performed in the course of a semi-structured clinical interview similar to an interview for the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1976). The interview requires approximately 20 to 30 minutes to conduct. The items were developed by reviewing the relevant literature on differentiating suicidal and non-suicidal individuals. In addition, the authors of the scale independently generated items. Those items on which there was agreement among the raters as well as the literature were included in the scale. The scale items tend to be grouped in five areas: affect, bodily states, control and coping, emotional reactivity, and suicide thoughts and behavior. Table 1 shows the items on the scale.

Items 16 through 20 are the suicide ideation and behavior items. Item 1: sadness and despondency, Item 2: hostility, Item 9: anxiety, Item 12: low self esteem, conceptualized as a sense of failure, and Item 13: hopelessness are the items related to affect. Items 3: anergia, 8: tension, and 10: somatic concern are the bodily states items. Emotional reactivity is evaluated on items 4: hypersensitivity, 5: emotional withdrawal, and 14: inability to feel. The last grouping of items clusters around control and coping. These items are resourcefulness (6), perceived loss of control (7), impulsivity (11), and poor frustration tolerance (15).

Scale Development

In evaluating interrater reliability for total SAS scores, correlations among three raters (two for each patient evaluation) on a set of 37 ratings were computed. Interrater reliability was found to be adequate ranging from .78 to .88. In attempting to examine the validity of the SAS, we administered the scale to a group of 62 suicide attempters and 47 non-attempters who were hospitalized on a psychiatry service (Table 2).

The groups were matched for age and education. We had a higher proportion of males in the non-attempter category, principally as a consequence of the patient population at the time of data collection. Diagnosis did not differ significantly between the groups.

In examining the construct validity of the SAS, a comparison of scores for suicide attempters and non-attempters was made (Table 3). The results show suicide attempters scored significantly higher than non-attempters.

Table 4 differentiates between attempters and non-attempters on the other scales administered. The SSI, the HAM-D Scale, and the suicide item which assesses current suicidal state on the Hamilton Scale distinguished attempters from non-attempters. The BPRS and the Hamilton Anxiety (HAM-A) scale did not.

Table 5 shows the SAS scores for the three diagnostic groups represented in the study: Major Affective Disorder, Schizophrenia, and Personality Disorder. The diagnostic groups do not differ in SAS scores. This is consistent with the finding that suicide cuts across psychiatric diagnoses. Table 6 shows the correlation of the SAS with other scales. As can be seen, the SAS correlates moderately with depression as reflected by the HAM-D scores and moderately with suicide ideation as reflected by the SSI and the suicide item on the HAM-D. The scale shows somewhat of a correlation with psychotic symptomatology as measured by the BPRS. Furthermore, we find that the presence of suicide ideation within the past week and recent attempt in the past 6 months correlates with SAS scores.

TABLE 1

Suicide Assessment Scale

Item	Symptoms
1. Sadness and Despondency	Sad mood; low spirits; feels miserable
2. Hostility	Hostile; angry; belligerent; antagonistic; provoked to rage; easily provoked
3. Anergia	Lack of energy; weariness; tired; fatigued; worn down; harried; sense of weakness
4. Hypersensitivity	Sensitive to criticism; easily hurt; feels easily rejected; easily offended; touchy; takes things personally; suspicious; distrustful
5. Emotional Withdrawal	Lack of emotional contact; socially isolated; retreating; insulated; distrustful
6. Resourcefulness	Inability to solve problems effectively; lack of flexibility in coping with problems; sees few options and alternatives
7. Perceived Loss of Control	Feels lack of control over self or own destiny; feels at mercy of external events; feeling of lacking influence over environment
8. Tension	Physically tense; nervous; ill at ease; inability to relax; jumpy (exclude autonomic symptoms)
9. Anxiety	Worry; overconcern for present or future; fearfulness; dread; uneasiness (exclude autonomic symptoms)
10. Somatic Concern	Concern over physical health; preoccupation with physical symptoms (including aches and pains; sleeplessness; gastrointestinal and cardiovascular symptoms); generalized worries or delusions about body
11. Impulsivity	Acts on impulses; acts without planning or considering consequences; has irresistable urges; acts on spur of moment
12. Low Self Esteem	Low self esteem; feelings of worthlessness and inferiority; feels like a failure
13. Hopelessness	Feels hopeless and despairing; gloomy outlook; pessimistic; feels that the worst will happen; nihilistic thoughts
14. Inability to Feel	Depersonalization; lack of feelings; inability to feel emotions (not lack of empathy)
15. Poor Frustration Tolerance	Easily frustrated or irritated; readily discouraged
16. Suicidal Thoughts	Preoccupied with suicidal thoughts; thinks about being dead; thinks of reactions of others to suicide; finds it difficult to think of anything other than suicide
17. Purpose of Suicide	Suicide is a solution to the problem; suicide is the only alternative to problems; wants to relieve others of burden; reunion with someone who is deceased (as opposed to suicide attempt as attention-seeking and manipulative)
18. Wish to Die	Strong desire to die; feels that he/she doesn't deserve to live; feels that life isn't worth living
19. Lack of Reasons for Living	Feels that there is no one to live for; feels that no one cares; feels that there is no purpose to life
20. Suicidal Actions	Actively plans method for committing suicide; has written a note or informed others; needs to be supervised to prevent attempt

TABLE 2

Demographic Characteristics of Suicide Attempters and Non-Attempters

	Suicide Attempters ($N = 62$)	Non-Attempters ($N = 47$)	Significance Test^a
Age $\bar{X}$	33.1 ± 10.5	30.3 ± 7.6	1.53^{NS}
Education			
$\bar{X}$	12.3 ± 2.2	12.94 ± 2.0	1.45^{NS}
Sex			
% Male	45.8	70.2	5.98*
Diagnosis (%)			
Bipolar, Manic	19.4	23.4	5.37^{NS}
Bipolar, Depressed	3.2	2.1	
Unipolar, Depressed	24.2	8.5	
Schizophrenia	29.0	38.3	
Personality	21.0	21.3	
Other	3.2	6.4	

^{a}For age and education variables, a t-test for independent groups was performed; for sex and diagnosis, a χ^2 test.
*$p < .05$
NS = Nonsignificant

Lethality and seriousness of the most recent attempt did not correlate with SAS scores nor did the level of aggressive behavior in the patient's past.

Table 6 shows the decline in SAS scores for a group of 8 suicidal patients who took part in a study using fenfluramine to treat suicidality. Although not a significant decline, possibly due in part to the small sample size, it appears that the scale will be sensitive to change and can reflect the effect of drugs on patients' conditions.

Discussion

The SAS is a measure that is designed to assess changes in level of suicidality for use in pharmacologic studies as well as other studies of suicidal behavior. The SAS may be useful to investigators studying suicidal behavior when it is important to use a rating that evaluates observable as well as reported symptomatology. The inclusion of observable symptoms on a suicide rating scale is particularly important for inpatient studies of suicidal behavior because suicidal ideation can be readily denied. Patients in psychiatric hospitals may be more motivated to deny suicidal thoughts than other psychiatric symptoms, since hospital privileges (e.g., passes) are often linked to a lack of suicidal ideation.

Furthermore, the development of the SAS represents an effort to identify and assess symptomatology associated with suicidal behavior (e.g., impulsivity and poor frustration tolerance) that go beyond suicidal ideation and diagnosis-specific symptoms. This effort parallels other scales that are commonly used in pharmacologic studies. These scales include the BPRS and the HAM-D and HAM-A scales.

The present study reports preliminary findings on the utility and validity of the SAS. Findings indicate that a high degree of reliability can be achieved in overall ratings. Furthermore, the scale appears to have construct validity, in that it correlates with suicidal ideation. In addition, those patients who have previously attempted suicide and are not cur-

TABLE 3

SAS Scores for Suicide Attempters and Non-Attempters

	Suicide Attempters ($N = 62$)	Non-Attempters ($N = 47$)	
SAS† $\bar{X}$	29.5 ± 13.2	17.3 ± 9.7	5.34*

*$p < .01$
† possible range = 0-80

TABLE 4

Comparison of Psychopathology Scores for Suicide Attempters and Non-Attempters

	Suicide Attempters ($N = 62$)	Non-Attempters ($N = 47$)	t
SSI (range = 0–38) $\bar{X}$	7.2 ± 9.5	1.7 ± 4.7	3.62*
BPRS (range = 18–126) $\bar{X}$	42.4 ± 10.2	38.6 ± 9.7	1.94^{NS}
HAM-A† (range = 0–56) $\bar{X}$	27.4 ± 12.6	25.2 ± 18.6	.56^{NS}
HAM-D (range = 0–64) $\bar{X}$	22.5 ± 8.9	16.8 ± 7.4	3.53*
Suicide Item (range = 0–4) $\bar{X}$	1.6 ± 1.3	.34 ± .8	5.73*

$^{*}p < .01$
NS = Nonsignificant
†sample size = 47; NA = 18

rently suicidal tend to obtain somewhat higher scores on the SAS. This difference between those with and without a history of a suicide attempt may indicate that the scale is detecting some behavioral trait difference between suicide attempters and non-attempters. It may also be that patients with a previous history of a suicide attempt may be more likely to be hospitalized again for suicide-related reasons although not currently suicidal. While these speculations may be valid, additional research needs to be conducted to determine the reasons for the difference between those with and without a history of a suicide attempt.

In addition, several other analyses need to be performed on the scale to determine its usefulness. First, a large-scale follow-up study of suicidal patients over the course of their hospitalization should be performed. This analysis will determine whether the scale reliably detects changes in suicidality.

Secondly, a factor analysis of the scale items is yet to be performed. While the scale has been grouped by item clusters on an a priori basis, a factor analysis is required to determine whether the statistical analysis yields the same factor grouping.

The data for these analyses are in the process of being collected and, thus, the current findings on the SAS are preliminary. At this point, the SAS appears to be a promising instrument for use in evaluating the efficacy of pharmacologic treatments of suicidal behavior.

TABLE 5

Comparison of SAS Scores Across Diagnostic Classification

Diagnosis	$\bar{X}$, SD	t
Major Affective Disorders ($N = 45$)	23.7 ± 13.5	.60^{NS}
Schizophrenia ($N = 36$)	23.8 ± 13.4	
Personality Disorders ($N = 23$)	27.4 ± 12.5	

NS = Nonsignificant

TABLE 6

Correlation Between the SAS and Other Measures of Psychopathology

Other Measures	SAS
Overall Psychopathology	
Brief Psychiatric Rating Scale ($N = 109$)	.543*
Depression and Anxiety	
Hamilton Depression Scale ($N = 109$)	.655*
Hamilton Anxiety Scale ($N = 65$)	.332*
Suicidal Thoughts and Behavior	
Suicidality (HAM-D item) ($N = 109$)	.708*
Scale of Suicidal Ideation ($N = 106$)	.682*
Ideation within 1 week of SAS ($N = 109$)	−.587*
Total Number of Attempts in Past ($N = 109$)	.418*
Attempt within 6 months of SAS ($N = 109$)	−.304*
Seriousness of Recent Attempts ($N = 91$)	.173^{NS}
Medical Lethality of Recent Attempt ($N = 91$)	.175^{NS}
Aggression	
Aggression History Total Score ($N = 66$)	.118^{NS}

$^{*}p < .01$
NS = Nonsignificant

References

Åsberg, M., Träskman, L., and Thorén, P. 5-HIAA in the cerebrospinal fluid: A biochemical suicide predictor? *Arch. Gen. Psychiatry*, 33:1193–1197, 1976.

Beck, A.T., Kovac, M., and Weisman, A. Suicidal intention: The scale for suicidal ideation. *Consult. Clin. Psychol.*, 47:343–352, 1979.

Beck, A.T., Schuyler, D., and Herman, I. Development of suicide intent scales. In: Beck, A.T., Resnik, H.L.P., and Lettieri, D. (eds.), *The Prediction of Suicide*. Baltimore, Md.: Charles Press Publishers, Inc., 1974, pp. 45–56.

Beck, A.T., Weissman, A., Lester, D., and Trexler, L. The measurement of pessimism: The hopelessness scale. *J. Consult. Clin. Psychol.*, 42(6):861–865, 1974b.

Hamilton, M. Hamilton Depression Scale. In: Guy, W. (ed.), *ECDEU Assessment Manual for Psychopharmacology*, Washington, D.C., DHEW Publ. No. (ADM) 76-338, 1976, pp. 180–192.

Linehan, M. Reasons for Living Inventory. Suicidal Behaviors Research Clinic, Washington, D.C., 1983.

Overall, J.E., and Gorham, D.R. Brief Psychiatric Rating Scale. In: Guy, W., (ed.), *ECDEU Assessment Manual for Psychopharmacology*, Washington, D.C., DHEW Publ. No. (ADM) 76-338, 1976, pp. 158–169.

Robins, E., Murphy, G.E., Wilkinson, R.H., Jr., et al. Some clinical considerations in the prevention of suicide based on a study of 134 successful suicides. *Am. J. Public Health*, 49:889, 1959.

Stanley, M., Virgilio, J., and Gershon, S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science*, 216:1337–1339, 1982.

Zung, William. Index of Potential Suicide. In: Beck, A., Resnik, H., and Lettieri, D. (eds.), *The Prediction of Suicide*. Baltimore, Md.: Charles Press Publishers, Inc., 1974.

A Retrospective Clinical Analysis of the Overall-Rhoades Classification of Hamilton Depression Scale Profiles

Robert H. Lenox, M.D.,[1] Lelon A. Weaver, Ph.D.,[1] James E. Shipley, M.D.,[1] and Stephen Cohen, M.D.[1]

Introduction

Overall and Rhoades (1982a,b) described an empirical method of classifying depressed patients based on the profile of ratings on the Hamilton Depression Rating Scale (HAM-D). The profiles of 420 patients selected for participation in antidepressant medication trials were subjected to cluster analysis. Five phenomonological subtypes, designated "Anxious," "Suicidal," "Vegetative," "Paranoid," and "Somatizing" were identified. Discriminant functions were calculated to maximize the separation of the subtypes, resulting in five sets of weights for each Hamilton item. Classification was achieved by multiplying each Hamilton rating by these weights, summing algebraically within subtype, and assigning the patient to the subtype with the greatest positive sum. Rating profiles which result in only negative sums cannot be classified, i.e., the score profile does not fit any of the subtypes. No clinical validation data were included in their original publications.

The purpose of this study was to examine the distribution of the Overall-Rhoades classifications in the pre- and posttreatment data from depressed patients participating in clinical investigations of major depressive disorder. We examined two such groups of patients: an Inpatient population treated in our Clinical Research Center, and an Outpatient group followed in the ambulatory care setting at the University of Vermont College of Medicine.

Methods

Patients

The Inpatient group consisted of 24 patients, 7 males and 17 females, with an age range of 28 to 73 years; mean ±SEM = 53.8±3.0 years (Table 1). All patients were diagnosed as Major Depressive Disorder, Endogenous Subtype, in accordance with Research Diagnostic Criteria (Spitzer et al., 1977). This group was screened from a much larger sample of depressed patients referred for treatment to the psychiatric unit of a general hospital. All were returned to the community following treatment.

The Outpatient study group consisted of 13 patients, 4 males and 9 females, with an age range of 21 to 59 years; mean ± S.E.M. = 38.2±2.8 years (Table 1). These patients are selected from a larger group of physician and self-referrals. All were diagnosed as Major Depression according to DSM-III criteria. All patients completed the prescribed course of treatment without significant complications.

Measures

In both groups each patient was administered a battery of clinical assessment instruments. For our present purpose, the data for the pre- and posttreatment HAM-D and the

TABLE 1

Demographic Data for the Inpatient and Outpatient Study Groups

	Inpatient			Outpatient		
	N	Mean	SE	*N*	Mean	SE
Age Group	24	53.8	3.0	13	38.2	2.8
Male	7	50.4	6.7	4	37.0	2.1
Female	17	55.2	3.3	9	38.7	4.0
Duration Prior to Treatment (wks)		19.4	4.5		66.8	17.3
History of Previous Manic Depressive Disorder			50%			92%

---

[1] Department of Psychiatry, College of Medicine, University of Vermont, Burlington, VT 05405.

Physician's Global Impressions (PGI) scales will be considered. The latter instrument contains a 7-category scale (ranging from 1 = "Normal, not at all ill" through 7 = "Among the most extremely ill patients"). We have defined a patient as "Improved" if a final PGI rating of 1 or 2 ("Normal" or "Borderline ill") was given. In the Inpatient study, the ratings on both scales are the mean of two independent raters. The interrater correlations were +.91 for the HAM-D data and +.89 for the PGI. In the Outpatient study, all ratings on both scales were carried out by a single psychiatrist who did not participate in the Inpatient study and who was unacquainted with the Overall-Rhoades classification system.

Results

The first step was to determine the appropriate classification for each patient on the pre- and posttreatment Hamilton profiles according to the method detailed by Overall and Rhoades (1982b). Table 2 contains a sample output from our Inpatient group in which the highest positive score is underlined to indicate the category to which the patient was assigned. Thus, patient #629 was classified "Vegetative" during the pretreatment period and "Anxious" at posttreatment with an overall improvement of 67% in the HAM-D. On the other hand, patient #275 was classified "Suicidal" for both pre- and posttreatment with an overall improvement in the HAM-D of only 17%.

The results of the application of the method to our data are summarized in Table 3 which contains the distribution of the Inpatient and Outpatient groups across the six possible classifications for both the initial and final ratings. For ease of comparison, frequency data has been converted into group percentages. On the initial rating, the Inpatient group was heavily represented in the Vegetative and Suicidal classes with very modest frequencies in the other four categories. Following treatment, the final ratings showed a substantial increase in the Anxious and Not-Classifiable categories. These results are consistent with expectations for a group of moderately to severely ill patients, only some of whom responded to treatment.

For the Outpatient group, the initial (pretreatment) data showed a preponderance of patients classified in the Anxious category, some in the Vegetative, and a minor representation in the others; again consistent with expectations for a less severely ill group of patients. The final rating was heavily concentrated in the Not-Classifiable category, due largely to the reduction in the total HAM-D score and the substantial number of items rated zero.

A classification table using the Overall-Rhoades categories assigned to each patient for both initial and final Hamilton profiles was constructed. Each patient could be assigned to only one cell. In Table 4, the cell entries are the mean total Hamilton scale scores for the initial and final ratings of the Inpatient group. Each pair of entries represents a single patient. The table may be read as follows: The patient classified as Vegetative initially and Anxious finally had an initial Hamilton score of 30.0 and a final Hamilton score of 10.0.

There were 11 patients initially classified as Vegetative with a mean HAM-D rating of 30.1. At the time of final rating (posttreatment), 3 of the original 11 remained in the Vegetative category, while the others had shifted into Anxious (3) or Not-Classifiable categories (5). Here again, it is apparent that patients in the Inpatient study shifted from predominantly Vegetative/Suicidal/Somatizing categories pretreatment to Anxious/Not-Classifiable posttreatment. It is clear that those shifting into the Not-Classifiable category represented the patients showing the most improvement with a mean overall reduction in HAM-D of 81%.

Table 5 utilizes the identical format and contains the data for the Outpatient group. Three patients were initially classified as Vegetative with a mean HAM-D score of 24.8. Two of the three patients shifted into the Non-Classifiable category during the posttreatment rating with an overall reduction in HAM-D of 84%. As indicated in Table 2, the preponderance of patients were initially classified as either Anxious or Vegetative with the majority of these (77%) classified as Not-

TABLE 2

Sample Output of the Overall-Rhoades Classification Function Program Using Pre- and Posttreatment Hamilton Depression Rating Scale Profiles

		Overall-Rhoades Classification Functions						
Patient No.	Phase	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not Classifiable	Total Hamilton Score
275	Pre	−6.82	8.03	−5.99	−9.72	−2.75		27.00
	Post	−5.81	2.22	−5.36	−8.81	1.93		22.50
678	Pre	−1.60	−0.56	−4.23	−9.11	−1.08	•	23.50
	Post	0.96	−3.02	−3.51	−7.26	−0.45	•	7.00
363	Pre	3.12	−1.88	−5.80	−6.33	−5.05		26.00
	Post	−2.13	−1.20	−3.68	−8.32	−0.69	•	1.50
269	Pre	5.24	−1.14	−7.07	−6.57	−7.24		24.50
	Post	−0.07	−2.69	−5.52	−6.63	−0.22	•	17.00
604	Pre	−0.92	−5.63	3.88	−6.28	−7.06		41.00
	Post	−3.72	−3.48	−3.46	4.05	−1.27		22.50
161	Pre	−0.78	−4.84	−3.15	−10.99	2.80		19.00
	Post	−2.65	−2.87	−3.04	−11.76	2.77		11.00
965	Pre	−3.32	4.75	−6.24	−10.49	−2.76		31.50
	Post	−2.81	−2.03	−4.94	−5.44	1.22		11.00
629	Pre	1.36	−3.63	−5.05	−10.68	0.42		30.00
	Post	0.84	−4.54	−3.08	−6.78	0.57		10.00

Classifiable following treatment, with a mean score of 5.8.

Data shown in Tables 6 and 7 utilize the same format to show the initial and final PGI ratings for the Inpatient and Outpatient groups classified according to the Overall-Rhoades system. Patients were placed in the same cells as in Tables 4 and 5. A final rating that is underlined indicates that the patient was judged clinically "improved." Of the five patients in the Inpatient group classified as Vegetative or Suicidal both initially and finally, only one was rated as "improved" on the final PGI rating. Inspection of the HAM-D data (Table 4) for these patients indicated that this patient had the lowest final HAM-D rating, well below the mean of the other four patients. Similarly, only one patient initially classified as Vegetative and finally as Anxious showed significant improvement on the PGI, and the HAM-D rating reflected this improvement. Consistent with our findings in Tables 4 and 5, all patients found Not-Classifiable on the final HAM-D were found to be improved according to the PGI.

TABLE 3

Summary of Pre- and Posttreatment HAM-D Profile Classification by Groups

Overall-Rhoades Classification	Inpatient (*N* = 24) Initial	Inpatient (*N* = 24) Final	Outpatient (*N* = 13) Initial	Outpatient (*N* = 13) Final
Vegetative	46	17	24	8
Suicidal	33	8	8	0
Somatizing	12	0	8	8
Paranoid	0	4	0	0
Anxious	4	29	54	8
Not-Classifiable	4	42	8	76

(Cell Entries Are in Percent of Patient Groups)

As part of the design of the original inpatient study, the dexamethasone suppression test (DST) was administered to all patients pre- and posttreatment. Patients were administered the DST as described previously (Lenox et al., 1985). At the initial (pretreatment) period there were 11 suppressors and 13 non-

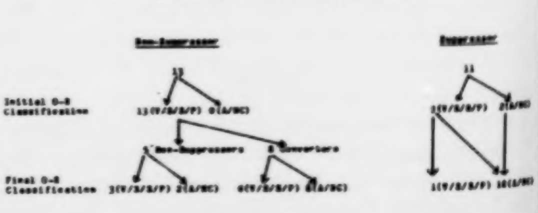


FIGURE. Flow diagram of changes in status on the DST as related to the Overall-Rhoades (O-R) classification system. Patients were administered the DST both during the pretreatment period (initial) and following at least 3 weeks of treatment (final). At the same time, HAM-D ratings were carried out and the O-R classifications were determined. (*See* text for definition of abbreviations.)

TABLE 4

The Overall-Rhoades Classification of the Inpatient Group on the Initial and Final Administration of the HAM-D

			Final					
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	36.0/22.5 33.0/13.0 24.5/17.0				30.0/10.0 39.5/23.0 35.0/26.0	27.5/8.5 28.5/5.5 26.0/1.5 20.0/0.0 31.0/9.0	11	30.1/12.4
Suicidal		27.0/22.5 34.0/21.0			31.5/11.0 26.0/30.0 22.0/24.0	39.0/8.0 28.5/5.5 24.0/6.0	8	29.0/16.0
Somatizing	45.0/28.5			41.0/22.5		36.0/3.5	3	40.7/18.2
Paranoid							0	
Anxious					19.0/11.0		1	19.0/11.0
Not-Classifiable						23.5/7.0	1	23.5/7.0
N	4	2		1	7	10	24	
Mean	34.6/20.2	30.5/21.7		41.0/22.5	29.0/19.3	28.4/5.4		30.3/14.0

(Cell entries are the initial and final HAM-D ratings for each patient)

suppressors (*see* Figure). At the posttreatment (final) evaluation, of the 13 patients classified as non-suppressors pretreatment, 8 normalized while 5 continued to be non-suppressors. The 11 original DST suppressors remained suppressors at the final evaluation. For the purpose of examining the relationship of Overall-Rhoades classifications, we created two category groups, Vegetative/Suicidal/Somatizing/Paranoid (V/S/S/P) and Anxious/Not-Classifiable (A/N-C). It may be remembered that the Vegetative and Suicidal categories contain 19 of the 24 Inpatients classified during the pretreatment period. All 13 of the initial DST non-suppressors and 9 out of the 11 suppressors were found in the V/S/S/P categories while only 2 of the 24 fell into A/N-C group. Of the five patients designated DST non-suppressors posttreatment, 3 remained in the V/S/S/P classification and 2 in the A/N-C category. All 8 patients who normalized the DST posttreatment were in the A/N-C category. Of the 9 suppressors who were initially categorized in the V/S/S/P, 8 shifted into the A/N-C category at final posttreatment evaluation.

TABLE 5

The Overall-Rhoades Classification of the Outpatient Group on the Initial and Final Administration of the HAM-D

			Final					
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	26.0/17.0					22.5/5.0 26.0/3.0	3	24.8/8.3
Suicidal						19.0/3.0	1	19.0/3.0
Somatizing						22.0/3.0	1	22.0/3.0
Anxious	23.0/10.0				24.0/18.0	19.5/4.0 23.0/1.0 25.0/0.0 34.0/7.0 26.0/2.0	7	24.9/6.0
Paranoid							0	
Not-Classifiable						21.5/11.0	1	21.5/11.0
N	2				1	10	13	
Mean	24.5/13.5				24.0/18.0	23.8/4.0		24.0/6.50

(Cell entries are the initial and final HAM-D ratings for each patient)

TABLE 6

The Relationship Between the Overall-Rhoades Classification and the PGI Ratings for the Inpatient Group.

	Final							
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	6.0/5.5 6.0/2.0 5.0/5.5				4.0/2.0 5.0/4.0 6.0/6.0	4.0/2.0 6.0/2.0 5.5/2.0 5.0/1.0 5.0/2.0	11	5.3/3.2
Suicidal		6.0/5.0 5.5/4.5			6.0/3.0 5.0/5.0 4.0/4.0	4.0/2.0 5.0/2.0 5.0/2.0	8	5.1/3.6
Somatizing	7.0/6.5			6.0/6.0		6.5/1.5	3	6.5/4.7
Paranoid							0	
Anxious					4.0/2.0		1	4.0/2.0
Not-Classifiable						4.5/2.0	1	4.5/2.0
N	4	2	0	1	7	10	24	
Mean	6.0/4.9	5.8/4.8		6.0/6.0	4.9/3.7	5.1/1.8		5.3/3.4

(Cell entries are initial and final PGI ratings. Underlining of final rating indicates patient was considered "improved")

Discussion

First, it is important to point out that these data were collected as part of a psychopharmacological research program and hence cannot be regarded as a designed prospective validation study. Rather, it represents a retrospective study of the distribution of the Overall-Rhoades classification in pre- and post-treatment data from two groups of patients with diagnosis of major depressive disorder. Both Inpatient and Outpatient studies were carried out independently of each other and the Overall-Rhoades classification scheme.

We have noted several problems incidental to the Overall-Rhoades classification system which are worthy of discussion. It will be remembered that each HAM-D item rating is multiplied by a different positive or negative weight in each of the categories. The algebraically summed categories will thus be either positive or negative and the patient assigned to the category with the highest positive sum. But since the same item may have

TABLE 7

The Relationship Between the Overall-Rhoades Classification and the PGI Ratings for the Outpatient Group.

	Final							
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	5/3					6/1 6/1	3	5.7/1.7
Suicidal						3/1	1	3.0/1.0
Somatizing						4/1	1	4.0/1.0
Paranoid							0	
Anxious	4/2				4/1	4/1 6/3 4/1 5/4 7/4	7	4.9/2.3
Not-Classifiable						6/2	1	6.0/2.0
N	2				1	10	13	
Mean	4.5/2.5				4.0/1.0	5.1/1.9		4.9/1.9

(Cell entries are initial and final PGI ratings. Underlining of final rating indicates patient was considered "improved") both positive and negative weights in the several categories, a patient rated high on several different items may cancel out the patterns, resulting in a high HAM-D total but fitting no specific category.

A still unresolved problem concerns the number of HAM-D items which are required to produce a valid categorization. The effectiveness of the discrimination of classification types depends upon the presence of both positive and negative weights; thus, if only a few items are non-zero rated, it is probable that no positive profile will emerge. Such a result, i.e., a finding of Not-Classifiable, is acceptable in logic, but a more serious question arises when a positive classification does emerge when only a few items are rated, since a chance combination of loaded items becomes more likely. This usually results when one or more of the rated items has a high positive loading in one category. Thus, even a rating of 1 on the HAM-D items #1 (Depressed Mood) and #4 (Early Insomnia) would ensure an Anxious categorization. Part of the problem is the dearth of negative offsetting scores when a large percentage of the items are rated zero. We have addressed these issues in this study by applying two decision rules:

1. If a profile results in "Not-Classifiable," it stands without regard to the number of items rated.
2. If a profile is categorized, the HAM-D must have at least one-third non-zero ratings for the categorization to be accepted as valid. If less than one-third of the items were rated, the profile was considered "Not-Classifiable."

The basic question is whether the Overall-Rhoades classification system results in clinically relevant data. Overall and Rhoades originally noted that the Vegetative type loaded onto items with symptoms of sleep disturbance, weight loss, and diurnal variation, consistent with endogenous features most responsive to somatic treatment intervention (tricyclics, ECT, etc.). The Anxious type is weighted for early (but not middle or late) insomnia, and psychic anxiety consistent with anxious depression or minor depression with anxiety, often responding to anxiolytics and thought to have a higher placebo response. The suicidal type was weighted heavily in the suicide item while the paranoid type was weighted heavily for paranoid symptoms and lack of insight. Both our Inpatient and Outpatient studies attempted to exclude psychotic depressions, but we would expect that the more seriously ill Inpatients would classify into the "sicker" categories, Vegetative and Suicidal. As shown in Table 3, 79% were so classified with high initial HAM-D (29.6) and PGI (5.2) ratings. Thus, the Overall-Rhoades classification did reflect the known severity of symptomatology in a carefully selected Inpatient group.

The Outpatient sample was not as severely ill as the Inpatient group since they were judged not to require hospitalization. There was a significant difference between the mean initial HAM-D scores of the Inpatient and Outpatient groups; 30.3 vs. 24.0, respectively. It is important to note that the same total score on the HAM-D can be produced by high ratings on different sets of items. From Table 3 it is apparent that this in fact occurred. Contrasting the Inpatient and Outpatient groups on the initial classification, the Vegetative and Suicidal categories comprised 78% of the Inpatient group but only 32% of the Outpatient group. For the Anxious and Not-Classifiable categories, the respective percentages were 8% and 62%. It can be concluded that the two groups of patients clinically judged to be different demographically (Table 1) and in degree of illness were differentially and properly categorized by the Overall-Rhoades classification.

Another question concerns the ability of the Overall-Rhoades classification scheme to reflect a change in clinical status. If a patient is judged to have improved significantly in terms of clinical criteria, this change should be reflected in posttreatment categorization. As noted in Table 3, the Inpatient group underwent a marked shift from Vegetative/Suicidal categories to Anxious/Not-Classifiable categories, with a similar shift occurring in the Outpatient group from Anxious to Not-Classifiable. The predominant shift in the Inpatient group would appear to be consistent with the suggestion of an affective spectrum, i.e., that patients with Vegetative/Suicidal depression profiles may pass through the stage described as an "Anxious Depression" prior to clinical recovery. These data might also suggest that some of the patients designated "Anxious" during pretreatment in the Outpatient study may represent an early stage of the Vegetative/Suicidal disorders treated in the Inpatient group.

Inspection of Table 4 shows that the final HAM-D rating of the patients remaining in the Vegetative/Suicidal categories did not differ from those moving into the Anxious category. Those moving into the Not-Classifiable category, however, had a significantly lower final HAM-D rating. There is, of course, an element of circularity present: patients with low HAM-D ratings are likely to fall into the Not-Classifiable category since there may not be enough non-zero item ratings to permit establishment of any pattern. However, inspection of the detailed PGI data of Table 6 confirmed the HAM-D data: all eight patients with a final classification of Not-Classifiable were judged "Improved" on the PGI scale. While it may be argued that since the HAM-D and PGI ratings were carried out by the same raters, agreement is only to be expected; cell-by-cell comparisons of the HAM-D and PGI ratings on the same patients showed numerous discrepancies.

It is concluded that the Overall-Rhoades classification reflects the clinical changes seen in both the HAM-D and PGI ratings. A shift into the Anxious category is not necessarily accompanied by a significant change in the HAM-D but movement into the "Not-Classifiable" is. Clinical improvement on the PGI is no more frequent in the Anxious category than in any other, but all patients rated "Not-Classifiable" showed significant clinical improvement. The data for the Outpatient group shows substantially the same trend.

We examined the possibility that the DST response might segregate according to the Overall-Rhoades classification scheme. Our findings would seem to indicate that patients classified into the "sicker" categories of Vegetative/Suicidal/Somatizing/Paranoid were as likely to be suppressors as non-suppressors. However, there was an indication that patients showing improvement by shifting into Anxious or Not-Classifiable categories were more likely to be the same patients whose DST converted to suppression. These data would be consistent with evidence showing a link between clinical improvement and DST conversion (Greden et al., 1980; Nemeroff & Evans, 1984). However, one must be cautious in light of our recent report that normalization of DST may be dependent upon long-term factors affecting the ability of the hypothalamic-pituitary-adrenal axis to revert to normal homeostatic control (Lenox et al., 1985).

In a recent study reported by Overall (1984), he examined the classification of patients enrolled in a series of 11 studies examining the clinical efficacy of nomifensine. Interestingly, while the initial classification type did not predict response reliably, it was apparent that patients in the Somatizing category appeared to be more responsive to placebo. However, the investigators did not study changes in classification profile as a function of treatment response.

The utility of the Overall-Rhoades classification scheme to prospectively screen and follow patients in psychopharmacological/behavioral/or even psychotherapeutic studies requires further investigation. These studies might address the early exclusion of placebo responders from major drug trials; the predictive value of suicidal classification; or the selection of patients more likely to respond to psychotherapy versus pharmacotherapy. Since the HAM-D is an instrument widely accepted and utilized in clinical studies, the potential application of this classification system requires further study.

References

Greden, J., Albala, A., Haskett, R., et al. Normalization of Dexamethasone Suppression Test: A laboratory index of recovery from endogenous depression. *Biol. Psychiatry*, 15:449–458, 1980.

Lenox, R., Peyser, J., Rothschild, B., et al. Failure to normalize the dexamethasone suppression test: Association with length of illness. *Biol. Psychiatry*, 20:333–337, 1985.

Nemeroff, C., and Evans, D. Correlation between the dexamethasone suppression test in depressed patients and clinical response. *Am. J. Psychiatry*, 141(2):247–249, 1984.

Overall, J. Efficacy of nomifensine in different depressive syndromes. *J. Clin. Psychiatry*, 45:85–89, 1984.

Overall, J., and Rhoades, H. Refinement of phenomenological classification in clinical psychopharmacology research. *Psychopharmacology*, 77:24–30, 1982a.

Overall, J., and Rhoades, H. Use of the Hamilton Rating Scale for classification of depressive disorders. *Compr. Psychiatry*, 23:370–376, 1982b.

Spitzer, R., Endicott, J., and Rabins, E. Research diagnostic criteria for a selected group of functional disorders, 3rd ed. New York: New York Biometrics Research Division, New York State Psychiatric Institute, 1977.

Understanding the Response Lag to Tricyclics. I. Application of Pulse-Loading Regimens With Intravenous Clomipramine[1]

Bruce G. Pollock, M.D.,[2,3] James M. Perel, Ph.D.,[3] Michael Shostak, M.D.,[3] Seymour M. Antelman, Ph.D.,[3] Barbara Brandom, M.D.,[4] and David J. Kupfer, M.D.[3]

The slow, gradual therapeutic onset of tricyclic antidepressants (TCAs) is difficult to explain by their reuptake-blocking properties alone, because these effects occur acutely. Recent research on the mode of action of TCAs has focused primarily on chronic modification of rat postsynaptic β-adrenergic receptors manifesting decreases in density (Sulser, 1983) and dopamine autoreceptors displaying subsensitivity (Chiodo & Antelman, 1980). These time-dependent phenomena may help to explain the enigma of the therapeutic delay in antidepressant treatment. Conversely, the explanation might be pharmacokinetic. Retrospective analyses of plasma level/response data have revealed that optimal effects are observed within 5 days after attaining adequate steady-state levels of orally administered antidepressants (Perel, 1983). Furthermore, it has been found that continuous intravenous infusions of TCAs in rats produce β-receptor down-regulation within 16 to 48 hours as opposed to intraperitoneal (i.p.) or oral routes which produce changes after 10 days (Sethy & Day, 1985).

The variable, extensive hepatic pre-systemic clearance and relatively long half-lives of TCAs militate against the rapid achievement of therapeutically effective steady-state blood levels via the oral route. Intravenous (i.v.) medication circumvents this limitation and, in addition, provides an opportunity to test whether continuous medication is necessary after the administration of a sufficiently large initial dose. The relative contribution of pharmacokinetic versus pharmacodynamic factors in the therapeutic onset of TCAs was examined using a pulse-loading dose strategy with i.v. clomipramine (CMI). I.V. clomipramine is a commonly employed treatment in many European centers. Treatment, however, is typically initiated with 25 to 50 mg in a morning dose, and gradually increased to 150 to 200 mg over a 7- to 10-day period, with an attendant therapeutic lag, thereby precluding observations of more rapid onset of action. Pulse-loading may be defined as the rapid attainment of transient therapeutic plasma concentrations.

Methods

Those studied were inpatients on the Clinical Research Unit at Western Psychiatric Institute and Clinic. All patients had a minimum duration of their current illness of 2 weeks and a maximum current episode duration of 1 year prior to hospitalization. A psychiatric interview and physical examination were carried out at admission, and collateral information was obtained from the families and records of prior treatment. During a 2-week drug-free period, patients underwent routine tests, including blood chemistry, EEG, and EKG, and any other tests suggested by their history and physical examination. They were then evaluated by two independent psychiatrists to ensure criteria of the Diagnostic and Statistical Manual (3rd ed.) for either Major Depressive Episode with Melancholia or Bipolar Disorder, Depressed, were met. If patients met these diagnostic criteria and were not delusional, were physically

---

[1] This study was supported in part by USPHS Grant No. MH-30915 from the National Institute of Mental Health.

[2] Centennial Fellow, Medical Research Council of Canada.

[3] Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213.

[4] Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA 15213.

healthy, had a minimum rating of 15 on the 17-item Hamilton Depression Rating Scale (HAM-D) at the end of the 2-week drug-free period, and gave written informed consent, they entered the protocol.

An overview of the protocol is shown in the Table. EEG sleep and cardiac rhythm were recorded via remote cable while patients slept in their own rooms on 11 nights during the protocol. The first 2 nights of EEG sleep were considered as facilitating adaptation to the procedure while data for the next 2 nights were averaged and represent baseline sleep. EEG sleep was recorded on the nights of clomipramine or saline infusions and 7, 8, and 10 nights after the infusions and for 2 nights at the start of any additional infusions. All sleep records were scored independently without knowledge of the clinical diagnosis or drug status of the patient. In addition to the standard classification of sleep into stages, automated delta analyses were performed according to methods previously described (Kupfer et al., 1981a). Patients were rated by an independent observer with the HAM-D at the start of the protocol, the day following the second infusion of CMI or saline, and twice weekly thereafter.

On the fifth evening of the protocol, at 9:30 p.m., 75 mg of CMI diluted in 250 cc of normal saline was administered via a butterfly cannula. This procedure lasted approximately 45 minutes. The following evening 200 mg of CMI in 500 cc of saline was administered over a 90-minute period. No additional medication was given for 11 days. Ten patients completed the above protocol. Four patients received i.v. saline only, in a double-blind fashion, on protocol nights 5 and 6. These patients were then offered active CMI infusions on nights 11 and 12. A minimum of six timed plasma samples were taken up to 80 hours after the second CMI infusion for pharmacokinetic analysis and twice weekly thereafter. Plasma samples were analyzed by radioimmunoassay and high performance liquid chromatography using methods developed in our laboratory (Stiller et al., 1985). Pharmacokinetic treatment of plasma level data was performed utilizing curve fitting by our version of the computer program ESTRIP (Brown & Manno, 1978) for the Hewlett Packard 9836, followed by nonlinear regression analysis (Yamaoka et al., 1981). Half-lives were calculated using a modification of a program written by Niazi (1977). Paired *t*-tests and Wilcoxon's signed rank test (two-tailed) were used in the statistical analyses.

Results

One male and 9 females (mean age 40.6 s.d. ± 11.2 years) with an average duration of illness of 7.5 months, were admitted to and completed the protocol. The infusions of clomipramine were well tolerated. All patients experienced a pleasant sedation during these infusions, but were kept awake until the infusions were completed because of the sleep studies. Six patients experienced mild to moderate nausea on receiving the first infusion of 75 mg CMI, while 3 of these patients subsequently had milder nausea with the second infusion of 200 mg. Two patients experienced myoclonic jerks and 4 complained of a transient restlessness shortly after the initation of the infusions. Three patients complained of mild headache on the morning af-

TABLE

I.V. Clomipramine Protocol Schedule

Day**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
EEG Sleep Studies	X	X	X	X	X	X							X	X		X	X	X			
I.V. Dose in mg: CMI or placebo 9:30-11:00 p.m.					25 50	200											*				
Blood Levels			X		X	X	X X	X X	X X	X X			X			X			X		X
Clinical Ratings			X				X			X			X			X			X		X

*If placebo is given on Days 5 and 6, I.V. CMI was offered here.

**Days represent period following 2 weeks medication-free in hospital.

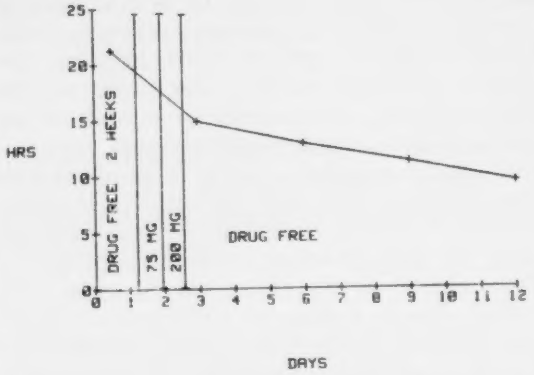


FIGURE 1. Mean Hamilton rating scale for 10 patients treated with IV clomipramine pulse-loading.

ter the second infusion. There was one report of blurred vision and three of dry mouth from patients receiving CMI, while 2 patients who received saline initially also complained of these side effects. Blood pressure remained stable throughout the infusions and there were no cardiographic changes post-infusion.

The HAM-D means changed over the course of the protocol as shown in Figure 1.

The mean HAM-D for the 10 patients just prior to the first CMI infusion was 21.5±SEM 2.8, as compared to 14.8±SEM 3.9 on the day (protocol day 7) following the second infusion ($p = .02$, Wilcoxon's signed rank test). Ten days after the second infusion of CMI (protocol day 16), the mean HAM-D had dropped further to 9.5±SEM 3.5 ($p < .02$ relative to protocol day 7). The immediate reduction in the HAM-D after the second infusion was primarily due to all patients reporting an improvement in their sleep. Eight patients, however, continued to report attenuation of their depressive symptoms over the ensuing 10 days. This progressive improvement occurred despite the fact that no additional medication was administered over this time. Only 2 of the 10 patients failed to clinically improve after the CMI infusions. Interestingly, one of these nonresponders became worse when sleep deprived for a pre-protocol EEG. At the conclusion of this study period, patients were placed on differing regimens of tricyclic therapy (either CMI or imipramine). Two of the 8 patients who had achieved near remission of their depression with i.v. CMI relapsed on oral CMI but improved again when lithium was added.

To control for the increased attention and nonspecific effects due to the procedures, 4 patients initially received two infusions of i.v. saline in a double-blind fashion. As shown by Figure 2, their mean HAM-D score slowly changed by 19% over a 10-day period following the second saline infusion. When these patients then received two CMI infusions, in an open fashion, their mean HAM-D score dropped rapidly by 43.4% within the ensuing 10 days.

Changes in EEG sleep were remarkable. The first REM period latency, after 2 weeks drug-free in hospital, was short (mean 40.5 SD±32.1 minutes); and sleep efficiency, the ratio of the time spent asleep to the total recording period, was less than expected for this age group (mean 73.5 SD±22.9%). Both these parameters are stigmata of moderate depression. Rapid-eye-movement (REM) sleep was completely suppressed on the 2 nights CMI was infused and then returned to the pre-infusion baseline over the ensuing 8 nights (Figure 3).

There was no significant change in sleep efficiency with the two CMI infusions ($p > .2$, $< .3$, paired *t*-test). This suggests that the considerable improvement which all patients reported in their sleep, after the CMI infusions, was due to a fundamental change in the quality of their sleep, rather than merely due to sedation. Delta sleep, subsequent to the CMI infusions, was not significantly altered.

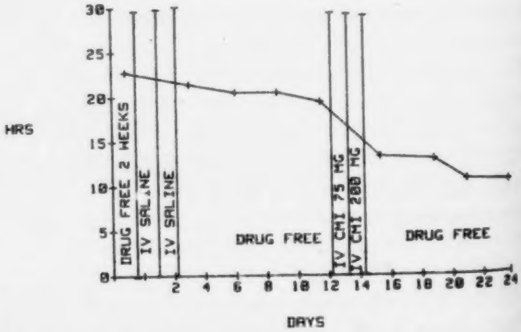


FIGURE 2. Mean Hamilton rating scale for 4 patients treated initially with IV saline.

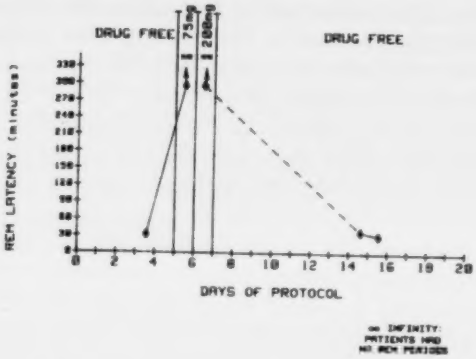


FIGURE 3. REM latency before and after treatment with IV clomipramine pulse-loading.

The saline infusions did not induce any significant changes in EEG sleep parameters.

Withdrawal pharmacokinetics performed after the second CMI infusion revealed a mean elimination half-life of 34 SD±3 hours, Concentration of zero time was 353 SD±127 ng/ml. Importantly, no significant amounts of desmethylclomipramine (>20 ng/ml) could be detected after the second infusion of CMI for at least 36 hours.

Discussion

Routine oral treatment with TCA's requires a minimum of 2 to 3 weeks at substantial doses to manifest optimal therapeutic effect (Hollister, 1983). It is well known that the extensive hepatic first-pass metabolism of orally administered TCAs prevents the rapid achievement of therapeutically effective blood levels (Evans et al., 1980). It is thus puzzling, as Klein et al. (1980) have noted, that there is such a paucity of studies on parenteral administration of these drugs. With respect to the i.v. administration of CMI, there have been several anecdotal reports and open studies attesting to its safety and superior efficacy in depression (Collins, 1970; Escobar et al., 1976; O'Flanagan, 1973; Symes, 1973), refractory depression (Dudley, 1980), and obsessive-compulsive disorder (Warneke, 1984).

There have been two double-blind controlled studies published in the English literature, comparing oral and i.v. routes of administration (Escobar, 1973; Faravelli, 1983). Both of these studies failed to show a significant difference in percent reduction in Hamilton ratings between i.v. and oral treatment groups. There is some cause, however, for caution in interpreting both of these studies. In the case of Escobar's 1973 study, there was considerable heterogeneity of diagnoses, e.g., only 43% of the i.v. group were diagnosed as suffering from endogenous depression versus 76% of the oral group. In spite of this, the authors concluded that there was a mean onset of action of 4 days for the i.v. group and 5 days for the oral. The same researchers in a subsequent paper (Escobar et al., 1976) commented on the importance of diagnostic criteria, and concluded "The results of this open trial, where specific diagnostic criteria were used, suggest i.v. administration of CMI to be a safe and feasible procedure, providing rapid therapeutic effects almost exclusively on unipolar and bipolar depressions, and a poor response in secondary affective disorders."

With regard to the more recent Faravelli paper, patients were begun at .5 mg/kg CMI, in a single a.m. dose, and raised to a maximum dose of 2 mg/kg after 10 days. At the end of 4 weeks, 30% of the patients had not achieved steady-state; combined plasma levels for CMI and its desmethyl metabolite were the same for both i.v. and oral groups and, thus, it is perhaps not entirely surprising that therapeutic response was equivalent. The authors suggest that a minimum, mean combined plasma level of 175 ng/ml is necessary for therapeutic improvement. Since it took 3 weeks to achieve these minimum levels in both groups of their patients, the important question still remained: If therapeutic levels are reached earlier, do patients improve earlier? Our data would appear to answer this question in the affirmative.

The evidence for impaired indoleaminergic functioning in subtypes of depressed patients, while not conclusive, remains as a highly viable hypothesis (Van Praag, 1984a). CMI, of all the TCAs, has consistently been shown to be the most potent inhibitor of the serotonin carrier pump in vitro (Tuck & Punell, 1973) and in vivo (Åsberg et al., 1977). Clinically, however, the significance of this has been obscured by the fact that the major metabolite of CMI, desmethylclomipramine (DCMI), is usually present in much greater concentrations (DCMI/CMI = 2.0–5.0) than CMI after oral administration and is a potent inhibitor of noradrenaline uptake (Mulgirigama et al., 1977). It has been suggested that increasing the serotonicity of orally administered CMI through the addition of 5-HTP and a peripheral decarboxylase inhibitor may shorten the latent period before a therapeutic response is observed (Van Praag, 1984b). Pulse-loading with i.v. CMI creates a system of moderate serotonicity, through the virtual absence of DCMI, and with extensive bioavailability to the central nervous system. It is also of interest to compare the results achieved by giving oral CMI at a dose of 225 mg/day (Van Praag, 1984b) as opposed to a total i.v. dose of 275 mg (Figure 4). Although there are obvious limitations to such a comparison, the effect nonetheless is striking and impels us to further investigation.

The magnitude of suppression of REM sleep by antidepressants may be predictive of clinical response (Kupfer et al., 1981b). Consistent with earlier preliminary work (Lacey et al., 1977), we found a profound suppression of REM sleep with parenteral CMI. The return of REM parameters to their pre-infusion state during the drug-free interval may herald an impending worsening of the patient's clinical status, which was aborted by initiating maintenance treatment. Alternatively, as has been suggested in sleep deprivation studies (Vogel et al., 1980), the buildup of REM pressure, i.e.. rebound itself, may be associated with clinical improvement. Of considerable interest is the finding that patients who respond to sleep deprivation have a greater likelihood of response to CMI infusions (Wirz-Justice, 1976). It is possible that this procedure may delineate a group of patients requiring serotonergic agents (Fahndrich, 1983).

Eight of the 10 patients in our pilot study began to evidence clinical improvement after achieving transient supra-therapeutic plasma levels of clomipramine, while their plasma levels were, in fact, declining. This paradox may be a manifestation of the activation of a time-dependent cellular process, as has been suggested for similar findings in animals (Chiodo & Antelman, 1980). Alternatively, it may represent a well-articulated pharmacodynamic process, anticlockwise hysteresis (Holford & Sheiner, 1981). This process occurs when there is an equilibration delay between systems (blood) concentrations and the effects (receptor) sites. The pattern of response observed in our patients seems to mirror that seen after the achievement of steady-state levels in patients treated with imipramine (Perel, 1983). This leads to the tentative conclusion that pharmacokinetic processes occuring in TCA therapy are mostly, but not entirely, the major determinants controlling the response lag time. Definition of the role of each factor awaits findings from a large-scale study currently underway.

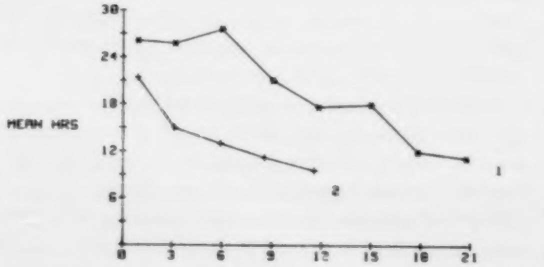


FIGURE 4. Comparative response of oral versus IV clomipramine.

References

Åsberg, M., Ringberger, V., Sjöqvist, F., et al. Monoamine metabolites in cerebrospinal fluid and serotonin-uptake inhibition during treatment with chlorimipramine. *Clin. Pharmacol. Ther.*, 21:201–207, 1977.

Brown, R., and Manno, J. ESTRIP: A basic computer program for obtaining initial polyexponential parameter estimates. *J. Pharm. Sci.*, 67:1687–1691, 1978.

Chiodo, L.A., and Antelman, S.M. Repeated tricyclics induce a progressive dopamine autoreceptor subsensitivity independent of daily drug treatment. *Nature*, 287:451–454, 1980.

Collins, G.H. I.V. Clomipramine in the treatment of severe depression. *Br. J. Psychiatry,* 117:211–212, 1970.

Dudley, D.D., Volberding, N., and Loebel, J.P. Intravenous chlorimipramine and refractory depression. *Gen. Hosp. Psychiatry,* 2:61–64, 1980.

Escobar, J.I., Flemenbaum, A., and Schiele, B.C. Chlorimipramine: A double-blind comparison of intravenous versus oral administration in depressed patients. *Psychopharmacologia,* 33:111–116, 1973.

Escobar, J.I., Teeter, R.R., Tuason, V.B., et al. Intravenous chlorimipramine and depressive subtypes. *Dis. Nerv. Syst.,* 37:325–328, 1976.

Evans, L.E., Bett, J.H., Cox, J.R., et al. The bioavailability of oral and parenteral chlorimipramine. *Prog. Neuro-Psychopharmacol.,* 4:293–302, 1980.

Fahndrich, E. Effect of sleep deprivation as a predictor of treatment response to antidepressant medication. *Acta Psychiatr. Scand.,* 68:341–344, 1983.

Faravelli, C., Broadhurst, A.D., Ambonetti, A., et al. Double-blind trial with oral versus intravenous clomipramine in primary depression. *Biol. Psychiatry,* 18:695–706, 1983.

Holford, N.H.G., and Sheiner, L.B. Understanding the dose-effect relationships: Clinical application of pharmacokinetic-pharmacodynamic models. *Clin. Pharmacokinet.,* 6:429–453, 1981.

Hollister, L.E. *Clinical Pharmacology of Psychotherapeutic Drugs,* 2nd Ed. New York: Churchill Livingston, 1983, p. 94.

Klein, D.F., Gittelman, R., Quitkin, F., and Rifkin, A. *Diagnosis and Drug Treatment of Psychiatric Disorders.* 2nd Ed. Baltimore, Md.: Williams & Wilkins, 1980, p. 275.

Kupfer, D.J., Shaw, D.H., Ulrich, R., et al. Application of automated delta analysis. *Sleep Res.,* 10:173, 1981a.

Kupfer, D.J., Spiker, D.G., Coble, P.A., et al. Sleep and treatment prediction in endogenous depression. *Am. J. Psychiatry,* 138:429–434, 1981b.

Lacey, J.H., Crisp, A.H., Crutchfield, M., et al. Chlorimipramine and sleep. A preliminary communication. *Post Grad. Med. J.,* 53:35–40, 1977.

Mulgirigama, L.D., Pare, C.M., Turner, P., et al. Tyramine pressor responses and plasma levels during tricyclic antidepressant therapy. *Postgrad. Med. J.,* (Suppl.4):30–34, 1977.

Niazi, S. Application of a programmable calculator in data fitting according to one and two compartment open models in pharmacokinetics. *Comput. Prog. Biomed.,* 7:41, 1977.

O'Flanagan, P.M. A Clomipramine (Anafranil) infusion unit. *J. Int. Med. Res.,* 1:375–381, 1973.

Perel, J.M. Tricyclic antidepressant plasma levels, pharmacokinetics, and clinical outcome. In: Grinspoon, L. (ed.), *Psychiatry Update,* Vol. 2. Washington, D.C.: American Psychiatric Press, 1983, pp. 491–511.

Sethy, V.H., and Day, J.S. Down-regulation of beta-adrenergic receptors within 24 hr after intravenous infusion of antidepressants. Abstract presented at the meeting of Society of Neuroscience, 1985.

Stiller, R.L., Perel, J.M., Pollock, B.G., and Foglia, J. Quantitative analysis of clomipramine. (In preparation, 1985).

Sulser, F. Mode of action of antidepressant drugs. *J. Clin. Psychiatry,* 44:14–20, 1983.

Symes, M.H. Oral and intravenous clomipramine (anafranil). *J. Int. Med. Res.,* 1:352–360, 1973.

Tuck, J.R., and Punell, G. Uptake of (^{3}H)5-hydroxytryptamine and (^{3}H)noradrenaline by slices of rat brain incubated in plasma from patients treated with chlorimipramine, imipramine or amitriptyline. *J. Pharm. Pharmacol.,* 25:573–374, 1973.

Van Praag, H.M. Depression, suicide, and serotonin metabolism in the brain. In: Post, R.M., and Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders.* Baltimore, Md.: Williams & Wilkins, 1984a, pp. 601–618.

Van Praag, H.M. In search of the mode of action of antidepressants: 5-HTP/tyrosine mixtures in depression. In: Usdin, E., Åsberg, M., Bertilsson, L., and Sjöqvist, F. (eds.), *Frontiers in Biochemical and Pharmacological Research in Depression.* New York: Raven Press, 1984b, pp. 301–314.

Vogel, G.W., Vogel, F., McAbee, R.S., and Thurmond, A.J. Improvement of depression by REM sleep deprivation. *Arch. Gen. Psychiatry,* 37:247–253, 1980.

Warneke, L.B. The use of intravenous chlorimipramine in the treatment of obsessive compulsive disorder. *Can. J. Psychiatry,* 29:135–141, 1984.

Wirz-Justice, A., Puhringer, W., and Hole, G. Sleep deprivation and clomipramine in endogenous depression. *Lancet,* 23:912, 1976.

Yamaoka, K., Tanigawara, Y., Nakagawa, T., and Uno, T. Pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobiodyn.,* 4:879–885, 1981.

Pharmacology of Combined Antidepressant/H_2-Blocking Drug Therapy

Stephen H. Curry, Ph.D.,[1] C. Lindsay DeVane, Pharm.D.,[1] and M. Michael Wolfe, M.D.[1]

Introduction

It has been observed that before the advent of antagonists of histamine-induced gastric acid secretion (H_2 blocking drugs), the treatment of ulcers with centrally acting drugs was common: nowadays, with H_2 blocking drugs available there is a tendency to treat psychiatric conditions with cimetidine. While this statement is clearly too broad to be universally true, it reflects increasing interest in two-pronged attack on human disease, and the combination of tricyclic antidepressants, and H_2 blocking drugs is an important component of this approach (Abernathy et al., 1984a; Somogyi & Gugler, 1979).

Little is currently known about the effects of individual tricyclic antidepressants and H_2 blocking drugs on each other. This is in spite of the well established fact that cimetidine inhibits hepatic microsomal enzymes and reduces hepatic blood flow (Puuronen & Pelkonen, 1979). Cimetidine is known to affect a wide variety of other drugs, including oral anticoagulants (Hetzel et al., 1979; Silver & Bell, 1979; Wallin et al., 1979; Willoughby, 1979), antipyrine (Roberts et al., 1981), phenytoin (Hetzel et al., 1981), ethanol (Feely & Wood, 1981), diazepam (Klotz & Reimann, 1980), chlordiazepoxide (Desmond et al., 1980), caffeine (May et al., 1982), theophylline (Campbell et al., 1981; Reitberg et al., 1981; Roberts et al., 1981), propranolol (Feely et al., 1981; Reimann et al., 1981), and lidocaine (Feely et al., 1982). In contrast, ranitidine appears less likely to affect other drugs (Abernathy et al., 1984a).

In one study with two oral antidepressants, administered separately, cimetidine decreased maximum plasma levels of imipramine, which is primarily metabolized by demethylation, but had no effect on plasma concentrations of nortriptyline, which is primarily metabolized by hydroxylation (Henauer & Hollister, 1984). With imipramine, the area under the curve of plasma levels against time was increased by cimetidine, implying inhibited metabolism. In another study, with imipramine only, after intravenous doses the elimination half-life of imipramine was increased, with no change in volume of distribution (Abernathy et al., 1984b). There was also no change in protein binding. After oral doses, the peak concentration, the area under the curve, and the half-life were all increased by cimetidine.

Methods

A recent study conducted at the University of Florida involved pretreatment with cimetidine or placebo for 2 days, amitriptyline test doses of 25 and 50 mg, blood samples for assay of amitriptyline and nortriptyline, measurement of blood pressure and pulse rate, and application of a digit symbol substitution test and a battery of visual analogue scales. Plasma concentrations were evaluated for time of maximum recorded concentration (T_{max}), maximum recorded concentration (Cp_{max}), half-life from 8 to 48 hours past amitriptyline dosage ($T_{1/2}$), and area under the curve (AUC). The AUC for amitriptyline included extrapolation to infinity using the formula $Cp_{(48)}/\beta$ where $Cp_{(48)}$ is the 48-hour concentration and β is the terminal phase rate constant for amitriptyline (AUC_{∞}). This was not done for nortriptyline, for which $AUC_{(0-48)}$ was calculated. Statistical analysis employed analysis of variance designed to identify differences between treatments, times, and subjects, and *t* tests for unrelated samples to determine significant differences between means. A level of $p<0.05$ was taken to indicate significance throughout. The methods and results of this work are presented in detail in two papers submitted for publication (Curry et al., in press; submitted, 1985).

---

[1] Colleges of Pharmacy and Medicine, University of Florida, Gainesville, FL 32610.

Results

In a pilot experiment, it was shown that Cp_{max} and AUC were linearly related to amitriptyline dose for both amitriptyline and nortriptyline, with both measurements higher after higher doses. T_{max} and $T_{1/2}$ were similar for both 25 and 50 mg doses. Digit symbol substitution showed a dose-dependent depression in performance, with the greater depression after the 50 mg dose. Visual analogue scales recording sedation were similarly affected, but with no difference at the two dose levels.

In the interaction experiment, pretreatment with cimetidine apparently doubled Cp_{max} and AUC for amitriptyline, but halved these two measurements for nortriptyline. T_{max} and $T_{1/2}$ data were not affected. Mean concentration data are in the Table. Digit symbol substitution results correlated with plasma amitriptyline changes, and visual analogue scale data correlated with plasma nortriptyline changes. Blood pressure and pulse rate changes were consistent with plasma amitriptyline changes.

Discussion

At the commencement of this experiment, a cimetidine-induced slowing of amitriptyline metabolism was anticipated, and this was expected to affect plasma concentrations of amitriptyline and nortriptyline. The observations support this hypothesis. There was no reason to expect changes in volumes of distribution, protein binding, or rate of transfer of amitriptyline from the gastrointestinal tract to the general circulation. Furthermore, there was no reason to expect a detectable effect on nortriptyline kinetics. Since T_{max} and $T_{1/2}$ stayed unchanged, and Cp_{max} and AUC were much affected, we consider that this impairment is primarily of presystemic metabolism of amitriptyline (first-pass effect) such that the fraction of the dose reaching the general circulation as unmetabolized amitriptyline increased.

Since this study was conducted with single doses in healthy volunteers, caution must be exercised in extrapolation to long-term treatment in patients. However, it is reasonable to predict that this interaction will occur in patients, with doubled steady-state amitriptyline concentrations and halved steady-state nortriptyline concentrations predicted. This clearly has implications for patient management, especially in regard to plasma level monitoring, and a need for a clinical study of the importance of this interaction is indicated.

Acknowledgments: We are grateful to our subjects for their participation in this project, to the staff of the Clinical Research Center of the J. Hillis Miller Health Center of the University of Florida for their supervision of dosing and blood sampling, and to Mrs. Sandy Sundlof and Mr. Ron Miller for their skilled technical assistance in the drug assays.

TABLE

Plasma Concentrations (ng/ml) of Amitriptyline and Nortriptyline After Single Doses of Amitriptyline (25 mg) With and Without Cimetidine Pretreatment

Pretreatment	Compound Measured	Time After Amitriptyline Dose (hours)													
		0	1	2	3	4	5	6	8	10	12	24	30	36	48
Placebo	Amitriptyline	0	4.1	10.0	13.7	9.8	8.7	7.1	5.4	4.8	3.8	2.7	2.0	1.9	1.0
		(-)	(1.2)	(1.9)	(1.8)	(1.1)	(1.1)	(0.9)	(0.7)	(0.7)	(0.6)	(0.4)	(0.3)	(0.4)	(0.3)
	Nortriptyline	0	0.3	2.1	4.2	4.6	6.2	4.8	4.4	3.8	4.4	2.4	2.8	2.5	1.6
		(-)	(0.2)	(1.0)	(1.0)	(1.1)	(2.1)	(1.3)	(1.1)	(0.9)	(1.4)	(0.7)	(0.6)	(0.6)	(0.4)
Cimetidine	Amitriptyline	0	3.6	13.9	18.8	15.9	13.3	12.8	9.5	7.5	7.6	6.2	5.7	3.9	1.9
		(-)	(1.0)	(2.1)	(2.9)	(2.4)	(1.7)	(2.6)	(1.9)	(1.2)	(1.8)	(1.9)	(1.7)	(1.1)	(0.7)
	Nortriptyline	0	0	1.0	2.2	2.1	2.1	3.1	1.9	1.2	2.0	1.5	1.8	1.7	1.0
		(-)	(-)	(0.9)	(1.6)	(1.2)	(1.1)	(1.3)	(0.8)	(0.7)	(0.5)	(0.5)	(0.4)	(0.5)	(0.4)

(Figures are means with S.E.M. in brackets)

References

Abernathy, D.R., Greenblatt, D.J., Eshelman, F.N., and Shader, R.I. Ranitidine does not impair oxidative or conjugative metabolism: Noninteraction with antipyrine, diazepam, or lorazepam. *Clin. Pharmacol. Ther.*, 35:188–192, 1984a.

Abernathy, D.R., Greenblatt, D.J., and Shader, R.I. Imipramine-cimetidine interaction: Impairment of clearance and enhanced absolute bioavailability. *J. Pharmacol. Exp. Ther.*, 229:702–705, 1984b.

Campbell, M.A., Plachetka, J.R., Jackson, J.E., et al. Cimetidine decreased theophylline clearance. *Ann. Intern. Med.*, 95:68–69, 1981.

Curry, S.H., DeVane, C.L., and Wolfe, M.M. Hypotension and bradycardia induced by amitriptyline in healthy volunteers. *Eur. J. Clin. Pharmacol.* (In press)

Curry, S.H., DeVane, C.L., and Wolfe, M.M. Hypotension and bradycardia induced by amitriptyline in healthy volunteers. *J. Clin. Psychopharmacol.* (Submitted, 1985)

Desmond, P.V., Patwardhan, R.V., Schenker, S., and Speeg, K.V., Jr. Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. *Ann. Intern. Med.*, 93:266–268, 1980.

Feely, J., and Wood, A.J. Effects of cimetidine interaction on the elimination and actions of ethanol. *JAMA*, 43:66–69, 1982.

Feely, J., Wilkinson, G.R., McAllister, C.B., and Wood, A.J.J. Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann. Intern. Med.*, 96:592–594, 1982.

Feely, J., Wilkinson, G.R., and Wood, A.J.J. Reduction in liver blood flow and propranolol metabolism by cimetidine. *N. Engl. J. Med.*, 304:692–695, 1981.

Henauer, S.A., and Hollister, L.E. Cimetidine interaction with imipramine and nortriptyline. *Clin. Pharmacol. Ther.*, 35:183–187, 1984.

Hetzel, D.J., Birkett, D., and Miners, J. Cimetidine interaction with warfarin. *Lancet*, 2:639, 1979.

Hetzel, D.J., Bochner, F., Hallpike, J.R., et al. Cimetidine interaction with phenytoin. *Br. Med. J.*, 282:1512, 1981.

Klotz, U., and Reimann, I. Delayed clearance of diazepam due to cimetidine. *N. Engl. J. Med.*, 302:1012–1014, 1980.

May, D.C., Jarboe, C.H., Van Bakel, A.B., and Williams, W.M. Effects of cimetidine on caffeine disposition in smokers and nonsmokers. *Clin. Pharmacol. Ther.*, 31:656–661, 1982.

Puurunen, J., and Pelkonen, O. Cimetidine inhibits microsomal drug metabolism in the rat. *Eur. J. Pharmacol.*, 55:335–336, 1979.

Reimann, I.W., Klotz, U., Siems, B., and Frohlich, J.C. Cimetidine increases steady-state plasma levels of propranolol. *Br. J. Clin. Pharmacol.*, 12:785–790, 1981.

Reitberg, D.P., Bernhard, H., and Schentag, J.J. Alteration of theophylline clearance and half-time by cimetidine in normal volunteers. *Ann. Intern. Med.*, 95:582–585, 1981.

Roberts, R.K., Grice, J., Wood, L., et al. Cimetidine impairs the elimination of theophylline and antipyrine. *Gastroenterology*, 81:19–21, 1981.

Silver, B.A., and Bell, W.R. Cimetidine potentiation of the hypoprothrombinemic effect of warfarin. *Ann. Intern. Med.*, 90:348–349, 1979.

Somogyi, A., and Gugler, R. Drug interactions with cimetidine. *Clin. Pharmacokinet.*, 7:23–41, 1982.

Wallin, B.A., Jacknowitz, A., and Raich, P.C. Cimetidine and the effect of warfarin. *Ann. Intern. Med.*, 90:993, 1979.

Willoughby, J.M.T. Cimetidine: Interaction with oral anticoagulants in man. *Lancet*, 2:317–319, 1979.

Free Communications—Session B

CHAIRS: *Hillary Lee, Ph.D.*
Food and Drug Administration
Rockville, Maryland

and

Thomas P. Laughren, M.D.
Food and Drug Administration
Rockville, Maryland

Methylphenidate: Rate-Dependent Effects on Hyperactivity

Mark D. Rapport, Ph.D.,[1] and George J. DuPaul, Ph.D.[1]

Hyperactivity is currently viewed as an Attention Deficit Disorder (ADD) characterized by a short attention span, impulsivity, and excessive, nongoal directed activity which is pervasive over time and across settings (American Psychiatric Association, 1980). In recent years, there has been an increasing urgency in establishing effective treatment protocols for ADD children owing to the relatively high prevalence rate (i.e., 3% to 5% of school-age children) and protracted nature (Satterfield et al., 1982) of the disorder.

The most popular treatment for this disorder over the past decade (Rapport, 1983) involves the prescription of psychostimulant medication (e.g., methylphenidate, dextroamphetamine and, more recently, pemoline), which improves the performance of most ADD children on laboratory tests of sustained attention (Sykes et al., 1973), reflection-impulsivity (Brown & Sleator, 1979; Rapport et al., 1985a), and short-term memory (Rapport et al., 1985b; Sprague & Sleator, 1977), as well as their classroom on-task and academic completion rates (Rapport et al., 1980, 1982, 1985b). Despite the widespread use of psychostimulants with this population (Safer & Krager, 1983), there remains a dearth of information regarding the underlying mechanisms and/or specific overt variables which may contribute to their effectiveness.

Conversely, studies of central nervous system (CNS) stimulant effects in animal species have consistently shown that the drug effect often depends upon the rate of occurrence (the control rate) of a given behavior in a drug-free state, i.e., that the behavioral effect of the drug is rate-dependent (Dews, 1977; Dews & Wenger, 1977).

The results of laboratory investigations examining the existence of the rate-dependency phenomenon with human adults have been equivocal thus far (Dews & Morse, 1958; Stitzer & Domino, 1974). Recent investigations, however, have shown preliminary evidence of rate-dependent effects of methylphenidate and/or D-amphetamine upon the in-seat activity (Robbins & Sahakian, 1977) and operant key-pressing (Rapport et al., 1985) behaviors of ADD children. Unfortunately, examinations of rate-dependent effects of stimulant medication have been confined thus far to behaviors exhibited under contrived conditions and/or laboratory settings, thus limiting the applicability and external validity of the findings.

The present investigation sought to extend previous findings by examining the effects of several doses of methylphenidate upon a behavior which is integrally related to the measurement of an attention deficit (viz., the frequency of on-task behavior) in a setting which is especially problematic for most ADD children: The classroom. The purpose of the study was to determine the extent to which an overt behavioral variable (i.e., the rate of on-task behavior in the absence of medication) contributes to the medication effect upon the frequency of classroom on-task behavior or, stated differently, whether stimulant effects upon an exigent behavior in *esse situ* could be explained via a rate-dependency analysis.

---

[1] Children's Learning Clinic, Department of Psychology, University of Rhode Island, Kingston, RI 02881-0808.

The order in which authors are listed was randomly determined. Both authors contributed equally to the manuscript.

Materials and Methods

Children with chronic problems of inattention, impulsivity, and overactivity were referred to the Children's Learning Clinic (CLC) of the University of Rhode Island by local pediatricians and school system personnel. A total of 20 (18 males and 2 females) children (weight range = 18.9 to 38.25 kg; median = 24.3 kg) between the ages of 6 and 11 years (mean = 8.1 years) participated in the study after obtaining informed consent from their parents and meeting each of the following criteria: a) an independent diagnosis by the child's pediatrician and CLC's directing clinical psychologist using DSM-III (American Psychiatric Association, 1980) criteria for Attention Deficit Disorder with Hyperactivity (ADD-H); b) a maternal report of a developmental history consistent with hyperactivity (Barkley, 1981); c) a maternal rating of at least two standard deviations above the mean for the child's age on the Werry-Weiss-Peters Activity Scale (Routh et al., 1981); d) a teacher rating on the Abbreviated Conners Teacher Rating Scale (ACTRS) above 15, the designated cutoff score for hyperactivity (Werry et al., 1975); e) performance on the Matching Familiar Figures (MFF) Test (Kagan et al., 1964) characteristic of a "fast-inaccurate or impulsive" responder, i.e., faster than average responses and higher than average error rates for the child's age; and f) free from any gross neurological, sensory, or motor impairment and not presently taking medication.

All children were of average or above average intelligence (mean IQ = 105; SD = 10.8) as assessed by the Peabody Picture Vocabulary Test-Revised, Form L (Dunn & Dunn, 1981), from families of low to middle socioeconomic status (Hollingshead, 1975), and "favorable responders" to methylphenidate according to recently defined criteria (Rapport et al., 1985a,b).

A double-blind, placebo-controlled, within-subject (crossover) design was used in which all children received each of the four doses following baseline measures. Order of drug administration was determined by randomly assigning each child to one of 24 possible counterbalanced drug orders. Methylphenidate was prescribed by each child's respective pediatrician in the following doses: placebo, 5 mg (range = .13 to .26 mg/kg), 10 mg (range = .26 to .53 mg/kg), and 15 mg (range = .39 to .79 mg/kg). Fixed doses (vs. mg/kg) were prescribed to reflect normal pediatric practice in the United States (Physician's Desk Reference, 1985) and because optimal dose has been shown not to depend on a child's body weight (Kinsbourne & Swanson, 1979; Rapport et al., 1985a,b). The methylphenidate was packaged in colored gelatin capsules by the pharmacist to avoid detection of dose and taste. Capsules were placed in individually dated envelopes to insure accurate dose administration.

Children were seen weekly at the CLC for individual testing using a battery of cognitive, learning, impulsivity, attention, and motor tasks during an intensive 8-week study period, which is detailed elsewhere (Rapport et al., 1985a,b). Only the classroom measures will be described herein.

The classroom phase of the experiment involved 5 consecutive weeks of observation. Following baseline data collection (1st week), parents were given a week's worth of medication in pre-dated envelopes at one dose level (i.e., placebo, 5, 10, or 15 mg methylphenidate). This procedure continued until a child received each dose for 7 consecutive days. All weekly dosage changes (e.g., switching from 15 mg to 5 mg) occurred on Saturdays to control for potential rebound effects. Parents were instructed to give their children a medication capsule each morning, 1/2 hr prior to breakfast, and to tell them it was a vitamin supplement (i.e., to help control for expectancy (Rapport et al., 1982). Both used and unused envelopes were returned to control for medication compliance.

Children were observed in their regular classrooms for 20 min intervals, 3 days per week across the 5-week evaluation period. Classroom observations began 1 1/2 to 2 hrs after the children's morning medication in an effort to improve upon previous dose response studies (Sprague & Sleator, 1977) by controlling for time after medication. Children completed in-seat academic work assigned by the teacher during this time and were unobtrusively observed by trained undergraduate and graduate students for 60 continuous intervals during each observation period throughout the study. Each interval was divided into 15 sec of observation followed by 5 sec for recording. Classroom teachers and observers were blind to both when medication was administered and specific doses.

A child's behavior was categorized as either on-task or off-task in a manner identical to that used in earlier studies (Rapport et al., 1980, 1982, 1985b). A response was defined as a discrete 15-sec interval in which a child was observed to be on-task. Response rate was obtained for each child by calculating the mean number of responses per 20 min interval (maximum daily response rate = 60 per 20 min) over the 3-day observation period within each experimental condition. Interobserver reliability checks of child behavior were taken on 33% of the observation days for all children, and at least once during each experimental phase. Obtained reliability estimates (Hopkins & Hermann, 1977) were computed for occurrence (mean = .95), nonoccurrence (mean = .88), and overall agreement (mean = .95) (Bijou et al., 1968), with a mean Kappa value of .83 obtained for all observations.

Results

The mean on-task response rates (responses per 20 min) and standard deviations for baseline, placebo, and the three methylphenidate (5, 10, 15 mg) conditions are presented in the Table. A one-way analysis of variance with repeated measures across the five conditions was significant ($F = 24.92$; d.f. = 4,76; $p < .001$), with a follow-up Newman-Keuls test revealing significantly greater mean on-task response rates in all three methylphenidate conditions compared to baseline and placebo ($p < .01$). The mean on-task response rate in the 15 mg condition was significantly greater than those in 5 ($p < .01$) and 10 ($p < .05$) mg. No further significant differences were found.

TABLE

Mean On-Task Response Rates (Responses per 20 min) and Associated Standard Deviations (SD) for Baseline, Placebo, and Three Active Methylphenidate Conditions (5, 10, 15 mg) in a Sample ($N = 20$) of ADD Children

Condition	On-Task Response Rate	
	Mean	SD
Baseline	32.37	12.32
Placebo	32.40	15.68
5 mg	41.90	11.21
10 mg	46.18	11.26
15 mg	51.96	4.63

Note: The maximum daily on-task response rate = 60.00.

Rate-dependent effects of psychostimulants upon behavior have been classically analyzed by examining the relationship between the control response rate (response rate under placebo) and the output ratio (the ratio of response rate after medication to control response rate) (Dews & Wenger, 1977). In keeping with tradition, Figure 1 was drawn with log control rate plotted on the abscissa and log output ratio (drug rate/control rate × 100) on the ordinate with regression lines for each dose fitted by the method of least squares. Correlations between the two variables were −.96, −.98, and −.99 for 5, 10, and 15 mg, respectively, with all three significantly different from zero ($p < .001$). Thus, a negative linear relationship was found between control rate and output ratio at all three doses. A test for equality of slopes, with control rate as the covariate and each dose treated as a separate group, revealed that the 15 mg slope was significantly steeper than both the 5 and 10 mg slopes ($F = 11.28$; d.f. = 2,54; $p < .001$).

A final analysis was performed owing to the controversy regarding whether fixed-dose or milligram per kilogram (mg/kg) plots

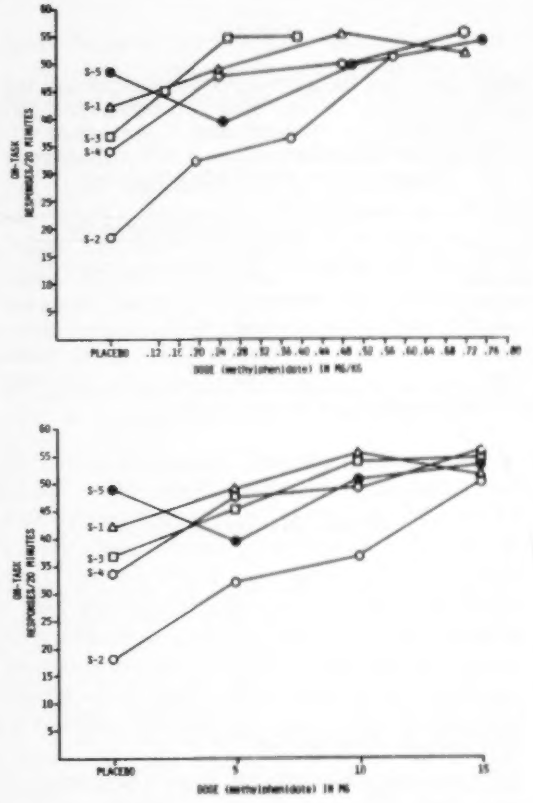


FIGURE 1. Log output ratio (drug rate/placebo control rate × 100) as a function of log placebo control rate for on-task response rate (responses per 20 min). Regression lines were fitted by the method of least squares for each dose. Individual scores across doses are represented by closed circles (5 mg), triangles (10 mg), and squares (15 mg).

should be used in evaluating dose effects in children receiving methylphenidate (Rapport et al., 1985a,b). Consequently, the on-task response rates of five children randomly selected from the participant group ($N = 20$) were plotted using both fixed-dose and mg/kg plots (*see* Figure 2). This procedure was used to facilitate graphical illustration and interpretation (i.e., drawn curves using all 20 children were too difficult to visually follow). A test of equality of the regression lines showed no signficant differences between the slopes of the dose-response curves obtained from the random subsample and the remaining 15 children, indicating that the former were representative of the total sample.

In examining the curves shown in Figure 2, it appears that children's on-task response rates show similar dose-related changes using both fixed-dose and mg/kg dose-response plots. Four of the five children (S-2, S-3, S-4, & S-5) performed optimally at the highest dose (compared with lower doses) regardless of whether fixed-dose or mg/kg plots were used; thus, corroborating the results of previous investigations showing individual responsivity to psychostimulant medication (Rapport et al., 1985a,b). Furthermore, weight calculated on a mg/kg basis does not appear to account for the obtained individual differences (e.g., note the differences in on-task behavior between S-2 and S-3 at .38 mg/kg).

Discussion

Our data have implications for both pediatric psychopharmacological research and the clinical practice of monitoring psychostimulants in ADD children. A review of the psychopharmacological research on ADD indicates that there have been no prospective empirical investigations which systematically assess whether a child's drug-free rate of behavior contributes to drug responsiveness (Reatig, 1984). The data presented herein establish this relationship by showing drug-induced proportional changes in ADD chil-

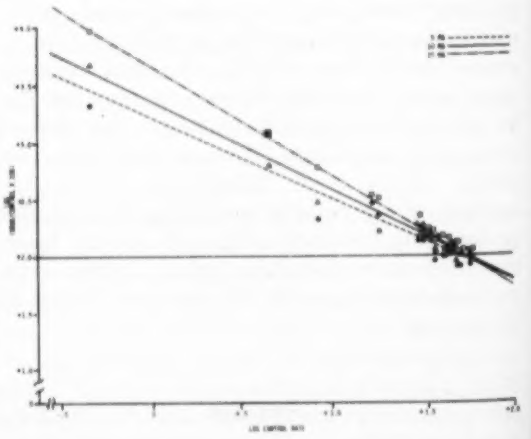


FIGURE 2. The mean on-task response rate per 20 min interval for five hyperactive children randomly chosen from the total group ($N = 20$) on placebo and three doses of methylphenidate. The top panel depicts dose-response curves in mg/kg. The lower panel shows dose-response curves in mg for comparison.

dren's attention which are consistent with the rate-dependency phenomenon found with lower species (Dews, 1977; Dews & Wenger, 1977). Thus, the rate of a child's overt behavior in a drug-free state clearly contributes to the effect of CNS stimulant on that behavior. The strength and shape of this relationship are affected by dose and the child's unique reaction to the drug, yet appear unrelated to body weight. Dosage should be directly manipulated in pediatric psychopharmacological studies and the cumbersome practice of using mg/kg dosage schedules may no longer be necessary (Rapport et al., 1985a).

The CNS stimulant methylphenidate is the most widely studied and prescribed medication for ADD children in the United States (Safer & Krager, 1983). Physicians typically use the titration method (Physician's Desk Reference, 1985) of increasing dosage until favorable reports are obtained by the parents and/or teacher. Both of these sources tend to base their judgments on the child's social behavior, which generally necessitates higher dosages for improvement than does cognitive performance (Sprague & Sleator, 1977). In order to assess the effects of methylphenidate on classroom performance, our data indicate that physicians need to obtain information regarding the child's rate of academic behavior both before and during clinical drug trials. School-based paraprofessionals may need to be recruited to provide this information to the pediatrician. The contribution of other variables (e.g., an individual's past history) and/or specific behaviors (academic completion and accuracy rates) to CNS stimulant effects in ADD children will need to be explicated in future studies.

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Washington, D.C.: Author, 1980.

Barkley, R.A. *Hyperactive Children: A Handbook for Diagnosis and Treatment.* New York: Guilford Press, 1981.

Bijou, S.W., Peterson, R.F., and Ault, M.H. A method to integrate descriptive and experimental field studies at the level of data and empirical concepts. *J. Appl. Behav. Anal.*, 1:175–191, 1968.

Brown, A.T., and Sleator, E.K. Methylphenidate in hyperkinetic children: Differences in dose effects on impulsive behavior. *Pediatrics*, 64:408–411, 1979.

Dews, P.B. Rate-dependency hypothesis. *Science*, 198:1182, 1977.

Dews, P.B., and Morse, W.H. Some observations on an operant in human subjects and its modification by dextroamphetamine. *J. Exp. Anal. Behav.*, 1:359–364, 1958.

Dews, P.B., and Wenger, G.A. Rate-dependency of the behavioral effects of amphetamine. In: Thompson, T., and Dews, P.B. (eds.), *Advances in Behavioral Pharmacology*, Vol. 1. New York: Academic Press, 1977.

Dunn, L.M., and Dunn, L.M. *Peabody Picture Vocabulary Test-Revised*. Circle Pines, Minn.: American Guidance Service, 1981.

Hollingshead, A.B. *Four Factor Index of Social Status.* New Haven: Yale University, 1975.

Hopkins, B.L., and Hermann, J.A. Evaluating interobserver reliability of interval data. *J. Appl. Behav. Anal.*, 10:121–126, 1977.

Kagan, J., Rosman, B.L., Day, D., et al. Information processing in the child: Significance of analytic and reflective attitudes. *Psychol. Monogr.*, 78, 1964.

Kinsbourne, M., and Swanson, J.M. Models of hyperactivity: Implications for diagnosis and treatment. In: Trites, R.L. (ed.), *Hyperactivity in Children: Etiology, Measurement and Treatment Implications.* Baltimore, Md.: University Park Press, 1979.

Physicians Desk Reference. Oradell, N.J.: Litton Industries, Inc., 1985.

Rapport, M.D. Attention deficit disorder with hyperactivity: Critical treatment parameters and their application in applied outcome research. In: Hersen, M., Eisler, R., and Miller, P. (eds.), *Progress in Behavior Modification*, Vol. 14. New York: Academic Press, 1983.

Rapport, M.D., DuPaul, G.J., and Smith, N.F. Rate-dependency and hyperactivity: Methylphenidate effects on operant responding. *Pharmacol. Biochem. Behav.*, 23:1–7, 1985.

Rapport, M.D., DuPaul, G.J., Stoner, G., et al. Attention deficit disorder with hyperactivity: The differential effects of methylphendiate on impulsivity. *Pediatrics*, 76:938–943, 1985a.

Rapport, M.D., Murphy, A., and Bailey, J.S. The effects of a response cost treatment tactic on hyperactive children. *J. School Psychol.*, 18:98–111, 1980.

Rapport, M.D., Murphy, A., and Bailey, J.S. Ritalin vs response cost in the control of hyperactive children: A within subject comparison. *J. Appl. Behav. Anal*, 15:205–215, 1982.

Rapport, M.D., Stoner, G., DuPaul, G.J., et al. Methylphenidate in hyperactive children: Differential effects of dose on academic, learning, and social behavior. *J. Abnorm. Child Psychol.*, 13:227–244, 1985b.

Reatig, N. Attention deficit disorder: A bibliography *Psychopharmacol Bull.*, 20(4):693–718, 1984.

Robbins, T.N., and Sahakian, B.J. "Paradoxical"effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behavioral pharmacology. *Neuropharmacology*, 18:931–950, 1979.

Routh, D.K., Schroeder, C.S., and O'Tauma, L. Development of activity level in children. *Dev. Psychol.*, 10:163–168, 1974.

Safer, D.J., and Krager, M.D. Trends in medication treatment of hyperactive school children. *Clin. Pediatr.*, 22:500–504, 1983.

Satterfield, J.H., Hoppe, C.M., and Schell, A.M. A prospective study of delinquency in 110 adolescent boys with attention deficit disorder and 88 normal boys. *Am. J. Psychiatry*, 139:795–798, 1982.

Sprague, R.L., and Sleator, E.K. Methylphenidate in hyperkinetic children: Differences in dose effects on learning and social behavior. *Science*, 198:1274–1276, 1977.

Stitzer, M., and Domino, E.F. Effects of d-amphetamine and secobarbital on key press rates in normal humans. *Arch. Int. Pharmacodyn. Ther.*, 207:288–297, 1974.

Sykes, D.H., Douglas, V.I., and Morgenstern, G. Sustained attention in hyperactive children. *J. Child Psychol. Psychiatry*, 14:213–220, 1973.

Werry, J., Sprague, R., and Cohen, M. Teacher rating scale for use in drug studies with children—An empirical study. *J. Abnorm. Child Psychol.*, 3:217–229, 1975.

The Therapeutic Effect of Clonidine in Attention Deficit Disorder With Hyperactivity: A Comparison With Placebo and Methylphenidate

Robert D. Hunt, M.D.,[1] Ruud B. Minderaa, M.D.,[2] and Donald J. Cohen, M.D.[1]

Introduction

Attention Deficit Disorder with Hyperactivity (ADD-H) has been estimated to affect approximately 250,000 children in the U.S.A. It is characterized by impulsivity, inattention, and hyperactivity (Hunt et al., 1982: Safer & Allen, 1976) which impairs academic learning, disrupts social and peer relations, and can greatly disturb functioning within the home and at school (Cantwell, 1975a: Halperin & Gittelman, 1982: Levy & Hobbes, 1981: Silver, 1981: Weiss & Hechtman, 1979). Recent evidence has established the persistence of this disorder into adolescence (Lerer & Lerer, 1977; Mendelson et al., 1971) and adulthood (Amado & Lustman, 1982: Weiss et al., 1979: Wood et al., 1976). ADD-H children may have an increased risk of developing anti-social behavior (Satterfield et al., 1982) and alcoholism and substance abuse (Eyre et al., 1982).

A genetic component to this disorder has been described (Cantwell, 1975b; Deutsch et al., 1982; Mendelson et al., 1971), which may suggest that it has a biological substrate. Altered noradrenergic functioning has been suggested by the low levels of urinary 3-methoxy 4-hydroxyphenylglycol (MHPG) (Shekim et al., 1979, 1982), and in increased human growth hormone (hGH) response to a clonidine challenge (Hunt et al., 1984).

Need for Alternative to Stimulant Medication

In spite of the excellent response of many children with ADD-H to stimulant medications such as methylphenidate and D-amphetamine, a substantial percent do not respond to or develop significant side effects from stimulants. Approximately 40% of well-diagnosed children have no response or exhibit a decrement in response on paired associate learning tasks following an acute dose of methyphenidate or cylert (Swanson & Kinsbourne, 1976). Their cognitive and social behavior may become exceedingly constricted and rigid. Although stimulant medication improves performance on selected cognitive laboratory tasks, the medication alone does not improve academic grades nor substantially alter other outcome measures (Gittelman-Klein, 1976, Quinn & Rapoport, 1974). Coupled with psychotherapy and special education, stimulants may improve academic adjustment and performance (Satterfield et al., 1979).

However, stimulant medications have multiple side effects and some specific contraindications for use. Transient side effects include anorexia, insomnia, stomach aches, afternoon withdrawal, and explosiveness (Cantwell, 1975a). Long-term side effects of stimulants may include growth suppression (Greenhill et al., 1980; Millichap, 1978), development of tics (Lowe et al., 1982), and hallucinosis (Young, 1981). Compliance with methylphenidate treatment is frequently low (Firestone, 1982; Sleator et al., 1982). There is a need for an alternative medication that would have the following characteristics: 1) fewer side effects and a more consistent duration of action; 2) therapeutic benefit for children whose ADD-H is associated with explosiveness, motor tics, personality rigidity; 3) safety in ADD-H adolescents who are at risk for substance abuse; 4) improvement in patient acceptance and compliance; and 5) more effective enhancement of academic performance.

---

[1] Yale Child Study Center, New Haven, CT 06510.
[2] Sophia Children's Hospital, Rotterdam, The Netherlands.

Clonidine

Clonidine is an alpha-adrenergic stimulating agent which acts preferentially on presynaptic alpha-2 neurons to inhibit noradrenergic activity (Aghajanian & Bunney, 1977; Cedarbaum & Aghajanian, 1977; Titeler & Seeman, 1980). It stimulates release of hGH (Gold et al., 1979; Hunt, 1984), and inhibits norepinephrine (NE) release which decreases the level of the NE metabolite MHPG in the urine (Charney, 1982; Hunt, in press). Clonidine is useful as an antihypertensive agent (Manheim et al., 1982), an inhibitor of opiate withdrawal (Gold et al., 1980), and it may have some short-term antianxiety effects (Redmond, 1979).

Many patients with Tourette's Syndrome (TS) frequently share with ADD-H children problems of impulsivity, inattention, and motor restlessness (Cohen et al., 1980). Children with TS demonstrate decreased tics and improved calmness and attention on clonidine (Cohen et al., 1980; Leckman et al., 1983).

Following good results with an open pilot study of 7 ADD-H boys treated with clonidine (4 ng/kg/day), we performed a double-blind placebo-crossover in 10 children.

Method

Subjects

Ten children, ages 11.6±0.54 (mean±SE) years, participated in 12 weeks of active treatment with clonidine.

All of the children had received special education; half were predominantly treated in this fashion. Four of the children had one or more first-degree relatives with a distinct history of ADD-H or learning disabilities. The families in this study were in the 3.2±0.4 socioeconomic status (Hollingshead, 1965).

Seven (70%) of those completing the study had previously been treated with stimulant medication for 3.2±.7 (mean±SE) years at a dose of 0.35±.12 mg/kg. Three of the parents reported that the stimulant medication had been beneficial; four had discontinued stimulants because of significant side effects.

Subject Selection

To be eligible for the study, a child had to meet DSM-III criteria for ADD-H and score at least 2.0 standard deviations (s.d.) above normal on the Hyperactivity Index (Barkley, 1981) of the Connors Behavior Rating Scale (C-BRS) as rated by either parent or teacher (Conners, 1969). All subjects had an IQ greater than 80 and had no symptom of psychosis or primary mood disturbance. All were medically healthy with no cardiac, endocrine, or neurological disorder.

An additional baseline assessment included two weekly ratings on the Parents' and Teachers' version of the Parents' Child Behavior Checklist (Achenbach, 1978), a standardized psychiatric interview using the Diagnostic Inventory for Children and Adolescents (DICA) by Herjanic and Weiner (1981), and a developmental and personal history (Personal Data Inventory developed by Shaywitz, 1982). Academic and behavioral records describing academic performance, behavior, and psychological and educational testing were obtained from their schools. Physical and neuromaturational exams, a complete blood count, thyroid indices, lead levels, ceruloplasm, electrolytes, blood urea nitrogen, and an electrocardiograph were also performed. The children were either drug-naive or were drug-free for 1 month prior to beginning clonidine. Informed consent from parents and assent from the children was obtained after they received a detailed description of the study.

Double-Blind Treatment Design and Implementation

Since the effects of clonidine require several weeks to stabilize, active clonidine was administered for 8 consecutive weeks. After 2 weeks of baseline assessment, subjects were randomly assigned to begin with either active clonidine or placebo for 2 weeks. The group initially treated with placebo ended their treatment with 2 additional weeks of placebo; the group initially treated with clonidine ended with 4 weeks of placebo. Subjects were randomly assigned to a treatment group by a research assistant, leaving clinicians blind to the treatment sequence. Parents were given coded tablets with computer-generated instructions specifying the tablet to be taken for each dose. Parents, teachers, children, and one clinician rater remained blind to the study design.

Medication Dose and Rate of Increase

The dose of clonidine was increased by 0.05 mg every other day until a dose of 4-5 µg/kg/d (about 0.05 four times a day) was achieved. Clonidine was tapered off gradually when children were returned to placebo in order to avoid a hypertensive reaction. Blood pressure and pulse were measured monthly at each clinic visit.

Evaluation of Therapeutic Response

Every 2 weeks parents and teachers completed the revised Conners Parents' Behavior Rating (48-item) and the Teachers' Behavior Rating (28-item) scales, respectively. *Every month* parents and children had a videotaped interview and repeated behavioral ratings. Two clinicians blind to the treatment condition rated the children using a scale which quantitatively scores the DSM-III specified symptoms for ADD-H; all raters also completed a global rating of improvement. A brief neuromaturational assessment battery was repeated monthly to monitor visual-motor coordination as evidenced by: sequential finger tap, the peghole test, the marble sorting, printing, and the Coding and Digit Symbol tasks from the Wechsler Intelligence Scale for Children—Revised (WISC-R). Auditory attention was assessed using Digit Span (forward and backwards). The Kagan Matching Familiar Figures Test provided an index of impulsivity, visual scanning, and frustration tolerance.

Data Analysis

Behavior and neuromaturational rating scores were compared at baseline, 1 month, 2 months, and during placebo withdrawal using a one-way analysis of variance with repeated measures. Comparisons between baseline and final week of clonidine (2 months) and clonidine and placebo were analyzed using a two-tailed t test.

Results

Clonidine's Effect On Conners' Behavior Ratings (*See* Table 1, Figures 1 and 2.)

Composite Ratings: Eight of the 10 children were rated as at least mildly (10 to 24%) improved by one observer. Seven children were rated as at least moderately (25 to 49%) improved by two observers; this rating was considered the minimal criteria for definite improvement. Six showed a substantial (50 to 74%) improvement as rated by at least one observer; 5 were rated as at least 50% improved in the classroom. Four subjects were reported to be substantially improved in two settings.

Teachers' Ratings

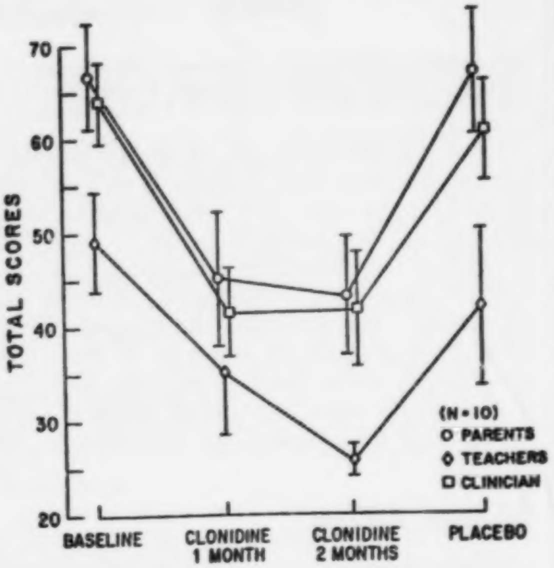
Before treatment with clonidine, teachers' total behavior rating on the Conners' 28-item scale for the group was 49.00±5.20 (mean±SE). After 8 weeks of treatment with clonidine the bi-weekly average of the teachers' behavior ratings demonstrated progressive improvement, with a final rating of 25.79 ±1.31 ($p = 0.001$). Similarly, the teachers' "Hyperactivity Index" (Barkley, 1981) dropped from pretreatment level of 1.99±0.16 to 1.12±0.06 at the end of active clonidine treatment ($p = 0.001$). Significant changes in conduct ($p = 0.4$) and inattention

TABLE 1

Overall Improvement for Individual Subjects During Treatment

Subject No.	Rater		
	Parent	Teacher	Clinician
1	1	2	1
2	2	3	1
3	4	3	3
4	2	2	2
5	2	3	3
6	2	0	1
7	3	2	3
8	0	NA	—
9	2	2	2
10	2	NA	2

Key:
0 = no significant change (less than 25% improvement or deterioration)
1 = mild improvement (10 to 24%)
2 = moderate improvement (25 to 49%)
3 = substantial improvement (50 to 74%)
4 = extreme improvement (more than 75%)
— = 25% overall deterioration
NA = not ascertained



p-VALUES	PARENTS	TEACHERS	CLINICIAN
BASELINE - CLON 2 mo	0.003	0.001	0.01
CLON 2 mo - PLACEBO	0.02	0.05	0.04

FIGURE 1. Total scores. Behavioral response to clonidine and placebo (crossover).

($p = 0.5$) were also noticed by teachers. Five of the 8 children on whom ratings were completed demonstrated at least moderate (25%) improvement in overall behavior ratings; 5 were substantially (75%) improved. During the post-clonidine placebo period, the teachers observed at least a moderate (25 to 50%) deterioration in all but one child. Teachers' written comments indicated that children appeared "more relaxed," and had much more "on-task activity" during clonidine treatment and exerted more purposeful effort at school. They reported that children seemed less easily distracted or frustrated. Teachers described these children as being "better accepted by peers" and "less aggressive and explosive."

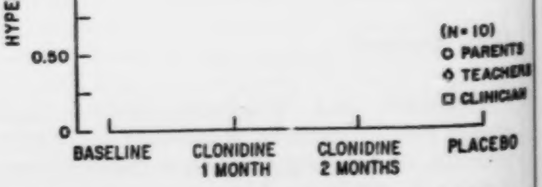
Parents' Ratings

Parents documented a similar response to clonidine treatment. Parents' overall behavior ratings (Conners' 48-item scale) for the group declined from a pretreatment level of 66.85±5.75 to 43.00±6.29 ($p = 0.003$) after 8 weeks of clonidine. Parents rated significant improvement in the following areas: "Hyperactivity Index" (2.03±0.16 to 1.34±0.21; $p = 0.004$); "Conduct Problems" (1.38±0.16 to 0.99±0.10; $p = 0.01$); and improvement in "Learning Problems" (2.36 ±0.17 to 1.53±0.28; $p = 0.007$); but no significant improvement occurred in factor scores for Anxiety or Psychosomatic problems.

During clonidine treatment, 3 children demonstrated a substantial decrease (50%), while 4 had a moderate (25%) decrease, in ADD-H symptoms. Three of the children, including both girls, showed no overall change according to their parents. Parents' ratings of children's overall behavior on subsequent *placebo* showed a substantial deterioration in 4 children, a moderate deterioration in an additional 2 children, and a mild deterioration in 2 more children; 1 child demonstrated slightly improved behavior. Ratings for "Hyperactivity" deteriorated to about the same degree during placebo.

Clinicians' Ratings

Based on direct clinical interviews and a review of the behavioral ratings, the clinicians reported a significant improvement in 8



p-VALUES	PARENTS	TEACHERS	CLINICIAN
BASELINE - CLON 2 mo	0.004	0.001	0.03
CLON 2 mo - PLACEBO	0.002	0.04	0.12

FIGURE 2. Hyperactivity index. Behavioral response to clonidine and placebo (crossover).

subjects in the primary DSM-III symptoms of ADD-H. Three children improved moderately and 5 improved mildly in overall symptoms of ADD-H.

On withdrawal from clonidine, clinicians also reported that 7 of 10 children developed more severe ADD-H symptoms, which were extreme in 4 subjects and moderate in 1. Ratings of "Hyperactivity" showed deterioration in 6 subjects; inattention and impulsivity worsened in 7 subjects on placebo. Clinicians' ratings of "Impulsivity" showed a similar response to placebo.

By direct clinicians' observation, these children were more cooperative during interviews while taking active clonidine. They performed the neuromaturational and cognitive tasks with less resistance and protest. Their mood appeared improved. They frequently described experiences of feeling more in control of anger and irritability, and having greater ability to solve problems. They expressed increased pride in their achievements and experienced less conflict and oppositionality at home and at school. They described an increase in their efforts to resolve conflicts and solve problems. They appeared more thoughtful, psychologically minded, and self-confident. This was most impressive in 3 children who otherwise had experienced minimal therapeutic benefit from their prior treatment with methylphenidate.

Placebo Withdrawal

When subjects returned to the placebo condition, their behavior rapidly deteriorated; symptoms usually returned within 2 to 4 days. Three of the children were unable to remain off medication for the full 4 weeks due to profound worsening of behavior that threatened to disturb classroom performance and placement. A significant deterioration in overall behavior for the group was noted by teachers ($p = 0.05$), parents ($p = 0.02$), and clinicians ($p = 0.04$).

Neuromaturational Testing

The scores for the neuromaturational tests showed that clonidine tended to improve performance in some tests beyond the effect of practice, but none of these changes reached significance. Clonidine's main effect on neuromaturational tasks was to diminish variability. This may indicate reduced distractibility and off-task behavior on clonidine. Clonidine did not impair subjects' performance of psychomotor tasks.

Side Effects

The main side effect was *sleepiness*, which occurred primarily for 30 to 60 minutes beginning about 1 hour after clonidine administration. In all but one child, this sleepiness subsided after 3 weeks and was dose dependent. For this child, sleepiness limited clonidine's usefulness. The mean *blood pressure* decreased 10% on clonidine; this produced no subjective symptoms other than occasional light-headedness immediately after standing or strenuous exertion. One child who had symptoms of mild *depression* prior to clonidine became more tearful and unhappy on clonidine. Children without prior symptoms of depressive disorder did not become depressed on clonidine.

Discussion

Clonidine significantly improved the overall behavior ratings of "Hyperactivity," "Impulsivity," and "Inattention" in children with ADD. Two children improved moderately (10 to 25%) on clonidine, while 5 improved substantially (25 to 50%). One subject showed no change or a slight deterioration on clonidine. The two girls were among the three poorest responders.

Clinical Impressions

Clonidine seemed to facilitate a maturational development characterized by increased reflectivity, heightened purposeful, goal-directed behavior, and less oppositional behavior. Clonidine enhanced children's frustration tolerance and enabled them to sustain effort toward age-appropriate objectives without feeling overwhelmed, inadequate, or incompetent.

Clinical Differentiation of Good and Poor Responders to Clonidine

The ADD-H children who responded best were those who had been overactive and lacked inhibition. Their capacity for social-relatedness and purposeful activity appeared intact but had been under-utilized due to their impulsivity. One child who did not benefit from clonidine met DSM-III criteria for both ADD-H and schizoid personality disorder. While this child was calmer on clonidine, he also became more disorganized, passive, and undirected. The poor response of two ADD-H girls may suggest a slightly different clinical or neurochemical process in these individuals.

Noradrenergic Mechanisms in ADD-H

The finding of therapeutic benefit from clonidine in ADD-H is of heuristic as well as practical significance, since it may advance our understanding of the role of noradrenergic mechanisms in this disorder.

Clonidine not only directly inhibits noradrenergic excitation, as evidenced by decreased firing of the locus coeruleus (Aghajanian & Bunney, 1977; Starke & Altman, 1973), and by diminished MHPG production (Cedarbaum & Aghajanian, 1976, 1977; Hunt et al., 1984; Leckman et al., 1980). Clonidine also has a modulating effect on the firing of dopaminergic neurons under conditions of stress (Antelman & Caggiula, 1977). Clonidine's effect in children with ADD-H may reflect both direct noradrenergic effects on cognition and anxiety—leading to improved frustration tolerance and performance—and secondary modulating effects on other monoamine systems. Chronic administration of a noradrenergic agent such as clonidine may alter the sensitivity of non-adrenergic receptors, such as dopamine, to their neurotransmitters (Cooper et al., 1978).

Norepinephrine (NE) mediates the expression of anxiety which may occur during phobic or panic states or during opiate withdrawal. NE activity of the locus coeruleus as measured by implanted electrodes in unanesthetized cats increased during arousal from sleep to wakening and in response to the introduction of a novel stimulus (Aston-Jones & Bloom, 1981; Foote & Bloom, 1979). This NE activation increased arousal and external vigilance of the animal. The symptoms of ADD-H may suggest a state of increased arousal that causes stimuli to seem excessively novel and engaging.

Biochemical factors may distinguish these children from normal, and may eventually contribute to predicting medication response. Clonidine may be preferentially useful in a biologically definable subgroup of noradrenergically over-responsive ADD-H children, who may be identified by levels of urinary MHPG or by response to a clonidine or yohimbine challenge.

Clonidine may be preferable to methylphenidate in children who have chronic tics, decreased appetite (anorexia), sleep disturbance (insomnia), excessive afternoon withdrawal, or growth retardation. It may also be beneficial to ADD-H children who are primarily impulsive, unreflective, and easily emotionally overwhelmed.

Further subtyping of ADD-H according to diagnosis of conduct disorder (Satterfield et al., 1982), aggression (Milich et al., 1982), degree of motor activity (Porrino et al., 1983), the presence of specific learning disabilities (Andrulonis et al., 1982; August and Stewart, 1982; Kupietz et al., 1982; O'Brien, 1982), and the extent of affective lability, explosiveness, or depression may clarify clinical or biological differences in ADD-H children.

We are performing an open-ended comparison of methylphenidate and clonidine on an additional 20 ADD-H children using similar behavioral and neuromaturational measures. Our clinical impressions support our earlier observations that clonidine treatment improves compliance, task orientation, and frustration tolerance, and reduces oppositional behavior. Parents especially appreciate the fact that clonidine can be given in the late afternoon or evening without interfering with the child's appetite or sleep. In some cases of extreme distractibility a combination of clonidine and low doses of methylphenidate appears safe and effective.

Further research is needed to compare clinical response of ADD-H children to clonidine and methylphenidate and to identify biochemical and clinical predictions of differential response.

References

Achenbach, T.M. The child behavior profile: I. Boys aged 6-11. *J. Consult. Clin. Psychol.*, 46:478–488, 1978.

Aghajanian, G.K., and Bunney, B.S. Dopamine "autoreceptors": Pharmacological characterization by microintophoretic single cell recording studies. *Arch. Pharmacol.*, 297:1–7, 1977.

Amado, H., and Lustman, P.J. Attention deficit disorders persisting in adulthood: A review. *Compr. Psychiatry*, 23:200–214, 1982.

Andrulonis, P.A., Glueck, B.C., Stroebel, C.F., et al. Borderline personality subcategories. *J. Nerv. Ment. Dis.*, 170:670–679, 1982.

Antelman, S.M., and Caggiula, A.R. Norepinephrine-dopamine interactions and behavior. *Science*, 194:646–653, 1977.

Aston-Jones, G., and Bloom, F.E. Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *J. Neurosci.*, 1:887–900, 1981.

August, G.J., and Stewart, M.A. Is there a syndrome of pure hyperactivity? *Br. J. Psychiatry*, 140:305–311, 1982.

Barkley, R.A. *Hyperactive Children: A Handbook for Diagnosis and Treatment*. New York: Guilford Press, 1981.

Cantwell, D.P. *The Hyperactive Child: Diagnosis, Management and Current Research*. New York: Spectrum Publications, 1975a.

Cantwell, D.P. Genetic studies of hyperactive children: Psychiatric illness in biological and adopting parents. In: Fieve, R., Rosenthal, D., and Brill, H. (eds.), *Genetic Research in Psychiatry*. Baltimore: Johns Hopkins University Press, 1975b, pp. 273–280.

Cedarbaum, J.M., and Aghajanian, G.K. Noradrenergic neurons of the locus coeruleus: Inhibition by epinephrine and activation by the alpha-antagonist piperoxane. *Brain Res.*, 112:412–419, 1976.

Cedarbaum, J.M., and Aghajanian, G.K. Catecholamine receptors on locus coeruleus neurons: Pharmacological characterization. *Eur. J. Pharmacol.*, 44:357–385, 1977.

Charney, D.S., Heninger, G.R., Sternberg, D.E., et al. Adrenergic receptor sensitivity in depression: Effects of clonidine in depressed patients and healthy subjects. *Arch. Gen. Psychiatry*, 39:290–294, 1982.

Cohen, D.J., Detlor, J., Young, J.G., et al. Clonidine ameliorates Gilles de la Tourette Syndrome. *Arch. Gen. Psychiatry*, 34:1350–1357, 1980.

Conners, C.K. A teacher rating scale for use in drug studies with children. *Am. J. Psychiatry*, 126:152–156, 1969.

Cooper, J.R., Bloom, F.E., and Roth, R.H., (eds.) Catecholamines II: CNS aspects. In: *The Biochemical Basis of Neuropharmacology*. New York: Oxford University Press, 1978, pp. 161–196.

Deutsch, C.K., Swanson, J.M., Cantwell, D.P., et al. Overrepresentation of adoptees in children with attention deficit disorder. *Behav. Genet.*, 12:231–238, 1982.

Eyre, S.L., Rounsaville, B.J., and Kleber, H.D. History of childhood hyperactivity in a clinic population of opiate addicts. *J. Nerv. Ment. Dis.*, 170:5229, 1982.

Firestone, P. Factors associated with children's adherence to stimulant medication. *Am. J. Orthopsychiatry*, 52:44757, 1982.

Foote, S., and Bloom, F.E. Activity of norepinephrine-containing locus coeruleus neurons in the unanesthetized squirrel monkey. In: Usdin, E., Kopin, I., and Barchas, J. (eds.), *Catecholamines: Basic and Clinical Frontiers*. New York: Pergamon Press, 1979, pp. 625–627.

Gittelman-Klein, R., and Klein, D.F. Methylphenidate effects in learning disabilities: Psychometric changes. *Arch. Gen. Psychiatry*, 33:655–664, 1976.

Gold, M.S., Redmond, D.E. Jr., and Kleber, H.D. Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Am. J. Psychiatry*, 136:100–102, 1979.

Gold, M.S., Pottash, A.L., Sweeney, D.R., et al. Clonidine decreases opiate withdrawal-related anxiety: Possible opiate noradrenergic interaction in anxiety and panic. *Substance Alcohol Actions Misuse*, 1:239–246, 1980.

Greenhill, L.L., Puig-Antich, J., Halperin, F., et al. Growth disturbances in hyperkinetic children. *Pediatrics*, 66:152–154, 1980.

Halperin, J.M., and Gittelman, R. Do hyperactive children and their siblings differ in IQ academic achievement? *Psychiatry Res.*, 6:253–258, 1982.

Herjanic, B., and Weiner, J. *Diagnostic Interview for Children and Adolescents*. Working document. Washington University Medical School, St. Louis, Mo., 1981.

Hollingshead, A.B. *Two-Factor Index of Social Position*. New Haven, Conn.: Yale Station, 1965.

Hunt, R.D., Cohen, D.J., Shaywitz, S.E., et al. Strategies for study of the neurochemistry of attention deficit disorder in children. *Schizophr. Bull.*, 8:236–251, 1982.

Hunt, R.D., Cohen, D.J., Anderson, G.M., and Clark, L. Possible change in noradrenergic receptor sensitivity with attention deficit disorder and hyperactivity: Response to chronic methylphenidate treatment. *Life Sci.*, 35:885-897, 1984.

Hunt, R.D., Cohen, D.J., Anderson, G.M., et al. Noradrenergic mechanisms in attention deficit disorder with hyperactivity. In: L. Bloomingdale (ed.), *Attention Deficit Disorder and Hyperactivity*, Vol. 3. New York: Spectrum Publications. (In press)

Kupietz, S.S., Winsberg, B.G., and Sverd, J. Learning ability and methylphenidate (ritalin) plasma concentration in hyperkinetic children: A preliminary investigation. *J. Am. Acad. Child Psychiatry*, 21(1):27–30, 1982.

Leckman, J.F., Detlor, J., Harcherik, D.F., et al. Acute and chronic clonidine treatment in Tourette's Syndrome: A preliminary report on clinical response and effect on plasma and urinary catecholamine metabolites, growth hormone, and blood pressure. *J. Am. Acad. Child Psychiatry*, 5:433–440, 1983.

Leckman, J.F., Maas, J.W., Redmond, D.E. Jr., et al. Effects of oral clonidine on plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) in man: Preliminary report. *Life Sci.*, 26:2179–2185, 1980.

Lerer, R.J., and Lerer, M.P. Response of adolescents with minimal brain dysfunction to methylphenidate. *J. Learn. Disabil.*, 10:223–228, 1977.

Levy, F., and Hobbes, G. The diagnosis of attention deficit disorder (hyperkinesis) in children. *J. Am. Acad. Child Psychiatry*, 20:376–384, 1981.

Lowe, T.L., Cohen, D.J., Detlor, J., et al. Stimulant medications precipitate Tourette's Syndrome. *JAMA*, 247:1729–1731, 1982.

Manheim, P., Paalzow, L., and Hökfelt, B. Plasma clonidine in relation to blood pressure, catecholamines, and renin activity during long-term treatment of hypertension. *Clin. Pharmacol. Ther.*, 31:445–451, 1982.

Mendelson, W., Johnson, N., and Stewart, M. Hyperactive children as teenagers: A follow-up study. *J. Nerv. Ment. Dis.*, 153:273–279, 1971.

Milich, R., Loney, J., and Landau, S. Independent dimensions of hyperactivity and aggression: A validation with playroom observation data. *J. Abnorm. Psychol.*, 91:183–198, 1982.

Millichap, J.G. Growth of hyperactive children treated with methylphenidate. *J. Learn. Disabil.*, 11:567–570, 1978.

O'Brien, J. School problems: School phobia and learning disabilities. *Psychiatr. Clin. No. Am.*, 5:297–307, 1982.

Porrino, L.J., Rapoport, J.L., Behar, D., et al. A naturalistic assessment of the motor activity of hyperactive boys. *Arch. Gen. Psychiatry*, 40:681–693, 1983.

Quinn, P.O., Rapoport, J.L., Bradbard, G., et al. Imipramine and methylphenidate treatments in hyperactive boys: A double-blind comparison. *Arch. Gen. Psychiatry*, 30:789–793, 1974.

Redmond, D.E. Jr. New and old evidence for the involvement of a brain norepinephrine system in anxiety. In: Fann, W.E., Pokorny, A., Karacan, I., et al. (eds.), *Phenomenology and Treatment of Anxiety*. New York: Spectrum, 1979, pp. 153–203.

Safer, D.J., and Allen, R.P. *Hyperactive Children: Diagnosis and Management*. Baltimore, Md.: University Park Press, 1976.

Satterfield, J.H., Cantwell, D.P., and Satterfield, B.T. Multimodality treatment: A one-year follow-up of 84 hyperactive boys. *Arch. Gen. Psychiatry*, 36:965–974, 1979.

Satterfield, J.H., Hoppe, C.M., and Schell, A.M. A prospective study of delinquency in 110 boys with attention deficit disorder and 88 normal adolescent boys. *Am. J. Psychiatry*, 139:795–798, 1982.

Shaywitz, S.E. The Yale Neuropsychoeducational Scales. *Schizophr. Bull.*, 8(2):360–424, 1982.

Shekim, W.O., Davis, L.G., Bylund, D.B., et al. Platelet MAO in children with attention deficit disorder and hyperactivity: A pilot study. *Am. J. Psychiatry*, 139:936–938, 1982.

Shekim, W.O., Dekirmenjian, H., and Chapel, J.L. Urinary catecholamine metabolites in hyperactive children treated with D-amphetamine. *Am. J. Psychiatry*, 134:1276–1279, 1979.

Silver, L.B. The relationship between learning disabilities, hyperactivity, distractibility and behavioral problems: A clinical analysis. *J. Am. Acad. Child Psychiatry*, 20:385–391, 1981.

Sleator, E.K., Ullmann, R.K., and Von Neumann, A. How do hyperactive children feel about taking stimulants and will they tell the doctor? *Clin. Pediatr.*, 21:474–479, 1982.

Starke, K., and Altman, K.P. Inhibition of adrenergic neurotransmission by clonidine: An action on prejunctal α-receptors. *Neuropharmacology*, 12:339–349, 1973.

Swanson, J.M., Sandman, C.A., Deutsch, C., et al. Methylphenidate hydrochloride given with or before breakfast. I. Behavioral, cognitive, and electrophysiologic effects. *Pediatrics*, 72:49–55, 1983.

Swanson, J.M., and Kinsbourne, M. Stimulant related state-dependent learning in hyperactive children. *Science*, 192:1254–1256, 1976.

Titeler, M., and Seeman, P. Presynaptically acting catecholamines bind to alpha 2-adrenoreceptors labelled by 3H-clonidine. *Eur. J. Pharmacol.*, 67:187–92, 1980.

Weiss, G., and Hechtman, L. The hyperactive child syndrome. *Science*, 205:1348–1353, 1979.

Wood, D.R., Reimherr, F.W., Wender, P.H., et al. Diagnosis and treatment of minimal brain dysfunction in adults. *Arch. Gen. Psychiatry*, 33:1453–1460, 1976.

Young, J.G. Methylphenidate-induced hallucinosis: Case histories and possible mechanisms of action. *Dev. Behav. Pediatr.*, 2:35–37, 1981.

The Use of MK-801, a Novel Sympathomimetic, in Adults With Attention Deficit Disorder, Residual Type

Fred W. Reimherr, M.D.,[1] David R. Wood, M.D.,[1] and Paul H. Wender, M.D.[1]

Introduction

Attention Deficit Disorder (ADD) is one of the most frequently treated psychiatric disorders of childhood. However, of the diverse treatment approaches available, only the stimulant medications, particularly methylphenidate and dextroamphetamine, are generally accepted as effective. Unfortunately, treatment with stimulants presents several very significant problems.

One of the most serious is the risk of abuse. This is particularly true with adolescent or adult patients and makes physicians reluctant to consider clinical trials of stimulants if ADD is suspected. In the younger patient with ADD, parents may use the medication intended for their children. As a result, many patients who might be strongly responsive to medication are not treated with stimulant medication.

A second problem is the partial or complete unresponsiveness to stimulants of a significant percentage of patients with ADD. Although unexplained, this variability in response may reflect "artificial" factors such as misdiagnosis, poor compliance, or social conditions. Conversely, a significant percentage of these patients may represent "true" pharmacologic failures.

Finally, even when they are effective, the stimulants have a number of undesirable features. The requirement that they be taken two to four times per day promotes noncompliance. Pemoline, an alternative longer acting stimulant, is associated with liver problems, is a difficult medication to start, and has questionable long-term efficacy. Many patients or their families are not comfortable with regular use of stimulant medication. In children there is the possibility that all three medications will lead to diminished growth.

In the past it was felt that ADD disappeared with the onset of adolescence and did not occur in adulthood. Recent evidence suggests that it may continue through adolescence and into adulthood. The American Psychiatric Association has officially recognized this possibility by including ADD, Residual Type (ADD,RT) in the DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980). This development facilitates conducting clinical trials of experimental medications in ADD, since it allows one to avoid the special requirements attached to the use of experimental medications in children.

Collectively, these factors have led us to seek new pharmacologic approaches to the treatment of ADD. Preliminary work with a novel experimental compound developed by Merck Research Laboratories, MK-801, suggested that it merited testing in patients with ADD. Chemically, it is considered a dibenzocycloalkenimine, but it cannot be classified as a member of any accepted family of pharmacologic agents. In preliminary animal studies it is unique among chemical agents in possessing anticonvulsant, sympathomimetic, and anxiolytic actions. No other chemical is known to possess this cluster of properties.

In studies of radio-ligand binding, MK-801 does not compete with apomorphine, spiroperidol, serotonin, LSD, WB 4101 (measuring norepinephrine binding sites), quinuclidinyl benzilate (QNB) (measuring scopolamine binding sites), muscimol (measuring GABA binding sites), or 2-chloroadenosine. It does compete with diazepam binding acutely, but not chronically.

Central sympathomimetic activity has been assessed by measuring the induction of rota-

---

[1] Department of Psychiatry, University of Utah Medical Center, Salt Lake City, UT 84132.

The authors wish to thank David Tomb, M.D., of the University of Utah for his help in preparation of this report and Scott Reines, M.D., of Merck Research Laboratories for his support of this project.

tion in rats with unilateral nigrostriatal lesions produced by 6-hydroxydopamine (Clineschmidt, 1982b). MK-801 produced ipsilateral rotation which is usually produced by indirect dopamine agonist agents such as amphetamine, amfonelic acid, or methylphenidate. This effect was reduced by pretreatment with haloperidol, clozapine, prazosin (an alpha adreno-receptor antagonist), and alpha-methyl-paratyrosine. It was blocked completely by reserpine.

MK-801 also produced an increase in locomotor activity similar to that observed in animals treated with amphetamine, amfonelic acid, and methylphenidate (Clineschmidt, 1982b). Reserpine blocked this effect when it was produced by MK-801, methylphenidate, and amfonelic acid, but only partially inhibited the increase in activity produced by amphetamine. Alpha-methyl-para-tyrosine markedly reduced the increase in locomotor activity seen with amphetamine, but did not change the effect occurring with MK-801, methylphenidate, and amfonelic acid. All were blocked by haloperidol. Prazosin only blocked MK-801 and amphetamine.

Its anxiolytic properties have been examined in two different studies with rats (Clineschmidt, 1982c). Animals were taught to obtain food by pressing a lever; this response was then punished with electroshock. The rate of lever pressing following food deprivation was measured after treatment with diazepam, MK-801, and placebo. Both MK-801 and diazepam produced an increase in the rate of lever pressing. In a second study, fluid-deprived rats were given electrical shocks when they took sips of water. The number of sips of fluid was measured in rats treated with placebo, MK-801, and chlordiazepoxide. Both active agents produced an increase in the number of sips of water that the rats took. In a similar experiment done with squirrel monkeys, MK-801 produced no anxiolytic effect.

MK-801 has shown significant anticonvulsant activity in mice, preventing seizures induced by bicuculline and with electroshock (Clineschmidt, 1982a). This effect occurred at a dose of MK-801 that was lower than any of the comparison medications [clonazepam, phenobarbital, diazepam, phenytoin, (Y)-acetylenic GABA (gamma-aminobutyrate), sodium valproate, or trimethadione]. MK-801 also blocked seizures induced in rats with electroshock, pentylenetrazol (Metrazol), strychnine, or bicuculline. In this second set of studies with rats, MK-801 showed a spectrum of activity similar to phenytoin and unlike clonazepam. The anticonvulsant action of MK-801 was not affected by anticholinergics, antihistamine H1 receptor blockers, cimetidine, or antiserotonin agents (cyproheptadine, cinanserin, methylsergide, or methergoline). The action was antagonized by naloxone, theophylline, and haloperidol (most strongly). Its anticonvulsant action was completely reversed by HEAT and phenoxybenzamine, alpha-adrenoceptor blockers. Its anticonvulsant action was potentiated by propranolol.

Several small, open trials have been conducted in human subjects. In patients with seizure disorders, MK-801 appears to have anticonvulsant activity. Additional studies are being conducted. In 14 patients with anxiety disorders, a majority reported that it aggravated their symptoms and produced feelings of agitation. In a small number of patients with retarded depressions, one patient developed a confusional state and the others showed only modest improvement before termination of treatment.

Methods

This study was an open 6-week, outpatient trial limited to 10 patients. Treatment for more than 6 weeks with MK-801 was not available under any conditions. This project was approved by the Institutional Review Board of the University of Utah Medical Center.

Potential patients had to meet the following inclusion criteria:

1. ADD in childhood as defined by DSM-III;
2. Presence of attention difficulties as an adult;
3. Presence of hyperactivity as an adult; or
4. Two of the following:
   a. Quick or excessive temper,
   b. Poor organization or difficulty completing tasks,
   c. Over-reactivity to stress,

d. Excessive mood lability with dysphoric episodes, or

e. Impulsivity.

5. Females were required to be infertile;

6. Ages 21 to 65;

7. Five days drug-free; or

8. History of positive response to stimulant medication.

Potential patients were rejected if they met any of the following exclusion criteria:

1. Recent use of neuroleptics;

2. Major medical or neurological disease;

3. Recent history consistent with alcoholism, antisocial personality disorder, or drug abuse;

4. Significant abnormality on entry electrocardiogram (ECG), complete blood count (CBC), urine analysis (UA), blood chemistry, or physical examination;

5. History of allergic reaction to multiple drugs; or

6. Current or past history of major mood disorder, schizophrenia, psychotic symptoms, borderline personality, schizotypal personality, organic brain syndrome, or mental retardation.

Patients meeting these criteria were given a copy of the informed consent agreement containing a detailed description of the study. This document had been approved by the Institutional Review Board of the University of Utah Medical Center. Patients were instructed to review this document carefully and an appointment was made in 4 to 7 days to begin the study.

Patients initially received 7 days of placebo and then continued in the study if they still met the criteria for inclusion. Visits were at 1, 2, 3, 4, and 6 weeks. The following psychiatric rating instruments and medical measures were used:

1. Physician's global ratings of improvement (CGI) was obtained at each visit. This scale is a 7-point scale ranging from very much improved to very much worse.

2. Physician's global ratings of severity (CGS) was obtained at each visit. This is a 7-point scale ranging from no sign of illness to extremely symptomatic.

3. The Attention Deficit Disorder Scale (TADDS), a weighted scale of hyperactive behavior, was obtained at each visit. This scale assigns the following points for each area of symptoms:

12 points for inattention,
8 points for overactivity,
8 points for temper,
4 points for emotional reactivity, and
4 points for mood instability.

4. The Global Assessment Scale (GAS) at 0 and 6 weeks.

5. Vital signs at each visit.

6. Physical examination at 0 and 6 weeks.

7. ECG, UA, blood chemistry, and CBC at 0, 1, 2, 4, and 6 weeks.

The starting dose of MK-801 was .025 mg three times a day (t.i.d.). Maximum dose was .150 mg t.i.d. A flexible dosing schedule was followed.

Results

Ten adults, 6 males and 4 females, with ADD,RT were treated with MK-801. The average age of the subjects was 33. No patients were dropped during the placebo washout period and 8 completed the entire 6 weeks. Two dropped out at the third week because of an inadequate response to the medication.

We used TADDS, the CGI, and the CGS to classify patients as either responders or nonresponders. On the CGI, patients had to be rated as moderately or markedly improved to be considered treatment responders. On TADDS they had to show a 50% or greater improvement. On the CGS, they had to be rated no more than mildly ill. (We were unable to use the GAS to categorize the response of our patients.)

All three measures (TADDS, the CGI, and the CGS) produced similar results. For instance, on the CGI patients fell into two groups. Five of 10 patients were consistent responders. They improved and maintained their improvement for the full duration of the study. Five of the 10 patients were transient responders. These patients (including 2 who dropped out after 3 weeks of treatment) responded for 1 to 3 weeks in the beginning of the study, but did not maintain their improvement. The other two measures (TADDS and the CGS) produced the same groups, but the numbers of patients in each group changed by plus or minus 1 patient.

Three characteristics of the pattern of response are noteworthy. First, although our sample sizes are quite small, women responded better to MK-801. Three out of the 4 women (75%) in the study were rated as consistent responders. Conversely, only 2 out of the 6 men in the study (33%) were consistent responders.

Second, our patients showed a response within 1 to 2 weeks. This is similar to the effect observed with other stimulant medications which produce their response with no latency. The percent of symptoms on TADDS remaining each week is presented in Figure 1. The total score has been corrected to give equal weighting to each of the five factors on TADDS (concentration, hyperactivity, temper, mood, and emotional over-reactivity) because the raw score gives relatively greater weighting to concentration. Zero represents complete remission of all symptoms measured by TADDS. Within a week of treatment most patients had obtained a steady state of improvement.

Third, there seemed to be differences in the relative amount of improvement occurring in each of the symptoms measured by TADDS. Mood was most strongly affected. Concentration was least improved while hyperactivity, temper, and emotional reactivity fell in between. This is illustrated in Figure 2 which shows the average improvement at weeks 2, 3, 4, and 6. A 68% improvement occurred in mood. Hyperactivity, temper, and emotional reactivity averaged a 57% improvement. Concentration showed only a 43% improvement.

Medication side effects were minor. Six subjects maintained the same weight while two lost and two gained weight. There were no changes on the ECG or in pulse rate. Mean diastolic blood pressure dropped from 80 to 76. Mean systolic blood pressure dropped from 121.5 to 115.4. All side effects were mild to moderate in intensity. Additional side effects included dizziness (reported on four occasions), headache (reported on two occasions), diarrhea (reported on two occasions), increased appetite (reported on two occasions), insomnia (reported on two occasions), jitteriness (reported on two occasions), and confusion, memory loss, difficulty with ejaculation, fatigue, tinnitus, heart burn, and itching (all reported once). At the final visit, 5 patients reported side effects and 5 reported none. One patient had his dosage reduced to a relatively low level due to side effects. In this patient the trial was terminated at the third week due both to the presence of these side effects and the lack of a therapeutic response to MK-801.

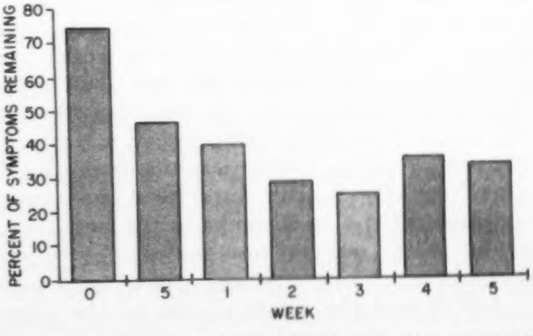


FIGURE 1. Percent of symptoms remaining at each visit as measured by the TADDS.

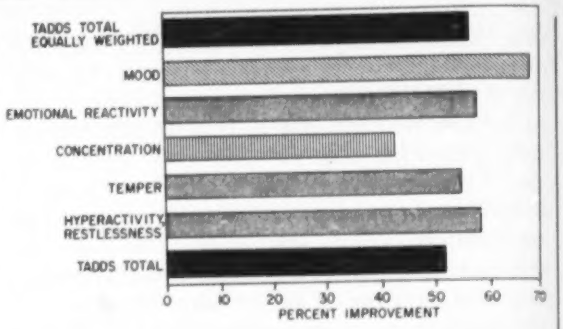


FIGURE 2. Percent improvement reported at weeks 2, 3, 4 and 6.

Although the dosing schedule was flexible, the majority of the patients were on .15 mg to .3 mg per day in three divided doses. Figure 3 contains a plot of the distribution of the total daily doses of MK-801 reported at weeks 2, 3, 4, and 6. The darker bars show the frequency of a particular dosage range in the patients classified as consistent responders with the CGI. The median dosage of the responders was .2 mg per day. The median dosage of the nonresponders was .225 mg per day. This plot shows that although most responders were in the .1 to .3 range, several responders were well above this range. A dosage plan that may be used in future studies will be discussed below.

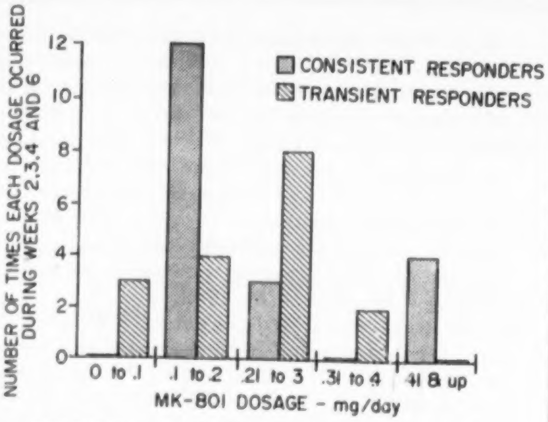


FIGURE 3. **Dosage distribution of MK-801.**

Conclusion

Several factors encourage optimism about the possible therapeutic value of MK-801, although the findings of this open, uncontrolled investigation must be interpreted with caution. First, there was no evidence that the patients abused or increased the dose of MK-801. Nor did they report any feelings of euphoria or increased energy.

Second, MK-801 appeared "different," not merely a less effective substitute for dextroamphetamine or methylphenidate. If one views ADD as having both a cognitive and an emotional component, MK-801 would appear to be more effective on the emotional component.

Third, several of our patients were outspoken in favor of MK-801. Even months later, several felt that they did better on MK-801: that with it they were more calm, in better control, and less reactive. As noted above, this was particularly true among our women patients. Two would not return to stimulants after being on MK-801.

Finally, in recent years we have conducted a number of open trials and controlled trials with small numbers of patients testing potential alternative medications for the treatment of ADD. These trials have focused on two classes of drugs: the monoamine oxidase inhibitors and metabolic precursors (Wender, 1983; Wood, 1985). This trial of MK-801 has been one of the most encouraging of these investigations.

The inclusion criteria that we adopted for this study present an important question concerning methodology in future drug studies of ADD. Should one select potential patients with ADD who are drug naive or should one select patients who have in the past been treated with stimulant medications? This question is more complex than it might appear initially. One would normally feel more confident about the diagnosis in a patient whom he had known for a significant period of time and had treated successfully in the past. Conversely, taking a patient off a medication which is producing a significant positive response is not easy. Research protocols usually require a drug-free interval of at least 1 week before starting the experimental treatment. However, it is difficult to know if this is an adequate period of time to allow a potential patient to recover from the lingering effects of past treatment with a psychoactive medication.

What dosage of MK-801 should be used in later studies? There appeared to be a bimodal dosage distribution among the consistent responders. One tenth of an mg per day in divided doses would be a reasonable starting dose. This should be raised very slowly to .25 mg per day over the next several weeks. If there has been no response after 3 weeks at this level, and if the patient can tolerate a higher dose, then a 1-week trial at a substantially higher dose such as .4 mg per day should be tried. This scheme would allow patients to be tried on both dosage levels which produced successful results in this study.

In light of a response rate of at least 50%, we feel additional studies with this agent in ADD,RT and normal childhood ADD are indicated. There might also be a role for this compound in other illnesses characterized by excessive temper, emotional reactivity, or impulsivity, such as borderline personality disorder or other personality disorders, particularly in women.

In summary, this was a short-term, open trial of MK-801. Half the patients were considered to be positive consistent responders to MK-801. The other half demonstrated a transient positive response to MK-801. Among the specific symptoms we monitored, mood showed the greatest relative improvement with MK-801. Temper, emotional reactivity, and over-activity all improved more than concentration. MK-801 appeared to be effective in the treatment of ADD,RT and its response appeared to be qualitatively different from that observed with the normal stimulant medications.

References

Clineschmidt, B.V., Martin, G.E., and Bunting, P.R. Anticonvulsant activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. *Drug. Dev. Res.*, 2:123–134, 1982a.

Clineschmidt, B.V., Martin, G.E., Bunting, P.R., et al. Central sympathomimetic activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. *Drug. Dev. Res.*, 2:135–145, 1982b.

Clineschmidt, B.V., Williams, M., Witoslawski, J.J., et al. Restoration of shock-suppressed behavior by treatment with (+)-5-methyl-10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5, 10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. *Drug. Dev. Res.*, 2:147–163, 1982c.

Wender, P.H., Wood, D.R., Reimherr, F.W., et al. An open trial of pargyline in the treatment of attention deficit disorder, residual type. *Psychiatry Res.*, 9:329–336, 1983.

Wood, D.R., Reimherr, F.W., and Wender, P.H. Amino acid precursors in the treatment of attention deficit disorder, residual type. *Psychopharmacol. Bull.*, 21(1):146–149, 1985.

The Prevalence of Tardive Dyskinesia in a Mentally Retarded Population[1]

Mary Ann Richardson, Ph.D.,[2] Gary Haugland, M.A.,[2] Raymond Pass, Ph.D.,[2] and Thomas J. Craig, M.D., M.P.H.[3]

Introduction

Mentally retarded (MR) patients comprise a nonpsychiatric population that has routinely been exposed to long-term neuroleptic treatment as a behavioral control measure. Rates of neuroleptic use among MR patients have been substantial in the past (25 to 60%) and, though in recent years there has been a trend to reduce dosage or discontinue treatment, these agents are still commonly used in these patients (Davis et al., 1982; Lipman et al., 1978). Unfortunately, there is a scarcity of data concerning the true prevalence of tardive dyskinesia (TD) and risk factors for its development across the full range of the MR. One study reported a 20.4% rate of the disorder among institutionalized MR children (ages 11 to 16) (Paulson et al., 1975). In that investigation the presence or absence of TD was not studied in relation to other patient characteristics. Another report, of parallel studies in two locations ($N = 95$), reported a 33% prevalence of TD (Gualtieri et al., 1982). However, that study dealt with a patient population that was highly restricted since subjects were all referred by treating physicians who felt a trial neuroleptic withdrawal should be attempted, and further used inclusionary criteria such as an educational or workshop placement. A multiple regression analysis was performed on the data collected at one of the locations ($N = 38$). The patients at that location were characterized by a mean age of 19.4 years, a mean treatment duration of 8.3 years, a mean IQ of 31.2 and a mean chlorpromazine (CPZ) equivalent dose of 239.9 mg. The analysis used moderate to severe TD as a dependent measure and isolated three significant independent variables; total lifetime exposure to neuroleptics, IQ, and the age at which neuroleptic treatment began. A review of TD studies in the MR including the report just described, with a total subject pool of 122, found rates for TD prevalences ranging from 29 to 36% (Kalachnik, 1983). The present study sought to add to this literature by a large-scale investigation in an institutionalized MR population. The investigation was also undertaken to study the presence or absence of TD in relation to risk variables that are peculiar to the MR and others that are shared with psychiatric patient populations. The facility studied provided a unique opportunity to evaluate the effect of drug discontinuation on TD prevalence because a policy had been instituted during the years prior to study initiation which encouraged the discontinuation of neuroleptics. The research team used criterion measures and methodology refined through several studies in psychiatric populations to help in the definition of commonalities and distinctions across these two neuroleptic-treated populations which might provide new information about the pathophysiology of the disorder itself.

Methods

A point prevalence study of TD was carried out among the residents of a state facility

---

[1] This study was supported in part by a grant from the Health Research Council of the New York State Health Planning Commission (HRC #13092). The authors wish to acknowledge the assistance of Frances Simpson and Ida Summers at the Nathan S. Kline Institute and the staff of the Staten Island Developmental Center.

[2] Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY 10962.

[3] State University of New York at Stony Brook, Stony Brook, NY 11794.

for the developmentally disabled with a total resident population of 721 individuals. All patients who had received a minimum of 1 year's neuroleptic treatment in the 5 years prior to study initiation ($N = 299$) were eligible to be included in the study, providing consent could be obtained. The TD evaluation was performed by using the Simpson Abbreviated Dyskinesia Scale (ADS) (Simpson et al., 1979) and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). The primary criterion measure of TD for the study was a dichotomy based on a global score derived from a subset of ADS items (lip chewing and lateral jaw movements, bon-bon sign, tongue protrusion, choreoathetoid movements of the tongue, cheek puffing, and choreoathetoid movements of the finger/wrists and ankle/toes). This score, which has been described previously (Richardson & Craig, 1982), classified subjects as having TD if they demonstrated evidence of the disorder in the mild-severe range. Other dependent measures employed were a restricted dichotomous global score based on the same ADS subset as above, which classified subjects as having TD only if they achieved a moderate-severe score, a total TD score which was a summation of the scores for the items rated in the global score, and a criterion measure for TD (RD-TD) based on the AIMS scale which required the presence of at least moderate movements in one body area or mild movements in two body areas for a positive TD score (Schooler & Kane, 1983).

Additionally, three data collection instruments were specifically developed for studying this population. The first was a checklist of 66 conditions known to produce mental retardation (Brain, 1977; Robinson & Robinson, 1976) which was completed during the review of the patients' medical records prior to the TD rating. The second was a listing of 19 conditions known to cause retardation whose phenomenology includes neuromuscular symptoms. These conditions were also identified at the time of record review, and descriptions of their associated symptoms were used by the raters during the TD evaluation sessions to aid in differential diagnosis. The third was a checklist of 29 stereotyped movements (such as rocking) and mannerisms reported to be seen in the MR (Baumeister et al., 1980; Meir-Koll & Pohl, 1979; O'Gorman, 1979) for which the patient was rated during the course of the TD evaluation.

A computerized drug-ordering system in place at the facility for approximately 5 years prior to study initiation was used to extract the variables of total number of days on neuroleptics and days off neuroleptics immediately prior to rating day. The complete facility record was studied for each patient, and patient characteristics were extracted and studied as independent variables. These characteristics included: IQ; sex; age; length of time since first facility admission; abusive to self; abusive to others; nonverbal/speech problems; hyperactivity; epilepsy; and neurological problems other than epilepsy. Also included were the DSM-II MR etiological categories of: Infection and/or Intoxication; Trauma or Physical Agent; Disorders of Metabolism, Nutrition or Growth; Gross Brain Disease (postnatal); Unknown Prenatal Influence; Chromosomal Abnormality; Prematurity; Major Psychiatric Disorder; and Psychosocial Deprivation.

A reliability study on the Simpson ADS and the AIMS was performed between the first author and the primary rater (G.H.) among psychiatric inpatients ($N = 25$) with satisfactory results (Kappas .633–.744; Pearson r's .788-.925). The first phase of the project consisted of a pilot study ($N = 19$) during which the first author rated concurrently with the primary rater. During this phase, it was determined that the validity of the ratings would be enhanced by observing the patients in their usual settings (i.e., dayroom, classroom) with an evaluation session of approximately 30 minutes. During the course of the study, 55% of the study population were rated twice; first, by the primary rater alone and then at a second session by both raters with the first author blind to the first rating, and with a consensual rating of both raters obtained at that second session.

Statistical methods used to analyze the data included chi-square analysis for categorical variables and the t-test statistic for continuous variables. Multivariate analyses were carried out using stepwise linear discriminant function analyses for the dichotomous dependent variables (Dixon et al., 1981; Nie et al., 1975) and a multiple linear regression was used for the continuous TD measure.

Results

Consents were obtained for 211 of the 299 eligible patients (70.6%). Chi-square analyses performed comparing the study population to the 88 clients for whom consents were not obtained on the variables of sex, age and DSM-II categories of retardation levels (mild, moderate, severe, or profound) revealed no significant differences. Of the 211 clients studied, 65.9% were male ($N=139$) and 34.1% female ($N=72$). The mean age of the subjects was 35.2 years with the mean length of time since first admission being 27.3 years. The mean IQ for the group was 15.5.

The prevalence of TD using the ADS mild-severe criterion measure was 29.9%. Using this measure, the TD positive group was characterized by a 92% rate of buccolingual-masticatory movements and an 80% rate of mild abnormal movements in at least two body areas or a moderate movement in at least one body area. The ADS moderate to severe criterion measure yielded a prevalence rate of 15.6% and the AIMS RD/TD, a rate of 48.8%. This latter criterion was highly correlated with the stereotypy, rocking (chi-square = 23.00, $p<.001$) which inflated the prevalence while the other two criterion measures were not affected by these movements (mild-severe, chi-square = 0.22, NS; moderate-severe, chi-square = 1.21, NS). The designation of TD-YES and TD-NO used for the remainder of this paper is based on the ADS mild-severe criterion measure.

The TD-YES group was significantly older than those without TD and significantly more likely to be female (*see* Tables 1 and 2). Residents with TD had experienced longer periods of institutionalization which was primarily an age-related phenomenon as the correlation between age and length of time since first admission was highly significant ($r=.63, p=.0001$).

Variables having to do with neuroleptic use on the day of TD evaluation were significantly associated with TD, while those having to do with neuroleptic history up to that day were not so associated. The rate of neuroleptic use at evaluation was significantly lower for the TD-YES group as was CPZ equivalent dose at evaluation (*see* Tables 1 and 2). These two drug-use variables were significantly correlated ($r=.47, p<.001$). However, the number of days receiving neuroleptics in the 5 years prior to evaluation, and the number of days continuously off neuroleptics prior to rating day for those not receiving medication at evaluation, were not significantly associated with the presence or absence of TD. The time interval off neuroleptics was also studied as a categorical variable with the following breakdown (months): 0-12, 12-24, 24-36, 36-60. There was no significant difference in TD status found for these breakouts (chi-square = 1.915, NS). Of the 84 residents not being treated with neuroleptics at evaluation, 57% had not received that class of drugs for 2 years or more.

The prevalence of TD varied according to DSM-II categories of retardation classified by etiology as shown in Table 1. Two of the categories showed a significant association with TD, one in a positive direction—Disorders of Metabolism, Nutrition, and Growth—and the other in a negative direction—Psychosocial Deprivation.

There was no association between the TD designation and epilepsy, and the category of other neurological problems.

The behavioral characteristics studied also showed no association with TD (abusive to self or others, nonverbal or having speech problems, hyperactivity, and the presence of the stereotyped movements rated).

The results of the stepwise discriminant function analysis carried out on the ADS mild-severe measure as shown in Table 3 indicated that the following variables were significant discriminators for TD (in order of entrance): Age (positive); Disorders of Metabolism, Nutrition, or Growth (positive); Psychosocial Deprivation (negative); and with a marginal association, Sex (female). Group membership was significantly predicted—F $(2.206)=20.28$ $p<.01$, and the resulting canonical correlation was—$R=.53$. Table 3 also shows the classification matrix. This represents the accuracy (77.3%) in classifying each case into either TD-YES or TD-NO groups, compared to actual group membership when using the resultant classification function. A jackknifed procedure was used for internal cross-validity checking which produced an accuracy rate close to the original at 76.3%. Variables that did not reach significance as discriminators in this analysis, though they did show a significant association with TD in the bivariate comparisons were: neuroleptic use at evaluation, CPZ dose at evaluation, and length of time since first admission.

Discussion

The prevalence rate of 30% in this population, using the same phenomenological criteria applied in psychiatric patients, casts doubt on the assertion made by some investigators that TD is closely associated with the disease process of schizophrenia (Crow et al., 1983; Owens & Johnstone, 1982).

This study presents the first reported significant association of TD and age in an MR population. Age has been positively associated with TD in psychiatric inpatients by the current authors with the same criterion measure (Richardson et al., 1984) and by several other investigators in both psychiatric inpatients and outpatients (Kane & Smith, 1982). The commonality of this risk factor between these MR patients and psychiatric populations suggests a similar age factor in the TD vulnerability of both groups.

The status of the risk factor of female sex in this study presents still another similarity to the TD psychiatric literature in which female sex is an acknowledged risk factor but possibly secondary to age (Kane & Smith, 1982). While female sex was significantly associated with TD status in a bivariate comparison, sex entered only as a marginally significant variable in the multivariate analysis where age was highly significant. The sex designation, however, did add to the power of the linear combination to discriminate TD status, and for that reason was kept in the analysis despite its marginal association.

The two diagnostic categories that significantly contributed to the TD discrimination in the multivariate analysis deserve careful study. The category that was positively associ-

TABLE 1

Comparison of TD-YES* and TD-NO* Groups for Categorical Variables

Variables	Total Group	TD-YES		TD-NO		Test Statistics	
	N	N	%	N	%	Chi-Square	p-value
Sex							
Males	139	32	23.0	107	77.0	9.09	<.01
Females	72	31	43.1	41	56.9		
DSM-II Etiological Classification							
Infection & Intoxication	21	4	19.0	17	81.0	1.30	NS
Trauma or Physical Agent	42	12	28.6	30	71.4	0.04	NS
Disorders of Metabolism, Nutrition, or Growth	12	11	91.7	1	8.3	23.29	<.01
Gross Brain Disease	16	5	31.3	11	68.8	0.02	NS
Unknown Prenatal Influence	89	28	31.5	61	68.5	0.19	NS
Chromosomal Abnormality	15	5	33.3	10	66.7	0.09	NS
Prematurity	28	8	28.6	20	71.4	0.03	NS
Major Psychiatric Disorder	1	1	100.0	0	0.0	2.36	NS
Psychosocial Deprivation	16	0	0.0	16	100.0	7.37	<.01
Medical Conditions							
Epilepsy	83	23	27.7	60	72.3	0.30	NS
Other Neurological Problems	48	13	27.1	35	72.9	0.23	NS
Behavioral Problems							
Abusive to Self	118	33	28.0	85	72.0	0.48	NS
Abusive to Others	107	26	24.3	81	75.7	3.20	NS
Nonverbal/Speech Problems	133	36	27.1	97	72.9	1.95	NS
Hyperactivity	112	29	25.9	83	74.1	1.79	NS
Stereotypies (Observed)	161	48	29.8	113	70.2	0.00	NS
Score on Neuroleptics at Evaluation	127	31	24.4	96	75.6	4.52	<.05

*TD status determined using ADS mild-severe criterion measure.
NS–Not Significant.

TABLE 2

Comparison of TD-YES* and TD-NO* Groups for Continuous Variables

Variables	Total Group		TD-YES		TD-NO		Test Statistic	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	*t*-Test	*p*-value
Age (years)	35.2	9.9	41.4	12.3	32.5	7.3	5.36	<.01
IQ	15.5	10.7	15.5	10.5	15.5	10.9	0.05	NS
No. Stereotypies	2.3	2.1	2.6	2.3	2.1	1.9	1.57	NS
Duration—Years Since 1st Admission	27.3	7.6	29.9	8.3	26.3	7.1	3.23	<.01
CPZ Equivalent Dose (mg)	192.0	306.5	127.0	218.1	220.0	334.0	2.38	<.05
Days on Neuroleptics in 5 Years Prior	1416.0	516.6	1339.0	526.4	1449.0	510.7	1.41	NS
Continuous Days Off Neuroleptics Prior to Rating Day**	784.0	464.7	822.0	448.1	761.0	477.5	0.58	NS

*TD status determined using ADS mild-severe criterion measure.

**Only patients *not* on neuroleptics on TD Rating Day are included in this variable ($N = 84$)

NS - Not significant

ated with TD (Disorders of Metabolism, Nutrition, and Growth) ($N = 12$), was composed primarily of females (75%), had a mean age of 39.9, a mean IQ of 9.2, and a 50% rate of neuroleptic use at a 127.8 mg mean CPZ equivalent dose. The modal medical condition ($N = 7$) in this category was phenylketonuria (PKU). The TD prevalence among the PKU patients was 86% while the prevalence in the remainder of the study population was 27%. All of the 6 PKU patients given a positive TD rating displayed buccolingual/masticatory movements, such as tongue protrusion, choreoathetoid tongue movements, lip movements (pouting, puckering, or smacking), and chewing movements. These patients also displayed other abnormal motor behaviors which were not counted toward the TD designation. These included: rocking, fidgeting, trunk-twisting, self-biting, toe-walking, tension spasms, and surface stroking. Some of these behaviors have been described as part of the symptom picture of PKU (Knox, 1966; Walton, 1977). Despite the small sample size,

TABLE 3

Multivariate Analysis - Stepwise Discriminant Function

Variables Entered:
DSM-II Category of Disorders of Metabolism, Nutrition and Growth
DSM-II Category of Psychosocial Deprivation
NL Use at Evaluation
CPZ Dose at Evaluation
Age
Sex
No. of Days On NL in Prior 5 Years
No. of Days Off NL Prior to Evaluation
Duration

Significant Discriminators

Variables in Order of Entrance	*F*-Statistic
Age (Positive)	36.182
Disorders of Metabolism, Nutrition, and Growth (Positive)	17.597
Psychosocial Deprivation (Negative)	5.830
Sex (Female)	3.575

Canonical Correlation: $R = .53$

Accuracy of Predicting Group Membership = 77.3% Overall

Classification Matrix

Actual Group Membership	Classified Group Membership: TD-NO	Classified Group Membership: TD-YES
TD-NO	128 (86.5%)	20 (13.5%)
TD-YES	28 (44.4%)	35 (55.6%)

this particular vulnerability of PKU cases to develop TD is of interest since it is the first report of a single medical condition being associated with TD. This finding may have heuristic value in terms of the pathophysiology of TD and deserves further study.

The other diagnostic category related to TD, psychosocial deprivation, carried a significant negative association. None of the 16 patients in this category manifested symptoms of TD. The characteristics of this group differed markedly from the prior group (Disorders of Metabolism, Nutrition, or Growth) in that there was a lower rate of females (31%), a younger mean age (32.9), a higher mean IQ (19.3), and a higher rate of neuroleptic use (93.8%) at a higher mean CPZ dose (445.9 mg). Patients were most likely given this diagnosis in the absence of any physical cause for their retardation and in the presence of evidence of nurturance deprivation. This finding could be read as a weak organic risk factor for TD, as this was the category least likely to contain patients with structural brain deficits. The fact, however, that TD was not significantly associated with any of the diagnostic categories indicative of neurological trauma and/or neurological structural deficits such as infection or intoxication, trauma or physical agent, gross brain disease (postnatal), chromosomal abnormality, and prematurity, or medical conditions such as epilepsy or other neurological problems, argues against a strong association of TD and structural neurological impairments.

The lack of association between the primary TD designation (ADS mild-severe) and stereotypies was due to the highly specific phenomenological approach of the criterion measure, the simultaneous rating of well-specified stereotypical movements known to occur in untreated MR patients, and by the rigor of the rating session.

In summary, this study establishes a 30% prevalence of TD in a medically heterogeneous mentally retarded population. Risk-factor analyses demonstrated similarities to the TD psychiatric literature and provided information on the disorder not possible within psychiatric populations.

References

Baumeister, A.A., MacLean, W.E., Kelly, J., et al. Observational studies of retarded children with multiple stereotyped movements. *J. Abnorm. Child Psychol.*, 8(4):501–521, 1980.

Brain, W.R. *Brain's Diseases of the Nervous System*. 8th Ed. (Revised by J.N. Walton) Oxford: Oxford University Press, 1977.

Crow, T.J., Owens, D.G.C., Johnstone, E.C., et al. Does tardive dyskinesia exist? *Mod. Probl. Pharmacopsychiatry*, 21:206–219, 1983.

Davis, V.J., Cullari, S., and Breuning, S.E. Drug use in community foster group homes. In: Breuning, S.E., and Poling, A.D. (eds.), *Drugs and Mental Retardation*. Springfield, Ill: Charles C Thomas, 1982.

Dixon, W.J., Brown, M.B., Engelman, L., et al. (eds.), *BMDP Statistical Software, 1981*. Berkeley: University of California Press, 1981.

Gualtieri, C.T., Breuning, S.E., Schroeder, S.R., et al. Tardive dyskinesia in mentally retarded children, adolescents and young adults: North Carolina and Michigan studies. *Psychopharmacol. Bull.*, 18(1): 62–65, 1982.

Kalachnick, J. Tardive dyskinesia and the mentally retarded: a review. In: Breuning, S. (ed.), *Advances in Mental Retardation and Developmental Disabilities*, Vol. 2, New York: Raven Press, 1983.

Kane, J.M., and Smith, J.M. Tardive dyskinesia prevalence and risk factors, 1959 to 1979. *Arch. Gen. Psychiatry*, 39:473–481, 1982.

Knox, L.E. Phenylketonuria. In: Stanbury, J.B., Wyngaarden, J.B., and Fredrickson, D.S. (eds.), *The Metabolic Basis of Inherited Disease*. New York: McGraw-Hill Book Company, 1966, pp. 258–294.

Lipman, R.S., DiMascio, A., Reatig, N., et al. Psychotropic drugs and mentally retarded children. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978.

Meir-Koll, A., and Pohl, P. Chronobiological aspects of stereotyped motor behavior in mentally retarded children. *Int. J. Chronobiol.*, 6:191–209, 1979.

Nie, N.H., Hull, C.H., Jenkins, J.G., et al. *Statistical Package for the Social Sciences*, 2nd ed. New York: McGraw-Hill Book Co., 1975.

Owens, D.G.C., and Johnstone, E.C. Spontaneous involuntary disorders of momement. *Arch. Gen. Psychiatry*, 39:452–461, 1982.

Paulson, G.W., Rizvi, C.A., and Crane, G.E. Tardive dyskinesia as a possible sequel of long-term therapy with phenothiazines. *Clin. Pediatr.*, 14(10):953–955, 1975.

Richardson, M.A., and Craig, T.J. The coexistence of parkinson-like symptoms and tardive dyskinesia. *Am. J. Psychiatry*, 139(3):341–343, 1982.

Richardson, M.A., Pass, R., Craig, T.J., et al. Factors influencing the prevalence and severity of tardive dyskinesia. *Psychopharmacol. Bull.*, 20(1):33–38, 1984.

Robinson, N.M., and Robinson, H.B. *The Mentally Retarded Child, A Psychological Approach*, 2nd ed. New York: McGraw-Hill Book Company, 1976.

Walton, J.N. *Brain's Diseases of the Nervous System*, 8th Ed. (Revised by J.N. Walton) Oxford: Oxford University Press, 1977, pp. 832–833.

Neuroleptic-Induced Tardive Dyskinesia and Parkinsonism: Changes During Several Years of Continuing Treatment[1]

Daniel E. Casey, M.D.,[2,3] Uffe J. Povlsen, M.D.,[3] Birgit Meidahl, M.D.,[3] and Jes Gerlach, M.D.[3]

Tardive dyskinesia (TD), a syndrome of abnormal involuntary hyperkinetic movements, usually involves the mouth, tongue, and face, but may also cause choreoathetoid dyskinesias in the limbs and trunk. It occurs in predisposed individuals during or following the cessation of long-term neuroleptic treatment (Casey & Gerlach 1984). Since this disorder may occur in 15% of patients receiving extended neuroleptic therapy—and at even higher rates in the elderly—there is appropriate concern about the proper indications for using these highly effective antipsychotic drugs (Casey, 1985).

Difficult clinical choices must be made when managing patients with TD who benefit from neuroleptic drugs. Since these agents are the purported cause of TD, it is widely believed that they will also inevitably worsen TD if neuroleptic treatment is continued. However, there are few data either to corroborate or refute this commonly held belief. Reports about the natural history of TD noted several possible outcomes, including improvement, stabilization, or aggravation, either with or without continued treatment, but these evaluations tended to be of short duration (Pyke & Seeman, 1981; Schonecker, 1957; Smith et al., 1981; Urhbrand & Faurbye, 1960).

The long-term (5 years or more) outcome of TD has seldom been evaluated. In the few available studies, it was not always possible for the investigators to quantify or monitor the effects of adjustments in drug treatment, such as decreased, stable, or increased dose. Furthermore, changes in other neuroleptic-induced symptoms, such as parkinsonism, were not simultaneously assessed to account for the possible interaction of these two treatment-induced side effects. Therefore, this study evaluated long-term changes in TD and neuroleptic-induced parkinsonism in chronically ill psychiatric patients who required neuroleptic treatment for control of psychosis.

Methods

Patients

Thirty-three patients (6 females, 27 males) with chronic psychiatric illnesses and living in an institutionalized setting were assessed. The mean age was 65.6 years (range, 31 to 99 years).

Medications

The neuroleptic dose for each patient was recorded at the beginning of the evaluation and at 6-month intervals. Drug treatment was tailored to the individual patient's psychiatric needs. Neuroleptic doses were converted to chlorpromazine equivalents (CPZE) (Baldessarini, 1977). Mean daily dose at the end of the study period was 316 mg/day of CPZE (range, 0-1500 mg/day).

Design and Evaluation

Patients were evaluated at the time of entry into the study (baseline) and at one of 3-, 5-, 8-, 10-, or 11-year follow-up assessments in May 1984. A standardized examination for TD and parkinsonism was videotaped at the beginning and end of follow-up assessments. These tapes were randomly sequenced and scored by experienced raters who were blind to the year of assessment and drug treatment. TD was scored on the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) and parkinsonism was evaluated with the Sct. Hans Dyskinesia Scale (Gerlach, 1979). TD was defined by the recently proposed research criteria (Schooler & Kane, 1982). Data are presented as changes in group mean total scores.

---

[1] This study was supported in part by funds from the Veterans Administration Research and Merit Review Programs, and USPHS Grant MH-36657 from the National Institute of Mental Health. Marian Karr prepared the manuscript.

[2] Psychiatry Service, VA Medical Center, Departments of Psychiatry and Neurology, Oregon Health Sciences University, Portland, OR 97201.

[3] Departments AEH/H, Sct. Hans Mental Hospital, 4000 Roskilde, Denmark.

Reprint requests to: Daniel E. Casey, M.D., Psychiatry Service (116A), VA Medical Center, Portland, OR 97207.

Results

Over the follow-up period, a consistent pattern of outcome emerged. In the whole group of 33 patients, TD decreased 27% and parkinsonism increased 34% (*see* Table). There was a significant ($p<.05$) positive correlation between length of follow-up and TD improvement. Neuroleptic dosages increased modestly from 265 mg/day to 316 mg/day CPZE (*see* Table). Variable degrees of symptom changes were evident when the treatment was categorized by dosage changes of decreased, stable, and increased. In those patients whose neuroleptic decreased (from 646 mg/day to 230 mg/day) TD was unchanged and parkinsonism increased minimally by 9%. In patients receiving a stable neuroleptic dose (±100 mg/day CPZE average daily dose increased by 9% from 195 mg/day to 214 mg/day); TD decreased 24% and parkinsonism increased 31%. Increased dose (from 128 mg/day to 681 mg/day) was necessary to control psychotic symptoms in some patients. This group showed a 55% decrease in TD and a 21% increase in parkinsonism. In summary, TD remained stable or improved in most patients continuing neuroleptic treatment. No systematic or generalized increase in TD was observed. Furthermore, parkinsonism increased in about the same proportion as TD decreased.

Three of the 33 (9%) patients showed increased AIMS scores, but these were modest changes of +1 to +2 in the total AIMS assessments. These changes were unrelated to treatment status: medicines were discontinued in one patient, dosage was increased by 100 mg/day CPZE in another, and decreased by 75 mg/day in the third. None of these increased scores was of clinical significance and no patient had an increase in global ratings from mild or moderate categories.

Discussion

This study of the long-term outcome of TD indicates that this syndrome remains stable or gradually improves in the majority of patients receiving extended low to moderate neuroleptic dosage. These results are consistent with other studies which have evaluated changes in TD over periods of 5 years or more (Casey & Toenniessen 1983; Gardos et al. 1985; Yagi & Itoh 1984). Furthermore, the few patients who experience increases in TD show only modest changes in symptoms.

The lack of TD aggravating effect by neuroleptics is seen in all the treatment groups. The decreased dose group would be most likely to show an increase in TD, as reduced neuroleptic dose would further unmask existing symptoms and lead to the appearance that TD increased. This was not the case. However, the lack of substantive change in TD at the study end point may be accounted for by offsetting effects of unmasking which would tend to increase symptoms and gradual improvement which would have the effect of decreasing symptoms. The stable dose group provides the best opportunity to evaluate the effects of continuing neuroleptic therapy because the masking or unmasking effects are minimized. The decrement in AIMS scores refutes the proposal that continued neuroleptic treatment will inevitably aggravate TD. Finally, the increased dose group might be expected to show more TD in later years after the initial masking or suppressive effect of neuroleptics was subsequently unmasked by "breakthrough" phenomena. However, this again was not the case.

Some caveats must be emphasized. Most importantly, these conclusions cannot be extended to groups of patients which are substantively different from this study cohort. It is not possible to predict the outcome of a similar study if much higher neuroleptic doses were employed. Similarly, different age groups may have different outcomes. Though increasing age is generally correlat-

TABLE

Changes in Drug Dose, AIMS, and Parkinsonism

Dose Group	No. Pts	CPZE[a] BL[d]-5/84[e]	AIMS[b] BL[d]-5/84[e]	PARK[c] BL[d]-5/84[e]	Percent Change		
					CPZE[a]	AIMS[b]	PARK[c]
All	33	265–316	6.7–4.9	6.8–9.0	↑20	↓27	↑34
Decrease	6	646–230	6.0–5.9	8.4–9.1	↓64	↓1	↑9
Stable	20	195–214	6.9–5.2	6.3–8.3	↑9	↓24	↑31
Increase	7	128–681	6.8–3.0	5.2–6.3	↑432	↓55	↑21

[a] Chlorpromazine equivalent;
[b] Abnormal Involuntary Movement Scale;
[c] Parkinsonism;
[d] Baseline;
[e] May, 1984

ed with decreasing improvement in TD (Casey & Toenniessen, 1983: Smith & Baldessarini, 1980), this group of patients, averaging 65.6 years of age, still showed considerable symptom amelioration over many years. Thus, irreversible TD may not be as pervasive as is widely believed. This time course suggests that combining the concepts of gradually resolving and persisting TD are worthwhile, as TD improvement correlated with length of follow-up.

The role of drug-induced parkinsonism in TD requires further discussion. Other long-term TD investigations have not concomitantly evaluated these syndromes, so opportunities for comparing and contrasting these findings are not yet available. The large majority of patients in this study had coexisting TD and drug-induced parkinsonism, though this point is seldom discussed (Richardson & Craig 1982). The hypothesis that dopaminergic function occurs along a unidimensional continuum of a relative deficit (parkinsonism) to relative excess (TD) is insufficient to explain these coexisting syndromes. However, the inverse changes of TD decrease and parkinsonian increase do support the proposal that these disorders share, at least in part, some reciprocally functioning or dysfunctioning mechanisms. Perhaps the decreased TD is due to a masking bradykinetic effect of parkinsonism.

Increasing age may be an important contributor to the decreasing TD and increasing parkinsonism, as idiopathic parkinsonism occurs with increasing age. Though it is not possible to distinguish whether patients had idiopathic or drug-induced parkinsonism, it must be assumed that patients had at least the drug-induced syndrome because they were receiving neuroleptics. Some of these patients might currently have or eventually go on to develop idiopathic parkinsonism. Furthermore, it may be that the addition of neuroleptics is sufficient to increase subclinical parkinsonism to the level of clinically obvious symptoms, which would subsequently revert to subclinical phenomena if drugs were discontinued.

In summary, TD remains stable or gradually improves in patients receiving long-term, low to moderate dose neuroleptics. TD seldom increases—and then only moderately in this treatment setting. Neuroleptic therapy as an "aggravating agent" of existing TD is unproven. These drugs, at least in conservative doses, are not contraindicated in TD patients with psychosis that is responsive to neuroleptic therapy. TD and parkinsonism change reciprocally, though slowly, over several years. Further study of these coexisting and covarying syndromes is required.

References

Baldessarini, R.J. *Chemotherapy in Psychiatry*. Cambridge: Harvard University Press, 1977, pp. 12–56.

Casey, D.E. Spontaneous and tardive dyskinesia: clinical and laboratory studies. *J. Clin. Psychiatry*, 46 (4, Sec. 2):42-47, 1985.

Casey, D.E., and Gerlach, J. Tardive dyskinesia: management and new treatment. In: Stancer, H.C., Garfinkel, P.E., and Rakoff, V.M. (eds.), *Guidelines for the Use of Psychotropic Drugs*. New York: Spectrum Publications, 1984, pp. 183–203.

Casey, D.E., and Toenniessen, L.M. Neuroleptic treatment in tardive dyskinesia: can it be developed into a clinical strategy for long-term treatment? In: Ban, T.A., Pichot, P., and Poldinger, L.W. (eds.), *Modern Problems of Pharmacopsychiatry*, Vol. 21. Basel: S. Karger, 1983, pp. 65–79.

Gardos, G., Cole, J.O., Perenyi, A., et al. Five-year follow-up study of tardive dyskinesia. In: Kemali, D., and Racagni, G. (eds.), *Chronic Treatments in Neuropsychiatry*. New York: Raven Press, 1985, pp. 37–42.

Gerlach, J. Tardive dyskinesia. *Dan. Med. Bull.*, 26:209-245, 1979.

Guy, W. *ECDEU Assessment Manual for Psychopharmacology*. Washington, D.C.: U.S. Government Printing Office, 1976, pp. 534–537.

Pyke, J., and Seeman, M.V. Neuroleptic-free intervals in the treatment of schizophrenia. *Am. J. Psychiatry*, 138:1620–1621, 1981.

Richardson, M.A., and Craig, T.J. The coexistence of parkinsonism-like symptoms and tardive dyskinesia. *Am. J. Psychiatry*, 139:341-343, 1982.

Schonecker, M. Ein eigentumliches Syndrom im oralen Bereich bei Megaphenapplikation. *Nervenarzt*, 28:35, 1957.

Schooler, N.R., and Kane, J.M. Research diagnoses for tardive dyskinesia. *Arch. Gen. Psychiatry*, 39:486-487, 1982.

Smith, J.M., and Baldessarini, R.J. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. *Arch. Gen. Psychiatry*, 37:1368–1373, 1980.

Smith, J.M., Burke, M.P., and Moon, C.O. Long-term changes in AIMS ratings and their relation to medication history. *Psychopharmacol. Bull.*, 17(1):120–121, 1981.

Uhrbrand, L., and Faurbye, A. Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine, and electroconvulsive therapy. *Psychopharmacologia*, 1:408-418, 1960.

Yagi, G., and Itoh, H. A ten-year follow-up study on tardive dyskinesia, with special reference to the influence of neuroleptic administration on the long-term prognosis. Proceedings of the Collegium Internationale Neuro-Psychopharmacologicum, 1984.

Integrating Incidence and Prevalence of Tardive Dyskinesia[1]

John M. Kane, M.D.,[2] Margaret Woerner, Ph.D.,[2] Michael Borenstein, Ph.D.,[2] James Wegner, Ph.D.,[2] and Jeffrey Lieberman, M.D.[2]

Introduction

Epidemiologic studies of tardive dyskinesia (TD) are important in clarifying the scope of the problem and identifying potential risk factors with the ultimate aim of prevention, i.e., reducing the incidence of the condition.

Considerable difficulty remains, however, in integrating available information. We have previously reviewed the wide range of prevalence estimates in the literature and suggested possible explanations for the degree of variation (Kane & Smith, 1982). Prevalence estimates appear to vary enormously from population to population, and most explanations for this have focused on putative risk factors for the development of the condition. In addition, however, it is also important to consider risk factors contributing to the persistence of the condition once it has developed, since variations between populations in the course of TD will also have an important impact on point prevalence.

In this report we will discuss our current findings with regard to incidence and prevalence in the same population and present some findings with regard to risk factors which might influence the incidence and/or persistence of TD.

Incidence of TD

We have previously reported preliminary findings from an ongoing prospective study of TD development (Kane et al., 1982, 1984). This report presents more recent data analyses for the first 616 neuroleptic-treated patients from the main sample in this study, and for 52 patients entered into the study specifically because they had shown severe extrapyramidal side effects (EPS) to neuroleptic drugs upon examination by the research team.

The Table presents the demographic characteristics of the two groups. The most important feature is that these patients are relatively young and have been followed from early in their treatment course (the median exposure to neuroleptics at study entry is 12 months for the main sample, 5 months for the EPS sample).

Figure 1 displays the results of life-table analyses which present the incidence of TD as a function of time on neuroleptics for the main sample. Three survival curves are plotted on this figure. The first shows the incidence of any TD; the second shows the incidence of TD which persisted for 3 months or more; the third shows the incidence of cases which persisted for 6 months or more.

TABLE

Prospective Study of Tardive Dyskinesia Characteristics of the Neuroleptic-Treated Samples at Study Entry

		Regular Sample ($N = 616$)	EPS Sample ($N = 52$)
Sex:	Male	57%	65%
	Female	43%	35%
Age:	Mean	28	27
	S.D.	10	11
	Range	14-72	16-76
Diagnosis:	Affective Disorder	19%	25%
(Hospital)	Schizoaffective	11%	10%
	Schizophrenia	58%	56%
	Other	12%	9%
Total Months Exposure to Neuroleptics:			
	Mean	22	15
	S.D.	26	20
	Range	0-143	0.25-72
	Median	12	5
Age at First Neuroleptic Treatment:	Mean	24	23
	S.D.	9	8
	Range	7-71	15-64

---

[1] This work was supported by USPHS Grant MH-32369 and Contract 278-81-0032 from the National Institute of Mental Health.

[2] Hillside Hospital, a Division of Long Island Jewish Medical Center, Glen Oaks, NY 11004.

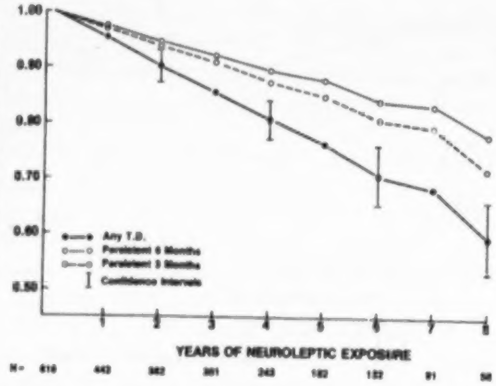


FIGURE 1. Tardive dyskinesia over eight years of neuroleptic exposure.

The overall TD incidence (and 95% confidence intervals) is 18.5% (±4.5%) following 4 years of cumulative exposure to neuroleptics, and 40% (±7%) following 8 years of exposure. The incidence of TD which persists for at least 3 months is 13% (±3%) at 4 years and 29% (±7%) at 8 years. The incidence of TD which persists for at least 6 months is 11% (±3%) at 4 years and 22% (±6%) at 8 years.

The incidence figures presented here are somewhat higher than those we have presented in the past. This is primarily because these figures include data from patients who had TD the first time they were seen (Baseline TD). In the past we had eliminated these cases on the grounds that they had not been followed prospectively, and the point at which they had actually developed TD was not known. However, if we include cases that have *no* TD at baseline and exclude those that do, we will invariably underestimate the incidence. For this reason we have elected to include the Baseline TD cases in the current analyses, and have used their neuroleptic exposure prior to baseline as an estimate of the exposure prior to TD. This does include some error, making the curve higher than it should be. However, we estimate that the amount of this error is small since the Baseline TD cases make up only a third of the TD cases and therefore have a small impact on the total curve.

It is important to note that the hazard rates for any-TD and for persistent-TD appear to be proportional to each other; i.e., there is no evidence that the cases which develop after short exposure are all nonpersistent, while the cases which develop after long exposure are persistent.

Risk Factors for TD

We have conducted a number of analyses with the goal of identifying factors related to the incidence of TD. Except as noted, all analyses were conducted with the 616 patients who either had TD at baseline or were at risk (treated with neuroleptics) while under observation in the prospective study. These analyses are preliminary in nature; in particular, some of the relationships presented here could be due to confounds with other variables which may emerge as the data base increases.

Age. For any given level of exposure to neuroleptics the incidence of TD is higher among older than among younger patients (chi-square = 12.86, $df = 1$, $p = .0003$ by the Wald test). The relationship between age and TD is curvilinear: the risk of TD appears to remain fairly stable through ages 20 to 40, but then rises dramatically with increases in age (chi-square for curvilinear component = 3.72, $df = 1$, $p = .05$). Following 2 years of exposure, the likelihood of TD is about 10% for a 20-year-old and 18% for a 50-year-old patient. Following 4 years of exposure, these figures are 18% for a 20-year-old and 30% for a 50-year-old patient. The value of age as a predictor of TD remains significant when we control for sex (chi-square = 10.13, $df = 1$, $p = .0015$).

Sex. The hazard rate is slightly (but not significantly) higher for women than it is for men (chi-square = 2.20, $df = 1$, $p = .14$). The interaction of sex by age is not significant.

Diagnosis. The incidence of TD was significantly higher among patients diagnosed as affective disorders than it was among either schizoaffectives, paranoid schizophrenics, or other schizophrenics (DSM-II, hospital diagnosis). The most significant distinction was between the pure affective disorders versus the paranoid/other schizophrenics combined. The increased risk associated with the affective disorders in this case remained significant even when we controlled for sex, history of treatment with lithium, electroconvulsive therapy, and age (chi-square = 9.77, *df* = 1, *p* = .002).

Lithium. Within diagnostic category (affective disorder vs. any schizophrenic), prognosis was better for patients who had taken lithium at some point than for those with no history of lithium treatment (chi-square = 5.89, *df* = 1, *p* = .02). Note that lithium use was more common among the affective disorders (43% with history of lithium vs. 9% for schizophrenics), and the affective disorder patients in general appear to have a poor prognosis. Therefore, when we look at lithium without taking diagnosis into account, we find no relationship to incidence (chi-square = 0.61, *df* = 1, *p* = .43).

EPS. The 52 patients who had been entered specifically because of their severe EPS ratings on examination by the research team were compared with the 369 "at-risk" patients who had no history of EPS in their charts (Baseline TD cases were excluded). The TD incidence for the EPS patients is markedly higher than that of the comparison group. Overall the hazard rate for the EPS patients is 2.32 times that of the others (chi-square = 6.64, *df* = 1, *p* = .01), and there is some evidence that the risk ratio could be even higher (3.60) during the first 2 years of exposure. Following 4 years of exposure, the rate of TD is 15% in the comparison group and 37% in the EPS group (Figure 2).

Outcome of TD

Preliminary analyses on the course of TD have been conducted employing data from 96 patients who developed TD during the prospective study.

On the basis of the entire follow-up course, each patient was classified as either remitted, masked, or persistent. A patient was classified as remitted if his global TD ratings were less than 2 (mild TD) for at least two consecutive ratings encompassing at least a 3-month period. A patient could be classified as remitted if these criteria were met, even if the TD later re-emerged. The patient was classified as a "persistent remission" if these criteria were met and the patient never subsequently met criteria for TD. Patients were classified as masked if they met the criteria for remission only following an increase in medication dosage and were classified as persistent if they never met the criteria. In the analyses presented here, the masked cases were treated as persistent.

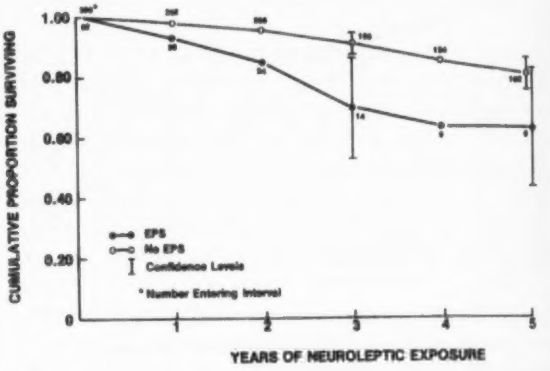


FIGURE 2. EPS as a risk factor for T.D.

Figure 3 presents TD outcome over 2 years of follow-up. When we look at any remissions (ignoring the possibility of a later re-emergence) a total of 32% (95% confidence interval ± 10%) of the patients remit over the first year, and a total of 47% (± 12%) remit over the first 2 years. When we look at persistent remissions only, these figures are 23% (± 10%) for the first year and 33% (± 14%) over the first 2 years.

Exploration of factors related to TD outcome indicate that, as reported based upon earlier analyses (Kane et al., 1984), prognosis is better for patients who develop TD following short-term exposure to neuroleptics than for those who developed TD following long-

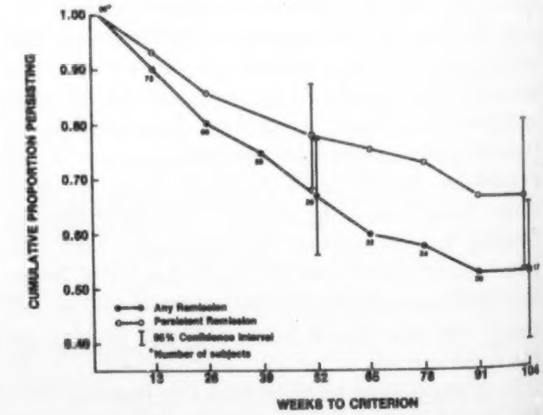


FIGURE 3. Tardive dyskinesia outcome.

er exposure ($p = .05$). There is a suggestion that the importance of prior exposure is greater for women than for men, but gender by itself is not significantly related to TD outcome.

Two measures of treatment after the development of TD have been found to predict outcome: prognosis is better for patients treated with neuroleptics for a smaller proportion of the follow-up period ($p = .05$), and for those treated with lower modal doses during follow-up ($p = .009$). These predictors of outcome are confounded with each other, and with the current sample size it is difficult to identify the unique contribution of each. Thus far, our analyses suggest that modal dose during follow-up is a critical variable with an impact over and above the effect of prior medication history. Proportion of time on medication during follow-up may be more critical for older than younger people; the former appear to have little chance of remitting if maintained on medication after TD develops.

Prevalence of TD

We have recently completed a large-scale survey of the prevalence of TD involving more than 2,000 subjects from two geriatric and three psychiatric populations, including Hillside Hospital. The methodology and some preliminary results were presented previously (Kane et al., 1985; Lieberman et al., 1984a,b). In this report we are focusing on the Hillside sample since the incidence figures discussed above are derived from this population.

Preliminary exploration of variables related to the presence of TD indicated that within each of the psychiatric samples the TD rate increases with increasing age. Further analyses revealed that the impact of age on TD prevalence varies as a function of sex, and of length of exposure to neuroleptics. Figure 4 illustrates the interaction of age and sex in relation to TD prevalence for the Hillside sample. Among women, TD is more prevalent among older than younger people ($r = .42$, $p = .001$). For men, there is a trend in the same direction ($r = .11$, $p = .12$). The fact that this correlation is smaller than the correlation for the women appears to reflect a real fact of risk; that it fails to reach significance for the men reflects in part the relatively narrow age range in the Hillside sample.

The other side of this coin is that sex is more important as a risk factor in older people than it is in younger people. Whether or not sex will prove significant as a risk factor depends upon the age range of the sample; in the Hillside sample it is significant. The following p values were obtained using multiple regression analysis: main effect for sex, $p = .036$; main effect for age, $p = .001$; interaction, $p = .012$.

Figure 5 graphs TD prevalence as a function of the interaction of age and length of neuroleptic exposure in the Hillside sample. It is evident that for the younger people (age<30) there is only a small increase in the probability of getting TD with longer expo-

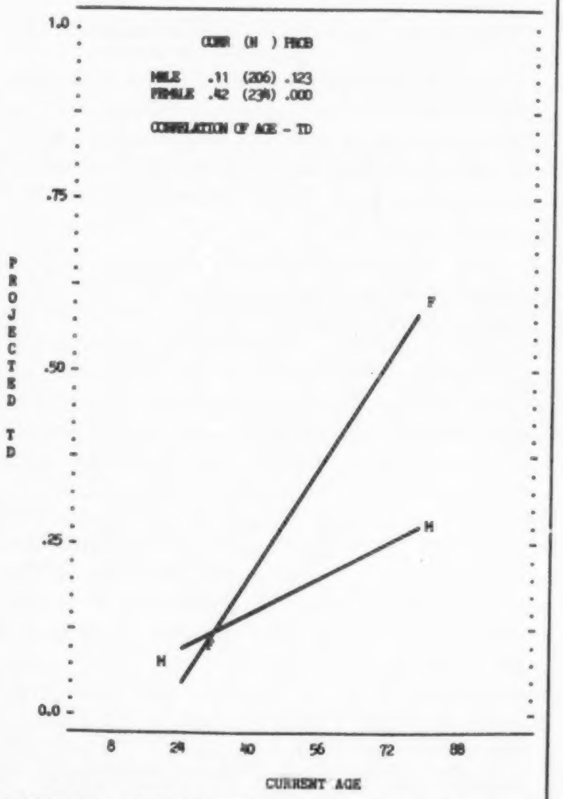


FIGURE 4. Hillside: TD as a function of age and sex.

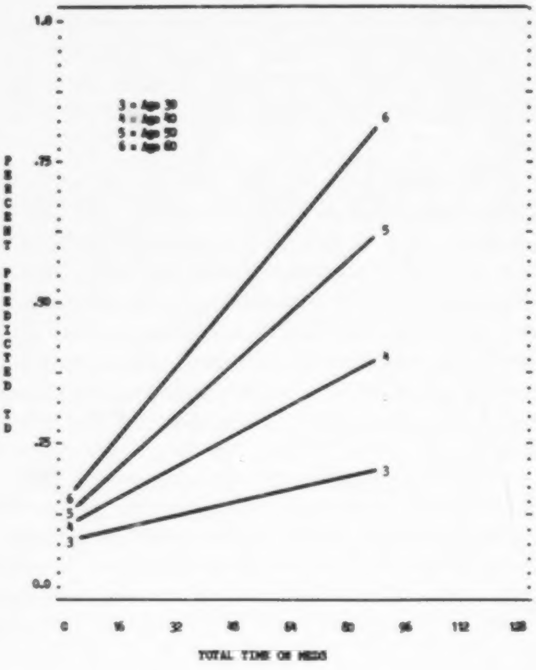


FIGURE 5. TD as a function of duration and age.

sure to neuroleptics, while for the older people TD prevalence increases sharply with increased exposure. The regression analysis yielded the following *p* values: main effect for age = .001; main effect for exposure = .019; interaction = .016.

It seems likely that the interaction reflects, in part, the fact that duration of exposure is truly a more important factor in TD development among older, than among younger people. However, this interaction could also partly reflect the findings presented above, from our study of outcome of TD among patients in the incidence study. Since the data under discussion stem from a prevalence survey, we do not know how long the individuals have had TD; i.e., how old they actually were when TD developed, and what length of drug exposure preceded it. However, it is clear that the duration of exposure employed in the analyses includes not only neuroleptic treatment *prior* to TD, but also some treatment *following* TD development. Our preliminary findings with regard to TD outcome suggest that treatment with neuroleptics following TD development is a more critical factor in TD persistence among older, than younger people. Thus, we would expect that even if the impact of neuroleptic exposure on the *development* of TD were equal across all ages, the TD would be less likely to remit, and *prevalence* would therefore be higher, among the older people.

Discussion

Our data suggest that the integration of incidence and prevalence requires knowledge about risk factors for the development of TD and risk factors for the persistence of TD once it develops. Certain findings are of particular clinical importance. Older individuals are not only more vulnerable to developing TD but also more likely to have it persist if neuroleptic medication is continued. Prognosis of TD is better for those patients treated for a smaller proportion of time during the follow-up period and for those treated with lower modal doses during follow-up.

By developing strategies to reduce the risk of TD in vulnerable individuals, and to increase the likelihood of a favorable outcome in those who have developed TD, we may be able to make meaningful progress in reducing the extent of this problem.

References

Kane, J.M., and Smith, J. Tardive dyskinesia: Prevalence and risk factors 1959-1979. *Arch. Gen. Psychiatry*, 39:473–481, 1982.

Kane, J.M., Woerner, M., Weinhold, P., et al. A prospective study of tardive dyskinesia development: Preliminary results. *J. Clin. Psychopharmacol.* 2:345–349, 1982.

Kane, J.M., Woerner, M., Weinhold, P., et al., Incidence of tardive dyskinesia: Five-year data from a prospective study. *Psychopharmacol. Bull.*, 20 (3):387–389, 1984.

Kane, J.M., Woerner, M., Lieberman, J.A., et al. The prevalence of tardive dyskinesia. *Psychopharmacol. Bull.*, 21(1):136–139, 1985.

Lieberman, J., Kane., J.M., Woerner, M., et al. Prevalence of tardive dyskinesia in elderly samples. *Psychopharmacol. Bull.*, 20(3):382-386, 1984a.

Lieberman, J., Kane, J.M., Woerner, M., et al. Prevalence of tardive dyskinesia in elderly patients. *Psychopharmacol. Bull.* 20(1):22–26, 1984b.

A Five-Year Follow-up Study of Tardive Dyskinesia

Guy Chouinard, M.D., M.Sc.(Pharmacol), F.R.C.P.(C), F.A.P.A.,[1,2,3] Lawrence Annable, B.Sc., Dip.Stat.,[1,2] Pierre Mercier, Ph.D.,[1,2] and Andree Ross-Chouinard, M.D.[1,2]

Introduction

Prevalence studies of tardive dyskinesia (TD) in neuroleptic-treated patients have investigated factors associated with the presence of the disorder. The most reliable finding is that TD is more prevalent in older patients. In 1975, we carried out a cross-sectional study of TD in all 256 schizophrenic patients receiving neuroleptic maintenance treatment in the outpatient clinic of the Allan Memorial Institute (Chouinard et. al, 1979b). At that time, we reported the prevalence of TD in the clinic to be 31% (in fact, 23% met the recently proposed Schooler and Kane research diagnostic criteria for TD) (1982). Stepwise multiple logistic regression analysis suggested the following risk factors for TD (in order of statistical significance): advanced age, long records of hospitalization, poor therapeutic response to neuroleptics, and fluphenazine medication [oral or intramuscular (i.m.)]. There was also an inverse relationship between parkinsonism and TD, patients tending to have one or the other disorder but usually not both.

We now report a 5-year follow-up of these patients, focusing in particular on an investigation of factors related to the subsequent development of TD in a cohort of 131 patients who did not present the disorder in 1975.

Method

In 1975 TD and parkinsonism were assessed by a neurologist (A.R.-C.) in all 256 schizophrenic outpatients receiving maintenance antipsychotic medication in the Special Follow-Up Clinic of the Allan Memorial Institute. The scale used was the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard and Ross-Chouinard (Chouinard et al., 1979a, 1980), and the presence of TD was determined according to the Schooler and Kane Research Criteria (1982) which require at least moderate dyskinetic movements in one body area or mild dyskinetic movements in two body areas. The presence of parkinsonism was also determined on a similar basis. Psychopathology was assessed by one of the authors (G.C.) who conducted a psychiatric interview. The schizophrenic illness of patients was classified as good or poor prognosis using the World Health Organization (WHO) scale for prognosis. Data were collected on demographic characteristics, treatment history, neuroleptic type and dosage converted to chlorpromazine equivalents (Davis, 1980), and antiparkinsonian drugs. Patients with a history of meningitis, brain trauma, neurosyphilis, or an abnormality on neurological examination associated with a neurological disease were classified by the neurologist as having brain damage.

In 1980, 169 of the original cohort of 256 patients (65%) were reassessed by the same neurologist and psychiatrist after 5 years of further neuroleptic treatment, using the same rating scales and criteria as before. At this time it was confirmed that all patients met the DSM-III criteria for schizophrenia. Eighty-seven of the original 256 patients (35%) were lost to follow-up because of either failure to return to the clinic, transfer elsewhere, or death. Table 1 compares the characteristics of patients lost to follow-up with those of patients who were reassessed in

---

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute, Royal Victoria Hospital, Montreal, Quebec, Canada.

[2] Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

[3] Research Department, Hôpital Louis-H. Lafontaine, Montreal, Quebec, Canada.

TABLE 1

Patient Characteristics (1975): Differences Between Follow-up Cohort of Patients and Those Lost to Follow-up

	Follow-up Cohort ($N = 169$)	Lost to Follow-up ($N = 87$)	Statistical Significance of Difference[a] p
Men/Women	83/86	54/33	0.07
Age	42 (23-67)[b]	39 (19-63)[b]	0.06
Treatment duration (yrs)	10.5 (0.1-22)[b]	8.0 (0.1-21)[b]	0.001
Dosage (CPZ equivalents)	487 (15-4000)[b]	506 (0-5000)[b]	0.82
Brain damage	25%	14%	0.05
Neuroleptic type			
p.o. only	61%	52%	0.20
i.m. only	18%	18%	0.96
p.o. and i.m.	20%	24%	0.48
Antiparkinsonian medication	55%	67%	0.10
Tardive dyskinesia (research criteria)[c]	22%	24%	0.89
Parkinsonism[d]	33%	44%	0.13

[a] Chi-square test with Yates' correction for percentages. t test for means (two-sided).
[b] Mean (minimum-maximum).
[c] Schooler and Kane (1982).
[d] At least two items with scores ≥ 2 or one item with score ≥ 3.

1980. Patients lost to follow-up were more likely to be male ($p = 0.07$), younger (mean difference = 3 years, $p = 0.06$), treated for a shorter period of time (mean difference = 2.5 years, $p = 0.001$), less likely to have brain damage ($p = 0.05$), and more likely to be receiving antiparkinsonian medication ($p = 0.10$). There were no significant differences between the two groups, however, with respect to prevalence of TD or parkinsonism in 1975.

TABLE 2

Patient Characteristics: Cohort of 131 Patients With No TD in 1975

	1975		1980
Men/Women		61/70	
Age	40 (23-67)[a]		45 (27-72)[a]
Duration of treatment (yrs)	9.5 (0.1-22)[a]		14 (4.4-26)[a]
Dosage (mg/day CPZ equivalents)	300 (15-4000)[a]		338 (6-4200)[a]
Poor schizophrenic prognosis		72%	
Brain damage		24%	
Neuroleptic type			
p.o. only	66%		36%
i.m. only	18%		60%
p.o. and i.m.	16%		5%
Antiparkinsonian medication	53%		68%

[a] Median (minimum - maximum).

The characteristics of the cohort of 131 patients who did not present TD in 1975 and who were reassessed in 1980 are shown in Table 2. During this period the policy in the clinic was to switch patients from daily oral (p.o.) neuroleptics to long-acting i.m. neuroleptics (mostly fluphenazine enanthate or decanoate) if feasible. Antiparkinsonian medication was prescribed only if necessary and not prophylactically. Polypharmacy was avoided as far as possible. The principal changes in treatment may be summarized as follows: 1) there was a switch from p.o. to i.m. medication in 45% of patients; 2) a reduction in neuroleptic dosage (chlorpromazine equivalents) (Davis, 1980) in 48% of patients;

TABLE 3

Prevalence of TD and Parkinsonism in 1975 and 1980: Cohort of 169 Patients Assessed in 1975 and 1980

		1975 (Percent)	1980 (Percent)
Tardive dyskinesia	(research criteria)[a]	22	44
Men	($N = 83$)	27	43
Women	($N = 86$)	19	45
Parkinsonism[b]		33	72
Men	($N = 83$)	39	76
Women	($N = 86$)	28	69

[a] Schooler and Kane (1982).
[b] At least two items with scores ≥ 2 or one item with score ≥ 3.

and 3) an increase in antiparkinsonian dosage in 45% of patients.

Results

Prevalence of TD in all reassessed patients (N = 169). Table 3 shows the prevalence of TD (Schooler & Kane, 1982) and parkinsonism in the 169 patients assessed in both 1975 and 1980. The prevalence of TD increased from 22% to 44% ($p<0.001$, McNemar's test) and that of parkinsonism from 33% to 72% ($p<0.001$, McNemar's test). There was no significant ($p<0.05$) difference between the sexes with respect to the prevalence of either TD or parkinsonism on either occasion. There was, however, a tendency ($p<.10$, $\chi^2 = 3.65$) for more parkinsonism in men than women in 1975, but not in 1980.

Development of TD in reassessed patients (N = 131). In the cohort of 131 patients who did not present TD in 1975, 46 patients (35%) developed TD, while the prevalence of parkinsonism increased from 32% to 71%. Stepwise multiple logistic regression analysis (Kleinbaum et al., 1982) was used to predict the development of TD (coded 0,1) during the period 1975 to 1980. The exploratory variables included for selection were of two types: those thought to be of possible etiological significance in the development of TD, and those known or suspected to uncover covert TD. The etiological variables included were: sex, age, duration of neuroleptic treatment (dichotomized and coded as follows: 0 = <5 yrs. 1 = ≥5 yrs), schizophrenic prognosis (0 = good, 1 = poor), brain damage (0 = none, 1 = present), and parkinsonism score (1975); the uncovering or confounding variables were: reduction in neuroleptic dosage, switch from daily p.o. to long-acting i.m. neuroleptic (the uncovering mechanism may be through a decline in blood level at the end of the injection interval when all patients were assessed), and an increase in antiparkinsonian dosage.

The model building strategy used was to start with all main effects in the model and then carry out forward selection to add any significant second-order product (i.e., interaction) terms (Kleinbaum et al., 1982). Second-order product terms were considered because we were unable to obtain a good fit with main effects only. An alpha level of 5% was used throughout. Because there were nine main effects and 36 second-order interaction terms as candidates for selection, this analysis should be regarded as exploratory, particularly where variables of marginal statistical significance were selected.

The results of the stepwise logistic regression analysis are shown in Table 4. Three main effects were significant at the 5% level: parkinsonism score (1975), poor schizophrenic prognosis, and treatment duration (>5 years). Also, two variables were significant at the 10% level: a switch from p.o. to i.m. medication and a neuroleptic dosage reduction. In addition to these main effects two interac-

TABLE 4

Variables Related to Development of TD (1975–1980): Results of Stepwise Logistic Regression Analysis ($N = 131$)

Variable	Coefficient	S.E.	χ^2	p
Intercept	−5.07	1.43	12.58	0.0004
Parkinsonism score (1975)	0.13	0.06	4.68	0.03
Poor schizophrenic prognosis	1.09	0.53	4.31	0.04
Treatment duration	1.42	0.73	3.75	0.05
p.o. to i.m. switch	1.12	0.61	3.37	0.07
Neuroleptic dosage reduction	0.80	0.45	3.18	0.07
Age	0.03	0.02	1.33	0.25
Antiparkinsonian dosage increase	−0.57	0.54	1.11	0.29
Sex	0.15	0.46	0.11	0.74
Brain damage	−0.01	0.66	0.00	0.98
p.o. to i.m. switch x parkinsonism score	−0.23[a]	0.09	7.08	0.008
Antipark. increase x brain damage	2.20	1.04	4.51	0.03

[a] Negative coefficient indicates that effect of presence of both risk factors is less than sum of each main effect (lack of additivity).

TABLE 5

Predictive Ability of Multiple Logistic Regression Model

		Predicted (1980)		
		No TD	TD	Total
	No TD	75	10	85
True	TD	23	23	46
(1980)	Total	98	33	131

Sensitivity (true positives) = 50%
Specificity (true negatives) = 88%

tion terms were added to the model: 1) that between the medication switch and parkinsonism score with a negative coefficient ($p = 0.008$), indicating that the risk of TD with both factors present is less than the sum of their separate risks and, more specifically, that the patients most at risk for developing TD were those with high parkinsonism scores in 1975 who remained on the same medication type (either p.o. only or i.m.) in 1980; and 2) that between an antiparkinsonian dosage increase and brain damage with a positive coefficient ($p<0.05$), indicating that brain-damaged patients were more vulnerable to the effect of antiparkinsonian increase. The effects of age and sex were not significant ($p>0.10$), although it is worth noting that age and duration of treatment were correlated somewhat ($r = 0.44$, $p<0.001$). We examined the goodness-of-fit of this model by comparing the predicted cases ($p>0.5$) with the true cases of TD (Table 5): sensitivity (true positives) was 50% which is fair, and specificity (true negatives) was 88%, which is good.

Because the 1975 parkinsonism score appeared to be the best predictor of subsequent TD development, we repeated the stepwise logistic regression analysis including the change in parkinsonism score (1975 to 1980) as an additional variable. The results of this analysis were that the new variable, change in parkinsonism score, became the best predictor of TD development ($p = 0.001$) with 1975 parkinsonism score second. The new model increased the sensitivity of prediction to 54% while the specificity remained at 88%.

Annual incidence rate of TD. The 5-year cumulative incidence rate of TD in the cohort of 131 patients who did not present TD at the 1975 assessment was 35% (46/131). This is equivalent to a mean annual incidence rate of 8.4% (Kleinbaum et al., 1982). However, this does not consider remissions (or misclassifications) among patients who presented TD in 1975 but not in 1980 of which there were 9/38 cases representing a 5-year cumulative remission rate of 24% or a mean annual remission rate of 5.5%. Thus the mean annual incidence rate of TD corrected for remissions was 2.9%.

Discussion

These results suggest that three etiologic factors may be important in the development of TD. The presence of severe parkinsonism which cannot be suppressed by antiparkinsonian medication appeared to be a precursor of TD development. There was also evidence that worsening of parkinsonism was associated with TD development. Whereas in 1975 we observed an inverse relationship between parkinsonism and TD, in 1980 both disorders were commonly present simultaneously. During this interval the patients had both grown older and been exposed to more neuroleptic treatment, so that a more advanced stage of extrapyramidal movement disorder had probably been reached. One contribution to the changed relationship may have been the decrease in dopamine synthesis with aging, especially in male patients, as found in PET scan studies.

The second risk factor for TD was poor schizophrenic prognosis, which tends to confirm our earlier finding (Chouinard et al., 1979b) of an association between poor therapeutic response to neuroleptics and TD. Duration of neuroleptic treatment also appeared to be a risk factor with 5 to 10 years of exposure being a critical period. This finding has intuitive appeal but has not generally been substantiated in prevalence surveys. The correlation between treatment duration and age in the present population probably explains why we failed to find age an important predictor here, although it was the first variable selected in our 1975 prevalence survey (Chouinard et al., 1979b). Another factor to be considered is that these patients may constitute a special subgroup inasmuch as they were those patients in the clinic who did not present TD in 1975, despite presence of risk factors in some cases.

Three variables that may perhaps be characterized as uncovering or, in statistical terminology, confounding factors rather than etiologic factors were also identified as associated with the manifestation of TD: a switch from p.o. to i.m. medication in those without parkinsonism, a neuroleptic dosage reduction, and an increase in antiparkinsonian medication in brain-damaged patients. The explanation for the appearance of the medication switch as a risk factor may be that blood levels tend to decline toward the end of the injection interval (when all these patients were assessed), and a decline in dopamine receptor blockade at this point would tend to uncover any covert dyskinesia. This may be the explanation for our previous finding of an association between fluphenazine treatment and TD (Chouinard et al., 1979b) as many patients were receiving i.m. fluphenazine. A study in two patients using neuroleptic radioreceptor assay measurements of neuroleptic blood levels at different points during the injection period supports this view (Chouinard et al., 1982). The uncovering effect on TD of neuroleptic dosage reduction is well-known: that of anticholinergic antiparkinsonian dosage increase has also been documented (for example, Chouinard et al., 1979c), but the finding of increased vulnerability of brain-damaged patients in this respect is new. In our earlier prevalence study of TD (Chouinard et al., 1979b) in this population, we found that brain-damaged patients tended to have more severe forms of TD than those without brain damage. Thus, there seems to be some evidence to suspect that brain-damaged patients are at greater risk for the disorder.

The estimated 2.9% annual incidence rate of TD corrected for remissions is similar to that reported by Kane et al. (1982) from a prospective study of TD development, although the latter study is of a younger and heterogeneous population of patients with schizophrenia or manic-depressive disorder.

We believe that a large-scale prospective study of TD development in a homogeneous population of newly-treated schizophrenic patients would clarify further the risk factors.

References

Chouinard, G., Annable, L., Ross-Chouinard, A., et al. Ethopropazine and benztropine in neuroleptic-induced parkinsonism. *J. Clin. Psychiatry*, 40:73–81, 1979a.

Chouinard, G., Annable, L., Ross-Chouinard, A., et al. Factors related to tardive dyskinesia. *Am. J. Psychiatry*, 136:79–83, 1979b.

Chouinard, G., de Montigny, C., and Annable, L. Tardive dyskinesia and antiparkinsonian medication. *Am. J. Psychiatry*, 136:228–229, 1979c.

Chouinard, G., Ross-Chouinard, A., Annable, L., et al. Extrapyramidal Symptom Rating Scale. *Can. J. Neurol. Sci.*, 7:233, 1980.

Chouinard, G., Creese, I., Boisvert, D., et al. High neuroleptic plasma levels in patients manifesting supersensitivity psychosis. *Biol. Psychiatry*, 17:849–852, 1982.

Davis, J.M. Antipsychotic drugs. In: Kaplan, H.I., Freedman, A.M., and Sadock B.J. (eds.) *Comprehensive Textbook of Psychiatry*, Vol. 3, 3rd ed., Baltimore, Md.: Williams & Wilkins, 1980, pp. 2257–2289.

Kane, J.M., Woerner, M, Weinhold, P., et al. A prospective study of tardive dyskinesia development: preliminary results. *J. Clin. Psychopharmacol.*, 2:345–349, 1982.

Kleinbaum, D.G., Kupper, L.L., and Morgenstern, H. *Epidemiologic Research*. Belmont, Calif.: Lifetime Learning Publications, 1982.

Plasma Fluphenazine Levels in Patients Receiving Two Doses of Fluphenazine Decanoate[1]

Stephen R. Marder, M.D.,[2] John W. Hubbard, Ph.D.,[3] Theodore Van Putten, M.D.,[2] Edward M. Hawes, Ph.D.,[3] Gordon McKay, Ph.D.,[3] Jim Mintz, Ph.D.,[2] Philip R.A. May, M.D.,[2] and Kamal K. Midha, Ph.D.[3]

Plasma level monitoring has the potential for being particularly useful in maintenance treatment. One of the serious problems in selecting a maintenance dose is that there are few guidelines available for deciding when a particular dose is adequate for a particular patient. This differs from the treatment of acute schizophrenia in that the clinician may not be able to titrate dose against active signs and symptoms. In this regard, anything which would help make dose selection in maintenance therapy less of a trial-and-error proposition would be welcome.

We explored the usefulness of plasma fluphenazine levels in the context of a double-blind comparison of what we defined as a very low (5 mg) and a conventional dose (25 mg) of fluphenazine decanoate (FD) administered every 14 days over a 1-year period (Marder et al., 1984).

Method

The subjects were 45 men referred to an outpatient research clinic at a large urban V.A. hospital. All were diagnosed as suffering from a Schizophrenic Disorder using DSM-III. The design of this study is described in detail in a prior publication (Marder et al., 1984).

After giving written informed consent, subjects were managed on a stable dose of FD for 2 or more months. Individuals who could not be stabilized on 25 mg or less every 14 days were dropped from the study. Following stabilization, all neuroleptics were stopped for 4 weeks. (This actually entailed missing one injection of FD.) At this point, all subjects were given a test dose of 5 mg of FD. Blood for plasma level measurement was drawn before and 24 hours after the injection. Two weeks after the test dose, patients were randomized to a double-blind trial of 5 or 25 mg of FD administered every 14 days. For the 5 mg group, FD was prepared in miglyoil; for the 25 mg group, in sesame seed oil. Further blood samples were drawn at 1, 2, 3, 6, 9, and 12 months following entry. Samples were drawn 2 weeks following the previous injection or just before the next injection was administered.

Plasma levels of fluphenazine were measured using a radioimmunoassay (RIA) (Midha et al., 1980) which was validated for specificity using gas chromatography with mass spectrophotometry (Dudley et al., 1983).

When patients demonstrated a worsening of 3 or more points on Brief Psychiatric Rating Scale (BPRS) cluster scores for thought disturbance or paranoia, they were considered to have a psychotic relapse. Most were rather mild and easily managed by adjusting the drug dose. (Relapses in this report were designated exacerbations in a prior publication.)

Results

The Figure describes the mean fluphenazine concentrations for patients treated with the two doses. Patients were dropped from this analysis when their dosage was adjusted as a result of relapse. Thus, the *N*'s reflect a diminishing sample due to dropout and relapse. However, results based only on com-

---

[1] This study was supported by the Veterans Administration Medical Research Service and the UCLA Mental Health Clinical Research Center for the Study of Schizophrenia (National Institute of Mental Health), R.P. Liberman, M.D., Director.

[2] West Los Angeles Veterans Administration Medical Center, Brentwood Division and the UCLA School of Medicine, Los Angeles, CA 90073.

[3] College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

Reprint requests to Dr. Stephen R. Marder, West L.A. V.A. Medical Center, 11301 Wilshire Blvd., Los Angeles, CA 90073.

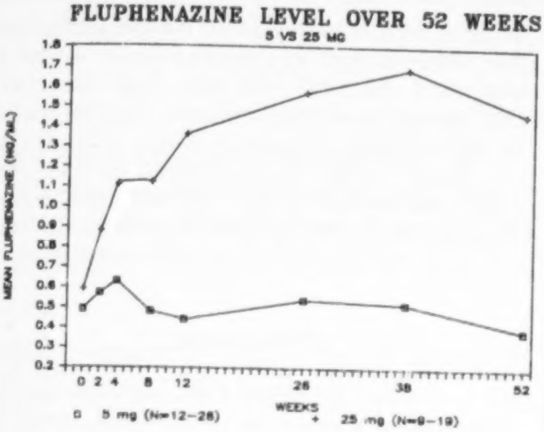


FIGURE. Mean plasma fluphenazine levels for patients treated with 5 or 25 ng of FD every 14 days. Differences between the two dosage groups are statistically significant at 8 weeks and thereafter.

plete cases through 52 weeks looked virtually identical. Although the values were similar at baseline and 2 weeks, by 8 weeks fluphenazine levels were significantly higher for patients treated with 25 mg—and remained significantly higher for the remainder of the year. For clarity, the standard deviations were left off this Figure. They were very large—often larger than the means. Levels for the 5 mg group remained reasonably stable over the year whereas the 25 mg group required 3 to 6 months to reach a stable level. Even though the high dose patients received fivefold the dose of low dose patients, there was some overlap.

We also examined the relationship between steady-state fluphenazine concentrations and vulnerability to psychotic relapse. We used the concentrations at 6 months since this was the amount of time it took plasma concentrations to reach steady state. We compared these levels with psychotic relapses during the next 18 months. The mean fluphenazine level was 0.57 ng/ml for relapsers and 1.01 ng/ml for nonrelapsers. This difference, however, was not statistically significant. Although 5 of the 10 patients who eventually relapsed had plasma levels below 0.5 ng/ml, 7 of the 19 patients who did not relapse were also in this range. None of the patients with plasma levels of greater than 1.5 ng/ml relapsed.

We also studied the relationships between fluphenazine levels at 3 months and side effects. Plasma concentrations correlated with the score for Akinesia ($r = .52$, $p = .002$), the BPRS cluster score for Retardation ($r = .52$, $p = .002$), and Total BPRS ($r = .39$, $p = .02$).

The relationship between side effects and plasma level was also examined in a pooled within-subject analysis of the ratings of side effects and fluphenazine levels over all rating occasions. For this analysis, "dummy" variables were forced into a hierarchical analysis of the side effect ratings to remove between-subject effects. We then computed the amount of variance which was explained by the addition of information about either fluphenazine (FLU) or log (FLU+1). For the log-transformed FLU, the relationship approached statistical significance at the $p = .097$ level for akinesia and reached significance at the $p = .016$ level for akathisia.

Discussion

We found that patients who received 25 mg of FD every 14 days required from 3 to 6 months to reach a stable steady state. This finding indicates that a dose of FD which may be appropriate during the first weeks of treatment may be excessive a few months later. It suggests that when a higher dose is given for maintenance, a reasonable practice might be to gradually decrease the dose or increase the interinjection interval during the first 6 months of treatment.

Although plasma fluphenazine concentrations were lower in patients who eventually relapsed, this difference did not reach statistical significance. Finding relationships between plasma concentration and clinical response probably requires a larger sample size when studying maintenance treatment as opposed to acute treatment. This is because of the greater variance related to such factors as the lengthy period of time during which patients may be exposed to environmental stressors and the unpredictable relationship between the time a dose is altered and the time to relapse. Our findings, however, do suggest that patients who have plasma levels of greater than 1.5 ng/ml are less likely to relapse than those with much lower plasma levels. The correlations between plasma levels and side effects suggest that this added protection may be at the cost of more personal discomfort. This finding is consistent with a previous report on the same population in which patients treated with 25 mg had higher side effect ratings than those treated with 5 mg—even though both groups were treated aggressively with antiparkinson medications (Marder et al., 1984). This suggests that finding the best maintenance dose may require a complex risk-benefit analysis in which the amount of protection given to the patient should be weighed against the amount of side effect-induced discomfort that the person can tolerate.

In conclusion, our data do not indicate that the measurement of fluphenazine level alone will be helpful in determining whether a patient is more vulnerable to relapse. Finding a reasonable threshold plasma level may require the measurement of parent fluphenazine as well as its psychoactive metabolites or the development of an even more sensitive analytical method. We did find, however, that plasma level measurement may be useful in determining when a patient is receiving too much drug. The correlations between fluphenazine levels and side effects indicate that patients with high plasma levels may benefit from having their drug dose reduced.

References

Dudley, J., Rauw, G., Hawes, E.M., et al. Correlation of fluphenazine plasma levels versus clinical response in patients: A pilot study. *Prog Neuro-Psychopharmacol. Biol. Psychiatry*, 7:791–795, 1983.

Marder, S.R., Van Putten, T., Mintz, J., et al. Costs and benefits of two doses of fluphenazine. *Arch. Gen. Psychiatry*, 41:1025–1029, 1984.

Midha, K.K., Cooper, J.K., and Hubbard, J.W. Radioimmunoassay for fluphenazine in human plasma. *Commun. Psychopharmacol.*, 4:107–114, 1980.

An Early Phase II Clinical Trial of Remoxipride in Schizophrenia With Measurement of Plasma Neuroleptic Activity

Guy Chouinard, M.D., M.Sc. (Pharmacol), F.R.C.P.(C),[1,2] and L. Turnier, M.D.[2]

A wide variety of chemical classes of drugs such as phenothiazines, thioxanthenes, butyrophenones, diphenylbutylpiperidines, and benzamides have been found to have antischizophrenic effects. Relative in vitro affinities for D_1 and D_2 dopamine receptors differentiate classical antipsychotics such as fluphenazine (relatively equivalent in blocking D_1 and D_2 receptors) from butyrophenones and diphenylbutylpiperidines. Haloperidol and pimozide, for example, have respectively 200 and 900 times more affinity for D_2 than D_1 receptors (Christensen et al., 1984). It is interesting to note that remoxipride, a new substituted benzamide, has no known affinity for D_1 receptors, and thus appears to be a selective D_2 receptor-blocking agent (Ogren et al., 1983). In addition, remoxipride was found to have a preferential effect in mesolimbic and extrastriatal dopamine containing neurons (Ogren et al., 1983). Remoxipride is an S(-)-3-bromo-N-[1-ethyl-2-pyrrolidinyl) methyl]-2,6-dimethoxy-benzamide monohydrate. We report an early Phase-II clinical trial of remoxipride in the treatment of chronic schizophrenia with and without acute exacerbation.

Method

Twenty patients satisfying the study criteria given below were selected for inclusion in the trial and transferred to our research ward of Hôpital Louis-H. Lafontaine. The selection criteria required that: 1) the patients be aged between 18 and 65 years; 2) a primary hospital diagnosis of schizophrenia be confirmed by the research psychiatrist on the basis of the DSM-III (American Psychiatric Association, 1980); and 3) patients with physical illness, childhood schizophrenia, organic brain syndrome, mental retardation, alcoholism, epilepsy, or drug addiction and women of childbearing potential be excluded from the study.

The study population consisted of 13 men and 7 women aged between 27 and 62 years (median: 48 years), who had been hospitalized on 1 to 18 occasions (median: 6), for a total duration of 2 to 30 years (median: 10.6 years). The schizophrenic disorder was classified by DSM-III criteria as paranoid in 13 patients, undifferentiated in 3 patients, and disorganized in 4 patients, of which 14 cases were chronic without acute exacerbation and 6 chronic with acute exacerbation.

Before entering the trial, all patients were receiving haloperidol (6 to 80 mg/day, median: 30) and a central anticholinergic antiparkinsonian, procyclidine (7.5–40 mg/day, median: 22.5). No other psychotropic drugs were taken by the patients before entering the trial. Haloperidol was abruptly discontinued and patients underwent a 4-day placebo single-blind washout period during which procyclidine was gradually decreased and discontinued.

Patients were then treated for 6 weeks with remoxipride at dosages determined according to therapeutic effect and side effects. The medication was given in the form of tablets prepared in a dosage strength of 50 mg and was administered in a twice-daily regimen. The initial dose varied between 50 mg and 100 mg/day. Thereafter, the dosage was adjusted according to therapeutic effect with the condition that individual dose increments did not exceed 100 mg/day and did not occur at intervals of less than 3 days.

Assessment of symptoms was based on

---

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute, Royal Victoria Hospital, Montreal, Quebec, Canada, and Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

[2] Research Department, Hôpital Louis-H. Lafontaine, Montreal, Quebec, Canada.

clinical interviews conducted by a single clinical investigator (G.C.). Mental status was scored on admission (while on haloperidol), at the end of washout (day 0) and weekly on the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) and a 7-point Clinical Global Impression (CGI) severity of illness. Factor scores were formed from the items of the BPRS (Overall & Klett, 1972). Extrapyramidal symptoms were recorded weekly on the Extrapyramidal Symptom Rating Scale of Chouinard and Ross-Chouinard (Chouinard et al., 1980, 1984); biochemistry, urinalysis, hematology, EEG, and ECG were done at regular intervals. Blood samples were taken in a fasting state before and 1 hour after ingestion of the morning dose of medication for measurement of plasma remoxipride concentrations and neuroleptic levels. Plasma neuroleptic activity was determined using a radioreceptor technique developed by Creese and Snyder (1977), Lader (1980), and Cohen et al. (1980), and remoxipride blood concentrations by a high performance-liquid chromatography method.

Results

Drug Dosages

Dosages of remoxipride were increased gradually from 50 mg/day to a maximum of 500 mg/day (the maximum daily dose permitted was 600 mg). At week 6 the doses varied between 75 mg/day and 500 mg/day (median: 225 mg/day). Eleven of the 20 patients were administered minimal doses of clonazepam, as needed, for agitation ($n = 8$), insomnia ($n = 2$), anxiety ($n = 1$), and aggressiveness ($n = 1$) that was not well-controlled by the study medication; the mean daily dosages of clonazepam in these patients ranged from .05 to .57 mg (median: .09 mg). Upon admission to the trial, all patients were receiving procyclidine to control parkinsonian symptoms (mean: 23.1 mg/day) while at the end of the treatment period with remoxipride 15 patients (75%) required procyclidine administration (mean: 17.4 mg/day). Comparison of week 6 and pre-washout doses of procyclidine shows a trend to a decline (paired t test, $t = 1.8$, $p < .10$, two-tailed) in patients' need for antiparkinsonian medication. No other psychotropic drugs were given during the trial.

Therapeutic Effect

All patients completed 42 days of active treatment. The Table shows the mean admission, baseline and weekly scores for all patients on the BPRS and CGI. There was a statistically significant deterioration (paired t test, $p < .001$) at the end of placebo washout in the BPRS total score and statistically significant improvement occurred at the end of the treatment period in the CGI (paired t: 2.8, $p = .01$, two-tailed) and the BPRS total score ($t = 2.3$, $p = .03$). The response of each patient was classified on a 7-point scale ranging from very much worse to very much im-

TABLE

Mean Admission, Baseline, and Weekly Scores for the BPRS, CGI, and Parkinsonism and Tardive Dyskinesia on the Extrapyramidal Symptom Rating Scale (ESRS)

	BPRS		CGI		ESRS Parkinsonism		ESRS Tardive Dyskinesia	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Admission	20.8	4.5	4.20	0.52	8.8	4.8	3.3	2.8
End of Washout	31.8**	11.4	4.60	0.75	8.5	4.7	3.5	3.1
Week 1	26.3	8.1	4.65	0.59	9.9	5.1	3.3	2.9
Week 2	25.9	11.2	4.45	0.95	11.3	5.6	3.4	3.3
Week 3	21.1	9.6	4.00	0.80	9.2	5.9	4.4	3.3
Week 4	23.4	12.8	4.10	0.91	9.5	5.5	4.4	3.9
Week 5	20.8	10.9	3.85	0.88	7.5	5.5	5.2	3.2
Week 6	24.5*	11.8	3.95*	0.89	7.3	4.1	4.3	3.6

*$p < .05$, paired t test, compared to End of Washout.

**$p < .001$, paired t test, compared to Admission.

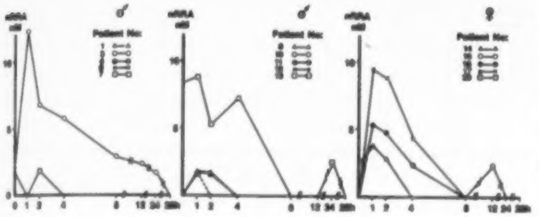


FIGURE 1

proved: 16 patients were considered to be improved (10 much improved, 6 minimally improved), and 4 patients minimally worse.

Extrapyramidal Symptoms and Adverse Effects

The admission, baseline, and weekly mean scores for parkinsonism and tardive dyskinesia (TD) on the Extrapyramidal Symptom Rating Scale are also shown in the Table. There was a decline in parkinsonism at Week 6 compared to admission while patients were on haloperidol treatment. Comparison of Week 6 with baseline scores shows a significant decline (paired *t* test: 2.65, *p* = .02, two-tailed) in hyperkinetic parkinsonian symptoms (factor formed by adding scores for tremors and akathisia) during remoxipride treatment. There was a tendency for an increase of overt TD in the total score for dyskinetic movements at baseline when patients had been withdrawn from neuroleptics compared to admission (when patients were on haloperidol); thus, after 6 weeks of drug administration remoxipride appeared to have little masking effect on TD.

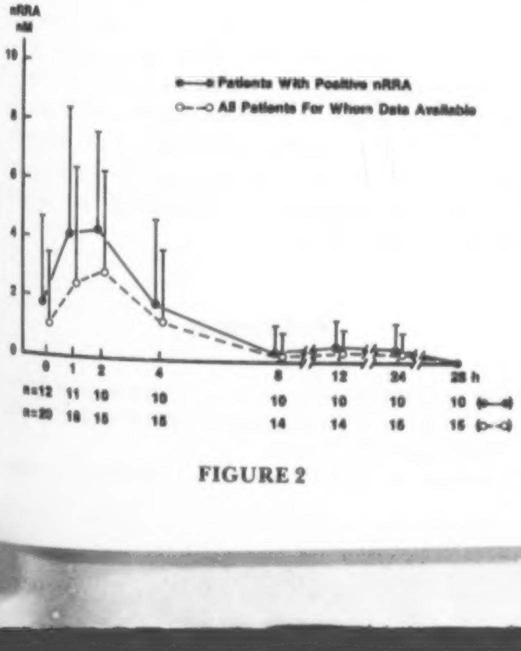


FIGURE 2

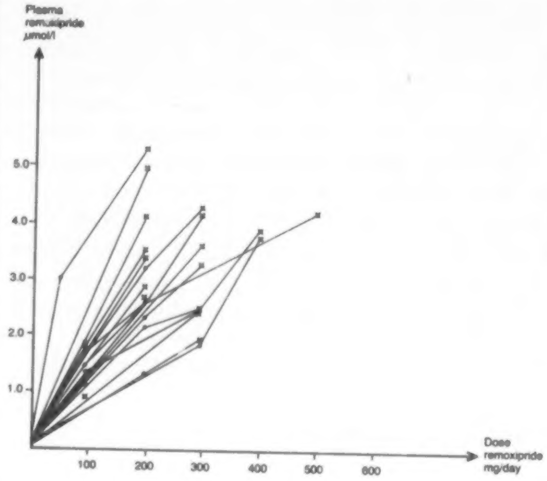


FIGURE 3

The following adverse experiences (of moderate intensity) were judged to be related to the study drug (number of cases in parentheses): akathisia (9), fatigue (7), insomnia (7). Remoxipride produced a statistically significant ($p<.05$, paired *t* test) lowering of the supine systolic blood pressure at the end of the clinical trial (mean admission—120.3 mm Hg, Day 42—111.8 mm Hg). There was a statistically significant ($p<.001$, paired *t* test) but small decrease in the mean body weight at the end of the trial (from 67.1 kg at admission to 65.1 kg at the end of the trial). Eight patients (40%) at the beginning of the clinical trial had mild EEG abnormalities, probably related to their prior neuroleptic intake. Of

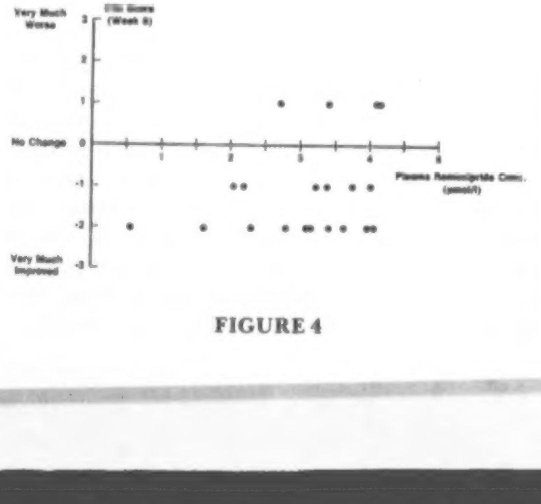


FIGURE 4

these patients, 2 had an improvement and 2 no changes, while in the 4 other patients there was some evidence of remoxipride producing EEG effects: mild irregular bitemporal theta activity, paroxystic activity induced by photic stimulation and increases in slow activity. On the ECG remoxipride produced nonspecific ST-T wave changes in 6 patients. Transient changes in white blood cell count (inversion of the proportion of neutrophiles upon lymphocytes) were noticed in 2 patients and transient vacuoles in lymphocytes (<1%) were observed in 3 patients.

Plasma Radioreceptor Activity

Baseline and day 42 blood samples were analyzed for neuroleptic activity using calf caudate homogenate and [^{3}H]spiperone as ligand. Activity was detected in the plasma of 5 patients at baseline (end of washout), whereas little or no activity could be demonstrated in the samples obtained on day 42. Indeed, analysis of serial blood samples drawn at 1, 2, 4, 8, 12, 24, and 28 hours after the last morning dose on day 42 showed 12 patients with maximum concentrations ranging from 1.7 to 12.3 nmol/l (median: 3) and 8 patients with no activity. Blood samples were analyzed in quadruplicate and the limit of the assay was 6 nmol/l haloperidol units. Results presented are the means of the four measurements (Figures 1 and 2).

Plasma Concentrations of Remoxipride

Serial plasma remoxipride concentrations in individual patients were measured following the last dose of remoxipride (Day 42). Maximum concentrations occurred within 2 hours after drug intake and ranged between 1.8 μmol/l (50 mg dose) and 10.8 μmol/l (250 mg dose). The mean elimination half-life was 5.9 hours (range: 4.1-10.7 hours). When individual patient steady-state plasma remoxipride concentrations were plotted against dose, steady-state concentration and dose were linearly related (Figure 3). There was no evidence of correlation between plasma remoxipride concentrations or drug dosage and therapeutic effect (Figures 4 and 5).

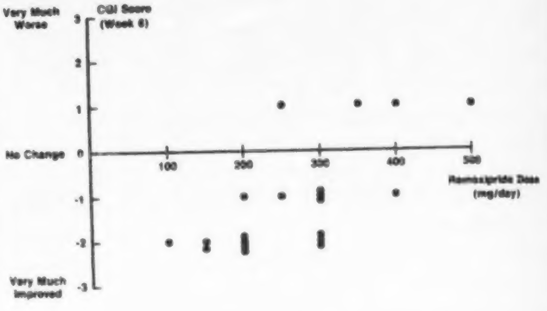


FIGURE 5

Discussion

The marked improvement seen in half of these schizophrenic patients suggests that remoxipride has an anti-schizophrenic effect. The decline in parkinsonism is consistent with the hypothesis that remoxipride has less effect on the nigrostriatal system (Ogren et al., 1983). Remoxipride was found to have little masking effect on TD. By the same token, this might suggest that remoxipride would have correspondingly less potential to induce TD in newly treated patients, but this would need to be investigated. The lack of serum neuroleptic activity in the majority of blood samples shows that the drug has low affinity for [^{3}H]spiperone binding which makes this method less useful for neuroleptic activity measurements, due to its low sensitivity versus remoxipride, when using calf caudate. Remoxipride can act with a configuration of the receptor other than the one labelled with spiroperidol, thus ligands such as [^{3}H]n-propylnorapomorphine could be used for D_2 receptors in human studies of remoxipride. These results underline the importance of a drug's D_2-dopamine receptor-blocking properties in achieving an anti-schizophrenic effect.

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III), 3rd ed., Washington, D.C., 1980.

Chouinard, G., Ross-Chouinard, A., Annable, L., et al.

Extrapyramidal symptom rating scale. *Can. J. Neurol. Sci.*, 7:233, 1980.

Chouinard, G., Ross-Chouinard, A., Gauthier, S., et al. An extrapyramidal rating scale for idiopathic and neuroleptic-induced parkinsonism and dyskinesia. 14th C.I.N.P. Congress. Abst. F-13, 1984.

Christensen, J., Arnt, J., Hyttel, J., et al. Pharmacological effects of a specific dopamine D-1 antagonist SCH 23390 in comparison with neuroleptics. *Life Sci.*, 34:1529–1540, 1984.

Cohen, B.M., Herschel, M., Miller, E., et al. Radioreceptor assay of haloperidol tissue levels in the rat. *Neuropharmacology*, 19:663–668, 1980.

Creese, I., and Snyder, S.H. A simple and sensitive radioreceptor assay for antischizophrenic drugs in blood. *Nature*, 270:180–182, 1977.

Lader, S.R. A radioreceptor assay for neuroleptic drugs in plasma. *J. Immunoassay*, 1:57–75, 1980.

Ogren, S.O., Hall, H., Kohler, C., et al. Remoxipride, a new potential antipsychotic compound with selective anti-dopaminergic actions in the rat brain. *Eur. J. Pharmacol.*, 102:459–474, 1983.

Overall, J.E., and Gorham, D.R. The brief psychiatric rating scale. *Psychol. Rep.*, 10:799–812, 1962.

Overall, J.E., and Klett, C.J. *Applied Multivariate Analysis.* New York: McGraw-Hill Book Co., 1972.

Measuring Adverse Drug Reactions in a Postmarketing Surveillance System[1]

Seymour Fisher, Ph.D.,[2] Stephen G. Bryant, Pharm. D.,[2] and Ronica M. Kluge, M.D.[3]

We have recently initiated a large-scale study aimed at developing new methods for collecting postmarketing surveillance data on prescription drug experiences in an ambulatory population. These new monitoring methods are designed to complement rather than replace existing physician-initiated voluntary reporting of adverse drug reactions (ADRs). The current study, while primarily oriented toward validating a patient-initiated monitoring system, actually compares two different approaches to ADR surveillance. One is based upon patient-initiated reports via toll-free telephone to a cadre of interviewers who have been trained to record in a standardized way the relevant information obtained from the patient. The second method utilizes computer-directed similar telephone interviews initiated by the interviewing staff.

Since many practitioners and researchers use some form of clinical interview to elicit potential ADRs, it is important to examine the validity of such interview information. These interviews may range from a casual inquiry about how the patient has been feeling since starting the drug to a detailed review of organ systems (e.g., Maclay et al., 1984: Mellinger, 1984: Rauch, 1979). The purpose of this paper is to show that, while spontaneously reported symptoms are uniformly reliable in detecting ADRs, symptoms elicited by system review may lead to gross overestimation of true ADRs.

Method

The study is based upon a cohort of patients receiving a new prescription for certain targeted drugs. The target drugs were selected from two classes of therapeutic agents with markedly disparate, well-documented ADR profiles (tricyclic antidepressants and antibiotics).

Study Design

At the time a targeted prescription is being dispensed at our outpatient pharmacies, cooperation is randomly solicited from half of the patients (Experimentals) via a printed notice attached to the outside of their medication bag: this patient package "outsert" provides a brief, concise statement of what the patient is being requested to do, the reason for the request, and a removable sticker (to be placed on the bathroom mirror or elsewhere) that gives our toll-free number along with a summary of details about how to report "*any* new or unusual symptoms" during the next 2 weeks. The other half of the patients (Controls) do not receive any outsert, but are interviewed approximately 2 weeks later by telephone. These Control interviews are computer-directed so that the questions and various response options appearing on the interviewer's video screen are almost completely determined by the patient's prior responses.

The Standardized Interview

If the ultimate goal is to be able to reliably detect the occurrence of postmarketing ADRs, then—as noted by Lasagna (1971) and Wardell et al. (1979)—the first step must be the development of a standardized method of collecting accurate reports of new or unusual "adverse clinical events" (ACEs) during or following a drug's use. An ACE

---

[1] This study is supported in part by USPHS Grant MH-39661 from the National Institute of Mental Health.

[2] Department of Psychiatry and Behavioral Sciences, The University of Texas Medical Branch, Galveston, TX 77550.

[3] Department of Internal Medicine, The University of Texas Medical Branch, Galveston, TX 77550.

may or may not turn out to be an ADR, depending upon additional information that permits inferences about potential causality; but all ADRs must first be valid ACEs.

When a call from an Experimental patient is received, or when we initiate a call to a Control patient, the ensuing interview tries to obtain complete information about all ACEs being reported. The standardized interview used to identify, describe, and quantify ACEs was developed from modifications of SAFTEE, the National Institute of Mental Health's "Systematic Assessment For Treatment Emergent Events" (Levine & Schooler, 1984). The modified telephone interview has four sections: a general inquiry for spontaneously reported ACEs, a systematic ACE inquiry, a post-spontaneous inquiry, and a medication inquiry.

The opening questions center only on spontaneously reported ACEs. With patient-initiated calls from Experimentals, the interviewer records verbatim the symptom(s) that prompted the patient to call. In staff-initiated Control interviews, the key initial question is simply "Have you noticed any new or unusual symptoms during the past 10 days or so?" For each symptom spontaneously mentioned by the patient, the interviewer records details about its onset, duration, frequency, pattern, and severity.

The general inquiry is followed by a systematic inquiry covering each of the specific organ systems or areas relevant to the two target drug classes. Special emphasis is again placed on eliciting only recent unusual changes: e.g., "Have you noticed any changes in your skin during the past 10 days or so?"; "Have you had any unusual problems with your mouth or tongue?" When a "No" response is elicited to any of these system-review questions, the interviewer does not pursue the area any further for fear of encouraging over-reporting through suggestion (i.e., unlike the original SAFTEE interview, we avoid asking leading questions like "Has your mouth been dry?" or "Have you had any rashes?").

At the end of the systematic inquiry the patient is offered one more opportunity to recall any other unusual changes. The final part of the interview then determines when the patient most recently started the target medicine; whether it is still being taken and with any significant dosage changes; whether and when it had been used previously; what other medicines were being taken regularly; and—if one or more ACEs were reported—whether starting the drug unequivocally preceded each ACE onset, and whether the patient attributed the new symptoms to any of the medications.

Data Analyses

The data presented here are based on 231 staff-initiated, computer-directed interviews with Control patients who a) were over 18 years old, b) did not receive an outsert or any other indication at the pharmacy of study participation, and c) when interviewed approximately 2 weeks later, reported having started the target drug and were not taking any drug from the other target class. The sample had a mean age of 45.0 years (s.d. = 15.6); 81.8% were female; 53.6% were Caucasian (38.9% were Black, 6.9% were Hispanic).

As noted previously, all ADRs must first be valid ACEs. A valid ACE is defined as any untoward reaction that began only after the patient started the target drug and within the specific allowable 14-day reporting period. A patient could have reported one or more valid ACEs during the general inquiry, the systematic inquiry, or the post-spontaneous inquiry; these ACEs are referred to as Spontaneous, Systematic, and Post-Spontaneous ACEs, respectively. In addition, because there is general agreement on a core set of expected side effects for the antibiotics and tricyclic antidepressants constituting our target drugs, we can single out those valid ACEs matching one of our assumed "true adverse drug reactions." Table 1 lists the symptoms defined as antibiotic and tricyclic ADRs prior to the study and reported by our Control patients in the three interview sections. Any one of the nine antibiotic ADRs reported by an antibiotic patient was recorded as an ACE+; similarly, any of the 12 tricyclic ADRs reported by a tricyclic patient was also recorded as ACE+. Conversely, any of the antibiotic ADRs reported by a tricyclic patient, or any of the tricyclic ADRs reported

TABLE 1

Pre-defined Adverse Drug Reactions[a]

Antibiotics[b]	Tricyclic Antidepressants[b]
Sore mouth	Dry mouth
Sore tongue	Daytime drowsiness or excessive sleeping
Itching	Light-headedness or dizziness
Rash	Fainting
Hives	Rapid or irregular heartbeat
Stomach ache or pain	Blurred vision
Nausea or vomiting	Headache or head pain
Cramps	Shakiness or tremor
Diarrhea	Constipation
	Delay in starting urination
	Decreased force of urine stream
	Numbness or tingling (extremity)

[a] These common adverse drug reactions were selected from Long (1977), USP (1983), and the approved labeling.

[b] Antibiotics: ampicillin, doxycycline, penicillin, tetracycline; tricyclics: amitriptyline, doxepin, imipramine.

by an antibiotic patient, are shown as ACE−'s.

Obviously, these pre-defined ADRs are not unique to the two target drug classes. However, since their ADR profiles have little overlap, and since patients could not be taking drugs from both classes concomitantly, in effect we have reduced the likelihood that our tricyclic patients would experience an antibiotic ADR or our antibiotic patients would experience a tricyclic ADR. It follows then that a) most of the true ADRs will be a subset of reported ACE+'s; b) true ADRs should be found where there are a minimum of ACE−'s, and c) therefore we can create an indicator of ADR sensitivity by comparing the presence of ACE+'s relative to ACE−'s within any defined group of patients:

$$\text{ADR Index} = \frac{(\text{ACE}+) - (\text{ACE}-)}{(\text{ACE}+) + (\text{ACE}-)}$$

This index can range from 1.00 (reflecting maximum sensitivity of a system in detecting the pre-defined ADRs) through 0.00 to −1.00 (indicating the extent to which ACE−'s are obscuring ADR detection).

In order to be able to conclude with a high level of confidence that a particular ACE was caused by a particular drug and is therefore a true ADR, it is first necessary to rule out attribution of the ACE to any one of the alternative causes listed in Table 2. Note that since the only condition under which no ACE−'s would be expected is when all six competing categories of potential causes can be ruled out (e.g., via statistical adjustment in a randomized controlled study), the primary validity tests are limited to whether a mean ADR Index is significantly positive or whether one mean is significantly larger (i.e., more sensitive) than another.

Results

Table 3 gives the frequency and rate per hundred of the 151 patients who had one or more valid ACEs. Each patient was classified as having either no valid ACEs or at least one valid ACE. Within each drug class ADR incidence estimates are first based upon ACEs reported anywhere in the interview, and are then shown cumulatively beginning with spontaneously reported ACE+'s during the general inquiry, and proceeding through the systematically elicited ACE+'s to the post-spontaneously reported ACE+'s.

Looking at the total group we see that almost two-thirds (65.4%) of all patients at some point in the interview reported at least one new or unusual symptom that appeared within 2 weeks after starting their target medication. When we limit the analysis to only ACE+'s (representing matches with a true ADR), we find that 30 to 40% of the patients are reporting symptoms that could indeed be true ADRs. Table 3 then shows in which sec-

TABLE 2

Competing Hypotheses to Account for an Adverse Clinical Event (ACE)

1. Natural course of the primary illness for which the target drug was prescribed.
2. Natural complications of the primary illness.
3. Onset of a new illness.
4. Independent environmental factors capable of producing the ACE.
5. Placebo effects associated with starting the target drug.
6. Other medications, foods, or substances taken concomitantly with the target drug.

TABLE 3

Frequency of Patients With One or More Valid ACEs

	Antibiotics		Tricyclics		Total	
	N	Rate*	N	Rate*	N	Rate*
Total Interviews	132		99		231	
Any ACE	89	67.4	62	62.6	151	65.4
Any ACE+	43	32.6	39	39.4	82	35.5
Spontaneous ACE+	23	17.4	11	11.1	34	14.7
Systematic ACE+	19	14.4	25	25.3	44	19.0
(cumulative)	42	31.8	36	36.4	78	33.8
Post-Spontaneous ACE+	1	0.8	3	3.0	4	1.7
(cumulative)	43	32.6	39	39.4	82	35.5

*Per 100 patients

tions of the interview these ACE+'s were elicited.

Spontaneous ACE+s reported during the general inquiry yielded only about a 15% incidence overall. However, when ACE+'s subsequently elicited during the systematic inquiry are added to the incidence rates obtained from the general inquiry alone, the overall rate is markedly increased: almost doubled for the antibiotics, and tripled for the tricyclics.

The final post-spontaneous inquiry augments the estimated incidence rates only slightly. Fewer than 2% of the total sample reported an ACE+ here when they had not already done so in either the general or systematic inquiry.

Thus, depending upon whether you focus on all ACEs, or only upon ACE+'s, and depending upon whether you base your estimates on the total interview or just the initial general inquiry, ADR incidences for these target drugs could range from a high of 67% to a low of less than 15%. To determine whether ACE+'s reported anywhere in the interview are equally valid, it is necessary to examine how ACE−'s are being reported along with ACE+'s. Table 4 presents these data for each of the three interview sections. During the general inquiry there were more patients in both drug classes with at least one spontaneous ACE+ than there were patients with one or more spontaneous ACE−'s. Although there were disproportionately more ACE− patients in the antibiotic group, the ADR Index means of .19 and .38 (not significantly different) indicate that both antibiotic and tricyclic groups were accurately discriminating true ADRs: the pooled mean ADR Index of .25 is significantly different from zero at the .03 level.

When we turn to the systematic inquiry, however, something is strikingly awry. The mean ADR Index for the total group is .00, stemming from very different results in the antibiotic and tricyclic samples. While tricyclic patients continued to discriminate as well as previously, an extraordinarily large number (32) of the antibiotic patients who had not spontaneously reported an ACE+ are now reporting ACE−'s, overwhelming the 19 patients now reporting one or more ACE+'s. The mean ADR Index for the antibiotics is negative and significantly different from the mean ADR Index of .42 for the tricyclics. Obviously, many of the pre-defined ADRs from the tricyclic target drug profile were being elicited from antibiotic patients throughout the systematic inquiry, even when they were reporting few new true antibiotic ADRs. Since there were three more pre-defined tricyclic ADRs than antibiotic ADRs, one has to consider the possibility that

TABLE 4

ADR Index for Different Interview Sections

	Antibiotics	Tricyclics	Total
Spontaneous ACEs			
Patients with at least 1 ACE+ or 1 ACE−	30	16	46
At least 1 ACE+	23	11	34
At least 1 ACE−	16	5	21
Mean ADR Index*	.19	.38	.25
t (df = 44)		<1 (p = N.S.)	
Systematic ACEs			
At least 1 ACE+ or 1 ACE−	40	30	70
At least 1 ACE+	19	25	44
At least 1 ACE−	32	12	44
Mean ADR Index	−.31	.42	.00
t (df = 68)		3.75 (p < .001)	
Post-Spontaneous ACEs			
At least 1 ACE+ or 1 ACE−	2	4	6
At least 1 ACE+	1	3	4
At least 1 ACE−	1	2	3
Mean ADR Index	.00	.25	.17
t (df = 4)		<1 (p = N.S.)	

*For each patient who had at least one ACE+ or one ACE−, an individual ADR Index is calculated based upon the total number of ACE+s and ACE−s reported by that patient. A different ADR Index, calculated by subtracting the frequency of patients with at least one ACE− from the frequency of patients with at least one ACE+ and dividing by the combined frequencies, yields almost identical results.
N.S. — Not Significant

antibiotic patients had more opportunity by chance to report an ACE that matched one of the tricyclic ADRs. However, that same opportunity was present for spontaneous ACEs during the general inquiry.

Table 4 further shows that during the final post-spontaneous inquiry only 6 patients mentioned an ACE+ or an ACE− for the first time. Despite the extremely small numbers, the data yield a tricyclic positive ADR Index consistent with accurate ADR detection while the two antibiotic patients, after having completed the systematic inquiry, yield an ADR Index of zero.

Discussion

We are not aware of any other postmarketing surveillance study that has so closely and systematically examined the incidence of *all* new symptoms during a 10- to 14-day period following the start of a drug. One of the clearest findings emerging from this study is that almost two-thirds of our patients did report a new ACE, and even when limiting the analysis to known ADRs, we find between 30% and 40% of our patients reported at least one "true" ADR (ACE+) at some point in the interview. The fundamental issue here centers on two interrelated questions: whether ACEs reported anywhere in the interview are equally likely to be ADRs, and whether the true ADR incidence for these target drugs is therefore really as high as is estimated by the total interview.

Our results clearly indicate that ADRs can be accurately detected for antibiotics and tricyclics using spontaneously reported ACEs, with incidence estimates of 17.4% and 11.1%, respectively. ACEs elicited by systematic inquiry increase the incidence estimates substantially, but totally destroy the discrimination of true antibiotic ADRs. On the other hand, tricyclic ADRs were effectively detected in all segments of the interview, and while the total estimate of 39.4% is within the range estimated by Klein et al. (1980), these authors qualify their figures by noting "that the data on (antidepressant) side effects are often confusing and show great variation from study to study."

Although it can be argued that only a comprehensive interview can detect possible ADRs, a systematic review of organ systems may be highly prone to eliciting ACEs consisting of more noise than signal. Huskisson & Wojtulewski (1974) have shown that inflated incidence estimates can occur and true side effects can be obscured when specific checklist questions are asked. But even without a checklist litany, a likely mechanism by which spurious ACEs may get unwittingly introduced is found in the realization that simply asking repeated "non-leading" questions focusing on possible side effects can exert subtle demands to reply positively—not so much by remembering distinctive symptoms that the patient forgot to report spontaneously, but by calling up perceptions associated with the illness or other drug-irrelevant causes. In the present study, out of 21 antibiotic patients reporting "decreased appetite," 19 were elicited during the systematic inquiry!

While our results do not unequivocally imply that incidence estimates based upon a systematic inquiry will necessarily overestimate the true incidence, the finding that inclusion of these ACEs drastically impaired the accurate detection of true antibiotic ADRs should dictate extreme caution for the investigator who is attempting either to detect new ADRs or to estimate true ADR incidences. Spontaneously reported ACEs appear to be the most reliable source for uncovering ADRs, although the actual population incidences may sometimes thereby be underestimated.

References

Huskisson, E.C., and Wojtulewski, J.A. Measurement of side effects of drugs. *Br. Med. J.*, 2:698–699, 1974.

Klein, D.F., Gittelman, R., Quitkin, F., and Rifkin, A. (eds.). *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*. Baltimore, Md.: Williams & Wilkins, 1980.

Lasagna, L. Decision processes in establishing the efficacy and safety of psychotropic agents. In: Levine, J., Schiele, B.C., and Bouthilet, L. (eds.), *Principles and Problems in Establishing the Efficacy of Psychotropic Agents*. Washington, D.C.: U.S. Government Printing Office, 1971, pp. 29–50.

Levine, J., and Schooler, N. SAFTEE (Systematic Assessment for Treatment Emergent Events): A new technique for detecting side effects in clinical trials. *Clin. Neuropharmacol.*, 7(Suppl.):856–857, 1984.

Long, J.W. *The Essential Guide to Prescription Drugs.* New York: Harper & Row, 1977.

Maclay, W.P., Cronder, D., Spiro, S., and Turner, P. Postmarketing surveillance: Practical experience with ketotifen. *Br. Med. J.*, 288:911–914, 1984.

Mellinger, G.D. Community survey methods for postmarketing drug monitoring. Presented at annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 1984.

Rauch, E.F. Data entry experience with the Flexeril surveillance program. *Drug. Inform. J.*, July-Sept.:75–83, 1979.

USP. USPDI: II. Advice for the patient. Rockville, Md.: U.S. Pharmacopeial Convention, 1983.

Wardell, W.M., Tsianco, M.C., Anavekar, S.N., and Davis, H.T. Postmarketing surveillance of new drugs: I. Review of objectives and methodology. *J. Clin. Pharm.*, 19:85, 1979.

Estazolam in the Treatment of Insomnia

Roberto A. Dominguez, M.D.,[1] Burton J. Goldstein, M.D.,[1] Alan F. Jacobson, Ph.D.,[1] and Richard M. Steinbook, M.D.[1]

In many cases of insomnia no overt medical, pharmacologic, or psychiatric cause can be found to explain this symptom. A poor sleep pattern often interferes with daytime activities. When non-pharmacologic treatments have been ineffective or insufficient, the judicious intermittent use of hypnotics is indicated. Hypnotics are most helpful when the disturbed sleep pattern is transient, as in acute situational reactions, hospitalization, jet lag, or after changes in work schedule. Because of their higher therapeutic index, lesser potential for abuse, and superior effectiveness, the benzodiazepines have replaced the barbiturates as the modern hypnotics. Three are currently marketed in the United States, and they differ in their pharmacokinetic profile and metabolism.

Estazolam is the generic name of a new triazolobenzodiazepine marketed in Japan since 1975 and presently under development as a hypnotic in the United States (*see* Figure). After single 2.0 mg oral doses, estazolam appears in the plasma within 30 minutes, and its mean peak plasma level occurs after 2.6 hours. Its mean elimination half-life is about 15 hours (Allen et al., 1983). It produces no long-acting metabolites or hepatic microsomal enzyme induction. After multiple doses, its accumulation is complete within 3 days. Placebo-controlled polysomnographic studies have demonstrated the hypnotic efficacy of estazolam in doses of 2 mg (Roehrs et al., 1983). Other clinical studies have confirmed its short-term efficacy in various doses against placebo (Walsh et al., 1984). This trial had as its objective the systematic assessment of estazolam's hypnotic efficacy and side-effect profile in comparison to flurazepam (Dalmane®) and placebo.

This was a double-blind, randomized study, using balanced parallel placebo and active control groups. Patients were assigned to receive either estazolam 2.0 mg, flurazepam 30 mg, or placebo and instructed to take the medication 30 minutes prior to bedtime for 7 consecutive nights. The trial was conducted in outpatient symptomatic volunteers (Brauzer & Goldstein, 1973). The demographics and presenting complaints of symptomatic volunteers are similar to those patients who are prescribed most hypnotics by their family physician. Subjects had to be in good health, had to be free from emotional or substance abuse disorders, and had to abstain from sedatives for at least 2 weeks. The inclusive age range was 21 to 65 years.

All patients suffered from at least a 3-month history of subjective complaints of insomnia. Those eligible for the study reported a history of daytime distress associated with insomnia plus an estimated total sleep time of 6 hours or less. Additionally, all patients complained of at least one of the following symptoms: a) difficulty in falling asleep of 60 minutes or more; or b) at least three nocturnal awakenings, or at least 1 hour of wakefulness during the night. A detailed written in-

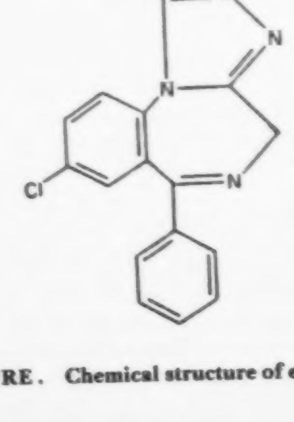


FIGURE. Chemical structure of estazolam.

---

[1] Department of Psychiatry, School of Medicine, University of Miami, Miami, FL 33136.

TABLE 1

Global Evaluation of Efficacy Results

	Treatment Comparison *P*-values		
	E vs. P	F vs. P	F vs. E
Sleep latency	0.008(E)[a]	0.006(F)[a]	0.966(NS)
Sleep duration	<0.001(E)[b]	<0.001(F)[b]	0.930(NS)
Nocturnal awakenings	<0.001(E)[b]	<0.001(F)[b]	0.425(NS)
Depth of sleep	<0.001(E)[b]	<0.001(F)[b]	0.587(NS)
Quality of sleep	<0.001(E)[b]	0.083(F)[c]	0.004(E)[a]
Overall improvement	<0.001(E)[b]	<0.001(F)[b]	0.289(NS)

[a, b, and c] indicate a significant difference at the 0.10, 0.01, 0.001 levels, respectively. The significant better treatment is indicated in parentheses.

Abbreviations: E = Estazolam, F = Flurazepam, P = placebo

formed consent was signed by each patient during the screening interview. Pre-study evaluations for eligibility were performed within 4 days prior to drug administration. Medications that could influence sleep were prohibited. Alcohol, caffeinated beverages, and napping were discouraged. Physical examinations and laboratory tests were performed at the screening visit and within 3 days of the last study dose. Also a comprehensive drug screen was obtained at baseline. Two questionnaires were completed by each patient each morning of the study, beginning on the morning after the first dose. During the final visit the investigator reviewed the study questionnaires with each patient and a global evaluation was made of efficacy and side effects. Drug compliance was confirmed by history, completed questionnaires, and a pill count during the final visit.

Seventy-four patients were screened and started the double-blind study. Four did not return for the final visit. Another 5 patients (2 on estazolam, 1 on flurazepam, and 2 on placebo) had a positive urine drug screen at baseline and their efficacy results were excluded from the analysis. Thus, data from 65 patients (20 on estazolam, 24 on flurazepam, 21 on placebo) were used for the efficacy analysis. Many patients deviated from the instructions given them relating to bedtime habits and ingestion of caffeinated and alcoholic beverages. Approximately 60% of the patients did not take their medication 30 minutes prior to bedtime or deviated from their stated usual bedtime by 1 hour at least one night during the study. Additionally some patients took caffeinated beverages (51%), or alcohol (54%), or napped (61%) at least once during the study. Data from these patients were included in the efficacy analysis on the basis that they closely resemble the general hypnotic-taking population, and the occurrence of these deviations was balanced among treatment groups. Statistical analysis showed the three treatments groups to be comparable with respect to all major demographic variables. All groups were also comparable at baseline regarding estimated sleep variables.

Global evaluations completed by the investigators demonstrated that both active treatments were significantly superior to placebo in all measurements used to assess quantity of sleep ($p<.01$). There were no significant differences between the active treatment groups (Table 1). A global rating of "quality of sleep" reflected how rested and refreshed patients reported they felt upon arising. Estazolam proved superior to placebo ($p<.001$) but improvement in the flurazepam group failed to reach significance ($p=.083$). In this measure estazolam was preferred over flurazepam ($p=.004$).

Results from the patient's daily sleep questionnaires paralleled those of the global assessments. Collective mean scores from the 7 treatment nights showed that both estazolam and flurazepam significantly reduced the number of nocturnal awakenings ($p<.01$), improved the total length of sleep, plus the depth and quality of sleep (all p's$<.001$). There were no significant differences among the active treatments. Patients reported that their length of time to fall asleep did not improve as much as other measures. Overall improvement in estimated sleep latency only showed a trend in favor of estazolam

TABLE 2

Global Evaluations of All Side Effects

	Estazolam (E) (*N* = 20)	Flurazepam (F) (*N* = 24)	Placebo (P) (*N* = 21)
Mean	1.6[a]	2.0	1.3
STD	0.8	0.8	0.6

Summary of statistical comparisons:
E vs. F = NS
E vs. P = NS
F vs. P = $p<.01$
1 = None, 2 = Mild, 3 = Moderate, 4 = Severe

TABLE 3

Total Number of Treatment-Emergent Symptoms (TES) Reported

	Estazolam	Flurazepam	Placebo
Residual daytime effects (% of total TES reported) (drowsy, fatigued, lethargic, drugged, exhausted, sleepy, decreased concentration, etc.)	15(71%)	30(73%)	0
Stomach discomfort/nausea	2	2	2
Headaches	1	1	1
Bitter taste	0	3	0
Irritability	0	2	0
Others	3	3	2
Total	21	41	5

($p = .088$) and flurazepam ($p = .093$) over placebo.

More patients reported adverse effects with flurazepam (83%) than with estazolam (50%). Residual daytime drowsiness and fatigue accounted for approximately 70% of all side effects reported for both active treatment groups. A significantly greater ratio of patients on estazolam ($p<.005$) and flurazepam ($p<.0001$) reported side effects than on placebo. Also, a significantly greater ratio of patients reported side effects on flurazepam than on estazolam ($p = .017$). Perhaps the most important measurement of side effects was a global assessment by the investigators of their severity (Table 2). There was no statistically significant difference in the global evaluations of side effects between estazolam and placebo treated patients, or between both active treatments. However, there was a significant difference ($p = .0018$) between flurazepam- and placebo-treated patients. Comparison of baseline and final vital signs and laboratory studies did not show any clinical or statistical significance.

As discussed, patients on both active treatment groups reported that their length of time to fall asleep did not improve as much as other measures. In interpreting this finding, it is important to note that most patients enrolled in this study (73%) complained of sleep maintenance problems, rather than a sleep latency disturbance. Therefore, given this population, it is not surprising that neither estazolam nor flurazepam treatment resulted in a statistical improvement in sleep latency. This interpretation is consistent with that of another published report (Roehrs et al., 1983) which concluded that the lack of statistical improvement of complaints of sleep latency with estazolam when compared to placebo was not surprising in a patient population in which 47% did not have an objective disturbance in sleep latency.

Not only does this study strongly confirm the hypnotic efficacy of estazolam, but it also shows that the new drug is better tolerated than flurazepam. In the literature, residual daytime effects have been more frequently reported with flurazepam than with other intermediate half-life benzodiazepines (Bliwise et al., 1984; Fillingim, 1982; Wesnes & Warburton, 1984). In the assessment used to measure how refreshed and rested each subject felt upon arising, estazolam was favored over flurazepam. Treatment-related side effects were less frequent with estazolam (Table 3). Also, the overall severity of these reactions favored the new drug. Additionally, significantly fewer patients complained of any side effects with estazolam than with flurazepam.

References

Allen, M.D., Greenblatt, D.J., and Arnold, J.D. Single- and multiple-dose kinetics of estazolam, a triazolobenzodiazepine. *Psychopharmacology,* 66:267–274, 1983.

Bliwise, D., Seidel, W.F., Greenblatt, D.J., et al. Nighttime and daytime efficacy of flurazepam and oxazepam in chronic insomnia. *Am. J. Psychiatry,* 141:191–195, 1984.

Brauzer, B., and Goldstein, B.J. Symptomatic volunteers: Another patient dimension for clinical trials. *J. Clin. Pharmacol.*, 13:89–98, 1973.

Fillingim, J.M. Double-blind evaluation of temazepam, flurazepam, and placebo in geriatric insomniacs. *Clin. Ther.*, 4:369–380, 1982.

Roehrs, T., Zorick, F., Lord, N., et al. Dose-related effects of estazolam on sleep of patients with insomnia. *J. Clin. Psychopharmacol.*, 3:152–156, 1983.

Walsh, J.K., Targum, S.D., Pegram, V., et al. A multicenter clinical investigation of estazolam: Short-term efficacy. *Curr. Ther. Res.*, 36:866–874, 1984.

Wesnes, K., and Warburton, D.M. A comparison of temazepam and flurazepam in terms of sleep quality and residual changes in performance. *Neuropsychobiology,* 11:225–229, 1984.

NCDEU Workshop/Microcomputer Interest Group

CHAIR: Joanne B. Severe, M.S.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Microcomputer Database Management Systems Concepts

David Robert Gastfriend, M.D.[1]

In the years since 1977, when microcomputers first became commercially available, the database management system (DBMS) has proven to be an efficient, cost-effective tool for clinical research. Microcomputer DBMS software programs are widely available commercially, offer a variety of powerful functions, and provide a range of ease of operation to suit any researcher, from the technophobe to the hacker. The selection of a particular DBMS for clinical research depends upon several factors, such as what kind of data will be stored, how much data will be stored, how the data storage will be organized, what kinds of analyses will be performed on the data, and whether more than one user will need to use the database at the same time.

What Is a Database? (Wiederhold, 1981)

At its simplest, a database is *a filing system.* Like a file card box for article references, or a Rolodex device for phone numbers, it is a tool for storing any data worth retrieving later. These examples have limited usefulness, however, because they use a physical structure to organize data.

Consider the situation in which one has each patient's name, address, and identification number listed vertically in that order on a Rolodex card, and the Rolodex deck is organized in alphabetical order by patient's last name. If it also became necessary to be able to look up patients just by identification numbers, one solution would be to photocopy each card, cut out the identification number line, paste it in at the top of a new card, then place the cards in the second Rolodex holder in numerical sequence. This example points out the limitations of a system that uses a physical layout to organize data. A computerized database would do this electronically and would allow both types of Rolodex card to be printed once the basic data are entered.

A computerized DBMS stores data in files, or lists, with a minimum of duplication. Each list can be used for a variety of purposes, because the program can reorganize it with relative independence of any physical layout. The *location* of any individual piece of data is indicated internally as a symbolic reference point rather than a physical reference point. This makes it possible a) to rearrange data to create a variety of useful reports with it; b) to perform complex searches called *queries*; and c) to add new types of data elements subsequently within existing records.

---

[1] Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114.

What Is "Data"?

The design of a computerized database begins by *listing what data are needed* for storage and analysis. The current range of microcomputer DBMS software makes it possible to store various kinds of data. Most DBMS programs are adept at managing numbers, formulae, and alphabetical characters, while a few have special qualities that treat words, sentences, paragraphs, and pictures (such as digitized drawings, x-rays, and scans) as discrete data elements.

How Are Data Represented in the Computer?

Data are represented by a set of microscopic switches which can exist in either a high or low voltage state (on or off). If a switch is off, this corresponds to 0; if it is left on, it stands for 1. Each switch is the electronic equivalent of a base two, or binary, digit. In computerese, a *binary digit* is called a *bit*.

Since real data elements are not adequately represented by only a 0 or 1, several bits are needed to represent the whole range of characters in use. There are about 100 distinct keys on the typewriter, including the digits from 0 to 9, all the characters in the alphabet, and punctuation symbols.

How many bits are required in order to represent all of these characters of real data? If we allot two bits per character, this allows us to represent four distinct characters: 0, 1, 2, and 3 (by the binary codes 00, 01, 10, and 11, respectively). Therefore, a set of 7 bits is needed in order to represent 100 distinct characters, and another bit is used as a marker for accuracy—altogether 8 bits. This set of 8 bits is the smallest number of switches that will represent all the decimal system characters, the alphabet, and punctuation symbols. Each *set of 8 bits* is called a *byte*. The coding system for all these characters is standardized throughout all microcomputers, and is called ASCII (pronounced "AS-key," for American Standard Code for Information Interchange).

Calculation of Data Storage Needs for a Study

Just as file cabinets vary in size, number of drawers, capacity, etc., DBMS programs vary in how much data can be stored. It is necessary to understand how data elements are stored and to calculate the total data storage needs a study will require, prospectively. For example, consider the design of a database for a study of the dose response to lithium. In order to represent a single lithium level, a value which can range from 0.0 to 9.9, the computer will need to allocate one byte for each digit, or two bytes per level to be stored. (The decimal point will be handled differently than a digit and need not be counted here.)

Each patient gets varying doses of lithium, and each week, for 10 weeks, each patient has lithium levels drawn and several rating scales recorded. The file containing all the study data will contain a record for each patient, and at the conclusion of the study each record will contain 10 different lithium levels, 1 for each week of the study. Since each lithium level will take up 2 bytes, this data field alone will use 20 bytes per patient. If 100 patients will participate in the study, we will be storing 2,000 bytes, or 2 kilobytes (K) of data just for this one variable. The variable, lithium dose, ranges from 0 to approximately 3,000 mg/day, for a total of 4 bytes (or characters) times 10 recordings times 100 patients. For this variable, then, we'll be storing another 4K of data. If we add a few scales on each patient, we must be careful in planning ahead of time how much data we will want to be storing. Here is a sample calculation:

$$5\ \frac{\text{scales}}{\text{subject}} \times 15\ \frac{\text{questions}}{\text{scale}} \times 2\ \frac{\text{characters}}{\text{question}} \times 10\ \text{weeks} \times 100\ \frac{\text{subjects}}{\text{week}} = 150{,}000\ \text{characters} = 150\text{K bytes}$$

Steps in Using Database Management

All database management systems operate using the same basic steps of 1) data and file definition, 2) data entry, and 3) data retrieval (Figure 1). Once one understands these in operation on one DBMS program, it becomes relatively easy to learn another program.

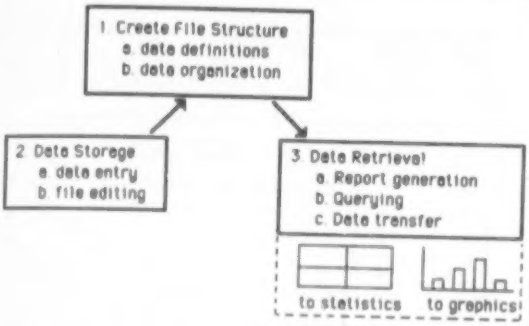


FIGURE 1. Steps in using database management.

The first and most important step in using a DBMS package is data and file definition. This consists of analyzing what data a study will gather, and defining and restricting which data items will be stored in order to construct what is known as a *data dictionary*. The data dictionary is a list of the data elements that will be stored, the *form* of data elements (e.g., "00/00/00" for dates), as well as the *content* of each element (so that a date of 11/35/85 should be excluded if the data dictionary is complete in its description of form and content of a date element).

Once the data dictionary is complete, data items can be organized into a database structure. To create a Rolodex file like the one above, each item must be stored in a set place whose location has to be defined (analogous to row and column of the Rolodex card). Every program has limits as to how many different data elements can be stored in a patient's record, how many records in a file. Therefore, in addition to the initial calculation of total data storage needs (shown above), it is necessary to map out whether one file will be sufficient to hold all data elements, or whether it will better to break up the data into several files—demographic data, medication data, lab data, scales, etc. The limitations of different DBMS programs in accommodating different file structures will be discussed below.

With a structure established for the database and definitions set for acceptable data elements, the process of data entry can begin. This is one area in which the computer's abilities enhance studies by promoting the capture of accurate data. As the user enters each value, the microprocessor can compare it with its respective data definition in form and content. In the event of an inconsistency, the computer prompts the user to correct the mistake. Only then will it store the new value in the patient's record.

An important feature of many DBMS programs is the ability to accept and store data from other programs (e.g., computer-administered psychometric tests), biofeedback instruments, and other computers. To do this, a DBMS program needs a function which accepts a stream of data in the same format as the output of the initial program. The standardized ASCII code is the most common format for sending a stream of data from one computer to another or one program to another within the same computer.

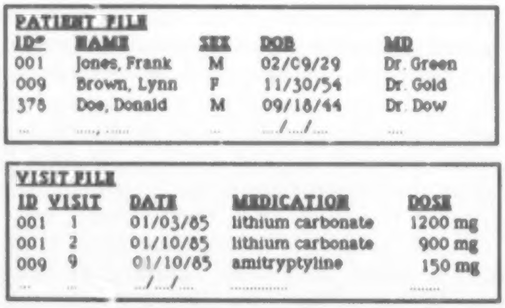
Data retrieval is the *raison d'etre* for database management systems. At its simplest, retrieval can be used to print a copy of each patient's record. Since DBMSs can reorganize data with relative independence from any physical layout, it is possible to do a more complex and very useful function called *searching*. Searching can be used to gather just the improvement scores from all patients' records, or to compile the data into a particular format for statistical analysis. Once initial data have been entered, searching can be used to review an entire file of records for missing data, prompting the user to complete the data entry process, and to allow editing of stored data which, although consistent in form and content, are still incorrect.

The ability to electronically rearrange or *sort* the order of data can also save considerable labor and time. In the example study 100 subjects are treated with lithium for 10 weeks and data are gathered from the history, mental status, lab tests, vital signs, and rating scales. Each data element is coded numerically and entered each week as it is obtained. At the conclusion of the trial we rearrange the order of the data set from the simple chronologic form in which it was gathered to the order needed for the analysis. In this final form, the patients are listed according to who entered the study first, then second, etc. After each subject is listed, then their baseline data is listed, then week 1 data, then week 2, etc. When subject 1's data are fully listed, then subject 2's follows. Sorting can be performed in different ways upon any data element in a record, such as chronologically by age of subject or date of visit, alphabetically by name of subject or clinician, or ordinally by lowest dose to highest.

Querying is a retrieval function which produces a more specialized search of the data, linking values from different data elements. An example of a query would be: "list all subjects with lithium levels greater than 1.2 who had global improvement scores of>3 for 2 or more consecutive weeks." Another important function of retrieval is the ability to extract data from the database to perform statistics or to graph. Few DBMSs are programmed to perform a full range of statistical tests, so additional software is usually required to do this (Crouch, 1985). However, if a·database can report its retrieved data in the same data transfer format as that accepted by the statistical package, time can be greatly reduced and errors can be eliminated by making an electronic transfer of the data.

Forms of File Organization (King et al., 1983)

The simplest microcomputer programs for constructing a database are called *file management systems.* These have a structure like a vertical list, making these programs easiest to learn for the new user. The variables of the list can be sorted in different ways to create different reports, but each list is separate. It is often useful or necessary (because of the finite capacities of a DBMS program) to use more than one file to store different types of data—demographic data might go into the "Patient" file, while treatment data might go into a "Visits" file. Figure 2 depicts a file management system with two different files (here in the format of tables), with no relation between the data in the patient file and the visit file. Each of these is just a two-dimensional file structure. Being able to store these data but not to be able to keep the two sets of files linked, is a ridiculous limitation. A better file organization is needed, necessitating a more flexible program that allows us to symbolically relate each patient in the first list to their respective visits and medications in the second list, and so on. This type of program is called a *relational database management system* (Figure 3).



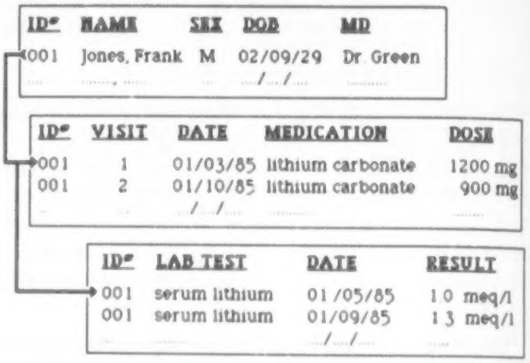
PATIENT FILE

ID#	NAME	SEX	DOB	MD
001	Jones, Frank	M	02/09/29	Dr. Green
009	Brown, Lynn	F	11/30/54	Dr. Gold
378	Doe, Donald	M	09/18/44	Dr. Dow
...	....., ...	...	.../.../...	....

VISIT FILE

ID	VISIT	DATE	MEDICATION	DOSE
001	1	01/03/85	lithium carbonate	1200 mg
001	2	01/10/85	lithium carbonate	900 mg
009	9	01/10/85	amitryptyline	150 mg
...	...	.../.../...	....	....

FIGURE 2. A file management system. Data from one file cannot be linked with that in another.



ID#	NAME	SEX	DOB	MD
001	Jones, Frank	M	02/09/29	Dr. Green
....	....., ...	...	.../.../...	....

ID#	VISIT	DATE	MEDICATION	DOSE
001	1	01/03/85	lithium carbonate	1200 mg
001	2	01/10/85	lithium carbonate	900 mg
...	...	.../.../...	....	....

ID#	LAB TEST	DATE	RESULT
001	serum lithium	01/05/85	1.0 meq/l
001	serum lithium	01/09/85	1.3 meq/l
...	....	.../.../...	.....

FIGURE 3. Relational database. The arrows indicate that relations can be drawn between data fields in different files, creating a three-dimensional file structure.

The relational database program is able to create relationships between data fields in different files, either right from the beginning or long after the initial format was laid out and even after much data has been stored in the system. A relational database management system allows users to create relations between data organized in different lists, e.g., as represented by the arrows. So while a file management system is like a two-dimensional list, a relational database is three-dimensional or more.

There is another form of organization that is multi-dimensional, and allows different files to relate to one another: the *hierarchical DBMS.* In hierarchical files, data elements are organized in several levels, structured one below another, like an inverted tree (Figure 4). This structure is set out from the beginning, however, and can't be changed once data are entered—the structure is fixed. This might seem a limitation, but is really an advantage for clinical researchers. The database for any given study should usually be laid out from the outset anyway, and a hierachical structure is easier to set up and to comprehend later. It also makes the data easier to search later. Finally, for clinical data, it is usually important that *one particular relationship be fixed: time.* Since we treat our patients over time, and they respond over time, any particular lab test or therapeutic intervention should always be forced to relate to time first, and to anything else second. DBMSs that fix certain relationships are called *hierarchical DBMS*s. When a hierarchical DBMS is designed to *fix the relationship of all items with respect to time,* it is called a *time-oriented DBMS*. A time-oriented DBMS is essential for building a clinical database.

Actual Use of Database Management Systems on Microcomputers

Some DBMSs let you select a task from a list of the possible alternatives, or *menu*; others require one to remember or look up a set of command codes. For the nonexpert user, *menu-driven* programs are much easier, because there is no need to memorize the options and less likelihood of forgetting how the program operates. The most popular DBMS in the world, dBase II, is only command-driven, but most of the newer programs offer a choice. DBase III, MetaFile, R:base 5000, and File Manager, allow the user to work from either menus or commands (Gresehover, 1984).

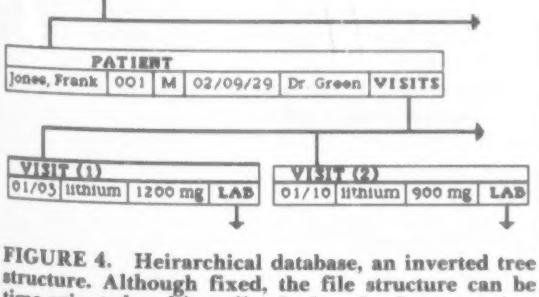


FIGURE 4. Heirarchical database, an inverted tree structure. Although fixed, the file structure can be time-oriented and is well suited to the data organization of clinical trials.

Some DBMSs have extensive statistical and graphics functions built in. These are called integrated DBMSs and their retrieval facilities include the transfer of data from the database subprogram to the statistical or graphics subprogram. Integrated DBMSs are time-saving because one doesn't have to rekey data from the database program to the statistical or graphics package. On the other hand, in the commercial software market, many integrated programs operate like a Swiss army knife—jack of all trades, master of none. While Lotus 1-2-3 might not meet the database needs of a research study, others such as Medlog (Layard, 1983) and Clinical Research System II (Crouch, 1985) are specifically designed for clinical trials.

In trials where more than one user will need to access records at one time, a multiuser DBMS is required. There are a growing number of general purpose microcomputer multi-user DBMSs on the market as well as some specifically developed for managing medical information, such as COSTAR (Barnett, 1984) and VA File Manager (Houser, 1984). These programs include additional features to protect information in the database from the vicissitudes of having multiple and simultaneous users. Two of these features are file lockout and security identification codes.

The following example demonstrates the need for *file lockout*: If a patient's chart folder is removed from the file drawer and then a lab slip is absent-mindedly dropped into the proper location, the slip falls to the bottom of the file drawer, forever misplaced. This mechanism of data loss can be prevented in a computerized database with file lockout. If a research assistant accesses a subject's file to enter a serum level while the researcher tries to update his assessment of the same subject, the system first updates the serum level, momentarily "locking" the file and holding the investigator's assessment entry. Once the level has been electronically updated, the investigator's entry is then recorded.

Security identification codes can be assigned for different levels of users, in the form of passwords. A secretary's password may gain access to demographic and schedule data (but not clinical), a clinician's may gain access to his own patients' clinical data (but hides placebo/drug status fields), and the principal investigator's password yields access to the aggregate.

Finally, the Veterans Administration File Manager program is worthy of special mention because it is a multi-user, hierarchical database (time oriented) and is designed to be a "programmerless system," allowing the user to set up his own complex flexible clinical database without extensive technical knowledge or time investment (Gastfriend et al., 1984).

Summary

With their increasing power and decreasing costs, microcomputers are proving a valuable tool for clinical research data management. A wide variety of database management systems is commercially available, offering differing levels of ease of use and capabilities (Bond, 1984). In selecting the best software program, the researcher must consider what types of data elements will be stored and must make an approximate calculation of total data storage needs. The three basic forms of file organization are: 1) file management systems; 2) relational DBMSs; and 3) hierarchical DBMSs. File management systems are easiest to learn but are too limited for most studies. Relational DBMSs allow free rearrangement of complex relations between different files, but these relations can become very abstract and learning to use them can be as difficult as learning a new programming language. Hierarchical DBMSs are more powerful than file management systems and are more understandable than relational DBMSs. For novice or casual users, menu-driven programs are more easily learned and used, but those accessing computerized files on a daily basis will appreciate newer programs that allow switching from menu mode to command mode of operation. Finally, options such as data transfer into the database or out of it, integration of statistical or graphics functions designed for clinical research, and multi-user operation are becoming available in microcomputer DMBS software and enhanced productivity as well as accuracy.

References

Barnett, G.O. The application of computer-based medical record systems in ambulatory practice. *N. Engl. J. Med.*, 319(25):1643–1650, 1984.

Bond, G. A database catalog. *Byte*, 9(11):227–238, 1984.

Crouch, M. PC clinical testing. *PC Mag.*, 19:263–264, 1985.

Gastfriend, D.R., Bauer, L., Bhatty, A., and Rosenbaum, J.F. Software considerations in the development of an integrated clinical-research database in psychopharmacology. *Comput. Psychiatry/Psychol.*, 6(2):19–22, 1984.

Gresehover, R.S. Metafile: One of the new breed of database management systems. *M.D. Computing*, 1(5):24–41, 1984.

Houser, W.R. End user software engineering: The experience of the Veterans Administration decentralized hospital computer program. *MUG Q.*, 13(3):3–11, 1984.

King, C., Manire, L., and Strong, R.M. Comparing data management systems in clinical research: 1983 survey. In: Dayhoff, R.E. (ed.), Proceedings of the Seventh Annual Symposium on Computer Applications in Medical Care. Silver Spring, Md.: IEEE Computer Society, 1983, pp. 715–719.

Layard, M.W. Medlog: A microcomputer-based clinical data management system. In: Lindberg, D.A.B., Van Brunt, E.E., and Jenkin, M.A. (eds.), AAMSI Congress 83, Proceedings of the Congress on Medical Informatics. Bethesda, Md.: American Association for Medical Systems and Informatics, 1983, pp. 464–468.

Wiederhold, G. *Databases for Health Care*. New York: Springer-Verlag, 1981.

SAFTEE: Data System for Side Effect Assessment Scale

Dean J. Clyde, Ph.D.[1]

The National Institute of Mental Health (NIMH) has developed a method for assessing side effects of drugs. The assessments are recorded on case report forms called Systematic Assessment for Treatment-Emergent Events (SAFTEE) (Levine & Schooler, 1984).

Clyde Computing Service[1] received a grant from the NIMH under the Public Health Service Small Business Innovation Research Program to develop software for handling SAFTEE data on microcomputers. Because of the variable length records resulting from data collection via the SAFTEE form, a specialized data entry system was required.

Most data collection instruments or case report forms used in clinical trials have a fixed number of questions generating the same fixed number of variables for each patient. For this type of data, software for the data entry (and verification) into microcomputers is widely available. The Clyde Statistical Analysis System (Clyde, 1984) for IBM Personal Computers is one available software system. However, SAFTEE forms permit a varying number of questions and answers for each patient. A number of specific adverse health events are printed on the forms and the clinician may also write in additional events that the patient reports. This results in data records of variable lengths.

The SAFTEE system software is written for use on the IBM Personal Computer. The program allows for data entry and data summarization as well as transfer to other software systems or database management packages. Use of other database software is the most efficient way to handle the statistical analysis of these data.

The microcomputer package R:base 5000 (Microrim, 1985) was selected from approximately 75 such available packages because of its power and capacity to accept variable length records. In order to save disk space on the microcomputer, the data generated by SAFTEE are compressed into one bit per data item before being transfered into R:base 5000 (which tries to store data in 32 bits per item).

Investigators who collect SAFTEE data in clinical trials can either obtain the programs from Clyde Computing Service and do their own data entry or make arrangements to send the forms to the Clyde Computing Service for entry and analyses.

References

Clyde, D.J. *Clyde Statistical Analysis System*. Fort Lauderdale, Fla.: Clyde Computing Service, 1984.

Levine, J., and Schooler, N.R. SAFTEE (Systematic Assessment for Treatment Emergent Events): A new technique for detecting side effects in clinical trials. *Clin. Neuropharmacol.*, 7(Suppl.):856–857, 1984.

Microrim, Inc. R:base 5000. Bellevue, Wash.: Microrim, Inc., 1985.

---

[1] Clyde Computing Service, P.O. Box 030398, Fort Lauderdale, FL 33303.

best copy available

Microprocessor-Based Assessment of Attention Deficit Disorders (ADD)

Michael Gordon, Ph.D.[1]

Dissatisfaction with formulating a diagnosis of ADD with hyperactivity (ADD-H) based almost entirely upon clinical judgment or the perception of raters has spawned the development of behavior-based assessment procedures. These efforts typically involve administration of the Continuous Performance Test (Rosvold et al., 1956) or related measures of attention and self-control (Davenport, 1972; Doyle et al., 1976; Hiscock et al., 1979; Margolis, 1972). Although bulky and expensive electromechanical devices had previously been required, researchers are now programming microcomputers to administer these laboratory tasks to children (Conners, 1980; Klee & Garfinkel, 1983).

Use of the microcomputer has certain advantages, including flexibility of administration, the ability to store multiple data points, and, if a microcomputer is already available, cost-effectiveness. This approach, however, does have drawbacks for the researcher and, in particular, the clinician. The size of even portable microcomputers can make testing in multiple sites cumbersome. It is perhaps for this reason that standardization samples for software-driven programs tend to be, at best, limited in number and breadth. The transport of disk drives, monitors, keyboards, and the computer itself from location to location often discourages use of the procedure in other than a single research or clinic setting.

Another potential limitation of microcomputer-based testing stems from concerns surrounding the reliability of administration. Computer monitors vary in the size, shape, intensity, and color of displayed characters. Each brand of computer presents to the child a different keyboard, and accepts different types of peripherals, such as "joysticks," which are often used as manipulanda. Without control over such critical factors as the amount of pressure necessary to actuate a switch, or the accuracy of timed sequences, repeatable administration across multiple microcomputers cannot be assured.

Finally, ADD-H children, despite a reputation for academic underachievement, routinely display a fine facility for disassembling delicate equipment. Unless the examiner is immediately present, the highly impulsive child will inevitably stick a finger in disk drives, unplug cables, adjust monitors, or in some other fashion interrupt standard administration of the task. Efforts to secure the microcomputer are often unsatisfactory because they usually involve additional hardware, cabling, and expense.

An alternative approach to testing attention and self-control has been developed by the author (Gordon & McClure, 1983, 1984). The goal of this project has been to establish a practical, reliable, and well-standardized procedure available to both researchers and clinicians. The Gordon Diagnostic System (GDS) is a microprocessor-based, portable unit which, without an external microcomputer, allows for the administration of multiple tasks. The Delay Task, based upon a DRL operant schedule, requires the child to inhibit responding in order to gain a reward. Specifically, the child is instructed to press a button, wait, and then press the button again. If she or he refrains from responding for at least 6 seconds, a light flashes and a reward counter increments. If the child responds before the interval elapses, then the timer resets and no reward points are recorded. The GDS Delay Task generates three major scores: the number of responses (button presses), the number of correct responses (i.e., Correct), and the Efficiency Ratio, which represents the percentage of correct responses.

The GDS also contains the Vigilance Task, which is a version of the Continuous Performance Test (Rosvold et al., 1956). The child is presented with a series of digits on the front display and is told to press the button every time a "9" appears that had been preceded by a "1." The GDS records the number of correct presses, the number of times the child fails to press the button when the "1/9" combination appears (i.e., errors of omission), and the number of extraneous button presses (i.e., errors of commission). For the testing of younger children, the GDS contains a "1" mode, which requires the subject to press the button every time a "1" appears. The same performance measures are recorded.

---

[1] SUNY-Upstate Medical Center, Syracuse, NY 13210.

Although normative data were gathered using standard settings for task parameters, the design allows the user to select a wide range of parameters. This feature enabled the modification of parameters for the testing of adults as well as very young children.

Because the GDS is controlled by a programmable microprocessor, additional tasks can be explored. One such enhancement being studied is a version of the Vigilance Task which assesses the impact of distraction on a child's ability to sustain attention. This Distractibility Task is identical to the standard Vigilance Task except that random digits flash at random intervals on the outer positions of the LED display. The subject is still required to press the blue button when a "9" comes right after a "1." The only difference is that numbers flash on either side of the center (i.e., relevant) digit. Other enhancements under development are designed to evaluate attention across sensory modalities.

Even though the GDS administers tasks independently of a microcomputer, it can communicate with external hardware via an RS232C communications port. Software is available which allows for the direct transmission of GDS data to a microcomputer where it can be tabulated, graphed, stored, and compared to normative data. Connection of the GDS to a microcomputer enables collection of some ancillary data which cannot be extracted from the stand-alone unit.

The portability and ease-of-operation of the GDS has allowed for large-scale data collection. The standardization sample is composed of 1,100 boys and girls from 3 to 16 years of age (Gordon & Mettelman, 1985). An additional 1,100 hyperactive and nonhyperactive protocols from various subject populations, including the deaf, blind, Spanish-speaking, emotionally disturbed, and learning disabled, have also been gathered.

A series of validational studies has shown that these game-like tasks differentiated accurately between hyperactive and nonhyperactive children from both outpatient and day treatment settings (Gordon, 1979; McClure & Gordon, 1984). In a sample of school-referred children, the GDS distinguished children with ADD from those classified as reading disabled, overanxious, and normal (Gordon & McClure, 1983). Over 20 university and medical center research sites are currently conducting investigations involving the GDS. Most studies concern the effectiveness of the GDS for determining drug responsivity and for evaluating the success of pharmacotherapy (Atkinson, 1985; Barkley, 1985; Rapport, 1985). Others are investigating the use of the GDS for evaluating children with known brain damage, preschoolers considered "at-risk" for impulsive behavior, and the relationship between GDS scores and observational measures of classroom behavior. The GDS is also being used by school systems and pediatric practices across the country for the clinical evaluation of ADD-H.

Comments and Conclusions

A chronic impediment in the field of ADD-H has been the paucity of universal criteria and procedures for subject selection and treatment monitoring. Even in the realm of behavioral assessment, where truly creative approaches to testing children have been developed, procedures have generally not been sufficiently practical or well-standardized to allow for acceptance by the majority of professionals (Loney, 1981). As such, most continue to rely on rating scales or tests, such as the Wechsler Intelligence Scale for Children (WISC-R) (Wechsler, 1974), which have been shown to be of limited usefulness in differentiating between groups (Douglas, 1972). Furthermore, comparison of studies across research programs has often been hampered by idiosyncratic measures or sets of criteria.

The GDS represents an effort to establish a standard procedure for evaluating certain aspects of attention and self-control. While it is more costly and, in certain respects, less flexible than software-driven approaches, its portability, ruggedness, and extensive base of normative data offer the user greater assurance of reliable administration and valid interpretation. The growing acceptance of the GDS within the professional community also permits greater comparison of data across studies.

It must be emphasized, however, that the GDS was never intended as a divining rod for ADD-H. This is a complex disorder which represents an array of subgroups and interactive diagnostic dimensions. The GDS is seen as an important tool to be used only in conjunction with other selection criteria and clinical judgment.

References

Atkinson, A.W., Cohen, P.C., and Kelly, P.C. Attention deficit disorder: The effects of ritalin on self-esteem—A comparison of ACTeRS teacher scale, Conners' parent scale, and Gordon Diagnostic System in diagnosis and management. Paper presented at the American Academy of Pediatrics Meeting, Atlanta, Georgia, April 1985.

Barkley, R.A. Assessment of stimulant drug responding in ADD-H children. Paper presented at the 93rd Annual Convention of the American Psychological Association, Los Angeles, California, August 1985.

Conners, C.K. *Continuous Performance Test* [Computer program]. Kensington, Maryland: Behavioral Medicine, Inc., 1980.

Davenport, W. Vigilance and arousal: Effects of different types of background stimulation. *J. Psychol.*, 82:339-346, 1972.

Douglas, V.I. Stop, look and listen: The problem of sustained attention and impulse control in hyperactive and normal children. *Can. J. Behav. Sci.*, 4:259-282, 1972.

Doyle, R.B., Anderson, R.P., and Halcomb, C.G. Attention deficits and the effects of visual distraction. *J. Learn. Disab.*, 9:59-65, 1976.

Gordon, M. The assessment of impulsivity and mediating behaviors in hyperactive and nonhyperactive children. *J. Abnorm. Psychol.*, 7:317-326, 1979.

Gordon, M., and McClure, F.D. The objective assessment of attention deficit disorder. Paper presented at the 91st Annual Convention of the American Psychological Association, Anaheim, California, 1983.

Gordon, M., and McClure, F.D. Assessment of attention deficit disorders using the Gordon Diagnostic System. Paper presented at the 92nd Annual Convention of the American Psychological Association, Toronto, Canada, 1984.

Gordon, M., and Mettelman, B.B. *Threshold Tables for the Gordon Diagnostic System.* (Available from Clinical Diagnostics, Inc., 300 E. Mineral Avenue, Suite 6, Littleton, Colorado 80122), 1985.

Hiscock, M., Kinsbourne, M., Caplan, B., and Swanson, J.M. Auditory attention in hyperactive children: Effect of stimulant medication on dichotic listening performance. *J. Abnorm. Psychol.*, 88:27-32, 1979.

Loney, J. Evaluating treatments for childhood hyperactivity: Some methodological considerations. In: Gadow, K.D., and Loney, J. (eds.), *Psychosocial Aspects of Drug Treatment for Hyperactivity.* Boulder, Colo.: Westview Press, 1981, pp. 77-103.

Klee, S.H., and Garfinkel, B.D. The computerized continuous performance task: A new measure of inattention. *J. Abnorm. Child Psychol.*, 11(4):489-496, 1983.

Margolis, J.S. *Academic Correlates of Sustained Attention.* (Unpublished thesis, University of California, Los Angeles, 1972.)

McClure, F.D., and Gordon, M. The performance of disturbed hyperactive and nonhyperactive children on an objective measure of hyperactivity. *J. Abnorm. Child Psychol.*, 12(4):561-572, 1984.

Rapport, M.D. Comparing classroom and clinic measures of ADD: Dose response effects. Paper presented at the 93rd Annual Convention of the American Psychological Association, Los Angeles, California, August 1985.

Rosvold, H.E., Mirsky, A.F., Sarason, I., et al. A continuous performance of brain damage. *J. Consult. Psychol.*, 20:343-350, 1956.

Weschsler, D. *Weschsler Intelligence Scale for Children-Revised.* New York: Psychological Corporation, 1974.

A Microcomputer-Based Psychophysiology Data Acquisition and Analysis System

C. Keith Conners, Ph.D.,[1,2] Roy Clymer, Ph.D.,[1] and Robert S. Sherrick, Ph.D.[1]

The recording of autonomic and electrophysiologic signals from patients under different conditions of drug treatment, cognitive tasks, or emotional states can provide an important source of information in clinical research settings. However, the considerable costs of the laboratory equipment, the degree of technical expertise required, and the labor-intensive requirements of analysis and display of information are all factors which have limited the application of psychophysiologic techniques to a relatively few dedicated laboratories. The advent of the microcomputer, however, promises to make these methods more widely available to psychopharmacologists and clinician-researchers.

In this article we describe a comprehensive, general purpose Apple computer-based psychophysiologic data analysis and acquisition system which was developed in the course of drug and nutrition studies with children. The software system is flexibly designed to allow for creation of a variety of testing paradigms which might require the simultaneous acquisition of data from several physiologic channels during active subject problem-solving and performance testing. The system allows for a comprehensive assessment of behavioral, cognitive, electrocortical, and autonomic variables, which has proven to be valuable in drug studies where it is desirable to examine the impact of a drug upon multiple response systems at different dosages and over different time periods. The system is menu-driven and easily learned by nontechnically oriented users.

Hardware

The most expensive part of a psychophysiologic system is the human operator, who, in addition to the time spent actually acquiring data, must usually spend many hours in the scoring and reduction of the vast quantities of data obtained during test sessions. The Apple II+ or Apple IIe, because of its remarkably low cost and flexibility, is a powerful tool for addressing this aspect of the psychophysiology problem.

After the operator, the most significant costs are usually associated with the equipment required to detect and transduce the physiologic signals into electrical energy which can be analyzed for its frequency and amplitude characteristics in relation to experimental parameters. Many companies now manufacture suitable and relatively inexpensive modular components for signal acquisition and transduction which obviates the need for expensive polygraphic equipment.* These components are designed for different physiologic signal characteristics and typically will amplify, shape, filter, integrate, or compare the analog physiologic signals which can then be used for further analysis.

Once acquired, such signals must be converted from their continuous (analog) voltage form into a numeric (digital) form suitable for further analysis. Analog-to-digital (A/D) conversion of input signals is greatly facilitated by an interface which utilizes pre-defined machine language routines which require only a simple BASIC-like higher-order interpretive computer language. This general re-

---

[1] Laboratory of Behavioral Medicine, Children's Hospital National Medical Center, Washington, D.C. 20010.
[2] Department of Psychiatry, George Washington University School of Medicine, Washington, D.C. 20016.

Address reprint requests to: C.K. Conners, Ph.D., Laboratory of Behavioral Medicine, Children's Hospital National Medical Center, 111 Michigan Avenue, N.W., Washington, DC, 20010.

*A high-quality, inexpensive source for modular signal processing equipment which we have used is Med Associates, Box 47, East Fairfield, VT 05448.

quirement can best be met by dedicated hardware which flexibly acquires many channels of information simultaneously, including binary (off-on) information such as button pushes or movement events: and which provides the timing and display requirements ordinarily available only on expensive polygraphs. We have used the Cyborg ISAAC Model 91a* for this purpose. The ISAAC™ system (Integrated System for Automated Acquisition and Control) includes 16 input channels for A/D conversion, and 16 binary input channels. It also contains computer-controllable binary and analog outputs which can be used to control an experiment, including four D/A and 16 binary outputs. The system also has four Schmitt Trigger inputs, a counter, and on-board 32-bit clock. All of these functions may be easily controlled by a high-level BASIC-like language, LABSOFT™ which consists of simple statements which can be added to Applesoft programs. Analog signals are processed as IRIG signals (1.4 volts full scale), a format compatible with most popular polygraphs, and FM tape recorders. Digital signals use standard 5-volt TTL logic.

Although the LABSOFT program is simple and fairly powerful, it has two important limitations which restrict its utility: 1) It does not allow easily for multiple functions to be performed in real time at once (e.g., taking A/D samples while monitoring for subject button presses). The LABSOFT program is fast when doing only a single task. For example, it can take A/D samples at 1,000 samples per second. When faced with performing multiple tasks simultaneously, however, it is considerably slower. A typical psychophysiological application might require measuring several channels of electroencephalograph (EEG), electrocardiograph (ECG) R-wave timing, subject button-press responses, activity level, and subject respirations all at the same time. Multiple functions can only be performed at a great sacrifice in speed. 2) LABSOFT is large, and allows only 4K bytes of computer memory for data storage in a 64K Apple if both high-resolution graphics pages of the Apple are being used for data display of incoming analog information.

Software

In order to circumvent the speed and memory size problems, a machine language software package called ISIINT was developed that requires only 2K of memory and can perform up to 14 functions simultaneously. ISIINT is like LABSOFT in that it consists of utility routines that can be called from Applesoft Basic programs. Applesoft integer arrays are used for passing parameters and data between the Applesoft Basic program and the ISIINT utilities. ISIINT uses one of the ISAAC timing elements to generate a real time clock that can be started and stopped under program control. Clock interrupts or "tics" can be set in software to occur as often as 1 per millisecond (msec) or as seldom as once every 65 seconds.

Through the use of the ISIINT utilities, any type of input or output that the ISAAC hardware is capable of performing can be scheduled to occur at a specified clock interrupt. For example, an A/D operation can be scheduled to occur at the 500th clock tic via a call to the ISIINT utilities. With another call to ISIINT, the clock can be started with a clock tic spacing of 10 msec. The A/D operation will then occur exactly 5 seconds after the clock is started without further interven-

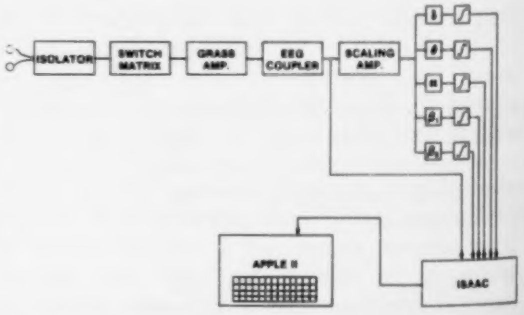


FIGURE 1. EEG/Evoked potential data collection system. Data from the subject electrodes passes through an optical isolator (required for subject protection), to a Grass EEG amplifier. The analog signal is then digitized by ISAAC and *stored in an* Apple array for EP measurement. The same signal is passed through sharp Butterworth bandpass filters for measurement of relative power in each of 5 frequency bands.

---

*ISAAC and LABSOFT are trademarks of the Cyborg Corporation, 55 Chapel Street, Newton, MA 02158.

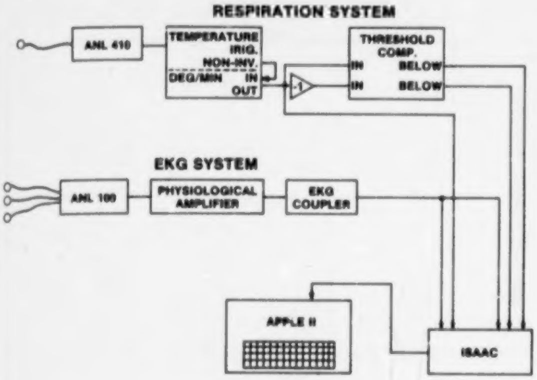


FIGURE 2. Respiration and heart rate data collection system. A thermistor attached to the nostril provides a temperature signal which changes with inspiration/expiration. The thermistor signal is amplified and transduced by a Med Associates ANL 410 module and converted to a value representing inspiration or expiration by a threshold comparator. The R-wave of the ECG (collected from the Med Associates ANL 100 module) is amplified and converted to a binary pulse used to activate an ISAAC Schmitt Trigger. The ISAAC and ISIINT routines are used to calculate interbeat intervals. The Apple-II+ can display the analog information in real time on the high-resolution screen during data collection.

tion by the Applesoft program. All ISIINT input/output operations occur in the "background" while an Applesoft Basic program is running in the "foreground." When many background input/output operations are scheduled, the foreground Basic program runs more slowly than normal, but it is not otherwise affected. When data become available via background input operations, they are placed into Basic integer arrays.

In addition to allowing all possible ISAAC input/output operations and real-time clock control, ISIINT also allows the user to schedule PEEK and POKE operations, read the clock, read background operation status information, and perform several useful functions not associated with the real time clock, such as adding two Basic integer arrays in a fraction of the time required by a similar routine in Applesoft Basic (this latter capability permits immediate display of averaged EEG-evoked potential data). Since all utility functions are accessed via Applesoft Basic "Call" operations, ISIINT is simple to use and does not require a knowledge of assembly language or a detailed understanding of the ISAAC hardware. Parameters and data are passed via integer arrays. Upon receiving a call, ISIINT may either perform a function immediately (such as clearing the counter, starting or stopping the clock), schedule a function, stop an already scheduled function, or enter a value (such as the time). The action taken by ISIINT depends upon the values passed to it in the parameter array.

Sample Application

A description of a study recently conducted using the Apple/ISAAC/ISIINT system may serve to demonstrate its capabilities. An experiment was conducted to ascertain the behavioral and physiological effects of a drug and a placebo given in two dosage regimens. In the single-dose condition a large dose of the investigational drug was given in the beginning of the experiment. In the distributed-dose condition the same quantity of drug was given, but in four equal doses 1 hour apart. In order to make the experiment double-blind, all dosages were matched for volume. Thus, in the distributed-dose condition the volume of the first drink, although containing one quarter of the drug, was equal to the first drink in the single-dose condition due to the addition of an appropriate quantity of placebo. Similarly, three placebo doses were given in the single-dose condition to match the quarter-doses given in the distributed dose condition. Subjects were 8- to 12-year-old normal children. It was desired to collect information on attentional set through the cardiac deceleration to a warned reaction-time task; on cortical alertness through quantitative EEG and visual evoked response; on behavioral attentiveness through a continuous performance task (CPT); on respiration rate associated with attention deployment; and on general activity obtained from counters attached to a stabilimiter in the subject's chair.

The primary performance measure was a "letter-form" version of the CPT. In this task the subject is required to press a response key whenever two letters appear in sequence from a series which includes both letters and letter-like forms matched for area (and consequently for brightness). This task, although an interesting measure of attending in itself,

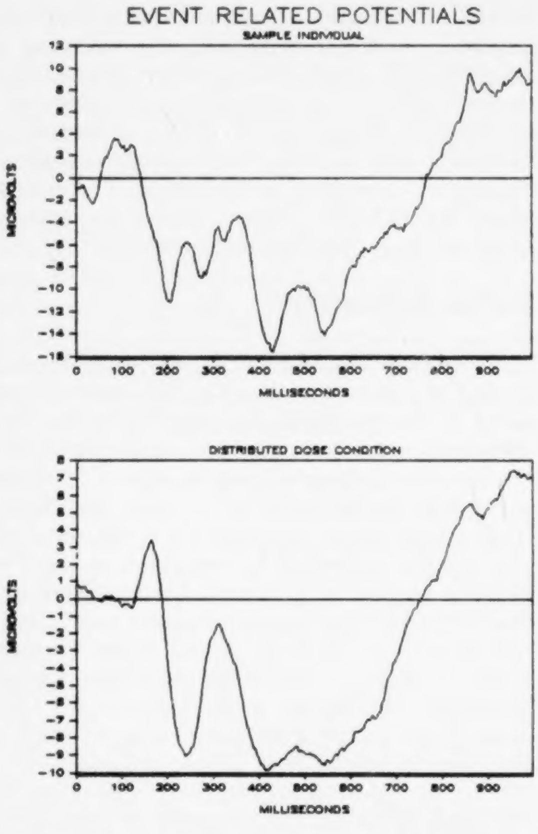


FIGURE 3. Individual and group-evoked potentials collected with ISIINT.

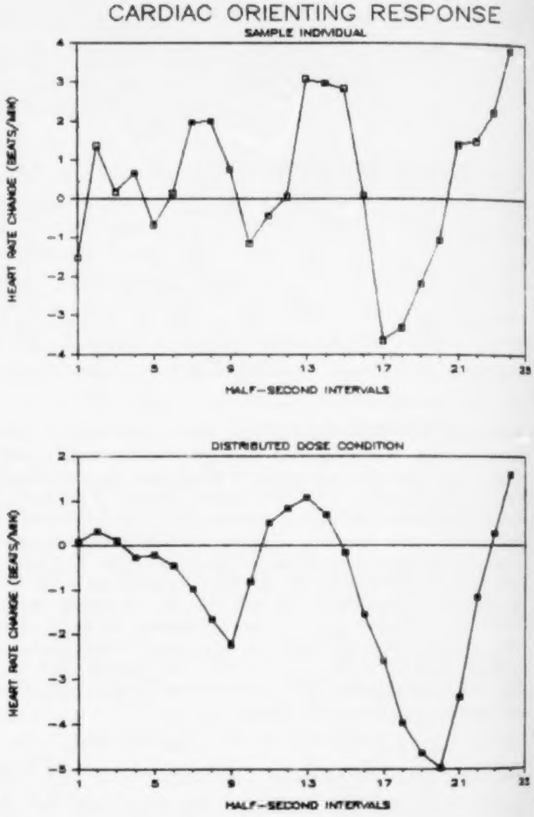


FIGURE 4. Individual and group cardiac changes during a 6-second warned reaction-time task.

has the added advantage of allowing the simultaneous gathering of averaged visual evoked potentials generated from both letter and form-stimuli, making it possible to ask interesting questions regarding hemisphere-specific processing. Figure 1 is a diagram of the hardware system used to gather EEG data.

A single input electrode (Cz referred to linked mastoids) was used to gather both ERP data and frequency band data. During the CPT task the Apple/ISAAC/ISIINT system was used to gather and average the EEG waveforms for 1,000 msecs following each visual stimulus presented on the monitor. The ISIINT program provided two averaged waveforms, one for the correct rejections and one for hits.

The CPT task also provided four performance measures: number of hits, number of correct rejections (targets which did not require and did not elicit a response by S), number of errors of commission (key presses to stimuli which were not the target), and the average reaction time to press the key after a target. Thus, a single task allowed monitoring of a variety of behavioral and psychophysiological variables.

A second task which also sampled two measurement levels was a warned reaction time task (Simons et al., 1979). The R-wave from a standard Lead II ECG activated one of the Schmitt trigger inputs of the ISSAC. The interbeat interval was recorded and converted to a rate per 1/2 second interval (Gatchel & Lang, 1973). A series of 20 reaction time trials was presented, with sampling beginning 3 seconds prior to the onset of a 6-second warning tone. The subject pressed a response

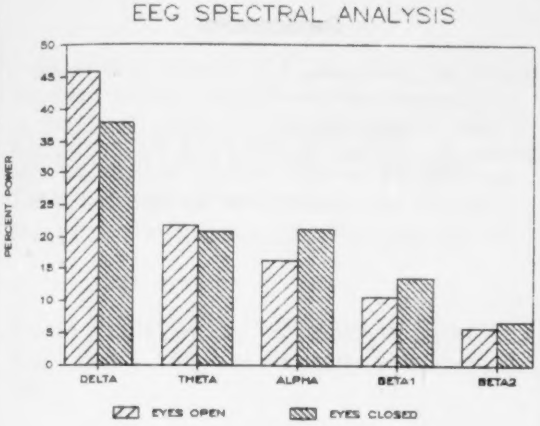


FIGURE 5. Changes in relative EEG power with eyes open and eyes closed.

key when a circle appeared on the monitor at the end of the warning tone. The heart rate was expressed as a deviation from the prestimulus average heart rate and an averaged evoked cardiac response was obtained by averaging across the 20 trials (Simons et al., 1979). In addition, the cardiac-orienting task yielded measures of misses, errors of commission, and warned reaction time. An automatic detection and correction routine removed artifacts created by movement.

Sixty-second samples of three additional psychophysiological measures were obtained periodically throughout the experiment. Respiration rate was obtained from a nasal thermistor taped near the nostril and peak change in temperature was used to identify respiratory influxes. Heart rate was obtained from the same Lead II ECG used in the warned reaction time task. Finally, the EEG from the Cz electrode was fed to a series of filters and integrators from the modular input equipment which provided on-line measurements of the relative proportion of power in each of the five EEG frequency bands (theta, delta, alpha, beta1, and beta2). Note that this "hardware" function could be easily obtained by software programmed to achieve the same goal. Each of these measures was sampled for 30 seconds with S's eyes open and then 30 seconds with their eyes closed. Figure 2 is a block diagram of the components used to obtain these measures.

Results

Since the purpose of this article is a description of the Apple/ISAAC/ISIINT system, the results of this experiment will be discussed only insofar as they are illustrative of the data gathering capabilities of the system.

Figure 3 displays some of the averaged evoked response data. The top panel is the ERP of a single subject, averaged across 88 correct hits. The bottom panel shows the evoked response to hits averaged across 20 subjects in the single-dose condition. The individual peak amplitudes and latencies were hand scored by a program which displays the EPs on the Apple high-resolution screen and allows the use of an adjustable cursor which reads out the time and amplitude of the wave wherever it is positioned. Subsequent statistical analyses may then be performed upon appropriate peaks.

Typical evoked cardiac response data are shown in Figure 4. Again the upper panel shows the data from a representative subject, while the lower panel shows the data averaged across all subjects. The data show the expected tri-phasic response (Gatchel & Lang, 1973).

In Figure 5 some of the EEG frequency band data is presented. The EEG was taken for 30 seconds with eyes open, then the eyes were closed and a minute later 30 seconds of EEG with eyes closed was taken. The data show the increase in alpha and expected shift to lower frequencies with eyes closed. (Not shown here are the sequential activity counts which were collected throughout the subject-day, or the respiration data.)

Conclusion

Most laboratories interested in psychophysiological recording will have access to the appropriate signal collection input modules, but the most difficult and expensive task is the computer storage, analysis, and display of the data. Typically, this has required mini-computers which are both expensive and difficult for the non-programmer to use. The system described here allows a comprehensive and sophisticated behavioral, electrophysiologic, and psychophysiologic experiment that is flexible and easy to use. Data are immediately displayed and graphed without long delay between the experiment and subsequent data reduction. The cost of this system compared to others may recommend it as a valuable experimental tool.

References

Gatchel, R.J., and Lang, P.J. Accuracy of psychophysical judgments and physiological response amplitude. *J. Exper. Psychol.*, 98:175–183, 1973.

Simons, R., Ohman, A., and Lang, P.J. Anticipation and response set and cortical, cardiac and electrodermal correlates. *Psychophysiology*, 16:222–233, 1979.

A Brain Function Diagnostic and Study Unit for Psychotropic Drug Development and Psychopharmacology Research

Turan M. Itil, M.D.,[1,3] Donald M. Shapiro,[2] Emin Eralp,[3] Ahmet Akman,[3] and Kurt Z. Itil[3]

Quantified electroencephalogram (EEG), evoked potential (EP), and neuropsychological tests have been proven to be reliable objective tests to study the effects of drugs on human brain function. In particular, when analyzed by digital computer, EEG can provide information about the minimum effective dose of a drug on the central nervous system (CNS), the onset and duration of CNS effects, and the mode of action of psychotropic drugs (Dolce & Kunkel, 1974; Fink, 1969; Itil, 1974). Recent investigations indicate that computer-analyzed EEG (CEEG™) can determine the type of psychotropic properties of the compound, its potency, and therapeutic window (Fink, 1974; Herrman, 1982; Itil et al., 1979). CEEG has also been applied successfully to determine the bioavailability and bioequivalency of psychotropic drugs and predicted therapeutic outcome in individual patients (Fink, 1974; Itil, 1974, 1977; Itil & Krynicki, 1983).

This paper summarizes a new system called the Brain Function Diagnostic Unit (BFDU™) (Itil et al., 1985) which provides information on brain function and its changes due to drug effects based on Quantitative Neurophysiological Testing results (EEG, EP, sleep), Interactive Neuropsychological and Psychometric tests, and integrative medical and neuropsychiatric summary data.

Quantitative Neurophysiological Testing

Computer EEG data collection and analysis system: The electrical phenomena of the brain, collected through a newly developed electrode helmet, are amplified via standard EEG machine amplifiers. The activity is recorded on a standard EEG strip chart by a conventional EEG writing system. (In the case of research, where the standard EEG strip chart may not be required, sensitive preamplifiers and laser printers may be used instead of the standard EEG machines.)

The same bioelectrical phenomena recorded on the strip chart are also first sent to the special 8-channel filter unit, then 8-channel analog-to-digital converter and, finally, to the microcomputer (IBM-PC/XT,AT or compatible). In addition to the EEG equipment and a microcomputer, some special peripheral hardware is required to conduct the EEG analysis with brain mapping:

a. Math Coprocessor
b. High Resolution Color Board
c. High Resolution Analog RGB Color Monitor
d. High-Speed Near Letter-Quality Printer

An extensive software package to conduct the following operations for these EEG data is also part of the BFDU:

1. A Clinical-Diagnostic EEG Program.

Provides quantitative outputs for each individual EEG lead, the frequency distribution of the mean of eight leads, and instant EEG reports with interpretation (unconfirmed). Simultaneously, colored hard copy topographic Dynamic Brain Map® are provided to help in the discrimination of abnormal or borderline records from normals.

2. Research EEG Programs.

For 8 to 16 channel power spectrum based on 6 to 22 variables and 8 to 16 channel period analysis (interval or zero-cross analysis) with 6 to 22 measurements.

---

[1] Division of Biological Psychiatry, New York Medical College, Tarrytown, NY 10691.
[2] Computer Center, New York Medical College, Tarrytown, NY 10691.
[3] HZI Research Center, Tarrytown, NY 10691.

3 Statistical Packages Which Yield:

Drug-induced changes (pre- minus post-drug) based on univariate statistics.

Drug versus placebo discrimination based on univariate and multivariate statistics.

Individual and group CEEG drug profiles based on *t* profiles.

Drug classification based on HZI's CEEG database using correlation statistics.

Time- and dose-related CNS effects for group and individual subjects based on regression analysis.

Classification of individual subjects' response with the HZI database to determine psychotropic potency of a drug and to predict the therapeutic outcome.

Graphic packages of the statistical outputs and database classifications (hard copy).

Serial comparisons (predrug minus post-drug) by statistical means and by topographic colored brain maps.

Evoked Potential Data Collection and Analysis System

The major part of hardware for EP data collection analysis such as EEG machine, microcomputer (IBM-PC/XT or AT) and electrode headset are the same as used for the EEG data collection and analysis. The only additional hardware required are different types of stimulators (acoustic, visual, and tactile), built specially for our EP system.

Software specific to EP data includes, for example, standard (conventional) 8- to 16-channel analyses with hard copy; an instant clinical report (unconfirmed); colored dynamic topographic brain maps based on different types of EP; and an automatic artifacting system.

There are also some unconventional features, including: high signal-noise ratio; separate analysis of EP based on different EEG frequency patterns; selective averaging, etc.

Interactive Neuropsychological Test System

For the interactive neuropsychological and cognitive test batteries, in addition to the IBM-PC/XT or AT, a psychological test station is required. This station includes another microprocessor (Z-80), a specially developed monitor, light pen, and control panel.

New programs were developed in collaboration with the computer center of the Austrian Road Safety Board to conduct the following tests:

Non-verbal intelligence test, concentration test, simple choice reaction time test, long-term memory test, speed-distance estimation test, optical memory test, sensor-motor coordination test (tracking test), tapping test, and a list of questions on current physical and mental state.

The results of these tests are provided in three different formats:

1. A graphic format, which includes the summary of raw data and the comparison of the data with age-related norms.
2. Interpretation of each individual test result (unconfirmed).
3. A summary report on neuropsychological test results as required by the clinician (unconfirmed interpretation).

Integrative Clinical Report

A series of medical, neuropsychiatric questions are asked about the past history and present symptomatology of the patient. The answers suspected to be related to brain dysfunction of the patient will be integrated into a clinical-practical acceptable format. For the questions, either a rating scale is used, or the patient is given a lap computer which has an interactive approach. The lap computer is a Radio Shack Model 100 with 24K memory, built in RS-232 port, and modem. The integrative summary is provided in a clinically useful format.

Conclusions

BFDU has the following major advantages:

1. The BFDU has been developed on a building-block principle. One can start with a computer EEG system which includes a standard EEG machine (any 8- to 16-channel with IRIG output), an IBM personal microcomputer (XT or AT), and some peripheral hardware (printer, monitor, sine wave generator). If one requires the EP system, one needs to purchase only a stimulator and additional

software. For neuropsychological tests, one needs to purchase a neuropsychological test station and additional programs. With a simple lap computer and additional software, one completes the BFDU system.

2. All three major tests, EEG, EP, and Neuropsychological Tests, are done by standard equipment and the output are also standard. Software provides much additional information to the standards, including quantitative data, statistical results, and color topographic Dynamic Brain Maps which are useful both for psychopharmacology and clinical research.

3. The system is self-monitored by software for technical problems and/or artifacts so that no special manpower for the computer or other test is required.

4. BFDU provides instant clinical-diagnostic EEG reports to determine whether psychiatric patients or subjects included in psychopharmacology trials exhibit any abnormal brain functions; thus computer EEG can be used to screen subjects with "organicity" to exclude from the psychopharmacology studies.

5. BFDU can be used in every phase of psychotropic drug studies, but most significantly during Phase I trials (Itil et al., 1972, 1977, 1979, 1984). Using CEEG, the following important CNS *efficacy* information of a new compound is obtained during Phase I *safety* trials:

- To determine the *CNS effectiveness* of a compound based on CEEG changes between pre- and postdrug administration. All marketed psychotropic drugs produce statistically significant CEEG changes.
- To establish the "*bioavailability*" of a compound on the CNS based on pharmacodynamic changes. In addition to the typical pharmacokinetic measurements (e.g., t_{max}, c_{max}, and AUPDC), CEEG parameters can also be used for time and dose response curves.
- To classify the quality of the CNS effects of a compound, thus to *predict* the type of the *psychotropic properties* using HZI's CEEG database. It was established that drugs with similar CEEG profiles produce equivalent therapeutic effects. Based on CEEG profiles of four major psychotropic drug groups (CNS depressants–neuroleptics; mood elevators–antidepressants; anxiety relievers–anxiolytics–hypnotics; cognitive activators–psychostimulants) and CEEG "prints" of 840 subclasses of 139 CNS effective drugs, the computer can classify the type of psychotropic properties of a new compound.
- To predict the *therapeutic window* of a new compound. The doses of which CNS effects can statistically be discriminated from placebo and also can be classified by the computer database as psychotropic are also therapeutically effective.
- To *predict the potency* of the psychotropic properties of a new compound. According to the studies, the more potent a compound the more patients show "typical" CEEG effects (CEEG profiles) within 1 to 3 hours after a single dose oral administration. The more typical CNS effects are, the better classified is a compound by the computer database to a psychotropic drug group. Among the 139 CNS effective drugs, Valium^R, Elavil^R, and dextroamphetamine are the most homogeneous CNS effective compounds. If a new compound is administered to 12 healthy subjects and more than 75% of the subjects are classified with a typical response, this indicates that the studied compound shall have homogeneous effects on the CNS; thus it will be a potent psychotropic.
- Last, but not least, CEEG can be useful to demonstrate the CNS effects of drugs in individual subjects or a group of subjects after single or multiple doses. Thus, CEEG can be used to monitor CNS effects of psychotropic drugs. If there is no significant change in EEG also, no therapeutic effects can be expected in psychiatric patient populations.

References

Dolce, G., and Kunkel, H. (eds.). *Computerized EEG Analysis*. Stuttgart: Gustav Fischer Verlag, 1974.

Fink, M. EEG and human psychopharmacology. *Ann. Rev. Pharmacol.*, 9:241–258, 1969.

Fink, M. EEG application in psychopharmacology. In: *Psychopharmacological Agents*, Vol. III. New York: Academic Press, 1974, pp. 159–174.

Fink, M. In: Itil, T. (ed.), *Psychotropic Drugs and the Human EEG* (Series: *Modern Problems of Psychopharmacology*). Basel: S. Karger, 1974, p. 76.

Herrman, W.M. *Electroencephalography in Drug Research*. Stuttgart/New York: Gustav Fischer Verlag, 1982.

Itil, T.M. (ed.) *Psychotropic Drugs and the Human EEG* (*Series: Modern Problems of Psychopharmacology*). Basel/New York: S. Karger AG, 1974.

Itil, T.M. Bioavailability and bioequivalence of psychotropic drugs based on computerized EEG measurements. *Drugs Exptl. Clin. Res.*, 1(1–2):251–257, 1977.

Itil, T.M., and Krynicki, V.E. Quantitative pharmaco-EEG in determining bioavailability and bioequivalency of psychotropic drugs. In: Garrett, E.R., and Hirtz, J.L. (eds.), *Drug Fate and Metabolism Methods and Technique*, Vol. 4, Chapt. 6. New York: Marcel Dekker, Inc., 1983.

Itil, T.M., Bhattachy, A., Polvan, N., et al. Fluvoxamine (DU-23,000), a new antidepressant. Quantitative pharmaco-electroencephalography and pilot clinical trials. In: Radouco-Thomas, C. (ed.), *Progress in Neuro-Psychopharmacology*, Vol. 1, Oxford/New York: Pergamon Press, 1977, pp. 309–322.

Itil, T.M., Polvan, N., and Hsu, W. Clinical and EEG effects of GB-94, a "Tetracyclic" and antidepressant effects of double-blind controlled trial. *Curr. Ther. Res.*, 14(7):395–413, 1972.

Itil, T.M., Soldatos, C., Bozak, M., et al. CNS effects of ISF-2522, a new nootropic (APhase) safety and CNS efficacy study with quantitative pharmaco-EEG and pharmaco-psychology. *Curr. Ther. Res.*, 26(5):525–538, 1979.

Itil, T.M., Michael, S.T., Baccari, S., et al. Antidepressant effects of flutracen, a long-acting patent thymoleptic (a double-blind controlled trial). *Curr. Ther. Res.*, 35(6):1014–1032, 1984.

Itil, T.M., Shapiro, D.M., Eralp, E., et al. A new brain function diagnostic unit, including the dynamic brain mapping of computer-analyzed EEG, evoked potential, and sleep (a new hardware/software system and its application to psychiatry and psychopharmacology). *New Trends in Exptl. Clin. Psychiatry*, C.I.C. Edizioni Internationali S.R.L., 21(2): Oct.–Dec., 1985.

BMDPC: BMDP Statistical Software for Microcomputers

MaryAnn Hill, Ph.D.[1]

In the fall of 1984, BMDP began distributing statistical software for IBM personal computers—the XT and AT, and compatibles such as the COMPAQ+. Since the BMDPC programs are the same as the BMDP mainframe programs, this development gives users the full power of a major, well-tested statistical package on a personal computer. The minimum requirements for a system to support BMDPC are a hard disk, an 8087 floating-point processor, 640 kilobytes of memory, and the capacity for double-sided, double-density floppy diskettes.

BMDPC is described in the following three sections: what is BMDP and how does it work, how does BMDPC differ from BMDP on the mainframe, and what is coming soon for BMDPC?

What Is BMDP and How Does It Work?

BMDP is a library of programs. Each program addresses a specific task or analysis: one program prints frequency tables and fits log linear models, another estimates a multiple linear regression equation, etc. BMDP provides a broad range of data description features and statistical analyses including *t* tests, analysis of variance (ANOVA) and covariance (ANCOVA) (repeated measures, multivariate ANOVA, mixed models), multiple regression (forward and backward stepping, all subsets, regression diagnostics), discriminant analysis, nonlinear regression, logistic regression, log linear models, cluster analysis, factor analysis, time series, and survival analysis including the Cox proportional hazards regression model. Most importantly, many procedures provide supports for the data analyst—graphical displays, diagnostics, and alternative tests that help the analyst estimate the degree to which assumptions (necessary for the analysis) are violated.

Each program uses the same basic set of instructions to describe the input data, name the variables, specify acceptable range limits and flags for missing data, select cases (old females from Clinic B in Boston), re-express data (change = baseline—week 4), and identify groups (male smokers, ... , female nonsmokers).

BMDP instructions are written in English sentences and are grouped into paragraphs. The most "basic set" of BMDP instructions (describing a data set containing pre- and post-exercise pulse measures) is shown in Figure 1. For many analyses, this basic set is all you need. For example, if these instructions were submitted to the factor analysis program, the output would contain a univariate data summary, a correlation matrix, eigenvalues associated with each factor, factor scores and Mahalanobis' distances for each case to the centroid of all cases, factor loadings with and without an orthogonal rotation, plots of loadings, and plots of factor scores. To limit the number of factors, or change the rotation type, the user adds instructions to the basic set.

Some programs require that paragraphs be added to the basic set. In Figure 2, a PLOT paragraph is added, requesting that the post-exercise pulse values be plotted against age in a bivariate scatterplot. The output, in addition to the scatterplot, includes the equation

```
/  INPUT            VARIABLES ARE 6.
                    FORMAT IS FREE.

/  VARIABLES        NAMES ARE ID, SEX, SMOKE,
                         AGE, PULSE_1, PULSE_2.

/  END
```

FIGURE 1. Basic BMDP instructions for data where each subject has an I.D., a code for sex and for smoking status, age, and pre and post exercise pulse values.

---

[1] Department of Psychiatry, UCLA School of Medicine, West Los Angeles VA Medical Center (Brentwood Division) and BMDP Statistical Software, Inc., Los Angeles, CA 90025.

```
/  INPUT         VARIABLES ARE 6.
                 FORMAT IS FREE.

/  VARIABLE      NAMES ARE ID, SEX, SMOKE,
                     AGE, PULSE_1, PULSE_2.

/  PLOT          YVAR IS PULSE_2.
                 XVAR IS AGE.

/  END
```

FIGURE 2. A PLOT paragraph is added to the basic set requesting a bivariate scatterplot of pulse versus age.

of the line of best fit (the location of this line is marked on the plot frame), the correlation (with tail probability), the residual mean square, and the means and standard deviations of pulse and age.

If, instead of a plot, the researcher wants a two-way table to test if the proportion of smokers is the same for males and females, the PLOT paragraph in Figure 2 is replaced by the TABLE paragraph in Figure 3.

A TRANSFORM paragraph, available in all programs, is useful for re-expressing data. All the usual arithmetic operators (multiplication, division, exponentiation) and functions (logs, square root, trigonometric) are available. Recently, for ease of data manipulation, more than 24 new transformation functions were added to the package. These functions produce results across variables on a record (e.g., SUM totals, say, 15 items on a record): other functions provide the mean, the minimum, the maximum, and the slope. Functions are also available to convert day-month-year dates to Julian form or to the number of days since January 1, 1960 (and vice versa).

How Does BMDPC Differ From BMDP on the Mainframe?

Researchers do not have to give up familiar mainframe options and features. Each BMDPC program (e.g., stepwise regression) has the *same* options, instructions, and documentation as its mainframe counterpart. But is the researcher handicapped with respect to size of problem and computational time? Yes, to problem size, if the analysis is on census data; no, for many of the studies in psychiatry, for which I am involved. Most BMDP programs do not require the data to be kept in memory—so problem size may be limited by the number of data items that can be stored on the hard disk. In Appendix B.2 of the *BMDP Statistical Software Manual, 1985 Reprinting*, formulas are given for the capacity of each particular analysis. For the standard mainframe installation, the maximum number "M" in these formulas is 15,000 (M is usually a function of the number of variables, number of groups, or number of cells in an ANOVA design). For BMDPC, the maximum value of "M" is 16,000. For example, if three megabytes are set aside on the hard disk for the data file, Program 1D could compute descriptive statistics for ten variables and 75,000 cases. More than 100 variables may be included in a stepwise regression run.

In sizable studies, millions of numbers may be collected when, say, for 200 subjects, many rating forms are administered repeatedly over time. Computing tasks for these studies may be distributed between the PC and the mainframe. For example, the data for each instrument could be cleaned separately on the micro at the center where they are collected, and later shipped or networked to a mainframe for merging with data from other centers. It should be pointed out that this distribution of computing also applies to the debugging of the BMDP instructions for analysis. The fine tuning of the instructions can be carried out on the micro for a subsample of the data and the instructions can then be shipped as text to the mainframe for final analysis of the complete file.

Of course, computation on the micro is slower than on the mainframe. However, the researcher is the only user on the micro, so the person sitting at a micro may not feel handicapped. On an IBM PC/XT, the time to execute the All Possible Subsets Regression searching algorithm for 23 variables is 45 seconds (by wrist watch). A factor analysis

```
/  TABLE         ROW IS SEX.
                 COLUMN IS SMOKE.
```

FIGURE 3. When a TABLE paragraph is added to the basic set of instructions the output contains a two-way frequency table plus the chi-square test of independence.

with 24 variables, including an orthogonal rotation, computation of factor scores, and other supplementary displays and supporting information, takes two minutes. Using the new BMDP Data Manager (described below), it took roughly 11 minutes by wrist watch to

—do *complex transformations* on each of 1,205 records in File A containing weekly clinic visits for 225 patients. For each record, transformation functions were used to check the number of missing values, sum 20 items, compare the total with another value, etc.

—use *aggregate functions* to generate 225, records with summary measures (i.e., one new record per patient summarizing his experience across weekly clinic visits).

—*join* this summary file *side-by-side* with File B, a 225-record demographic file, using the patient ID as a merge key.

In addition to the standard mainframe programs, BMDPC includes a line editor that allows the user to access both data and/or instruction files without leaving the program. With the new editor, the user loads the program once and makes a series of runs, inserting additional instructions or making corrections after each run, thus avoiding the delay of reloading the program after each error. The editor allows the user to get files from the system and to return modified files back to the system.

One difference between BMDPC and the mini and mainframe BMDP is the license procedure. Mainframe and mini-computer users lease the complete BMDP package for an annual fee—they have an annually renewable license. BMDPC users select a group or subset of the programs and pay a one-time-only fee—a perpetual license. Discounts are available for multiple copies of BMDPC leased to universities and research facilities.

What Is Coming Soon for BMDPC?

Each new release of BMDP includes modifications and enhancements. This year BMDP plans to introduce a new system: for managing data. This past year, BMDP began distributing the structural equations modeling program, EQS.

The Data Manager. An exciting new product to be released in 1985 is the data manager system that merges files, extracts summary information from sets of records that vary in number, and performs other file restructuring operations. In Figure 4, the procedures for merging files are illustrated. In Figure 4a, the subject ID is used as a key to merge records side-by-side from three files containing history, laboratory, and questionnaire data. In 4b, records from file B are

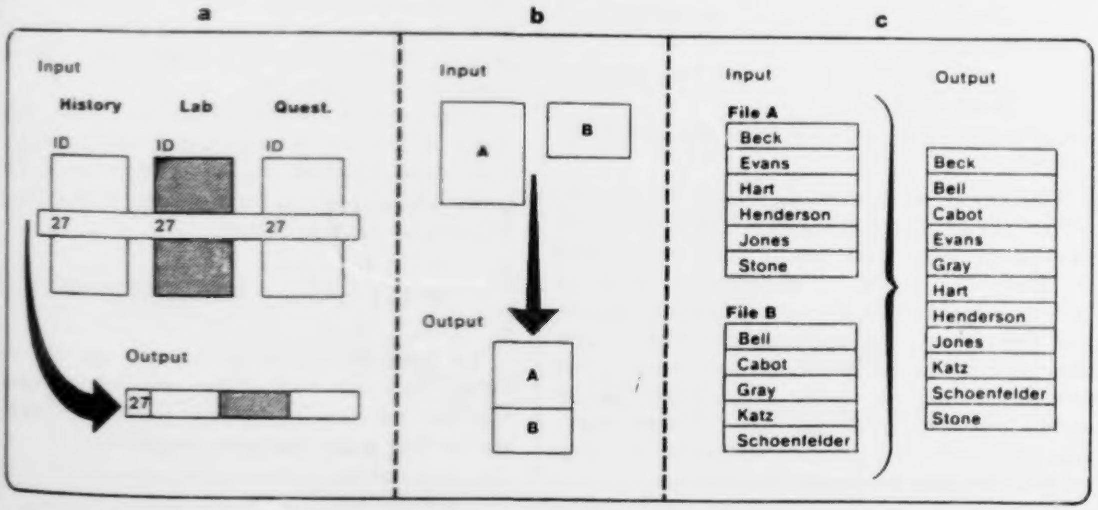


FIGURE 4. Merging files (a) side-by-side, (b) end-to-end, and (c) interleaving records.

Input

Family	Age	Income	Sex	Education
1	35	1500	1	12
1	33	1200	2	12
1	2	0	2	0
1	7	0	2	2
1	9	0	1	4
2	43	1800	2	16
2	39	1400	1	14
2	10	500	2	5

Output

Family	# in Family	Max. $	Total $	Max. $ Female	Education Max. $
1	5	1500	2700	1200	12
2	3	1800	3700	1800	16

FIGURE 5. Generating summary records.

added to the end of file A. In 4c, the subject's name is used to interleave records alphabetically from two input files. Output from more than two dozen summary functions can be 1) added to each input record, 2) used to generate summary records, or 3) added to records higher up in the hierarchy. For example, if a file contains records for individual family members with age, sex, education, monthly income, etc. (*see* Figure 5), you can use the summary functions to extract, for each family,

—the number of family members

—the total family income

—the maximum income for one member, the maximum for the males, the maximum for the females

—the education level of the member with the maximum income

—the sex of the member with maximum income

The development of measures to characterize social supports (social networks) of mental patients is an interesting illustration of how to extract information from a nonrectangular file. For each patient we collect one record for each person with whom the patient interacts. Thus, the number of records per patient varies. One patient has 18 in his network, while the next patient interacts with only two people. Variables on each member's record include the following:

—age, sex, frequency of contact, relationship to patient (relative, friend), etc.

—information about roles—the patient's interaction with each member (does he borrow money from the member, spend free time with him, etc.).

—a tally of the interaction with every member in the network (yes, Bill interacts with Jose; no, Bill does not interact with Sue, etc.).

The goal is to generate one record for each patient that summarizes the characteristics of his network: network size (the number of members), number of members interacting in at least one role, total number of roles experienced by the patient, the maximum number of interactions with one member, the member (e.g., mom) about whom the patient feels most negative and the contact score with this person, the number of "others" available for free-time activities, etc.

The generation of these summary measures is straightforward using the aggregate functions. To find the most negative feeling score among a patient's network members, we use the MIN function

MOST_NEG = MIN (FEELING).

To find who this person is, we use the FVAL function to find the value of the variable RELATION in the first record for which the feeling score was most negative.

WHO_NEG = FVAL (RELATION,
FEELING EQ MOST_NEG).

The ability to incorporate conditions in the summary functions also allows us to generate some measures using only the family records, other measures to summarize the nonfamily members. We did this for the number of family members and the number of others used in free time activities. Results were saved and plotted using the 9D miniplot options (*see* Figure 6). We grouped the patients by severity of illness (illness code 1 is severe, 4 is well) and ethnicity. The average number of friends is plotted on the vertical axis. A quick look at the plots provides a description of the results. Use of family members (F) for free time does not appear to be associated with severity of illness. However, use of "others" (O) does decrease markedly with illness, and the decrease is more dramatic for Anglos. The difference between family and "others" is smaller for the Hispanics—they appear to use more family members (probably because their families are larger).

Other data management supports are available to help produce the desired output file. You may *sort records* numerically and alphabetically; *select cases interactively*, e.g., male blue collar workers over 50 years of age who worked in an asbestos factory, *re-express data* using more than 30 functions and operators (LOG_WT = LOG (WEIGHT)), *convert dates* in day, month, and year form to Julian dates or days since January 1, 1960, report *univariate statistics* (n, $\bar{x}$, s, min, and max) for values of variables on input records or records created through file operations *print data* in user-specified fields or preassigned fields, etc. When limitations on computer funds make on-line data editing prohibitive, a batch edit capability is available also. Another feature the system provides is a *record map*—a

```
SYMBOLS -- F=FAMILY   O=OTHERS

       ...+....+....+....+....        ...+....+....+....+....
       -                     -        -                     -
       -                 O   -        -                     -
     3 +                     +      3 +                     +
V      -                     -        -                     -
A      -                     -        -                 O   -
R      -                     -        -                     -
I      -                     -        -                     -
A    2 +                     +      2 +                     +
B      -            O        -        -                     -
L      -                     -        -            O        -
E      -       O             -        -                     -
S      -                     -        -       O             -
     1 +                     +      1 +                     +
       -                     -        -  *    F         F   -
       -       F         F   -        -            F        -
       -  *         F        -        -                     -
       ...+....+....+....+....        ...+....+....+....+....
          1         3                    1         3
               2         4                    2         4
              ILLNESS                       ILLNESS

         ETHNICTY= ANGLO                ETHNICTY= HISPANIC
```

FIGURE 6. Number of family members (F) and others (O) available for free time activities (by illness and ethnicity).

graphical display in which each character represents the presence of a record.

The system was designed to handle the great majority of tasks encountered in research projects, while remaining reasonably easy to use. You should *not* require a programmer who is an expert in file structures in order to use it effectively. A data analyst can use the various data manipulation procedures interactively to learn both about the *structure of the records* (e.g., in a clinical trial, how many visits are missed for each patient? What is the pattern of return visits?) and the actual *data values* from cells defined by one or more grouping variables. For example, at 3 months, what is the change from baseline in clinical outcome scores for drug 1 completers (i.e., those subjects who remained on study 1 year), drug 1 dropouts, drug 2 completers, and so on.

Structural Equations Modeling Program. In 1985, BMDP began distribution of EQS (pronounced like the letter X), the structural equations modeling program developed by Professor Peter Bentler at UCLA. EQS permits distribution-free multivariate analyses, including multivariate regression, path analysis, simultaneous equation models, confirmatory factor analysis, latent variable models, etc. Structural equation models allow theory testing with nonexperimental data and for that reason are often called causal modeling methods. EQS is designed so that it requires no knowledge of matrix algebra. Models are specified using an equation language in the form

$$V1 = .5 * V2 + .8 * V3 + E1,$$

where variable V1 is regressed on variables V2 and V3, with error E1. The numbers preceding the asterisks are initial parameter estimates. In addition to parameter estimation using least squares, generalized least squares and maximum likelihood methods (based on elliptical theory) are available for nonnormal data. EQS is currently running on IBM and VAX computers as well as the IBM PC/XT and AT. Versions for other hardware will follow. Professor Bentler is widely published in the area of statistical methodology and is a past president of the Psychometric Society (1982–83).

Projects Under Development. As part of an NIMH research project at UCLA, a test program has been completed for repeated measures analysis of variance with incomplete data. W.J. Dixon is the principal investigator, and R. Jennrich and M. Schluchter are involved in design and programming for the project. In addition to handling incomplete data, the program allows a user-specified structure for the covariance parameters. This approach allows the data analyst to examine several different structures, each having important subject-matter interpretations.

Another program in design stage will allow the analysis of repeated measures categorical data, and at our office in Cork, Ireland, a program for correspondence analysis is under development.

How does BMDP decide what to include in the software? Suggestions come from several sources, including letters submitted by users. A panel of outside advisors meets twice a month to evaluate the suggestions. The panel includes members from the academic community and members actively involved in consulting in a variety of real world applications.

References

Dixon, W.J., Brown, M.B., Engelman, L., et al. (eds.). *BMDP Statistical Software, 1985 Reprinting*. Berkeley: University of California Press, 1985.

Hill, M.A. *BMDP User's Digest, 3rd Edition*. BMDP Statistical Software, Inc., Los Angeles, 1984.

Communications: Microcomputer/ Mainframe Interfacing

Pierre Mercier, Ph.D.[1]

There are a number of practical and technical aspects related to the use of microcomputers in communication with mainframes. In a typical session such as exemplified below, the user logs-on to a mainframe computer using an asynchronous terminal emulator program and issues the necessary commands to transfer to data file to the microcomputer's storage device.

The basic technical aspects involved in performing this task include the essential hardware components, ASCII coding, serial interfacing (RS–232C), and modulation-demodulation. Trapping and correction of transmission errors must also be performed.

A Sample Application

In order to establish communications between a microcomputer and some remote machine, the user must first load a Terminal Emulator Program and set the necessary parameters. The data communication parameters will be explained in detail later; let us assume that default values are appropriate for now. Turning on the communications line, a TERMINAL READY message appears at the top of the screen. The IDENTIFICATION and PASSWORD statements are then required to access the mainframe. The exact order and syntax of these steps may vary from installation to installation but they are typical of the process.

The user is now on-line and can issue any command that the mainframe understands, or use any program that runs on it, with the associated processing power. On the other hand, it may be desirable to take the content of a data file which resides on the mainframe storage device, list its content on the screen, and record it on the microcomputer's disk drive at the same time. Within the restrictions imposed by the size of the destination device (typically in the range 120–320 Kilobytes for floppy drives or 5–20 Megabytes for hard disks on microcomputers versus 100–317 Megabytes for a mainframe disk pack), these data are then available for processing by the micro (e.g., using a statistical analysis program), thus saving on-line costs and generally offering a more interactive environment.

To execute the transfer, the data destination is first identified by creating a new file on the microcomputer's disk directory. Next, the terminal is put in RECORD mode and a DISPLAY command is sent to the remote. At this point, a listing of the file is obtained which is then automatically saved on the local disk. It is now possible to terminate the session (OFF), and replace the terminal emulator program with the application program needed to process the newly acquired data (e.g., statistical analysis).

The Communication Process

The communication circuit used in the preceding example comprises a number of distinct elements. The circuit starts at one end with the mainframe computer or, more technically, the Data Terminal Equipment (DTE—a computer or machine which provides data in the form of digital signals at its output), continues with the front-end processor which acts as an interface between the Central Processing Unit (CPU) and the various input-output units, to the MODulator-DEModulator (MODEM—a type of Data Communication Equipment (DCE) that converts digital data to an analog signal for transmission on telephone circuits), to the telephone lines or any suitable transmission channel such as microwaves or radio waves, to another MODEM, to another interface (often such as the RS–232C serial interface), and finally to the microcomputer.

---

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada H3A 1A1

Along the communications circuit, the data (letters, numbers, and other symbols) are represented according to certain coding schemes. A scheme very widely used for computers to communicate with peripherals is the American Standard Code for Information Interchange or ASCII (Mackenzie, 1980). This code effectively uses 7 bits to represent 128 different symbols. These include the usual alphanumerical symbols found on a typewriter. For instance, upper case 'A' is represented as 100 0001 binary, corresponding to decimal value 65, whereas lower case 'a' is 110 0001, equivalent to decimal value 97, and so on. Some control characters are also available (decimal values 0–31), so called because they are acted upon by the computer rather than merely displayed. The most commonly used are probably 'carriage return' '(mnemonic: CR, decimal value = 13) and 'line feed' (LF, 12 decimal), which respectively bring the cursor or printhead to the leftmost position on a line and move to a new line. Other characters such as 'bell' (BEL, 7 decimal), 'backspace' (BS, 8 decimal) and 'form feed' (LF, 12 decimal) are fairly self-explanatory, but others are not so obvious.

In the case of a file transferred from a mainframe, each data line begins on a new line (LF) and terminates with a carriage return (CR). In addition, a device control character such as DC3 (19 decimal) might be inserted at the end of each line. It means 'reader-off,' i.e., the sender is not finished transmitting, more data is coming, and the sender will not accept input. The very last character, DC1 (17 decimal) means 'reader-on,' i.e., transmission has ended for now, input will be accepted. The communication protocol determines which control characters are used and how they are acted upon. It may vary from one system to another and it will be necessary to obtain that information from the system managers before establishing communications.

As mentioned before, ASCII is a widespread code for communications. Inside the computer at each end, the coding might be different. An IBM mainframe will use the Extended Binary Coded Decimal Interchange Code (EBCDIC) where 8 bits represent each symbol. Many microcomputers will use an 8 bit extended ASCII internally (the standard ASCII does not use the most significant bit which always has value 0). The necessary translation for communications will generally be done by the computer, in a manner transparent to the user.

There is another more important difference between internal data manipulation and external communications. The computer will generally move data around in a parallel manner. Each piece of information will typically be manipulated 8, 16, or 32 bits at a time, depending on the CPU word size. The electrical signals forming the bits each travel along a line or wire, but telephone lines and other channels do not have so many wires so the data need to be transmitted serially, one bit at a time. This conversion process is accomplished by a serial interface. There are more than one type of serial interface but the RS–232C is the most widely used on microcomputers. Simplifying to the extreme, this interface has a data register capable of parallel input (all bits of one character simultaneously) and serial output (all bits of one character one after the other) and vice-versa, with appropriate timing.

The telephone line not only forces serial transmission but it also requires that the digital pulses of the computer (e.g., 0 volts = 0, +5 volts = 1) be transformed or modulated using waves (e.g., 1070 Hz = 0, 1270 Hz = 1). This is accomplished by the modem. To obtain an orderly exchange of data, the modem needs to be controlled by the computer, via the serial interface and a wire cable allowing the use of up to 25 different signals.

Depending on the system you communicate with, transmission will take place in the either duplex or half-duplex. In duplex, the hardware allows sending and receiving of data at the same time (using different frequency bands) whereas in half-duplex, transmission occurs in one direction at a time. IBM mainframes use half-duplex communications.

In programming a serial interface or simply setting the parameters of a terminal emulator program, it is necessary to specify the speed at which the data will be transmitted along the channel. The RS–232C is designed to offer a range of 'Baud rates' between 50 and 19200. The Baud rate is the number of signaling elements per second. It can be understood as the number of bits per second (Bps) for the purpose of the current discussion, although the two are not always equivalent: techniques exist to transmit more than one bit per Baud.

A number of problems can arise during communication which can alter the nature of the signals and distort or destroy data. Noise on the telephone line, for instance, could interfere with the frequency of the signal and make a 0 appear as a 1 on arrival. The most reliable strategy would consist in sending the received message back to the sender and compare this copy with the original; but that would at least double transmission time, not to mention all the processing required to compare the messages.

Various methods exist to check for possible errors while maintaining a lower overhead (Lin & Costello, 1983). One is PARITY checking. Recall that the standard ASCII code uses only 7 bits while most microcomputers have a word length of at least 8 bits. During communications the eighth bit can be set or reset according to how many of the 7 character bits are set. For instance, enabling even parity would consist in setting the eighth bit when and only when there is an odd number of 1's in the remaining 7 bits such that overall there would always be an even number of 1's. This parity testing is usually carried out by the interface which will flag any problem.

Another method uses HAMMING CODES. This method associates a parity bit with bits 1, 3, 5, and 7, another parity bit with bits 2, 3, 6, and 7, and a third parity bit with bits 4, 5, 6, and 7. Upon character reception, these extra parity bits are computed from the received data and compared with those sent with the data. Depending on the pattern of change obtained, it can be determined which of the 7 character bits is faulty and correct it. For instance:

1) Data to be sent:
x1 x2x3 x4x5x6x7 = 1 00 0100
2) Transmitted data:
P1x1P2x2x3P3x4x5x6x7 = 0100010100
3) Data groups P1x1 x3 x5 x7 = 01 0 1 0
with even parity: P2x2x3 x6x7 = 000 00
P3x4x5x6x7 = 10100
4) Received data with error in bit x6:
0100010110
5) P's computed from received data:
P3 = 0 P2 = 1 P1 = 0
6) P's received with the data:
P3 = 1 P2 = 0 P1 = 0
7) Change in P's: C3 = 1 C2 = 1 C1 = 0
8) Decimal equivalent of C3C2C1 binary code: (110) = 6
9) Therefore bit 6 is incorrect:
received 1, change to 0
Data Code transmitted should be:
1 00 0100

The ability to isolate which bit was denatured during transmission costs two extra bits per character relative to simple parity checking. This overhead could become unacceptable: at low speed (e.g., 300 Bps), eight more minutes would be required to transfer an 80K characters file (80,000 char X 8 bits/300 Bps/60 seconds = 36 minutes, versus 44 minutes with 10 bits).

Data integrity is the crucial aspect of communications, particularly where file transfers are concerned. A number of protocols have been devised to achieve reliable communications. Here is a brief overview of the strategy used by KERMIT, a protocol developed at Columbia University (Da Cruz & Catchings, 1984):

- Communication takes place in half-duplex over ordinary transmission lines.
- ASCII characters are transmitted in packets of variable length (0–96) in alternate directions and a reply (positive or negative acknowledgment) is required for each packet.
- Only printable characters are used for transmission; non-printable characters (0 to 31) are prefixed with a special character (#) and converted for transmission by adding 32 to their decimal value.
- Each packet begins with a mark, normally SOH (ASCII 01 or CTRL-A), followed by a length field.
- The length is the number of ASCII characters in the packet following this field, including control characters (maximum = 94).
- The next character is the packet sequence number (0–63, wrapping around after a group of 64).
- Then comes a packet type identifier indicating whether the packet contains data, an acknowledgment, a command to be executed immediately, etc.

- Following is the actual contents of the packet, i.e., the data if any.
- The packet terminates with the block-check sequence.
- The system must react within a specified time interval; otherwise a time out occurs and the packet is retransmitted.

The standard error detection provided in the final block-check is an arithmetic checksum, which is the addition of the ASCII values of all the characters in the packet, excluding the mark and the check itself. The result can approach 12,000 (ASCII 127 × 94). The binary representation of this number is 14 bits long (10111011100000) thus two characters would be necessary to represent it fully. This represents a much lower overhead than the addition of 3 extra bits per character as in the Hamming code. The checksum method will leave some errors undetected since with up to 94 characters per sum, there are many combinations that can produce the same sum. According to the protocol designers, the probability of an undetected error is 1/4096 for a two-character checksum.

Another method of error detection allowed in the protocol is a 16 bit Cyclic Redundancy Check (CRC). Essentially, the CRC passes the characters through a shift register with feedback loops such that each bit of the transmitted message affects the block check character more than once. This method will detect all error bursts of 16 bits or less in length and 99.99% of longer ones (MacNamara, 1977).

With such a protocol, what would be the consequences of transmission errors?

- If the SOH is garbled, all characters become ignored until the next mark.
- If any other character in the packet is distorted into SOH, the rest of this packet is taken as a new one but its spurious nature will be caught at the length, sequence, or block-check level.
- If the length field is garbled into a larger value, the checksum will be absent or in any case wrong, leading to a retransmission. If the distortion causes a value smaller than the real length to arrive, then the system will hang, waiting for missing extra characters, until a preset time out is reached.
- If the sequence number, the type field, one or more data characters, or the checksum are distorted, the checksum should be wrong, causing retransmission of that packet.

Conclusion

Having a terminal emulator program at your disposal is certainly a cost efficient strategy since it allows your microcomputer to double up as a terminal.* This is fine if one simply needs access to a mainframe to execute sizable tasks. If the objective is to transfer data files between the two computers in order to use them on either machine, the program must provide reliability checks.

This text attempted to overview some of the basic technical aspects involved in terminal emulation. From the user's point of view at least, other aspects may be very significant such as full-screen editing capabilities (IBM 3270 emulation). These depend on such considerations as what the mainframe system supports and how extensively terminal-mode is used. Although not covered here, they would remain important aspects to consider in selecting or writing a program.

References

Da Cruz, F., and Catchings, B. KERMIT: A file transfer protocol for universities, Part 1: Design considerations and specifications. *Byte*, 9(6):255–278, 1984.

Lin, S., and Costello, D.J., Jr. *Error Control Coding: Fundamentals and Applications*. Englewood Cliffs, N.J.: Prentice-Hall, 1983.

Mackenzie, C.E. *Coded Character Sets, History and Development*. Reading Mass.: Addison-Wesley, 1980.

MacNamara, J.E. *Technical Aspects of Data Communications*. Maynard, Mass.: Digital Press, 1977.

---

*A documented listing of a minimal terminal emulator program is available from the author. This program is written in BASIC for a Hewlett-Packard 9816. It uses some machine-dependent features and performs error detection but not correction. It can be used to learn and build from.

Expert Systems in Psychiatry

Michael Feinberg, M.D., Ph.D.,[1] and
Robert K. Lindsay, Ph.D.[1]

There is a documented shortage of psychiatrists in the United States (GMENAC, 1980), and the estimates of the prevalence of psychiatric illness used to develop this report were lower than the figures in recent population surveys (Myers et al., 1984). Further, most prescriptions for antidepressants are written by non-psychiatrists (Johnson, 1974; Ketai, 1978; Kline, 1974), and the great majority of depressed patients seen by a sample of primary care physicians were treated inappropriately (Weissman et al., 1981). These data highlight the need for improving the treatment provided to the majority of mentally ill patients. We believe that computers can act as consultants to non-psychiatrist clinicians, resulting in improved patient care.

The appropriate computer technology is a form of applied artificial intelligence called *expert systems*. Expert systems are computer programs that encode some of the knowledge used by experts in a particular field and apply an inference-making procedure to this knowledge. There are now several hundred expert systems in various stages of development, covering a broad range of disciplines, a few of which are in active application. Examples of the more mature systems include those used for molecular structure elucidation in organic chemistry (Lindsay et al., 1980), configuration of computer systems (McDermott, 1982), mineral exploration (Campbell et al., 1982), and analysis of pulmonary function tests (Aikins et al., 1982); *see* also Duda and Shortliffe (1983), and Buchanan and Shortliffe (1983).

Expert systems can make accurate diagnoses in internal medicine, even when the patient has several diagnoses. The performance of the program Caduceus (nee Internist) was tested on a group of CPC's (clinical-pathological conferences) from the *New England Journal of Medicine*. The program was correct as often as were the referring physicians, but less often than the expert consultants who discussed the cases (Miller et al., 1982). This record should be considered in light of the fact that the human experts were particularly knowledgeable in a delimited area of internal medicine, while the program's performance was tested on a wide range of cases. Other expert systems can do as well as the best human consultant, but in a narrower domain. These include the Casnet program for the diagnosis of glaucoma (Kulikowski & Weiss, 1982) and programs for acid-base/electrolyte disorders (Patil et al., 1982).

Some expert systems can explain the reasons for asking a question, making a diagnosis, or recommending a therapeutic regimen, although the explanations have tended to be superficial rather than phrased in terms of basic principles. Caduceus, for example, works well but offers no amenities to the user; in the current jargon, it is not user-friendly. In particular, it cannot explain why it reached a diagnosis other than by displaying its initial probability data and its calculations. The program as written has no concept of time, and cannot make use of the order in which symptoms occurred, or of such concepts as episodes of illness or the rate of onset of a symptom. Fagan and his associates (Horvitz et al., 1984) have used a similar, Bayesian method in an expert system for the differential diagnosis of lymphomas using data gathered from inspection of a slide. In this situation, there are no temporal relationships to account for.

Shortliffe (1976; Buchanan & Shortliffe, 1984) wrote perhaps the best known medical expert system, MYCIN, which can diagnose and make treatment recommendations for meningitis and septicemia. The group at Stanford went on to separate the control structure of MYCIN from its knowledge about infectious diseases. The resulting program, called EMYCIN (Essential MYCIN), can "reason" in any domain and thus forms the basis of a wide variety of expert systems (van Melle, 1981, 1984). Each new expert system can be written by constructing a new knowledge base in the form of if-then (production) rules with a minimum of "program-

---

[1] Mental Health Research Institute, Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109-0010.

ming" required. The principles involved have shaped the design of expert systems and are central to the work we are doing.

As we have noted, it is extremely important that an expert system be able to explain its behavior to the client. This is so for two reasons. First, it is necessary for client acceptance. Second, it is necessary if the client and program are to work together in a manner that makes use of their complementary abilities. MYCIN, and EMYCIN-based systems in general, have a primitive explanation facility derived from the rule-based style of programming itself. Since rules are a more-or-less transparent and modular form of knowledge representation, informing the client that decisions were reached via such-and-such a rule is readily possible. Insofar as the rules succeed in encapsulating meaningful knowledge, these "explanations" are valuable.

The example below shows a rule from an expert system for the Hamilton Rating Scale and the explanation based on the rule:

RULE 003

[This rule is tried in order to find out whether retardation is severe or worse.]
If: 1) Retardation is moderate or worse, and
  2) A: Interview is prolonged by slowed speech,
    B: Gait is slow-with-decreased-associated-movements, or
    C: Time to complete self-ratings is abnormally long
Then: It is definite (1.0) that retardation is severe or worse.
  9) Does slowed speech prolong the interview to a marked degree?
  ** WHY
[i.e., WHY is it important to determine whether interview is prolonged by slowed speech?]
[3.0] This will aid in determining whether retardation is severe or worse. It has already been established that
  [3.1] retardation is moderate or worse
  Therefore, if
  [3.2] 1) Interview is prolonged by slowed speech,
    2) Gait is slow-with-decreased-associated-movements, or
    3) Time to complete self-ratings is abnormally long
then
it is definite (1.0) that retardation is severe or worse.
[RULE 003]

However, some rules are necessary simply to control certain record keeping functions in the program, and when these are offered as part of explanation the result is often puzzling (e.g., "I asked for that datum because that is one of the things I need to know."). Furthermore, the rule set does not contain the reasons for its own construction, and so a more global explanation cannot be obtained from it.

Swartout (1981, 1983) has developed a more sophisticated explanation facility for an expert system. He constructed an expert system that explains its questions and actions in terms of underlying knowledge, such as basic physiology and pharmacology, by having the expert system incorporate that information and literally build its own higher level knowledge on the foundation of the underlying concepts. The examples below show two explanations of the reason for asking about serum potassium before prescribing digoxin. The first is from a rule-based system; the second, from Swartout's explanation system.

1) What is the level of serum potassium?
Enter numerical value = = = > why?
My top goal is to begin therapy. One step in doing that is to check sensitivities. I am now trying to check sensitivity due to potassium.

2) Please enter the value of serum-k:why?
The system is anticipating digitalis toxicity. Decreased serum-k causes increased automaticity, which may cause a change to ventricular fibrillation. Increased digitalis also causes increased automaticity. Thus, if the system observes decreased serum-k, it reduces the dose of digitalis due to deceased serum-k.
Please enter the value of serum-k:3.7.

There have been a few recent attempts to apply expert systems methods to psychiatry, and interest in these applications has been growing. Heiser and Brooks (1978; Brooks & Heiser, 1980) began a project, called HEADMED, in the late 1970's. Their program used EMYCIN (van Melle, 1981) and was designed to work backward from available medications, attempting to select the one that was indicated by rules that related drugs to symptoms. This system was never fully implemented.

A small system applying knowledge engineering methods was constructed in 1983 by two medical externs at Stanford University Medical School. That program, called BLUEBOX (Mulsant & Servan-Schreiber, 1984), contained about 175 rules written in EMYCIN. We studied and ran this program and discussed it with its authors at length prior to beginning our own efforts. Neither HEADMED nor BLUEBOX was ever subjected to validation tests.

Erdman (1983) developed two computer-based diagnostic models for depression, based on the advice and expertise of a psychiatrist. One model was represented as a "flowchart" of questions and answers; the second "decision theoretic" model was based on statistical relations of symptoms and illness. These models were applied to a limited sample of (eight) actual cases that were also analyzed by a group of psychiatrists and a group physicians (non-psychiatrists). Neither model correlated well with the average of the psychiatrists' recommendations; the flow chart model doing no better than a random selection, the probabilistic model doing slightly better (kappa = .44). However, Erdman found a positive effect of these models on the confidence of non-psychiatric users.

We employed three programming tools for expert systems in the pilot studies. Two of these, EMYCIN (van Melle, 1981) and AGE (Nii & Aiello, 1979), were made available to us on the SUMEX national computer resource for artificial intelligence in medicine, located at Stanford University and accessed over computer network (Tymnet). The third is a commercial programming system for expert systems, KEE, developed by Intellicorp of Palo Alto, and used on a Xerox 1108 and a Symbolics 3600 scientific workstation. We first used EMYCIN to develop a system to consult in the use of the Hamilton Rating Scale, a standard tool for evaluation of depression (Hamilton, 1960, 1967). This expert system taught us several important lessons about constructing expert systems in general and about using EMYCIN to do so. We also developed a pilot version of a rule-based inference system for the diagnosis of depression, derived from observation of clinical interviews by an expert diagnostician (Feinberg). This system was initially developed on SUMEX using the AGE system. The AGE software is not maintained as a production tool by the SUMEX staff, and access over the network is slow and limited to standard keyboad/CRT interactions. Our experiences in using EMYCIN and AGE on SUMEX via Tymnet also convinced us that we would make more rapid progress using local machines, once past the pilot stages. SUMEX served us very well for pilot work, but will not be adequate for more intensive work with a larger knowledge base.

We sought a more efficient alternative, and one of us (RKL) was able to obtain an academic grant from Intellicorp allowing us to use the KEE system. This is a commercial product which runs on sophisticated workstations such as the Xerox 1108. Intellicorp provides documentation, maintenance (including bug reporting by electronic mail), and training. We have been using KEE to develop an expert system on the somatic treatment of depression.

An Expert System for the Diagnosis of Depression

There has been a growing emphasis in American psychiatry on careful diagnosis using clearly defined clinical criteria (APA, 1980; Feighner et al., 1972; Feinberg & Carroll, 1982, 1983; Spitzer et al., 1975). These efforts have led to several lists of criteria for the diagnosis of psychiatric disorders. The "St. Louis" criteria (Feighner et al., 1972) were succeeded by the Research Diagnostic Criteria (RDC), formulated by researchers from St. Louis and New York (Spitzer et al., 1975). The RDC led directly to the criteria that are now quasi-official in American psychiatry, DSM-III (APA, 1980). All of these lists of criteria were based on a combination of clinical opinion and literature review.

These diagnostic systems have been shown to be acceptably reliable, but their validity has not been as well demonstrated.

The criterion lists mentioned above have emphasized the diagnosis of affective disorders (e.g., depression), reflecting earlier evidence that American psychiatrists tended to overdiagnose schizophrenia in preference to affective disorders (Cooper et al., 1972). Several groups in England and the United States have used multivariate statistics to differentiate subtypes of depression. Roth and his colleagues (Carney et al., 1965) published a discriminant index (the Newcastle Diagnostic Index) for distinguishing "endogenous" from "neurotic" depressed patients. Kiloh et al. (1972) confirmed their results in a separate population. We have done similar work, deriving two discriminant indices for separating endogenous depressed (ED) patients (unipolar or bipolar) from those with nonendogenous ("neurotic") depression (ND). We cross-validated these indices in separate groups of patients, and also validated them against an external standard, the dexamethasone suppression test (Feinberg & Carroll, 1982, 1983). The Newcastle and Michigan Indices tend to contain the same symptoms, and both tend to differ from the criterion lists based on "clinical wisdom."

We have continued our work on the differential diagnosis of depression using an expert system written by Fagan and co-workers at Stanford (Horvitz et al., 1984). This program, Pathfinder, is being developed to distinguish among lymphomas on the basis of data gathered from inspection of a slide, using modified Bayesian statistics and logic similar to that of Internist–1 (Miller et al., 1982). We have applied Pathfinder to the task of distinguishing endogenous and nonendogenous depression. The knowledge base we provided includes marginal probabilities computed on data from the patients studied by Feinberg and Carroll (1982), specifically, the probability that a particular symptom will be present at a certain intensity in each diagnostic group and the probability that a patient with a given level of a symptom will belong to each diagnostic group. We used the Pathfinder program to assign diagnoses to a separate group of patients, with the results shown in the table. The program computes the probability of the patient's belonging to each diagnostic group, and we have assigned the patient to a group if the probability of his membership is above 0.66 (i.e., 2:1 odds or better). As expected, the results are almost exactly those obtained using the Michigan Discriminant Index for separating unipolar ED from ND patients (Feinberg & Carroll, 1982).

Pathfinder Diagnosis

		ED	?	ND	Total
Clinical	ED	17	5	4	26
Diagnosis	ND	6	4	15	25
					51

Forty-two of the 51 patients in this group were classified by the program (82%). Of these, 32 of 42 (76%) were classified correctly. This is far better than chance but we are trying to improve this by adding clinical features not included in the discriminant index.

The Pathfinder program can be run in two modes. The first, used to produce the results above, calculates the probability of each diagnosis from the (complete) data for each patient, based on the marginal probabilities in the knowledge base. In the second mode, more consistent with what one usually expects from an expert system, the program sequentially asks for the additional information that will be most useful in reaching a diagnosis until it can assign a sufficiently high probability to the patient's belonging to one diagnostic group. An example of computer-clinician dialogue for each mode is available from the authors. Our work to date has shown that the program can reach acceptably accurate diagnoses, but we will not have an accurate picture of its suitability for our particular problem until we have added more diagnoses and more clinical features to the knowledge base.

References

Aikins, J.S., Kunz, J.C., Shortliffe, E.H., and Fallat, R.J. PUFF: An expert system for interpretation of pulmonary function data. *Comput. Biomed. Res.*, 16:199–208, 1983. (Reprinted in Clancey, W.J., and Shortliffe, E.H., 1984.)

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Health Disorders*, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

Brooks, R.E., and Heiser, J.F. Some experiences with transferring the MYCIN system to a new domain. Correspondence. *IEEE Trans. Pattern Analysis Machine Intelligence PAMI*, 2:477–479, 1980.

Buchanan, B.G., and Shortliffe, E.H. (eds.). *Rule-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project*. Reading, Mass.: Addison-Wesley, 1984.

Campbell, A.N., Hollister, V.F., Duda, R.O., and Hart, P.E. Recognition of hidden mineral deposits by artificial intelligence programs. *Science*, 217:927–932, 1982.

Carney, M.W.P., Roth, M., and Garside, R.F. The diagnosis of depressive syndromes and the prediction of ECT response. *Br. J. Psychiatry*, 111:659–674, 1965.

Cooper, J.E., Kendell, R.E., Gurland, B.J., et al. *Psychiatric Diagnosis in New York and London*. London: Oxford University Press, 1972.

Duda, R.O., and Shortliffe, E.H. Expert systems research. *Science*, 220:261–268, 1983.

Erdman, H.P. A comparison of computer consultation programs for primary care physicians: Impact of decision-making model and explanation capability. Doctoral dissertation, University of Wisconsin-Madison, 1983.

Feighner, J.P., Robins, E., Guze, S.B., et al. Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiatry*, 26:57–63, 1972.

Feinberg, M., and Carroll, B.J. Separation of subtypes of depression using discriminant analysis: I. Separation of unipolar endogenous depression from nonendogenous depression. *Br. J. Psychiatry*, 140:384–391, 1982.

Feinberg, M., and Carroll, B.J. Separation of subtypes of depression using discriminant analysis. II. Separation of bipolar endogenous depression from nonendogenous ("neurotic") depression. *J. Affective Disord.*, 5:129–139, 1983.

GMENAC: Graduate Medical Education National Advisory Committee Summary Report to the Secretary of Health and Human Services. Washington, D.C.: U.S. Government Printing Office, 1980.

Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry*, 23:56–62 1960.

Hamilton, M. Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychol.*, 6:278–296, 1967.

Heiser, J.F., and Brooks, R.E. Design considerations for a clinical psychopharmacology advisor. Proceedings, Second Annual Symposium on Computer Applications in Medical Care. New York: IEEE, 1978, pp. 278–285.

Horvitz, E.J., Heckerman, D.E., Nathwani, B.N., and Fagan, L.M. Diagnostic strategies in the hypothesis-directed PATHFINDER system. *Proceedings of the first conference on artificial intelligence applications*, 1984, pp. 630–636.

Johnson, D.A.W. A study of the use of antidepressant medication in general practice. *Br. J. Psychiatry*, 125:186–192, 1974.

Ketai, R. Family practitioners' knowledge about treatment of depressive illness. *JAMA*, 235:2600–2603, 1978.

Kiloh, L.G., Andrews, G., and Neilson, M. The relationship of the syndromes called endogenous and neurotic depression. *Br. J. Psychiatry*, 121:183–196, 1972.

Kline, N.S. Antidepressant medication: A more effective use by general practitioners, family physicians, internists, and others. *JAMA*, 227:1158–1160, 1974.

Kulikowski, C.A., and Weiss, S.M. Representation of expert knowledge for consultation: The CASNET and EXPERT projects. In: Szolovits, P. (ed.), *Artificial Intelligence in Medicine*. Boulder, Colo.: Westview Press, 1982, pp. 21–55.

Lindsay, R.K., Buchanan, B.G., Feigenbaum, E.A., and Lederberg, J. *Applications of Artificial Intelligence for Organic Chemistry: The DENDRAL Project*. New York: McGraw Hill Book Co., 1980.

McDermott, J. Rl: A rule-based configurer of computer systems. *Artif. Intell.*, 19:39–88, 1982.

Miller, R.A., Pople, H.E., and Myers, J.D. INTERNIST–1, An experimental computer-based diagnostic consultant for general internal medicine. *New Engl. J. Med.*, 307:468–476, 1982. Reprinted in Clancey, W.J., and Shortliffe, E.H., (eds.), *Readings in Medical Artificial Intelligence*. Reading, Mass.: Addison-Wesley, 1984, pp. 190–209.

Mulsant, B., and Servan-Schreiber, D. Knowledge engineering: A daily activity on a hospital ward. *Comput. Biomed. Res.*, 17:71–91, 1984.

Myers, J.K., Weissman, M.M., Tischler, G.L., et al. Six-month prevalence of psychiatric disorders in three communities. *Arch. Gen. Psychiatry*, 41:959, 1984.

Nii, H.P., and Aiello, N. AGE (Attempt to Generalize): A knowledge-based program for building knowledge-based programs. *Proc. Int. Joint Conf. Artif. Intell.*, 6:645–655, 1973.

Patil, R.S., Szolovits, P., and Schwartz, W.B. Modeling knowledge of the patient in acid-base and electrolyte disorders. In: Szolovits, P. (ed.), *Artificial Intelligence in Medicine*. Boulder, Colo.: Westview Press, 1982, pp. 191–226.

Shortliffe, E.H. *A Computer-Based Medical Consultant: MYCIN*. Amsterdam: Elsevier, 1976.

Spitzer, R.L., Endicott, J., and Robins, E. *Research Diagnostic Criteria*, 2nd ed. New York State Department of Mental Hygiene, New York Psychiatric Institute, Biometric Research Divison, 1975.

Swartout, W.R. Explaining and justifying expert consulting programs. *Proc. of Seventh Inter. Joint Conf. on*

Artif. Intell., 2:815–823. Los Altos, Calif.: William Kaufmann, 1981.

Swartout, W.R. XPLAIN: A system for creating and explaining expert consulting programs. Marina del Rey, Calif.: Information Sciences Institute, ISI Reprint Series ISI/RS-83-4, 1983.

van Melle, W. The EMYCIN Manual. Stanford University: Heuristic Programming Project Report HPP-81-16, 1981.

van Melle, W. The structure of the MYCIN system. In: Buchanan, B.G., and Shortliffe, E.H. (eds.), *Rule-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project.* Reading, Mass.: Addison-Wesley, 1984, pp. 67–77.

Weissman, M.M., Myers, J.K., and Thompson, D. Depression and its treatment in a U.S. urban community: 1975–1976. *Arch. Gen. Psychiatry*, 38:417–421, 1981.

CUMULATIVE INDEX

Psychopharmacology Bulletin

A. Contents Index

Vol. 21, No. 1, 1985

1 **Annual NCDEU Meeting (1984)—Abridged Proceedings—Consensus Conferencing—**

2 Notes on the Consensus Development Process — *David J. Kupfer and Margaret C. McDonald*

7 An NIMH View of Consensus Conferencing — *Harold Alan Pincus*

Carbamazepine in Psychiatric Disorders —

10 Carbamazepine in Bipolar Illness — *Robert M. Post and Thomas W. Uhde*

18 Carbamazepine and Lithium: Different Profiles in Affective Disorder? — *Bernard Lerer, Norman Moore, Elaine Meyendorff, Sung-Ran Cho, and Samuel Gershon*

Medical Compliance —

23 Compliance in the Long-Term Treatment of Schizophrenia — *John M. Kane and Michael Borenstein*

28 Adherence to Methylphenidate Therapy in a Pediatric Population: A Preliminary Investigation — *Ronald T. Brown, Kathi A. Borden, and Stephen R. Clingerman*

37 Implications of Noncompliance on Research in Affective Disorders — *Ellen Frank, Robert F. Prien, David J. Kupfer, and Lisa Alberts*

Receptor Modulation as a Treatment Strategy —

43 Serotonin Agonists and Beta-Adrenergic Agonists as a Treatment for Depressive Disorder: A Direct Clinical Application — *Stephen M. Stahl*

Blood Levels of Haloperidol and Clinical Response —

48 Haloperidol Plasma Levels and Clinical Response: Basic Concepts and Clinical Data — *John M. Davis, Stephen E. Ericksen, Stephen Hurt, Sidney S. Chang, Javaid I. Javaid, Haroutune Dekirmenjian, and Regina Casper*

52 Haloperidol and Thioridazine Drug Levels and Clinical Response in Schizophrenia: Comparison of Gas-Liquid Chromatography and Radioreceptor Drug Level Assays — *Robert C. Smith, Richard Baumgartner, Alla Burd, G.K. Ravichandran, and Mary Maudlin*

59 Does a Therapeutic Window for Plasma Haloperidol Exist?: Preliminary Chinese Data — *Steven G. Potkin, Yucun Shen, Dongfeng Zhou, Herbert Pardes, Liang Shu, Bruce Phelps, and Russell Poland*

62 Plasma Haloperidol Levels and Clinical Response: Confounding Variables — *Michael L. Mavroidis, David L. Garver, Donald R. Kanter, and Jack Hirschowitz*

66 Absence of Relationship of Serum Haloperidol Concentration and Clinical Response in Chronic Schizophrenia: A Fixed-Dose Study — *Llewellyn B. Bigelow, Darrell G. Kirch, Tammy Braum, Esa R. Korpi, Richard L. Wagner, Steven Zalcman, and Richard Jed Wyatt*

69 Plasma Levels of Haloperidol and Clinical Response — *Theodore Van Putten, Stephen R. Marder, Philip R.A. May, Russell E. Poland, and Ronald P. O'Brien*

Free Communications—Session A —

73 An Early Phase II Clinical Trial with Follow-up of Tomoxetine (LY139603) in the Treatment of Newly Admitted Depressed Patients — *G. Chouinard, L. Annable, J. Bradwejn, A. Labonte, B. Jones, P. Mercier, and M.-C. Belanger*

77 The Dexamethasone Suppression and TRH Stimulation Tests in the Initial Phase of Depression Treatment — *Javier I. Escobar, Angelos Halaris, Lewis Baxter, Glenn Schwarcz, Mark Thompson, Margo Lea Hurwicz, MaryAnn Hill, Melinda Young, Kathleen Daugherty, and April Clemens*

81 A Prospective Study of Lithium-Induced Nephropathy: Preliminary Results — *Jay D. Amsterdam, Diane Jorkasky, Larry Potter, and Malcolm Cox*

85 A Controlled Study of the Effects of Antidepressants on Sexual Function — *Wilma M. Harrison, Jonathan Stewart, Anke A. Ehrhardt, Judith Rabkin, Patrick McGrath, Michael Liebowitz, and Frederic M. Quitkin*

89 Effects of Naloxone on Cognitive Deficits Following Electroconvulsive Therapy — *Henry A. Nasrallah, Nils Varney, Jeffrey A. Coffman, John Bayless, and Suzanne Chapman*

91 Efficacy and Withdrawal of Two Potent Benzodiazepines: Bromazepam and Lorazepam — *R. Fontaine, L. Annable, P. Beaudry, P. Mercier, and G. Chouinard*

93 Psychomotor Performance Following the Long-Term Use of Benzodiazepines — *Irwin Lucki, Karl Rickels, and Andrew M. Geller*

97 Brotizolam in the Treatment of Insomnia — *Roberto A. Dominguez, Burton J. Goldstein, Alan F. Jacobson, and Richard M. Steinbook*

101 A Clinical Rating Scale for Symptoms of Psychosis in Alzheimer's Disease — *Barry Reisberg and Steven H. Ferris*

Free Communications—Session B —

105 FDA's Monitoring of Clinical Trials — *Walter Sloboda and Carolanne Currier*

107 Attrition and its Consequence in a Clinical Trial of Placebo, Imipramine, and Phenelzine — *Jeffrey S. Markowitz, Judith G. Rabkin, Patrick J. McGrath, Jonathan Stewart, and Frederic M. Quitkin*

110 Psychopharmacologic Treatment and Informed Consent: Empirical Research — *Barbara Stanley, Michael Stanley, Judith Stein, Lisa Guido, and Roxanna-Pentland Transit*

114 A Trial of Adjunctive Imipramine in Post-psychotic Depression — *Samuel G. Siris, Arthur Rifkin, Gerard T. Reardon, Seshagiri R. Dotti, Patricia Foster, and Elaine Casey*

117 Experience with a Drug-Free Month in Schizophrenic Outpatients — *Douglas W. Heinrichs and William T. Carpenter, Jr.*

120 A Comparison of the Clinical Effects of Bromperidol, a New Butyrophenone Derivative, and Haloperidol on Schizophrenia Using a Double-Blind Technique — *Hitoshi Itoh*

123 Methylphenidate Challenge Tests and Course of Schizophrenia — *Jeffrey A. Lieberman, John M. Kane, Dominick Gadaletta, Jorge Ramos-Lorenzi, Kenneth Bergmann, James Wegner,and Hana Novacenko*

130 Tardive Dyskinesia and Depressive Symptoms in Schizophrenics — *Mary Ann Richardson, Raymond Pass, Zachary Bregman, and Thomas J. Craig*

136 The Prevalence of Tardive Dyskinesia — *John M. Kane, Margaret Woerner, Jeffrey Lieberman, Paul Weinhold, William Florio, Morton Rubinstein, John Rotrosen, Janos Kurucz, Sukdeb Mukherjee, Kenneth Bergmann, and Nina R. Schooler*

140 Neuroleptic-Related Dyskinesias in Autistic Children: A Prospective Study — *Richard Perry, Magda Campbell, Wayne H. Green, Arthur M. Small, Maria L. Die Trill, Karen Meiselas, Robert R. Golden, and Stephen I. Deutsch*

144 Desipramine in the Treatment of Attention Deficit Disorder in Adolescents — *David R. Gastfriend, Joseph Biederman, and Michael S. Jellinek*

146 Amino Acid Precursors for the Treatment of Attention Deficit Disorder, Residual Type — *David R. Wood, Frederick W. Reimherr, and Paul H. Wender*

150 A Controlled Trial of Clomipramine in Childhood Obsessive-Compulsive Disorder — *Martine F. Flament, Judith L. Rapoport, Carol J. Berg, and Clinton Kilts*

153 **Cumulative Index—Psychopharmacology Bulletin—1984—**

Contents Index

Authors Index

B-1 **Psychopharmacology—A Recurring Bibliography—**

Vol. 21, No. 2, 1985

167 **Introduction—***Natalie Reatig*

Pharmacotherapy for ADD-H Adolescents Workshop —

169 Follow-up Studies on Outcome of Hyperactive Children — *Gabrielle Weiss*

178 Adolescent Outcome of Hyperactive Children Treated with Stimulants in Childhood: A Review — *Lily Hechtman*

192 Pharmacotherapy in ADD Adolescents with Special Attention to Multimodality Treatments — *Ronald T. Brown, Kathi A. Borden, and Stephen R. Clingerman*

212 Prevalence of Medication Treatment for Hyperactive Adolescents — *Daniel J. Safer and John M. Krager*

216 A Review of Studies of Drug Treatment Efficacy with Attention Deficit Disorder with Hyperactivity in Adolescents — *Christopher K. Varley*

222 Pharmacological Treatment of Attention Deficit Disorder, Residual Type (ADDRT, "Minimal Brain Dysfunction," "Hyperactivity" in Adults) — *Paul H. Wender, David R. Wood, and Fred W. Reimherr*

232 New Drug Trials in Attention Deficit Disorder — *Judith L. Rapoport, Alan Zametkin, Maureen Donnelly, and Deborah Ismond*

237 Diagnosing ADD-H in Adolescents — *Rachel Gittelman and Salvatore Mannuzza*

243 Issues in the Study of Adolescent ADD-Hyperactivity — *C. Keith Conners*

A Summary of the Workshop Proceedings

251 Pharmacotherapy of ADD in Adolescents: What Do We Know, Where Should We Go, How Should We Do It? — *Dennis P. Cantwell*

Pharmacotherapy and Mental Retardation Workshop —

258 Emotional Problems in the Mentally Retarded: The Need for Assessment and Treatment — *Johnny L. Matson*

262 Issues in Pharmacology with the Mentally Retarded — *Susan Mouchka*

268 Psychoactive Drug Use in Public and Community Residential Facilities for Mentally Retarded Persons — *James Intagliata and Chris Rinck*

279 A National Study of Prescribed Drugs in Institutions and Community Residential Facilities for Mentally Retarded People — *Bradley K. Hill, Elizabeth A. Balow, and Robert H. Bruininks*

285 Establishing Socially Validated Drug Research in Community Settings — *Martin Agran and James E. Martin*

291 Prevalence and Efficacy of Stimulant Drug Use with Mentally Retarded Children and Youth — *Kenneth D. Gadow*

304 Psychopharmacology in the Mentally Retarded and a Few Related Issues — *C. Thomas Gualtieri and J.M. Keppel*

310 Behavioral Interactions Induced by Chronic Neuroleptic Therapy in Persons with Mental Retardation — *Stephen R. Schroeder and C. Thomas Gualtieri*

316 Diagnosis and Pharmacotherapy of Schizophrenia in the Retarded — *Frank J. Menolascino, Stephen L. Ruedrich, Charles J. Golden, Ph.D., and James E. Wilson, Pharm.D.*

Workshop Summary —

323 Issues and Future Research Directions of Pharmacotherapy in Mental Retardation — *Stephen R. Schroeder*

Brief Report —

327 An Applied Tardive Dyskinesia Monitoring System (ATDMS) — *John E. Kalachnik*

329 Pharmacotherapy and Mental Retardation/Developmental Disability: A Bibliography — *Natalie Reatig*

Adverse Drug Reaction —

334 "Time-less" Risks (A Hazard of Risk Assessment: The Example of Seizure and Antidepressants — *Paul Leber*

Articles —

339 ACTeRS Useful in Screening Learning Disables from Attention Deficit Disordered (ADD-H) Children — *Rina K. Ullmann*

345 Carbamazepine in Tardive Dyskinesia — *András Perényi and Dániel Sztanisz-láv*

347 Biochemistry of Alzheimer's Disease — *Ira R. Berry and Lionel Borkan*

B-1 **Psychopharmacology— A Recurring Bibliography—**

Vol. 21, No. 3, 1985

357 **In the Pipeline—***Barry Blackwell*

23rd Meeting of the ACNP—1984— Abridged Proceedings —

New Approaches to the Genetics of Psychiatric Disorders —

361 Additional Cerebrospinal Fluid Proteins Found in Schizophrenia and Creutzfeldt-Jakob Disease — *Michael G. Harrington and Carl R. Merril*

365 Cerebral Ventricular Enlargement as a Possible Genetic Marker for Schizophrenia — *Lynn E. DeLisi, Lynn R. Goldin, Joel R. Hamovit, M. Elizabeth Maxwell, David Kurtz, John I. Nurnberger, and Elliot S. Gershon*

Bright Light, Melatonin, and Biological Rhythms: Implications for the Affective Disorders —

368 Treating Phase Typed Chronobiologic Sleep and Mood Disorders Using Appropriately Timed Bright Artificial Light — *Alfred J. Lewy, Robert L. Sack, and Clifford M. Singer*

New Strategies in the Therapy of Affective Disorders —

373 The Serotonin/Norepinephrine-Linked Beta-Adrenoceptor System and the Mode of Action of Antidepressant — *Elaine Sanders-Bush, P. Jeffrey Conn, and Fridolin Sulser*

379 Serotonergic Modulation of Cortical Rat Noradrenergic System in the Mechanism of Action of Antidepressant Drugs — *N. Brunello, I. Mocchetti, A. Volterra, V. Cuomo, and G. Racagni*

385 The GABA Hypothesis of Depression and Antidepressant Drug Action — *G. Bartholini, K.G. Lloyd, B. Scatton, B. Zivkovic, and P.L. Morselli*

Do We Need CSF Studies in Clinical Pharmacology? —

389 CSF, Plasma, and Urine: What Do Concomitant Measurements of Norepinephrine and Its Metabolites Mean? — *Markku Linnoila, Elizabeth A. Lane, Sally Guthrie, Ioanis Parashos, Matthew Rudorfer, and William Z. Potter*

396 Can CSF Measures Distinguish Among Schizophrenia, Depression, Movement Disorders, and Dementia? — *Stephen M. Stahl*

400 Clinical Implications of Neurochemical Mechanisms of Appetite Regulation—Neuropeptidergic Regulation of Feeding — *John E. Morley, Blake A. Gosnell, Dean D. Krahn, James E. Mitchell, and Allen S. Levine*

406 Peptide-Catecholamine Interaction: Feeding and Satiety — *Robert D. Myers*

412 Brain Neurotransmitters and Appetite Regulation — *Sarah F. Leibowitz*

419 Disturbances of Norepinephrine Metabolism and α-2 Adrenergic Receptor Activity in Anorexia Nervosa: Relationship to Nutritional State — *Walter H. Kaye, Harry E. Gwirtsman, C. Raymond Lake, Larry J. Siever, David C. Jimerson, Michael H. Ebert, and Dennis L. Murphy*

Pharmacologic Model of Anxiety in Man —

424 Isoproterenol-Induced Anxiety States — *Robert Pohl, John Rainey, Aurelio Ortiz, Richard Balon, Heminder Singh, and Richard Berchou*

428 The Lactate Infusion Model — *Jack M. Gorman, Donald Dillon, Abby J. Fyer, Michael R. Liebowitz, and Donald F. Klein*

434 Panic Anxiety and Lactate Metabolism — *John M. Rainey, Jr., Charles E. Frohman, Ken Warner, Stewart Bates, Robert B. Pohl, and Vikram Yeragani*

Biological and Behavioral Reactions to Stress —

438 Regulation of Adrenocorticotropin Release From the Anterior Pituitary — *Terry Reisine*

443 Melancholia in Rodents: Neurobiology and Pharmacology — *Fritz A. Henn, Joel Johnson, Emmeline Edwards, and David Anderson*

447 Neurochemical Basis of Stress-Induced Depression — *Jay M. Weiss and Prudence Goodman Simson*

458 Serotonin-Behavior Interactions in Vervet Monkeys — *Michael T. McGuire and Michael J. Raleigh*

Enkephalin-Endorphins: Emotional Stress, Depression, and the Immune System —

464 Selectivity of Opioid Agonists and Antagonists for the Various Opioid Receptor Types — *A.E. Takemori and P.S. Portoghese*

466 Opioid Peptides in the Adrenal Pituitary Axis — *Christopher J. Evans, Elizabeth Erdelyi, and Jack D. Barchas*

472 The Alpha MSH-Specific and Arcuate Pro-Opiomelanocortin Neuronal Systems of the Hypothalamus: Observations on Their Connectivity and Response to Colchicine Treatment — *Karl M. Knigge, Diane T. Piekut, and Shirley A. Joseph*

476 Depression, Hypothalamic-Pituitary-Adrenocortical Activity, and Lymphocyte Function — *Ziad Kronfol and J. Daniel House*

479 Involvement of Opioid Peptides in the Analgesic, Immunosuppresive, and Tumor-Enhancing Effects of Stress — *James W. Lewis, Yehuda Shavit, Gregory W. Terman, Linda R. Nelson, Fredricka C. Martin, Robert Peter Gale, and John C. Liebeskind*

485 Endorphins, Immune Function, and Cancer — *John E. Morley, Neil Kay, John Allen, Timothy Moon, and Charles J. Billington*

489 The Ying-Yang Hypothesis of Opioid Peptide Immunomodulation — *Nicholas P. Plotnikoff*

Psychobiological Markers for Schizophrenia: State of the Art and Future Perspectives —

490 Introduction and Summary — *Joseph Zubin*

497 Are There State-Dependent Markers in Schizophrenia? — *Daniel P. van Kammen, Jules P. Rosen, Jeffrey Peters, Robert Fields, and Welmoet B. van Kammen*

503 Vulnerability to Schizophrenia: Childhood Indicators Predict Adult Outcome — *Ernest Hartmann, Walter Mitchell, Patricia Brune, and Daniel Greenwald*

509 Distractibility as a Marker of Vulnerability to Schizophrenia — *Bonnie Spring*

513 Neurophysiological Aspects of Information Processing in Schizophrenia — *Stuart R. Steinhauer*

518 Sensory and Perceptual Behavioral Markers of Schizophrenia — *Mitchell L. Kietzman*

Neuropeptides Modulating Dopaminergic Function: New Horizons for the Dopamine Hypothesis of Schizophrenia —

523 Cholecystokinin Potentiates Dopamine-Mediated Behaviors in the Nucleus Accumbens, a Site of CCK-DA Co-Existence — *Jacqueline N. Crawley*

Toxic Effects of Psychomotor Stimulants —

528 Persistent Effects of Amphetamine, *p*-Chloroamphetamine, and Related Compounds on Central Dopamine and Serotonin Neurons in Rodents — *Ray W. Fuller*

Alternate Treatment Strategies in Schizophrenia: Focus on the Deficit State —

533 High-Dose Versus Low-Dose Strategies in the Treatment of Schizophrenia — *John M. Kane, Arthur Rifkin, Margaret Woerner, Gerald Reardon, Dolores Kreisman, Richard Blumenthal, and Michael Borenstein*

Panic Disorder and Major Depression: Epidemiology, Family Studies, Biologic, and Treatment Response Similarities —

538 The Epidemiology of Anxiety Disorders: A Highlight of Recent Evidence — *Myrna M. Weissman, Philip J. Leaf, Charles E. Holzer III, and Kathleen R. Merikangas*

543 Major Depression and Panic Disorder: A Family Study Perspective — *James F. Leckman, Myrna M. Weissman, Kathleen R. Merikangas, David L. Pauls, Brigitte A. Prusoff, and Kenneth K. Kidd*

546 Neuroendocrine Abnormalities in Panic Disorder — *Peter P. Roy-Byrne, Thomas W. Uhde, Philip W. Gold, David R. Rubinow, and Robert M. Post*

551 Panic Disorder and Major Depression: Biological Relationships — *Peter P. Roy-Byrne and Thomas W. Uhde*

555 Lactate Infusion in Patients With Depression and Anxiety — *Patrick J. McGrath, Jonathan W. Stewart, Wilma Harrison, Frederic M. Quitkin and Judith Rabkin*

558 Effect of Panic Attacks on the Treatment of Atypical Depressives — *Michael R. Liebowitz, Frederic M. Quitkin, Jonathan W. Stewart, Patrick J. McGrath, Wilma Harrison, Judith Rabkin, Elaine Tricamo, Jeffrey S. Markowitz, and Donald F. Klein*

562 Panic Attacks in Outpatients With Depression: Response to Antidepressant Treatment — *Donald S. Robinson, Allen Kayser, John Corcella, Desmonde Laux, Kevin Yingling, and Diantha Howard*

Hormones and Depression—An Update —

568 Hormones and Depression—Conceptual Transitions — *Uriel Halbriech*

Peripheral Models for the Study of Neurotransmitter Receptors in Man —

573 Yohimbine and Clonidine Recognize Different States of Adrenergic Receptors on Human Platelets: Reconsideration of Studies on Platelet Alpha-2 Receptors in Depressive Illness — *John E. Piletz and Angelos Halaris*

579 Nocturnal Serum Melatonin in Major Depressive Disorder Before and After Desmethylimipramine Treatment — *Richard P. Brown, Stanley Caroff, James J. Kocsis, Jay Amsterdam, Andrew Winokur, Peter Stokes, and Alan Frazer*

Patterns of Cognitive Effects of Somatic Therapies —

582 Effect of Neuroleptic Treatments on Attention, Information Processing, and Thought Disorder — *Herbert E. Spohn, Lolafaye Coyne, Fred Mittleman, Jan Larson, Mary Johnston, Judy Spray, and Kenneth Hayes*

Brain Imaging in Psychiatry: New Developments —

588 Magnetic Resonance Imaging Studies of Schizophrenia — *Robert C. Smith, Richard Baumgartner, Marcos Calderon, Awatif Affas, G.K. Ravichandran, and I. Donald Peters*

595 Dopamine Receptor Binding of C-11-3-N-Methylspiperone in the Caudate in Schizophrenia and Bipolar Disorder: A Preliminary Report — *Dean F. Wong, Henry N. Wagner, Jr., Godfrey Pearlson, Robert F. Dannals, Jonathan M. Links, Hayden Ravert, Alan Wilson, Sudhir Suneja, Eythor Bjorvvinssen, Michael J. Kuhar, and Larry Tune*

Studies of Peripheral Monoamine Receptors in Affective Illness —

599 Platelet Alpha-Adrenergic Receptor Function in Affective Disorders and Schizophrenia — *Marian S. Kafka, Larry J. Siever, John I. Nurnberger, Thomas W. Uhde, Steven Targum, Dermot M.J. Cooper, Daniel P. van Kammen, and Nancy S. Tokola*

603 Studies of Beta-Adrenergic Receptors in Leukocytes of Patients With Affective Illness and Effects of Antidepressant Drugs — *Ghanshyam N. Pandey, Philip Janicak, and John M. Davis*

Social Phobias: Diagnosis, Pathophysiology, and Treatment —

610 Psychopharmacological Treatment of Social Phobia — *Michael R. Liebowitz, Jack Gorman, Abby Fyer, Raphael Campeas, Andrew Levin, Sharon Davies, and Donald F. Klein*

615 Behavioral Treatment of Social Phobia — *Isaac Marks*

Improvement With Antidepressants: Timing and Relationship to Biochemical Events —

619 Delayed Biochemical Changes Following Antidepressant Treatment — *Michael F. Sugrue*

Pharmacogenetics: A Preclinical and Clinical Perspective —

623 Molecular Basis of Drug-Resistance Mutations in C. Elegans — *James B. Rand and Richard L. Russell*

631 Biophysical Alterations in Cell Membranes Associated With Psychotherapeutic Drug Exposure, Psychopathology, and Aging — *George S. Zubenko and Bruce M. Cohen*

641 Relevance of Genetic Variability to Clinical Psychopharmacology — *Bruce M. Cohen and George S. Zubenko*

Noradrenergic Mechanisms and the Drug Withdrawal Syndrome —

651 Adrenergic Agonist Therapy in Alcohol Withdrawal States in Man — *Paul Cushman, Jr., William Lerner, and Michael Cramer*

Targeting the Central Nervous System: New Drug Delivery Technologies for Psychotropic Agents —

657 Chemical Approaches to Drug Delivery to the Central Nervous System — *Colin R. Gardner*

663 Peripheral Models for the Study of Neurotransmitter Receptors in Man — *Stephen M. Stahl*

672 Implantable Narcotic Antagonists: A Possible New Treatment for Narcotic Addiction — *C. Nora Chiang, Akira Kishimoto, Gene Barnett, and Leo E. Hollister*

Pharmacologic Challenge Strategies in Alzheimer's Disease: Basic and Clinical Issues —

676 Cognitive and Behavioral Sensitivity to Scopolamine in Alzheimer Patients and Controls — *Trey Sunderland, Pierre Tariot, Edward A. Mueller, Dennis L. Murphy, Herbert Weingartner, and Robert M. Cohen*

680 Low- and High-Dose Naloxone in Dementia of the Alzheimer Type — *Pierre N. Tariot, Trey Sunderland, Herbert Weingartner, Dennis L. Murphy, Martin R. Cohen, and Robert M. Cohen*

Poster Session —Editor's Choice

683 The Window of Vulnerability in the Ontogeny of the Dopamine Receptor — *Jeanette C. Miller and Arnold J. Friedhoff*

686 Depression in Adults With a History of Prenatal DES Exposure — *Heino F.L. Meyer-Bahlburg, Anke A. Ehrhardt, Jean Endicott, Norma P. Veridiano, E. Douglas Whitehead, and Felix H. Vann*

690 Cortisol and Prolactin Responses to Dexamethasone in Major Depression, Chronic Pain, and Chronic Pain With Major Depression — *Joseph H. Atkinson, Jr., Edwin F. Kremer, S. Craig Risch, and David S. Janowsky*

694 Evidence for a Daily Rhythm of Plasma HVA in Normal Controls But Not in Schizophrenic Patients — *Allen R. Doran, David Pickar, Rodrigo Labarca, Patrice Douillet, Owen M. Wolkowitz, John W. Thomas, Alex. Roy, and Steven M. Paul*

698 Imipramine for Treatment of Chronic Depression — *James H. Kocsis, Allen Frances, J. John Mann, John Sweeney, Carlyle Voss, Barbara Mason, and Richard P. Brown*

701 A New Postsynaptic Serotonin Receptor Agonist Suitable for Studies in Humans — *Edward A. Mueller, Dennis L. Murphy, Trey Sunderland, and Julia Jones*

705 Addition of Estrogen to Imipramine in Female-Resistant Depressives — *Joseph Zohar, Baruch Shapira, Gerald Oppenheim, Frank J. Ayd, and Robert H. Belmaker*

707 Lidocaine Kindling is Accompanied by an Increase in Apomorphine Stereotype and Mesolimbic Dopamine D Receptor Density — *John G. Csernansky, Cynthia A. Csernasky, Seth A. Glick, and Leo E. Hollister*

Vol. 21, No. 4, 1985

RATING SCALES AND ASSESSMENT INSTRUMENTS FOR USE IN PEDIATRIC PSYCHOPHARMACOLOGY RESEARCH

713 **From the Editor's Desk —**

714 **Introduction to This Issue —** ***Judith L. Rapoport and C. Keith Conners***

Demographic Data and Family History —

719 *Documentation of Demographic Data and Family History of Psychiatric Illness — *Magda Campbell and Michael Palij*

722 Demographic Template — *Magda Campbell*

728 ROS (Research Obstetrical Scale) — *Arnold J. Sameroff, R. Seifer, and M. Zax*

731 Prior Medication Record — *NIMH*

Psychiatric Interviews —

737 *Psychiatric Interviews Suitable for Use in Research With Children and Adolescents — *Helen Orvaschel*

747 CGAS (A Children's Global Assessment Scale) — *David Shaffer, Madelyn S. Gould, James Brasic, Paul Ambrosini, Prudence Fisher, Hector Bird, and Satwant Aluwahlia*

749 Rutter-Graham Psychiatric Interview for Children — *Michael Rutter and Philip Graham*

753 Children's Psychiatric Rating Scale (Scoring) — *Barbara Fish*

765 Children's Psychiatric Rating Scale — *NIMH*

Neurological Examinations —

773 Revised Physical and Neurological Examination for Subtle Signs — *Martha Bridge Denckla*

780 Scoring for Revised Physical and Neurological Examination for Subtle Signs — *Martha Bridge Denckla*

793 PANESS (Physical and Neurological Examination for Soft Signs) — *NIMH*

Diagnosis —

803 *DSM-III-R Pediatric Psychopharmacology — *Judity L. Rapoport*

Rating Scales and Checklists for Psychopharmacologic Trials —

809 *Rating Scales and Checklists for Child Psychopharmacology — *C. Keith Conners and Russell A. Barkley*

816 Parent Symptom Questionnaire — *C. Keith Conners*

823 Teacher Questionnaire — *C. Keith Conners*

828 Teacher Questionnaire (Follow-up School Report) — *C. Keith Conners*

832 IGRS (Inpatient Global Rating Scale) — *C. Keith Conners*

835 Child Behavior Rating Form — *Craig Edelbrock*

839 CGI (Clinical Global Impression) Scale — *NIMH*

845 The Aberrant Behavior Checklist — *Michael G. Aman, Nirbhay N. Singh, Alistair W. Stewart, and Carolyn J. Field*

851 GSS (General Scoring Sheet)—Basic — *NIMH*

Measures of Social Skills —

855 *Development of a Rating Scale to Measure Social Skills in Children: The Matson Evaluation of Social Skills With Youngsters (MESSY) — *Johnny L. Matson, Anthony F. Rotatori, and William J. Helsel*

861 Matson Evaluation of Social Skills With Youngsters (MESSY): (Teacher Rating Form) — *Johnny L. Matson and Karen Esveldt-Dawson*

865 Matson Evaluation of Social Skills With Youngsters (MESSY): (Self-Rating Form) — *Johnny L. Matson and Karen Esveldt-Dawson*

869 Social Interaction Observation Code — *Howard Abikoff, Diane Martin, and Rachel Gittelman*

Performance Measures —

**PLEASE NOTE: All references in this paper are presented in a single reference section to be found on pages 1111-1124.*

877 *Assessing Drug Effects on Academic Performance — Kenneth D. Gadow and H. Lee Swanson
887 *Measures of Cognitive Functioning Appropriate for Use in Pediatric Psychopharmacology Research Studies — James M. Swanson
891 *The Computerized Continuous Performance Test — C. Keith Conners
893 *Measuring Activity Level in Children — C. Keith Conners
898 Hillside Behavior Rating Scale (Behavior During Testing) — Rachel Gittelman and Donald Klein
901 Classroom Observation Code: A Modification of the Stony Brook Code — Howard Abikoff and Rachell Gittelman

Ratings for Attention Deficit Disorders —

913 *Some Thoughts on the Diagnosis of ADD-H in Adolescents — Rafael Klorman
915 Introduction to the Use of ACTeRS — Rina K. Ullmann, Esther K. Sleator, and Robert L. Sprague
917 ACTeRS (ADD-H Comprehensive Teacher's Rating Scale) —
921 ADD-H Adolescent Self-Report Scale — C. Keith Conners and Karen C. Wells
923 Parent Questionnaire of Teenage Behavior (Modified Conners) — Rachel Gittelman
925 Self-Evaluation (Teenager's) Self-Report — Rachel Gittelman
927 AQCC (Adult Questionnaire-Childhood Characteristics) Scale — Paul H. Wender
929 Bibliography on Rating and Assessment Instruments for Attention Deficit Disorder (ADD) — Natalie Reatig

Ratings for Anxiety Disorders —

933 Ratings for Anxiety Disorders — Rachel Gittelman
934 Children's Manifest Anxiety Scale: Parent Ratings — Rachel Gittelman
936 Children's Manifest Anxiety Scale: Child Ratings — Rachel Gittelman
939 Parent's Questionnaire (Modified Conners): Anxiety and Mood Items Added — Rachel Gittelman
945 Teacher Rating Scale ((Modified Conners): Anxiety and Mood Items Added — Rachel Gittelman

Ratings for Childhood Depression —

951 *Scales of Potential Use in the Psychopharmacologic Treatment of Depressed Children and Adolescents — Theodore A. Petti
957 DMS-III Symptom Checklist for Major Depressive Disorders — Javad Kashani, Donald McKnew, and Leon Cytryn
959 BID (The Bellevue Index of Depression) — Theodore A. Petti
969 PNID (Peer Nomination Index of Depression — M. M. Lefkowitz and E. Tesing
972 SADLI (School Age Depression Listed Inventory) — Theodore A. Petti
976 Interview for the SADLI — Theodore A. Petti
979 Children's Depression Rating Scale-Revised — Elva O. Poznanski
991 ISC (The Interview Schedule for Children) — Maria Kovacs
995 CDI (The Children's Depression Inventory) — Maria Kovacs

Ratings for Eating Disorders —

1001 *Rating Scales in the Eating Disorders — Katherine A. Halmi

---

*PLEASE NOTE: All references in this paper are presented in a single reference section to be found on pages 1111-1124.

1004 Anorexic Behavior Scale — *Peter D. Slade*

1005 Anorectic Attitude Questionnaire — *Solomon C. Goldberg, Katherine A. Halmi, and Elke D. Eckert*

1008 Eating Attitudes Test — *David M. Garner and Paul E. Garfinkel*

1009 Eating Disorder Inventory — *David M. Garner, M. P. Olmsted, and J. Polivy*

1011 Binge Scale Questionnaire — *Raymond C. Hawkins and Pamelia F. Clement*

1013 Binge-Eating Questionnaire — *Katherine A. Halmi, James R. Falk, and Estelle Schwartz*

1017 Bulimia Interview Form — *Timothy Walsh and Madeline Gladis*

1025 Eating Disorders Questionnaire — *James E. Mitchell*

Ratings for Autism —

1047 ***Behavioral and Cognitive Measures Used in Psychopharmacological Studies of Infantile Autism — *Magda Campbell and Michael Paliz***

1053 CARS (Childhood Autism Rating Scale) — *E. Schopler, R. J. Reichler, and B. R. Renner*

Ratings for Obsessive-Compulsive Disorders —

1057 The Leyton Obsessional Inventory-Child Version — *Carol J. Berg, Judith L. Rapoport, and Martine Flament*

Rating for Adverse Effects —

1063 ***Measurement of Side Effects Including Tardive Dyskinesia — *Magda Campbell***

1067 DOTES (Dosage Record and Treatment Emergent Symptom Scale) — *NIMH*

1069 TESS (Treatment Emergent Symptoms Scale—Write-In) — *NIMH*

1073 STESS (Subjective Treatment Emergent Symptoms Scale) — *NIMH*

1077 AIMS (Abnormal Involuntary Movement Scale) — *NIMH*

1081 Protocol for Rating Drug-Related AIMS, Stereotypies, and CPRS Assessments — *Magda Campbell*

1082 Timed Stereotypies Rating Scale — *Magda Campbell*

1085 **Laboratory Tests for Drug Studies — *Judith L. Rapoport***

Measures of Medication Compliance —

1089 *Measurement of Compliance — *Esther K. Sleator*

Grant Support and Ethical Issues —

1097 The Grant Support Program of the Pharmacologic and Somatic Treatment Research Branch — *Natalie Reatig*

1100 DHHS Internal Policies for Reviewing Protections to Human Subjects in Research — *Natalie Reatig*

1105 Ethical Issues in Research With Children: A Bibliography — *Natalie Reatig*

1111 **References for All Starred * Papers —**

***PLEASE NOTE:** *All references in this paper are presented in a single reference section to be found on pages 1111-1125.*

B. Author Index

Abikoff, Howard
  Vol. 21, No. 4, 1985, pp. 869, 901
Affas, Awatif
  Vol. 21, No. 3, 1985, p. 588
Agran, Martin
  Vol. 21, No. 2, 1985, p. 285
Alberts, Lisa
  Vol. 21, No. 1, 1985, p. 37
Allen, John
  Vol. 21, No. 3, 1985, p. 485
Aluwahlia, Satwant
  Vol. 21, No. 4, 1985, pp. 747
Aman, Michael G.
  Vol. 21, No. 4, 1985, pp. 845
Ambrosini, Paul
  Vol. 21, No. 4, 1985, pp. 747
Amsterdam, Jay D.
  Vol. 21, No. 1, 1985, p. 81
  Vol. 21, No. 3, 1985, p. 579
Anderson, David
  Vol. 21, No. 3, 1985, p. 443
Annable, L.
  Vol. 21, No. 1, 1985, pp. 73, 91
Atkinson, Joseph H., Jr.
  Vol. 21, No. 3, 1985, p. 690
Ayd, Frank J.
  Vol. 21, No. 3, 1985, p. 705

Balon, Richard
  Vol. 21, No. 3, 1985, p. 424
Balow, Elizabeth A.
  Vol. 21, No. 2, 1985, p. 279
Barchas, Jack D.
  Vol. 21, No. 3, 1985, p. 466
Barkley, Russell A.
  Vol. 21, No. 4, 1985, pp. 809
Barnett, Gene
  Vol. 21, No. 3, 1985, p. 672
Bartholini, G.
  Vol. 21, No. 3, 1985, p. 385
Baumgartner, Richard
  Vol. 21, No. 1, 1985, p. 52
  Vol. 21, No. 3, 1985, p. 588
Baxter, Lewis
  Vol. 21, No. 1, 1985, p. 77
Bayless, John
  Vol. 21, No. 1, 1985, p. 89
Beaudry, P.
  Vol. 21, No. 1, 1985, p. 91
Belanger, M-C
  Vol. 21, No. 1, 1985, p. 73
Belmaker, Robert H.
  Vol. 21, No. 3, 1985, p. 705
Berchou, Richard
  Vol. 21, No. 3, 1985, p. 424
Berg, Carol J.
  Vol. 21, No. 1, 1985, p. 150
  Vol. 21, No. 4, 1985, pp. 1057
Bergmann, Kenneth
  Vol. 21, No. 1, 1985, pp. 123, 136
Berry, Ira R.
  Vol. 21, No. 2, 1985, p. 347
Biederman, Joseph
  Vol. 21, No. 1, 1985, p. 144
Bigelow, Llewellyn B.
  Vol. 21, No. 1, 1985, p. 66
Billington, Charles J.
  Vol. 21, No. 3, 1985, p. 485
Bird, Hector
  Vol. 21, No. 4, 1985, pp. 747
Bjorvvinssen, Eythor
  Vol. 21, No. 3, 1985, p. 595
Blackwell, Barry
  Vol. 21, No. 3, 1985, p. 357
Blumenthal, Richard
  Vol. 21, No. 3, 1985, p. 533
Borden, Kathi A.
  Vol. 21, No. 1, 1985, p. 28
  Vol. 21, No. 2, 1985, p. 192
Borenstein, Michael
  Vol. 21, No. 1, 1985, p. 23
  Vol. 21, No. 3, 1985, p. 533
Borkan, Lionel
  Vol. 21, No. 2, 1985, p. 347
Bradwejn, J.
  Vol. 21, No. 1, 1985, p. 73
Brasic, James
  Vol. 21, No. 4, 1985, pp. 747
Braun, Tammy
  Vol. 21, No. 1, 1985, p. 66
Bregman, Zachary
  Vol. 21, No. 1, 1985, p. 130
Brown, Richard P.
  Vol. 21, No. 3, 1985, pp. 698, 579
Brown, Ronald T.
  Vol. 21, No. 1, 1985, p. 28
  Vol. 21, No. 2, 1985, p. 192
Bruininks, Robert H.
  Vol. 21, No. 2, 1985, p. 279

Brune, Patricia
  Vol. 21, No. 3, 1985, p. 503
Brunello, N.
  Vol. 21, No. 3, 1985, p. 379
Burd, Alla
  Vol. 21, No. 1, 1985, p. 52

Campbell, Magda
  Vol. 21, No. 1, 1985, p. 140
  Vol. 21, No. 4, 1985, pp. 719, 722,1047, 1063, 1081–1082
Campeas, Raphael
  Vol. 21, No. 3, 1985, p. 610
Cantwell, Dennis P.
  Vol. 21, No. 2, 1985, p. 251
Caroff, Stanley
  Vol. 21, No. 3, 1985, p. 579
Carpenter, William T., Jr.
  Vol. 21, No. 1, 1985, p. 117
Casey, Elaine
  Vol. 21, No. 1, 1985, p. 114
Casper, Regina
  Vol. 21, No. 1, 1985, p. 48
Chang, Sidney S.
  Vol. 21, No. 1, 1985, p. 48
Chapman, Suzanne
  Vol. 21, No. 1, 1985, p. 89
Chiang, C. Nora
  Vol. 21, No. 3, 1985, p. 672
Cho, Sung-Ran
  Vol. 21, No. 1, 1985, p. 18
Chouinard, G.
  Vol. 21, No. 1, 1985, pp. 73-91
Clemens, April
  Vol. 21, No. 1, 1985, p. 77
Clement, Pamelia F.
  Vol. 21, No. 4, 1985, pp. 1011
Clingerman, Stephen R.
  Vol. 21, No. 1, 1985, p. 28
  Vol. 21, No. 2, 1985, p. 192
Coffman, Jeffrey A.
  Vol. 21, No. 1, 1985, p. 89
Cohen, Bruce M.
  Vol. 21, No. 3, 1985, pp. 631, 641
Cohen, Robert M.
  Vol. 21, No. 3, 1985, p. 680
Conn, P. Jeffrey
  Vol. 21, No. 3, 1985, p. 373
Conners, C. Keith
  Vol. 21, No. 2, 1985, p. 243
  Vol. 21, No. 4, 1985, pp. 714, 809–832, 891, 893, 921
Cooper, Dermot M.J.
  Vol. 21, No. 3, 1985, p. 599
Corcella, John
  Vol. 21, No. 3, 1985, p. 562
Cox, Malcolm
  Vol. 21, No. 1, 1985, p. 81
Coyne, Lolafaye
  Vol. 21, No. 3, 1985, p. 582
Craig, Thomas J.
  Vol. 21, No. 1, 1985, p. 130
Cramer, Michael
  Vol. 21, No. 3, 1985, p. 651
Crawley, Jacqueline N.
  Vol. 21, No. 3, 1985, p. 523
Csernansky, Cynthia A.
  Vol. 21, No. 3, 1985, p. 707
Csernansky, John G.
  Vol. 21, No. 3, 1985, p. 707
Cuomo, V.
  Vol. 21, No. 3, 1985, p. 379
Currier, Carol Anne
  Vol. 21, No. 1, 1985, p. 105
Cushman, Paul
  Vol. 21, No. 3, 1985, p. 651
Cytryn, Leon
  Vol. 21, No. 4, 1985, p. 957

Dannals, Robert F.
  Vol. 21, No. 3, 1985, p. 595
Daugherty, Kathleen
  Vol. 21, No. 1, 1985, p. 77
Davies, Sharon
  Vol. 21, No. 3, 1985, p. 610
Davis, John M.
  Vol. 21, No. 1, 1985, p. 48
  Vol. 21, No. 3, 1985, p. 603
Dekirmenjian, Haroutine
  Vol. 21, No. 1, 1985, p. 48
DeLisi, Lynn E.
  Vol. 21, No. 3, 1985, p. 365
Denckla, Martha Bridge
  Vol. 21, No. 4, 1985, pp. 773, 780
Deutsch, Stephen I.
  Vol. 21, No. 1, 1985, p. 140
Die Trill, Maria L.
  Vol. 21, No. 1, 1985, p. 140
Dillon, Donald
  Vol. 21, No. 3, 1985, p. 428
Doddi, Seshagiri R.
  Vol. 21, No. 1, 1985, p. 114
Dominguez, Roberto A.
  Vol. 21, No. 1, 1985, p. 97

Donnelly, Maureen
  Vol. 21, No. 2, 1985, p. 232
Douillet, Patrice
  Vol. 21, No. 3, 1985, p. 694
Dovan, Allen R.
  Vol. 21, No. 3, 1985, p. 694

Ebert, Michael H.
  Vol. 21, No. 3, 1985, p. 419
Eckert, Elke D.
  Vol. 21, No. 4, 1985, pp. 1005, 1025
Edelbrock, Craig
  Vol. 21, No. 4, 1985, p. 835
Edwards, Emmeline
  Vol. 21, No. 3, 1985, p. 443
Ehrhardt, Anke A.
  Vol. 21, No. 1, 1985, p. 85
  Vol. 21, No. 3, 1985, p. 686
Endicott, Jean
  Vol. 21, No. 3, 1985, p. 686
Erdelyi, Elizabeth
  Vol. 21, No. 3, 1985, p. 466
Ericksen, Stephen E.
  Vol. 21, No. 1, 1985, p. 48
Escobar, Javier I.
  Vol. 21, No. 1, 1985, p. 77
Esveldt-Dawson, Karen
  Vol. 21, No. 4, 1985, pp. 855–865
Evans, Christopher J.
  Vol. 21, No. 3, 1985, p. 466

Falk, James R.
  Vol. 21, No. 4, 1985, pp. 1013
Ferris, Steven H.
  Vol. 21, No. 1, 1985, p. 101
Field, Carolyn J.
  Vol. 21, No. 4, 1985, pp. 845
Fields, Robert
  Vol. 21, No. 3, 1985, p. 497
Fish, Barbara
  Vol. 21, No. 4, 1985, p. 753
Fisher, Prudence
  Vol. 21, No. 4, 1985, pp. 747
Flament, Martine F.
  Vol. 21, No. 1, 1985, p. 150
  Vol. 21, No. 4, 1985, pp. 1057
Florio, William
  Vol. 21, No. 1, 1985, p. 136
Fontaine, R.
  Vol. 21, No. 1, 1985, p. 91
Foster, Patricia
  Vol. 21, No. 1, 1985, p. 114
Frances, Allen
  Vol. 21, No. 3, 1985, p. 698
Frank, Ellen
  Vol. 21, No. 1, 1985, p. 37
Frazer, Alan
  Vol. 21, No. 3, 1985, p. 579
Freeman, Linda N.
  Vol. 21, No. 4, 1985, p. 979
Friedhoff, Arnold J.
  Vol. 21, No. 3, 1985, p. 683
Frohman, Charles E.
  Vol. 21, No. 3, 1985, p. 434
Fuller, Ray W.
  Vol. 21, No. 3, 1985, p. 528
Fryer, Abby J.
  Vol. 21, No. 3, 1985, pp. 428, 610

Gadaletta, Dominick
  Vol. 21, No. 1, 1985, p. 123
Gadow, Kenneth D.
  Vol. 21, No. 2, 1985, p. 291
  Vol. 21, No. 4, 1985, pp. 877
Gale, Robert Peter
  Vol. 21, No. 3, 1985, p. 479
Gardner, Colin R.
  Vol. 21, No. 3, 1985, p. 657
Garfinkel, Paul E.
  Vol. 21, No. 4, 1985, pp. 1008
Garner, David M.
  Vol. 21, No. 4, 1985, pp. 1008, 1009
Garver, David L.
  Vol. 21, No. 1, 1985, p. 62
Gastfriend, David R.
  Vol. 21, No. 1, 1985, p. 144
Geller, Andrew M.
  Vol. 21, No. 1, 1985, p. 93
Gerard T. Reardon
  Vol. 21, No. 1, 1985, p. 114
Gershon, Elliot S.
  Vol. 21, No. 3, 1985, p. 365
Gershon, Samuel
  Vol. 21, No. 1, 1985, p. 18
Gittelman, Rachel
  Vol. 21, No. 2, 1985, p. 237
  Vol. 21, No. 4, 1985, pp. 869, 898, 901, 923–925,
933–945
Gladis, Madeline
  Vol. 21, No. 4, 1985, pp. 1017
Glick, Seth A.
  Vol. 21, No. 3, 1985, p. 707

Gold, Philip W.
  Vol. 21, No. 3, 1985, p. 546
Goldberg, Solomon C.
  Vol. 21, No. 4, 1985, pp. 1005
Golden, Charles J.
  Vol. 21, No. 2, 1985, p. 316
Golden, Robert R.
  Vol. 21, No. 1, 1985, p. 140
Goldin, Lynn R.
  Vol. 21, No. 3, 1985, p. 365
Goldstein, Burton J.
  Vol. 21, No. 1, 1985, p. 97
Gorman, Jack M.
  Vol. 21, No. 3, 1985, pp. 428, 610
Gosnell, Blake A.
  Vol. 21, No. 3, 1985, p. 400
Gould, Madelyn S.
  Vol. 21, No. 4, 1985, pp. 747
Graham, Philip
  Vol. 21, No. 4, 1985, p. 749
Green, Wayne H.
  Vol. 21, No. 1, 1985, p. 140
Greenwald, Daniel
  Vol. 21, No. 3, 1985, p. 503
Gualtieri, C. Thomas
  Vol. 21, No. 2, 1985, pp. 304, 310
Guido, Lisa
  Vol. 21, No. 1, 1985, p. 110
Guthrie, Sally
  Vol. 21, No. 3, 1985, p. 389
Gwirtsman, Harry E.
  Vol. 21, No. 3, 1985, p. 419

Halaris, Angelos
  Vol. 21, No. 1, 1985, p. 77
  Vol. 21, No. 3, 1985, p. 573
Halbreich, Uriel
  Vol. 21, No. 3, 1985, p. 568
Halmi, Katherine A.
  Vol. 21, No. 4, 1985, pp. 1001, 1005, 1013
Hamovit, Joel R.
  Vol. 21, No. 3, 1985, p. 365
Harrington, Michael G.
  Vol. 21, No. 3, 1985, p. 361
Harrison, Wilma M.
  Vol. 21, No. 1, 1985, p. 85
  Vol. 21, No. 3, 1985, pp. 555, 558
Hartmann, Ernest
  Vol. 21, No. 3, 1985, p. 503
Hatsukami, Dorothy
  Vol. 21, No. 4, 1985, p. 1025
Hawkins, Raymond C.
  Vol. 21, No. 4, 1985, pp. 1011
Hayes, Kenneth
  Vol. 21, No. 3, 1985, p. 582
Hechtman, Lily
  Vol. 21, No. 2, 1985, p. 178
Heinrichs, Douglas W.
  Vol. 21, No. 1, 1985, p. 117
Helsel, William J.
  Vol. 21, No. 4, 1985, pp. 855
Henn, Fritz A.
  Vol. 21, No. 3, 1985, p. 443
Hill, Bradley K.
  Vol. 21, No. 2, 1985, p. 279
Hill, Maryann
  Vol. 21, No. 1, 1985, p. 77
Hirschowitz, Jack
  Vol. 21, No. 1, 1985, p. 62
Hollister, Leo E.
  Vol. 21, No. 3, 1985, pp. 672, 707
Holzer, Charles E., III
  Vol. 21, No. 3, 1985, p. 538
House, J. Daniel
  Vol. 21, No. 3, 1985, p. 476
Howard, Diantha
  Vol. 21, No. 3, 1985, p. 562
Hurt, Stephen
  Vol. 21, No. 1, 1985, p. 48
Hurwicz, Margo Lea
  Vol. 21, No. 1, 1985, p. 77

Intagliata, James
  Vol. 21, No. 2, 1985, p. 268
Ismond, Deborah
  Vol. 21, No. 2, 1985, p. 232
Itob, Hitoshi
  Vol. 21, No. 1, 1985, p. 120

Jacobson, Alan F.
  Vol. 21, No. 1, 1985, p. 97
Janicek, Philip
  Vol. 21, No. 3, 1985, p. 603
Janowsky, David S.
  Vol. 21, No. 3, 1985, p. 690
Javaid, Javaid I.
  Vol. 21, No. 1, 1985, p. 48
Jellinek, Michael S.
  Vol. 21, No. 1, 1985, p. 144
Jimerson, David C.
  Vol. 21, No. 3, 1985, p. 419

Johnson, Joel
  Vol. 21, No. 3, 1985, p. 443
Johnston, Mary
  Vol. 21, No. 3, 1985, p. 582
Jones, B.
  Vol. 21, No. 1, 1985, p. 73
Jones, Julia
  Vol. 21, No. 3, 1985, p. 701
Jorkasky, Diane
  Vol. 21, No. 1, 1985, p. 81
Joseph, Shirley A.
  Vol. 21, No. 3, 1985, p. 472

Kafka, Marian S.
  Vol. 21, No. 3, 1985, p. 599
Kalachnik, John E.
  Vol. 21, No. 2, 1985, p. 327
Kane, John M.
  Vol. 21, No. 1, 1985, pp. 23, 123, 136
  Vol. 21, No. 3, 1985, p. 533
Kanter, Donald R.
  Vol. 21, No. 1, 1985, p. 62
Kashani, Javad
  Vol. 21, No. 4, 1985, p. 957
Kay, Neil
  Vol. 21, No. 3, 1985, p. 485
Kaye, Walter H.
  Vol. 21, No. 3, 1985, p. 419
Kayser, Allen
  Vol. 21, No. 3, 1985, p. 562
Keppell, J.M.
  Vol. 21, No. 2, 1985, p. 304
Kidd, Kenneth K.
  Vol. 21, No. 3, 1985, p. 543
Kietzman, Mitchell L.
  Vol. 21, No. 3, 1985, p. 518
Kilts, Clinton
  Vol. 21, No. 1, 1985, p. 150
Kirch, Darrell G.
  Vol. 21, No. 1, 1985, p. 66
Kishimoto, Akira
  Vol. 21, No. 3, 1985, p. 672
Klein, Donald F.
  Vol. 21, No. 3, 1985, pp. 428, 558, 610
  Vol. 21, No. 4, 1985, pp. 898
Klorman, Rafael
  Vol. 21, No. 4, 1985, pp. 913
Knigge, Karl M.
  Vol. 21, No. 3, 1985, p. 472
Kocsis, James H.
  Vol. 21, No. 3, 1985, pp. 579, 698
Korpi, Esa R.
  Vol. 21, No. 1, 1985, p. 66
Kovacs, Maria
  Vol. 21, No. 4, 1985, pp. 995
Krager, John M.
  Vol. 21, No. 2, 1985, p. 212
Krahn, Dean D.
  Vol. 21, No. 3, 1985, p. 400
Kreisman, Dolores
  Vol. 21, No. 3, 1985, p. 533
Kremer, Edwin F.
  Vol. 21, No. 3, 1985, p. 690
Kronfol, Ziad
  Vol. 21, No. 3, 1985, p. 476
Kuhar, Michael J.
  Vol. 21, No. 3, 1985, p. 595
Kupfer, David J.
  Vol. 21, No. 1, 1985, pp. 3, 37
Kurtz, David
  Vol. 21, No. 3, 1985, p. 365
Kurucz, Janos
  Vol. 21, No. 1, 1985, p. 136

Labarca, Rodrigo
  Vol. 21, No. 3, 1985, p. 694
Labonte, A.
  Vol. 21, No. 1, 1985, p. 73
Lake, C. Raymond
  Vol. 21, No. 3, 1985, p. 419
Lane, Elizabeth A.
  Vol. 21, No. 3, 1985, p. 389
Larson, Jan
  Vol. 21, No. 3, 1985, p. 582
Laux, Desmond
  Vol. 21, No. 3, 1985, p. 562
Leaf, Philip J.
  Vol. 21, No. 3, 1985, p. 538
Leber, Paul
  Vol. 21, No. 2, 1985, p. 334
Leckman, James F.
  Vol. 21, No. 3, 1985, p. 543
Lefkowitz, M.M.
  Vol. 21, No. 4, 1985, p. 969
Leibowitz, Sarah F.
  Vol. 21, No. 3, 1985, p. 412
Lerer, Bernard
  Vol. 21, No. 1, 1985, p. 18
Lerner, William
  Vol. 21, No. 3, 1985, p. 651
Levine, Allen S.
  Vol. 21, No. 3, 1985, p. 400

Levine, Andrew
  Vol. 21, No. 3, 1985, p. 610
Lewis, John W.
  Vol. 21, No. 3, 1985, p. 479
Lewy, Alfred J.
  Vol. 21, No. 3, 1985, p. 368
Lieberman, Jeffrey A.
  Vol. 21, No. 1, 1985, pp. 123, 136
Liebeskind, John C.
  Vol. 21, No. 3, 1985, p. 479
Liebowitz, Michael R.
  Vol. 21, No. 1, 1985, p. 85
  Vol. 21, No. 3, 1985, pp. 428, 558, 610
Links, Jonathan M.
  Vol. 21, No. 3, 1985, p. 595
Linnoila, Markku
  Vol. 21, No. 3, 1985, p. 389
Lloyd, K. G.
  Vol. 21, No. 3, 1985, p. 385
Lucki, Irwin
  Vol. 21, No. 1, 1985, p. 93

Mann, J. John
  Vol. 21, No. 3, 1985, p. 698
Mannuzza, Salvatore
  Vol. 21, No. 2, 1985, p. 237
Marder, Stephen R.
  Vol. 21, No. 1, 1985, p. 69
Markowitz, Jeffrey S.
  Vol. 21, No. 1, 1985, p. 107
  Vol. 21, No. 3, 1985, p. 558
Marks, Isaac
  Vol. 21, No. 3, 1985, p. 615
Martin, Diane
  Vol. 21, No. 4, 1985, pp. 869
Martin, Fredricka C.
  Vol. 21, No. 3, 1985, p. 479
Martin, James E.
  Vol. 21, No. 2, 1985, p. 285
Mason, Barbara
  Vol. 21, No. 3, 1985, p. 698
Matson, Johnny L.
  Vol. 21, No. 2, 1985, p. 258
  Vol. 21, No. 4, 1985, pp. 855–865
Maudlin, Mary
  Vol. 21, No. 1, 1985, p. 52
Mauroidis, Michael L.
  Vol. 21, No. 1, 1985, p. 62
Maxwell, M. Elizabeth
  Vol. 21, No. 3, 1985, p. 365
May, Philip R.A.
  Vol. 21, No. 1, 1985, p. 69
McDonald, Margaret C.
  Vol. 21, No. 1, 1985, p. 3
McGrath, Patrick J.
  Vol. 21, No. 1, 1985, pp. 85, 107
  Vol. 21, No. 3, 1985, pp. 555, 558
McGuire, Michael T.
  Vol. 21, No. 3, 1985, p. 458
McKnew, Donald
  Vol. 21, No. 4, 1985, p. 957
Meiselas, Karen
  Vol. 21, No. 1, 1985, p. 140
Menolascino, Frank J.
  Vol. 21, No. 2, 1985, p. 316
Mercier, P.
  Vol. 21, No. 1, 1985, pp. 73, 91
Merikangas, Kathleen R.
  Vol. 21, No. 3, 1985, pp. 538, 543
Merrill, Carl R.
  Vol. 21, No. 3, 1985, p. 361
Meyendorff, Elaine
  Vol. 21, No. 1, 1985, p. 18
Meyer-Bahlburg, Heino F.L.
  Vol. 21, No.3, 1985, p. 686
Miller, Jeanette C.
  Vol. 21, No. 3, 1985, p. 683
Mitchell, James E.
  Vol. 21, No. 3, 1985, p. 400
  Vol. 21, No. 4, 1985, pp. 1025
Mitchell, Walter
  Vol. 21, No. 3, 1985, p. 503
Mittleman, Fred
  Vol. 21, No. 3, 1985, p. 582
Mocchetti, J.
  Vol. 21, No. 3, 1985, p. 379
Mokros, Harmut B.
  Vol. 21, No. 4, 1985, p. 979
Moon, Timothy
  Vol. 21, No. 3, 1985, p. 485
Moore, Norman
  Vol. 21, No. 1, 1985, p. 18
Morley, John E.
  Vol. 21, No. 3, 1985, pp. 400, 485
Morselli, P. L.
  Vol. 21, No. 3, 1985, p. 385
Mouchka, Susan
  Vol. 21, No. 2, 1985, p. 262
Mueller, Edward A.
  Vol. 21, No. 3, 1985, p. 701
Mukherjee, Sukdeb
  Vol. 21, No. 1, 1985, p. 136
Murphy, Dennis L.
  Vol. 21, No. 3, 1985, pp. 419, 701

Myers, Robert D.
  Vol. 21, No. 3, 1985, p. 406

Nasrallah, Henry A.
  Vol. 21, No. 1, 1985, p. 89
Nelson, Linda R.
  Vol. 21, No. 3, 1985, p. 479
Novacenko, Hana
  Vol. 21, No. 1, 1985, p. 123
Nurnberger, John I.
  Vol. 21, No. 3, 1985, pp. 365, 599

O'Brien, Ronald P.
  Vol. 21, No. 1, 1985, p. 69
Olmsted, M.P.
  Vol. 21, No. 4, 1985, pp. 1009
Oppenheim, Gerald
  Vol. 21, No. 3, 1985, p. 705
Ortiz, Aurelio
  Vol. 21, No. 3, 1985, p. 424
Orvaschel, Helen
  Vol. 21, No. 4, 1985, pp. 737

Palij, Michael
  Vol. 21, No. 4, 1985, pp. 719, 1047, 1063
Pandey, Ghanshyam N.
  Vol. 21, No. 3, 1985, p. 603
Parashos, Ioanis
  Vol. 21, No. 3, 1985, p. 389
Pardes, Herbert
  Vol. 21, No. 1, 1985, p. 59
Pass, Raymond
  Vol. 21, No. 1, 1985, p. 130
Paul, Steven M.
  Vol. 21, No. 3, 1985, p. 694
Pauls, David L.
  Vol. 21, No. 3, 1985, p. 543
Pearlson, Godfrey
  Vol. 21, No. 3, 1985, p. 595
Perenyi, Andras
  Vol. 21, No. 2, 1985, p. 345
Perry, Richard
  Vol. 21, No. 1, 1985, p. 140
Peters, I. Donald
  Vol. 21, No. 3, 1985, p. 588
Peters, Jeffrey
  Vol. 21, No. 3, 1985, p. 497
Petti, Theodore A.
  Vol. 21, No. 4, 1985, pp. 951, 959, 972–976
Phelps, Bruce
  Vol. 21, No. 1, 1985, p. 59
Pickar, David
  Vol. 21, No. 3, 1985, p. 694
Piekut, Diane T.
  Vol. 21, No. 3, 1985, p. 472
Piletz, John E.
  Vol. 21, No. 3, 1985, p. 573
Pincus, Harold Alan
  Vol. 21, No. 1, 1985, p. 7
Plotnikoff, Nicholas P.
  Vol. 21, No. 3, 1985, p. 489
Pohl, Robert B.
  Vol. 21, No. 3, 1985, pp. 424, 434
Poland, Russell
  Vol. 21, No. 1, 1985, pp. 59, 69
Polivy, J.
  Vol. 21, No. 4, 1985, pp. 1009
Portoghese, P. S.
  Vol. 21, No. 3, 1985, p. 464
Post, Robert M.
  Vol. 21, No. 1, 1985, p. 10
Potkin, Steven G.
  Vol. 21, No. 1, 1985, p. 59
Potter, Larry
  Vol. 21, No. 1, 1985, p. 81
Potter, William Z.
  Vol. 21, No. 3, 1985, p. 389
Poznanski, Elva O.
  Vol. 21, No. 4, 1985, pp. 979
Prien, Robert
  Vol. 21, No. 1, 1985, p. 37
Prusoff, Brigitte A.
  Vol. 21, No. 3, 1985, p. 543
Pyle, Richard
  Vol. 21, No. 4, 1985, p. 1025

Quitkin, Frederic M.
  Vol. 21, No. 1, 1985, pp. 85, 107
  Vol. 21, No. 3, 1985, pp. 555, 558

Rabkin, Judith
  Vol. 21, No. 1, 1985, pp. 85, 107
  Vol. 21, No. 3, 1985, pp. 555, 558
Racagni, G.
  Vol. 21, No. 3, 1985, p. 379
Rainey, John M., Jr.
  Vol. 21, No. 3, 1985, pp. 424, 434
Raleigh, Michael J.
  Vol. 21, No. 3, 1985, p. 458

Ramos-Lorenzi, Jorge
  Vol. 21, No. 1, 1985, p. 123
Rand, James B.
  Vol. 21, No. 3, 1985, p. 623
Rapoport, Judith L.
  Vol. 21, No. 1, 1985, p. 150
  Vol. 21, No. 2, 1985, p. 232
  Vol. 21, No. 4, 1985, pp. 714, 803, 1057, 1085
Ravert, Hayden T.
  Vol. 21, No. 3, 1985, p. 595
Ravichandran, G.K.
  Vol. 21, No. 1, 1985, p. 52
  Vol. 21, No. 3, 1985, p. 588
Reardon, Gerald
  Vol. 21, No. 3, 1985, p. 533
Reatig, Natalie
  Vol. 21, No. 4, 1985, pp. 929, 1097–1105
Reichler, R. J.
  Vol. 21, No. 4, 1985, pp. 1053
Reimherr, Frederick W.
  Vol. 21, No. 1, 1985, p. 146
  Vol. 21, No. 1, 1985, p. 222
Reisberg, Barry
  Vol. 21, No. 1, 1985, p. 101
Reisine, Terry
  Vol. 21, No. 3, 1985, p. 438
Renner, B. R.
  Vol. 21, No. 4, 1985, pp. 1053
Richardson, Mary Ann
  Vol. 21, No. 1, 1985, p. 130
Rickels, Karl
  Vol. 21, No. 1, 1985, p. 93
Rifkin, Arthur
  Vol. 21, No. 1, 1985, p. 114
  Vol. 21, No. 3, 1985, p. 533
Rinck, Chris
  Vol. 21, No. 2, 1985, p. 268
Risch, S. Craig
  Vol. 21, No. 3, 1985, p. 690
Robinson, Donald S.
  Vol. 21, No. 3, 1985, p. 562
Rosen, Jules P.
  Vol. 21, No. 3, 1985, p. 497
Rotatori, Anthony F.
  Vol. 21, No. 4, 1985, pp. 855
Rotrosen, John
  Vol. 21, No. 1, 1985, p. 136
Roy, Alec
  Vol. 21, No. 3, 1985, p. 694
Roy-Byrne, Peter P.
  Vol. 21, No. 3, 1985, pp. 546, 551
Rubinow, David R.
  Vol. 21, No. 3, 1985, p. 546
Rubinstein, Morton
  Vol. 21, No. 1, 1985, p. 136
Rudorfer, Matthew
  Vol. 21, No. 3, 1985, p. 389
Ruedrich, Stephen L.
  Vol. 21, No. 2, 1985, p. 316
Russell, Richard L.
  Vol. 21, No. 3, 1985, p. 623
Rutter, Michael
  Vol. 21, No. 4, 1985, p. 749

Sack, Robert L.
  Vol. 21, No. 3, 1985, p. 368
Safer, Daniel J.
  Vol. 21, No. 2, 1985, p. 212
Sameroff, Arnold J.
  Vol. 21, No. 4, 1985, p. 728
Sanders-Bush, Elaine
  Vol. 21, No. 3, 1985, p. 373
Scatton, B.
  Vol. 21, No. 3, 1985, p. 385
Schooler, Nina R.
  Vol. 21, No. 1, 1985, p. 136
Schopler, Erik
  Vol. 21, No. 4, 1985, pp. 1053
Schroeder, Stephen R.
  Vol. 21, No. 2, 1985, pp. 310, 323
Schwarcz, Glenn
  Vol. 21, No. 1, 1985, p. 77
Schwartz, Estelle
  Vol. 21, No. 4, 1985, pp. 1013
Seifer, R.
  Vol. 21, No. 4, 1985, p. 728
Shaffer, David
  Vol. 21, No. 4, 1985, pp. 747
Shapira, Baruch
  Vol. 21, No. 3, 1985, p. 705
Shavit, Yehuda
  Vol. 21, No. 3, 1985, p. 479
Shen, Yucun
  Vol. 21, No. 1, 1985, p. 59
Shu, Liang
  Vol. 21, No. 1, 1985, p. 59
Siever, Larry J.
  Vol. 21, No. 3, 1985, pp. 419, 599
Simson, Prudence Goodman
  Vol. 21, No. 3, 1985, p. 447
Singer, Clifford M.
  Vol. 21, No. 3, 1985, p. 368
Singh, Heminder
  Vol. 21, No. 3, 1985, p. 424

Singh, Nirbhay N.
  Vol. 21, No. 4, 1985, pp. 845
Siris, Samual G.
  Vol. 21, No. 1, 1985, p. 114
Slade, Peter D.
  Vol. 21, No. 4, 1985, pp. 1004
Sleator, Esther K.
  Vol. 21, No. 4, 1985, pp. 915, 1089
Sloboda, Walter
  Vol. 21, No. 1, 1985, p. 105
Small, Arthur M.
  Vol. 21, No. 1, 1985, p. 140
Smith, Robert C.
  Vol. 21, No. 1, 1985, p. 52
  Vol. 21, No. 3, 1985, p. 588
Spohn, Herbert E.
  Vol. 21, No. 3, 1985, p. 582
Sprague, Robert L.
  Vol. 21, No. 4, 1985, pp. 915
Spray, Judy
  Vol. 21, No. 3, 1985, p. 582
Spring, Bonnie
  Vol. 21, No. 3, 1985, p. 509
Stahl, Stephen M.
  Vol. 21, No. 1, 1985, p. 43
  Vol. 21, No. 3, 1985, pp. 393, 663
Stanley, Barbara
  Vol. 21, No. 1, 1985, p. 110
Stanley, Michael
  Vol. 21, No. 1, 1985, p. 110
Stein, Judith
  Vol. 21, No. 1, 1985, p. 110
Steinbook, Richard M.
  Vol. 21, No. 1, 1985, p. 97
Steinhauer, Stuart R.
  Vol. 21, No. 3, 1985, p. 513
Stewart, Alistair W.
  Vol. 21, No. 4, 1985, pp. 845
Stewart, Jonathan W.
  Vol. 21, No. 1, 1985, pp. 85, 107
  Vol. 21, No. 3, 1985, pp. 555, 558
Stokes, Peter
  Vol. 21, No. 3, 1985, p. 579
Sugrue, Michael F.
  Vol. 21, No. 3, 1985, p. 619
Sulser, Fridolin
  Vol. 21, No. 3, 1985, p. 373
Sunderland, Trey
  Vol. 21, No. 3, 1985, p. 701
Suneja, Sudhir
  Vol. 21, No. 3, 1985, p. 595
Swanson, H. Lee
  Vol. 21, No. 4, 1985, pp. 877
Swanson, James M.
  Vol. 21, No. 4, 1985, pp. 887
Sweeney, John
  Vol. 21, No. 3, 1985, p. 698
Sztaniszlav, Daniel
  Vol. 21, No. 2, 1985, p. 345

Takemori, A. E.
  Vol. 21, No. 3, 1985, p. 464
Targum, Steven
  Vol. 21, No.3, 1985, p. 599
Terman, Gregory W.
  Vol. 21, No. 3, 1985, p. 479
Thomas, John W.
  Vol. 21, No. 3, 1985, p. 694
Thompson, Mark
  Vol. 21, No. 1, 1985, p. 77
Tokola, Nancy S.
  Vol. 21, No. 3, 1985, p. 599
Transit, Roxanna-Pentland
  Vol. 21, No. 1, 1985, p. 110
Tricamo, Elaine
  Vol. 21, No. 3, 1985, p. 558
Tesing, E.
  Vol. 21, No. 4, 1985, p. 969
Tune, Larry
  Vol. 21, No. 3, 1985, p. 595

Uhde, Thomas W.
  Vol. 21, No. 1, 1985, p. 10
  Vol. 21, No. 3, 1985, pp. 546, 551, 599
Ullmann, Rina K.
  Vol. 21, No. 2, 1985, p. 339
  Vol. 21, No. 4, 1985, pp. 915

Van Kammen, Daniel P.
  Vol. 21, No. 3, 1985, p. 497
Van Kammen, Welmoet B.
  Vol. 21, No. 3, 1985, p. 497
Van Putten, Theodore
  Vol. 21, No. 1, 1985, p. 69
Vann, Felix H.
  Vol. 21, No. 3, 1985, p. 686
Varley, Christopher K.
  Vol. 21, No. 2, 1985, p. 216
Varney, Nils
  Vol. 21, No. 1, 1985, p. 89
Veridiano, Norma P.
  Vol. 21, No. 3, 1985, p. 686

Volterra, A.
Vol. 21, No. 3, 1985, p. 379
Voss, Carlyle
Vol. 21, No. 3, 1985, p. 698

Wagner, Henry N., Jr.
Vol. 21, No. 3, 1985, p. 595
Wagner, Richard L.
Vol. 21, No. 1, 1985, p. 66
Walsh, Timothy
Vol. 21, No. 4, 1985, pp. 1017
Warner, Ken
Vol. 21, No. 3, 1985, p. 434
Wegner, James
Vol. 21, No. 1, 1985, p. 123
Weinhold, Paul
Vol. 21, No. 1, 1985, p. 136
Weiss, Gabrielle
Vol. 21, No. 2, 1985, p. 169
Weiss, Jay M.
Vol. 21, No. 3, 1985, p. 447
Weissman, Myrna M.
Vol. 21, No. 3, 1985, pp. 538, 543
Wells, Karen C.
Vol. 21, No. 4, 1985, p. 921
Wender, Paul H.
Vol. 21, No. 1. 1985, p. 146
Vol. 21, No. 2, 1985, p. 222
Vol. 21, No. 4, 1985, pp. 927
Whitehead, E. Douglas
Vol. 21, No. 3, 1985, p. 686
Wilson, Alan A.
Vol. 21, No. 3, 1985, p. 595
Wilson, Thomas E.
Vol. 21, No. 2, 1985, p. 316
Winokur, Andrew
Vol. 21, No. 3, 1985, p. 579
Woerner, Margaret
Vol. 21, No. 1, 1985, p. 136
Vol. 21, No. 3, 1985, p. 533
Wolkowitz, Owen M.
Vol. 21, No. 3, 1985, p. 694
Wong, Dean F.
Vol. 21, No. 3, 1985, P. 595
Wood, David R.
Vol. 21, No. 1, 1985, p. 146
Vol. 21, No. 2, 1985, p. 222
Wyatt, Richard Jed
Vol. 21, No. 1, 1985, p. 66

Yeragani, Vikram
Vol. 21, No. 3, 1985, p. 434
Yingling, Kevin
Vol. 21, No. 3, 1985, p. 562
Young, Melinda
Vol. 21, No. 1, 1985, p. 77

Zalcman, Steven
Vol. 21, No. 1, 1985, p. 66
Zametkin, Alan
Vol. 21, No. 2, 1985, p. 232
Zax, M.
Vol. 21, No. 4, 1985, p. 728
Zhou, Dongfeng
Vol. 21, No. 1, 1985, p. 59
Zivkovic, B.
Vol. 21, No. 3, 1985, p. 385
Zohar, Joseph
Vol. 21, No. 3, 1985, p. 705
Zubenko, George
Vol. 21, No. 3, 1985, pp. 631, 641
Zubin, Joseph
Vol. 21, No. 3, 1985, p. 490

Psychopharmacology—A Recurring Bibliography

The bibliography below is offered to our readers to alert them to recent papers on psychopharmacology from the world literature. It was computer-generated by the Medical-Literature Analysis and Retrieval System (MEDLARS) of the National Library of Medicine, National Institutes of Health, and represents papers which were entered into the system during the 3 months before the *Bulletin* went to press.

The subject headings from Index Medicus were selected by the National Institute of Mental Health to reflect significant current interest of the international scientific community. Some nonrelevant citations may appear, and some relevant ones may be absent, but this is usual for machine-generated searches.

BIBLIOGRAPHY

ACEPROMAZINE

Increased mortality in gray wolves captured with acepromazine and etorphine hydrochloride in combination. Tobey RW, et al. **J Wildl Dis** 1985 Apr;21(2):188-90

ACETYLCHOLINE

Modulation of choline transport and acetylcholine synthesis in synaptosomes from different brain regions. Nordberg A, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Mar;56(3):193-8

Cadmium inhibition of [3H]acetylcholine secretion in guinea-pig ileum myenteric plexus. Alberts P, et al. **Acta Physiol Scand** 1985 Jun; 124(2):313-6

The effects of adenosine and of some adenosine analogues on the concanavalin A-or acetylcholine-induced histamine release from human adenoidal mast cells. Delmich K, et al. **Agents Actions** 1985 Apr; 16(3-4):141-3

Immunological modulation of cholinergic histamine release in isolated rat mast cells. Masini E, et al. **Agents Actions** 1985 Apr; 16(3-4):152-4

The modulation of acetylcholine release by noradrenaline, GABA and related compounds. Beani L, et al. **Ann Ist Super Sanita** 1984; 20(1):17-9

Acetylcholine and histamine interact supra-additively on bronchomotor tone in guinea-pigs in vivo: a possible consequence of the relationship between airways resistance and calibre. Stewart AG, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):33-46

Declining catecholamine secretion in adrenal medulla on prolonged stimulation with acetylcholine. Bevington A, et al. **Biochem Pharmacol** 1985 May 1;34(9):1497-500

Thyroliberin (TRH), 6-methyl-5-oxothiomorpholinyl-3-carbonyl histidylproline amide and histidylproline diketopiperazine do not affect the release of [3H]-acetyl choline and [3H]-choline from rat brain tissue cubes. Hedley D, et al. **Biochem Pharmacol** 1985 Apr 15; 34(8):1341-3

Blockade of the diazepam-induced increase in rat striatal acetylcholine content by the specific benzodiazepine antagonists ethyl-beta-carboline-3-carboxylate and Ro 15-1788. Kolasa K, et al. **Brain Res** 1985 Jun 17;336(2):342-5

Light evoked release of acetylcholine in response to a single flash: cholinergic amacrine cells receive ON and OFF input. Massey SC, et al. **Brain Res** 1985 Mar 4;328(2):374-7

Synthesis of acetylcholine and gamma-aminobutyric acid by dissociated cerebral cortical cells in vitro. Thomas WE. **Brain Res** 1985 Apr 15; 332(1):79-89

Acetylcholine release from rat atria can be regulated through an alpha 1-adrenergic receptor. Wetzel GT, et al. **Circ Res** 1985 May; 56(5):763-6

Effect of secretagogues on pancreatic exocrine secretion in the monkey and the dog. Iwatsuki K, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):67-72

Comparative actions of GABA and acetylcholine on the Xenopus laevis lateral line. Bobbin RP, et al. **Comp Biochem Physiol [C]** 1985; 80(2):313-8

Action of acetylcholine and antagonists on somata isolated from locust central neurons. Suter C, et al. **Comp Biochem Physiol [C]** 1985; 80(2):221-9

Neurochemical evidence for the release of acetylcholine from the guinea-pig ileum myenteric plexus by capsaicin. Barthó L, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):125-7

Real-time measurements of acetylcholine-induced release of ATP from bovine medullary chromaffin cells. Rojas E, et al. **FEBS Lett** 1985 Jun 17;185(2):323-7

Human pancreatic acinar cells: studies of stimulus-secretion coupling. Petersen OH, et al. **Gastroenterology** 1985 Jul;89(1):109-17

Mast cell heterogeneity in response to cholinergic stimulation. Masini E, et al. **Int Arch Allergy Appl Immunol** 1985;77(1-2):184-5

Rapid changes in synaptic vesicle cytochemistry after depolarization of cultured cholinergic sympathetic neurons. Johnson MI, et al. **J Cell Biol** 1985 Jul;101(1):217-26

Nimodipine has an inhibitory action on neurotransmitter release from human cerebral arteries. Porter ID, et al. **J Cereb Blood Flow Metab** 1985 Jun;5(2):338-42

Determination of choline and acetylcholine levels in rat brain regions by liquid chromatography with electrochemical detection. Ikarashi Y, et al. **J Chromatogr** 1985 Mar 29;322(1):191-9

Chromatographic analysis of choline and acetylcholine by UV visualization. Jones RS, et al. **J Chromatogr** 1985 Feb 20; 319(3):454-60

Modulation of the acetylcholine system in the superior cervical ganglion of rat: effects of GABA and hypoglossal nerve implantation after in vivo GABA treatment. Kása P, et al. **J Neurochem** 1985 May; 44(5):1363-72

Newly synthesized and preformed acetylcholine are released from Torpedo synaptosomes by different pathways. Luz S, et al. **J Neurochem** 1985 Jul;45(1):43-50

Changes in presynaptic release of acetylcholine during development of tolerance to the anticholinesterase, DFP. Russell RW, et al. **J Neurochem** 1985 Jul;45(1):293-9

High-affinity binding of [3H]acetylcholine to muscarinic cholinergic receptors. Kellar KJ, et al. **J Neurosci** 1985 Jun;5(6):1577-82

Pharmacological and ionic characterizations of the muscarinic receptors modulating [3H]acetylcholine release from rat cortical synaptosomes. Meyer EM, et al. **J Neurosci** 1985 May;5(5):1202-7

Bombesin evoked acetylcholine release from the guinea pig antrum. Kantoh M, et al. **Life Sci** 1985 Jun 24;36(25):2445-52

Oxidative metabolism and acetylcholine synthesis during acetylpyridine treatment. Gibson GE, et al. **Neurochem Res** 1985 Apr;10(4):453-67

The compartmentalized hypothalamo-neurohypophysial system: evidence for a neurohypophysial action of acetylcholine on vasopressin release. Gregg CM. **Neuroendocrinology** 1985 May;40(5):423-9

The modulation of cortical acetylcholine release by GABA, GABA-like drugs and benzodiazepines in freely moving guinea-pigs. Tanganelli S, et al. **Neuropharmacology** 1985 Apr;24(4):291-9

State of adrenergic and cholinergic systems in schizophrenia patients during psychopharmacotherapy. Krupenina LB, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):1-8

Acetylcholine-induced currents at plasma membrane of the frog oocyte. Toselli M, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):179-84

Acetylcholine stimulates a Ca2+-dependent C1- conductance in mouse lacrimal acinar cells. Findlay I, et al. **Pflugers Arch** 1985 Mar; 403(3):328-30

The biophysical pharmacology of calcium-dependent acetylcholine secretion. Silinsky EM. **Pharmacol Rev** 1985 Mar;37(1):81-132 (282 ref.)

Neurochemical basis for the photic control of circadian rhythms and seasonal reproductive cycles: role for acetylcholine. Earnest DJ, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4277-81

Is an acetylcholine transport system responsible for nonquantal release of acetylcholine at the rodent myoneural junction? Edwards C, et al. **Proc Natl Acad Sci USA** 1985 May;82(10):3514-8

Chronotropic effects of the reversed carboxyl (RC) analogue of acetylcholine (beta-homobetaine methylester) at defined intraluminal pressures on isolated right rabbit atria. Rossberg F, et al. **Res Exp Med (Berl)** 1985;185(2):139-44

Effects of secretagogues on membrane potential and input resistance of pancreatic acinar cells of sheep. Katoh K, et al. **Res Vet Sci** 1985 Mar; 38(2):250-1

Inhibitory effects of dopamine and isoprenaline on antral motor activity stimulated by acetylcholine or physostigmine in vitro. Ulvestad A, et al. **Scand J Gastroenterol** 1985 Mar;20(2):243-6

The release of acetylcholine. Dunant Y, et al. **Sci Am** 1985 Apr; 252(4):58-66

Immunocytochemical detection of acetylcholine in the rat central nervous system. Geffard M, et al. **Science** 1985 Jul 5;229(4708):77-9

[Relationship between cholinesterase activity and acetylcholine of the brains of mice acutely intoxicated with soman] Zhang X, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar;6(1):16-9 (Eng. Abstr.) **(Chi)**

[Regulation of the cell cycle of B-lymphocytes in mice by substances elevating the levels of intracellular cAMP and cGMP] Ado AD, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):455-8 (Eng. Abstr.) **(Rus)**

[Changes in the response to the extracellular application of acetylcholine during the intracellular perfusion of isolated neurons with biogenic amines] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985; 280(6):1495-8 **(Rus)**

[Effect of RNAse inhibitors and activators on acetylcholine interaction with the cholinoreceptor in a tissue extract] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985;281(2):500-2 **(Rus)**

[Catecholamine levels in pancreatic tissue after intraperitoneal administration of acetylcholine] Gal'kiv MA, et al. **Fiziol Zh** 1985 Mar-Apr;31(2):230-4 **(Rus)**

[Correlation between the plasticity of monosynaptic inputs of command neurons of Helix lucorum and the plastic properties of the chemoreceptive membrane during rhythmic stimulation] Norekian TP, et al. **Neirofiziologiia** 1985;17(2):279-82 (Eng. Abstr.) **(Rus)**

[The effect of acetylcholine and histamine on blood flow through the abdominal organs] Antal J, et al. **Bratisl Lek Listy** 1985 Mar; 83(3):218-28 (Eng. Abstr.) **(Slo)**

ACHIEVEMENT

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227-43

AFFECTIVE DISORDERS

Treatment of affective disorders. Lader MH. **Br J Clin Pharmacol** 1985; 19 Suppl 1:29S-30S

The relationship between antisocial behavior and affective illness. Reich J. **Compr Psychiatry** 1985 May-Jun;26(3):296-303 (47 ref.)

Consensus development summaries. Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health. **Conn Med** 1985 Mar;49(3):157-63

Compliance with outpatient lithium therapy. Connelly CE. **Perspect Psychiatr Care** 1984 Apr-Jun;22(2):44-50

AFFECTIVE DISORDERS, PSYCHOTIC

Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health Consensus Development Conference Statement. **Nat Inst Health Consensus Dev Conf Consensus Statement** 1984; 5(4):8 p.

AFFECTIVE SYMPTOMS

Nomifensine for 'emotional incontinence' of the pseudobulbar type [letter] Sandyk R. **J Am Geriatr Soc** 1985 May;33(5):375

AGGRESSION

Treatment of an aggressive, compulsive adolescent with sultopride [letter] Bucci L. **Am J Psychiatry** 1985 Jul;142(7):882-3

Differential effects of electroconvulsive shock on four models of experimentally-induced aggression in rats. Liou SY, et al. **Jpn J Pharmacol** 1985 Feb;37(2):167-72

Effects of chronic LiCl and RbCl on muricide induced by midbrain raphe lesions in rats. Yamamoto T, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):559-63

Target biting associated with a gustatory avoidance response. Wagner GC, et al. **Physiol Behav** 1985 Mar;34(3):465-9

Serotonergic control of experimental aggression. Valzelli L, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):495-503

Biogenic amine alterations in limbic brain regions of muricidal rats. Broderick PA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr; 48(1):3-15

AMINO ACIDS

Effects of jejunoileal bypass on food intake, amino acid levels, and indoleamine metabolism in rats. Herlin PM, et al. **Am J Surg** 1985 Jun; 149(6):739-44

Synthesis of side chain-protected amino acid phenylthiohydantoins and their use in quantitative solid-phase Edman degradation. Steiman DM, et al. **Anal Biochem** 1985 Feb 15;145(1):91-5

Effects of diazinon on nucleotide and amino acid contents of chick embryos. Teratogenic considerations. Kushaba-Rugaaju S, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1937-43

Aromatic amino acid metabolites as potential protein binding inhibitors in human uremic plasma. Tavares-Almeida I, et al. **Biochem Pharmacol** 1985 Jul 15;34(14):2431-8

Determination of the relative positions of amino acids by partial specific cleavages of end-labeled proteins. Jue RA, et al. **Biochemistry** 1985 Jan 1;24(1):162-70

Antagonism of inhibitory amino acids by the steroid derivative RU5135. Simmonds MA, et al. **Br J Pharmacol** 1985 Mar;84(3):631-5

Quantitative review of optimum amino acid intakes for young laying pullets. McDonald MW, et al. **Br Poult Sci** 1985 Apr;26(2):253-64 (32 ref.)

Effects of excitatory amino acids on calcium transport by brain membranes. Harris RA. **Brain Res** 1985 Jun 24;337(1):167-70

Modulatory effects of prostaglandin D2, E2 and F2 alpha on the postsynaptic actions of inhibitory and excitatory amino acids in cerebellar Purkinje cell dendrites in vitro. Kimura H, et al. **Brain Res** 1985 Mar 25;330(2):235-44

Isocratic separation of PTH-amino acids at picomole level by reverse-phase HPLC in the presence of sodium dodecylsulfate. Tsunasawa S, et al. **J Biochem (Tokyo)** 1985 Feb;97(2):701-4

Determination of neurotransmitter amino acids by high-performance liquid chromatography with fluorescence detection. Zecca L, et al. **J Chromatogr** 1985 Feb 8;337(2):391-6

An artifact in urinary amino acid analysis produced by tris(hydroxymethyl)aminomethane (THAM). Wilson WG, et al. **J Inherited Metab Dis** 1985;8(1):24

Orally active and potent inhibitors of gamma-aminobutyric acid uptake. Ali FE, et al. **J Med Chem** 1985 May;28(5):653-60

Synthesis and structure-activity studies on excitatory amino acids structurally related to ibotenic acid. Krogsgaard-Larsen P, et al. **J Med Chem** 1985 May;28(5):673-9

Ibotenic acid analogues. Synthesis, molecular flexibility, and in vitro activity of agonists and antagonists at central glutamic acid receptors. Lauridsen J, et al. **J Med Chem** 1985 May;28(5):668-72

An excitant amino acid projection from the medial prefrontal cortex to the anterior part of nucleus accumbens in the rat. Christie MJ, et al. **J Neurochem** 1985 Aug;45(2):477-82

Potassium-induced release of endogenous amino acids in the guinea pig cochlea. Jenison GL, et al. **J Neurochem** 1985 Jun;44(6):1845-53

Afferent facilitation induced by iontophoretic application of acidic amino acids in the ampullary electroreceptors of Plotosus. Nagai T, et al. **J Neurophysiol** 1985 Apr;53(4):853-67

Pharmacological characterization of postsynaptic receptors for excitatory amino acids in Purkinje cell dendrites in the guinea pig cerebellum. Kimura H, et al. **J Pharmacobiodyn** 1985 Feb;8(2):119–27

Release of endogenous dopamine, 3,4–dihydroxyphenylacetic acid, and amino acid transmitters from rat striatal slices. Flint RS, et al. **Neurochem Res** 1985 Apr;10(4):515–27

Transport of monoamine and amino acid neurotransmitters by primary astroglial cultures. Hansson E. **Neurochem Res** 1985 May; 10(5):667–75

Glutamine–induced alterations in the content of brain amino acid neurotransmitters in rats with different alcohol motivation. Ostrovsky SYu. **Subst Alcohol Actions Misuse** 1984;5(5):247–53

Electrophysiological studies on neuronal transmission in the frog's photosensory pineal organ. The effect of amino acids and biogenic amines. Meissl H, et al. **Vision Res** 1984;24(12):1727–34

[Observations on the use of amino–acid mixtures in severe burn patients] Wang QF, et al. **Chung Hua Wai Ko Tsa Chih** 1985 Feb; 23(2):69–71, 125 (Eng. Abstr.) **(Chi)**

[Biochemistry of the brain. b. Amino acids, polypeptides, and proteins] Nishimura T, et al. **Nippon Rinsho** 1985 Feb;43(2):253–7 (30 ref.) **(Jpn)**

[Differential spectrophotometry of iodinated proteins and amino acids in heavy water] Gussakovskii EE, et al. **Biofizika** 1985 Mar–Apr; 30(2):208–10 (Eng. Abstr.) **(Rus)**

AMITRIPTYLINE

Chlordiazepoxide toxicity in Limbitrol overdose [letter] Goethe JW, et al. **Am J Psychiatry** 1985 Jun;142(6):774

Comparison of the effects of binodaline and amitriptyline on peripheral autonomic functions in healthy volunteers. Longmore J, et al. **Br J Clin Pharmacol** 1985 Mar;19(3):295–300

A comparison of the cardiovascular effects and subjective tolerability of binedaline and amitriptylene in healthy volunteers. Joubert PH, et al. **Eur J Clin Pharmacol** 1985;27(6):667–70

Why is amitriptyline much weaker than desipramine at decreasing beta–adrenoceptor numbers? Wise H, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):137–41

Tricyclic antidepressants antagonize prostaglandin (PG) E2–induced contractions of the guinea pig ileum and hypomotility in the mouse. Tayo FM. **Experientia** 1985 Apr 15;41(4):474–6

Determination of cyclobenzaprine in plasma and urine using capillary gas chromatography with nitrogen–selective detection. Constanzer ML, et al. **J Chromatogr** 1985 May 3;339(2):414–8

Plasma levels of amitriptyline: effect of age and sex. Preskorn SH, et al. **J Clin Psychiatry** 1985 Jul;46(7):276–7

Amitriptyline and contact lenses [letter] Troiano G. **J Clin Psychiatry** 1985 May;46(5):199

Amitriptyline and hydroxylated metabolite plasma levels in depressed outpatients. Robinson DS, et al. **J Clin Psychopharmacol** 1985 Apr; 5(2):83–8

Comparison of limbitrol (chlordiazepoxide/amitriptyline) and amitriptyline alone as a single night–time dose for the treatment of depression with anxiety. James RT, et al. **J Int Med Res** 1985; 13(2):84–7

Inhibition of the retrograde axonal transport of acetylcholinesterase by the anti–calmodulin agents amitriptyline and desipramine. Tiberi M, et al. **J Neurobiol** 1985 May;16(3):245–8

Responsibilities of prescribing. Avery JK. **J Tenn Med Assoc** 1985 May; 78(5):297

Effects of acute and chronic treatment with amitryptyline on the sleep–wake activity of rats. Obál F Jr, et al. **Neuropharmacology** 1985 Mar;24(3):223–9

Mianserin versus amitriptyline for depression: a double–blind 6–week trial. Rabkin JG, et al. **Neuropsychobiology** 1984;12(4):224–8

AMOBARBITAL

[Attempted suicide with barbiturate after glue sniffing] Sami HO, et al. **Orv Hetil** 1985 Mar 31;126(13):781–3 (Eng. Abstr.) **(Hun)**

[Barbamyl distribution in human blood] Kudrin AN, et al. **Farmakol Toksikol** 1985 Mar–Apr;48(2):113–5 (Eng. Abstr.) **(Rus)**

AMPHETAMINE

Pre–school children of amphetamine–addicted mothers. II. Environment and supportive social welfare. Eriksson M, et al. **Acta Paediatr Scand** 1985 Mar;74(2):185–90

Differential response to amphetamine in schizophrenia. Cesarec Z, et al. **Acta Psychiatr Scand** 1985 May;71(5):523–38

Effects of D– and L–amphetamine on dopamine metabolism and ascorbic acid levels in nucleus accumbens and olfactory tubercle as studied by in vivo differential pulse voltammetry. Louilot A, et al. **Brain Res** 1985 Jun 17;336(2):253–63

Single–reagent polarization fluoroimmunoassay for amphetamine in urine. Colbert DL, et al. **Clin Chem** 1985 Jul;31(7):1193–5

Opposite effects of sulpiride and metoclopramide on amphetamine–induced stereotypy. Robertson A, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):81–9

Liquid chromatographic determination of the enantiomeric composition of amphetamine and related drugs by diastereomeric derivatization. Barksdale JM, et al. **J Chromatogr Sci** 1985 Apr;23(4):176–80

Reserpine–induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31–8

Norepinephrine–dependent and independent mechanisms of persistent effects of amphetamine in rat cerebellum. Sorensen SM, et al. **Life Sci** 1985 Jun 24;36(25):2383–9

Hypothalamic involvement in the locomotor stimulant or satiety action of thyrotropin–releasing hormone and amphetamine. Shian LR, et al. **Pharmacology** 1985;30(5):259–65

Development of mouse activity, stimulus reactivity, habituation, and response to amphetamine and scopolamine. Alleva E, et al. **Physiol Behav** 1985 Apr;34(4):519–23

Amphetamine response and relapse risk after depot neuroleptic discontinuation. Angrist B, et al. **Psychopharmacology (Berlin)** 1985; 85(3):277–83

Specific opioid–amphetamine interactions in the caudate putamen. Woo SK, et al. **Psychopharmacology (Berlin)** 1985;85(3):371–6

The effect of previous d–amphetamine treatment on the disposition and lethality of fenfluramine in the rat. Hunsinger RN, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):236–45

[Comparative effect of the psychostimulants sidnocarb and fenamin on the tyrosine hydroxylase activity of the brain synaptosomes in rats] Ganiev MM, et al. **Farmakol Toksikol** 1985 Mar–Apr;48(2):27–32 (Eng. Abstr.) **(Rus)**

[Effect of stable strontium on spontaneous and drug–induced motor activity in the rat] Escanero JF, et al. **Arch Farmacol Toxicol** 1985 Apr; 11(1):33–9 (Eng. Abstr.) **(Spa)**

[Is the combination of amphetamine and chloroquine the cause of unexpected psychological symptoms?] **Lakartidningen** 1985 May 22; 82(21):1962 **(Swe)**

AMPHETAMINES

4–Bromo–2,5–dimethoxyphenethylamine: identification of a new street drug. Ragan FA Jr, et al. **J Anal Toxicol** 1985 Mar–Apr;9(2):91–3

Board of Medicine proposes new amphetamine rules. **Mich Med** 1985 Feb;84(2):100–2

Psychobiological foundations of behaviors induced by amphetamines. Groves PM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:356–66

p–Chloroamphetamine: effect on sleep and respiration in the rat. DeMesquita S. **Pharmacol Biochem Behav** 1985 May;22(5):889–91

Structure–activity studies on methoxy–substituted phenylisopropylamines using drug discrimination methodology. Glennon RA, et al. **Pharmacol Biochem Behav** 1985 May;22(5):723–9

[Microanalysis of amphetamines III. Detection of amphetamines in the hair of monkeys treated with methamphetamine] Takahashi K, et al. **Eisei Shikenjo Hokoku** 1984;(102):21–4 (Eng. Abstr.) **(Jpn)**

ANOREXIA NERVOSA

Chlorpromazine–associated haemolysis in anorexia nervosa. Van der Weyden MB, et al. **Acta Haematol (Basel)** 1985;73(2):111–3

Activity measures in anorexia nervosa. Falk JR, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):811–4

Anorexia nervosa: aetiological theories and treatment methods. Bryant R, et al. **J Adolesc** 1985 Mar;8(1):93–103

Behavior therapy, pimozide treatment and prolactin secretion in anorexia nervosa. Weizman A, et al. **Psychother Psychosom** 1985;43(3):136–40

ANTIDEPRESSIVE AGENTS

1st Czechoslovak Conference on Biological Psychiatry. Karlovy Vary (Karlsbad), September 1983. Abstracts. **Act Nerv Super (Praha)** 1985 Mar;27(1):60–72

Alteration of histamine metabolism in the rat brain under influence of various antidepressive treatments. Zawilska J, et al. **Agents Actions** 1985 Apr;16(3–4):105–8

Qualitative and quantitative analysis of the action of typical and atypical antidepressants in the experimental animal. Kozlovskaya MM, et al. **Ann Ist Super Sanita** 1984;20(1):73–7

Effects of long–term drug treatments on the sensitivity of presynaptic receptors regulating neurotransmitter release. Raiteri M, et al. **Ann Ist Super Sanita** 1984;20(1):57–64

Membrane–related effects of atypical antidepressants. Valdman AV, et al. **Ann Ist Super Sanita** 1984;20(1):65–72

Resting metabolic rate is reduced in patients treated with antidepressants. Fernstrom MH, et al. **Biol Psychiatry** 1985 Jun;20(6):692–5

Comparison of the effects of binodaline and amitriptyline on peripheral autonomic functions in healthy volunteers. Longmore J, et al. **Br J Clin Pharmacol** 1985 Mar;19(3):295–300

Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: studies on the olfactory bulbectomized rat model of depression. O'Connor WT, et al. **Br J Clin Pharmacol** 1985;

19 Suppl 1:49S–56S

A comparison of the cardiovascular effects and subjective tolerability of binedaline and amitriptylene in healthy volunteers. Joubert PH, et al. **Eur J Clin Pharmacol** 1985;27(6):667–70

Interindividual differences in the binding of antidepressives to plasma proteins: the role of the variants of alpha 1-acid glycoprotein. Tinguely D, et al. **Eur J Clin Pharmacol** 1985;27(6):661–6

Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behavioural 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):253–6

Drug response as a predictor of transmission of non-bipolar major depression within families. Prusoff BA, et al. **J Affective Disord** 1985 Mar–Apr;8(2):171–6

1-Azacycloalkyl-1,4-benzodiazepin-2-ones with antianxiety-antidepressant actions. Sugasawa T, et al. **J Med Chem** 1985 Jun;28(6):699–707

Synthesis and antidepressant profiles of phenyl-substituted 2-amino- and 2-[(alkoxycarbonyl)amino]-1,4,5,6-tetrahydropyrimidines. Weinhardt K, et al. **J Med Chem** 1985 Jun;28(6):694–8

Neurochemical profile of Lu 19-005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615–22

5-Hydroxytryptamine-stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: pharmacological characterization and effects of antidepressants. Kendall DA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):473–9

Effects of clenbuterol and antidepressant drugs on beta adrenergic receptor/N-protein coupling in the cerebral cortex of the rat. O'Donnell JM, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):30–6

Enhanced signal transduction by adenylate cyclase in platelet membranes of patients showing antidepressant responses to alprazolam: preliminary data. Mooney JJ, et al. **J Psychiatr Res** 1985;19(1):65–75

Elevation of mood due to antidepressants [letter] Pearce PL. **JAMA** 1985 Jun 7;253(21):3091–2

On acute and chronic CNS effects of antidepressants in normals: neurophysiological, behavioral and pharmacokinetic studies with pirlindol. Saletu B, et al. **Methods Find Exp Clin Pharmacol** 1985 Mar;7(3):137–51

Antidepressants and endogenous opioid peptide systems. Przewłocki R, et al. **Neuropeptides** 1985 Feb;5(4–6):575–8

Serotonin and antidepressant drugs antagonize melatonin-induced behavioural changes after injection into the nucleus accumbens of rats. Gaffori O, et al. **Neuropharmacology** 1985 Mar;24(3):237–44

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar;24(3):217–22

The olfactory bulbectomized rat as a model of depression. Leonard BE. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):561–9 (30 ref.)

Characterization of the bupropion cue in the rat: lack of evidence for a dopaminergic mechanism. Blitzer RD, et al. **Psychopharmacology (Berlin)** 1985;85(2):173–7

The tail suspension test: a new method for screening antidepressants in mice. Steru L, et al. **Psychopharmacology (Berlin)** 1985;85(3):367–70

The activation of mice's behavior and reduction of brain beta-adrenergic receptor binding following repeated administration of antidepressant drugs. Nomura S, et al. **Yakubutsu Seishin Kodo** 1984 Nov;4(3):237–41

[Effect of acute administration of antidepressive agents at 2 P.M. on plasma and pineal levels of melatonin in the rat] Mouren P, et al. **Encephale** 1985 Jan–Feb;11(1):29–30 (Eng. Abstr.) **(Fre)**

[Drug flush. Possible role of indalpine overdosage (letter)] Manigand G, et al. **Presse Med** 1985 Apr 13;14(15):841 **(Fre)**

[Therapeutic strategy in depression] Scotto JC, et al. **Rev Prat** 1985 May 11;35(27):1633–8 (Eng. Abstr.) **(Fre)**

[Action of indalpine on the pupil diameter in the healthy volunteer] Brion N, et al. **Therapie** 1985 Jan–Feb;40(1):9–11 (Eng. Abstr.) **(Fre)**

[Treatment of depressive syndrome with antidepressants] Woggon B, et al. **Med Monatsschr Pharm** 1985 May;8(5):130–6 **(Ger)**

[Inhibition of brain monoamine oxidase in the rat by multiple pyrazidol administration] Verevkina IV, et al. **Biull Eksp Biol Med** 1985 May;99(5):583–4 (Eng. Abstr.) **(Rus)**

[Comparative study of the indices of the antidepressive activity of potassium orotate and piracetam] Karkishchenko NN, et al. **Farmakol Toksikol** 1985 Mar–Apr;48(2):32–5 (Eng. Abstr.) **(Rus)**

[The effect of psychopharmacologic agents on the passive transport of Ca2+ induced by vanadate in human erythrocytes] Pogády J, et al. **Bratisl Lek Listy** 1985 Apr;83(4):345–52 (Eng. Abstr.) **(Slo)**

ANTISOCIAL PERSONALITY DISORDER

The relationship between antisocial behavior and affective illness. Reich J. **Compr Psychiatry** 1985 May–Jun;26(3):296–303 (47 ref.)

ANXIETY

A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. Davison K, et al. **Br J Clin Pharmacol** 1985;19 Suppl 1:37S–43S

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445–51

Brief review of published alprazolam clinical studies. Straw RN. **Br J Clin Pharmacol** 1985;19 Suppl 1:57S–59S (22 ref.)

Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety. Power KG, et al. **Br Med J [Clin Res]** 1985 Apr 27;290(6477):1246–8

Drugs in dentistry. Agents for anxiety disorders. Ciancio SG. **Dent Manage** 1985 Jun;25(6):66, 68, 70

Animal models for the study of anti-anxiety agents: a review. Treit D. **Neurosci Biobehav Rev** 1985 Summer;9(2):203–22

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: punished barpressing. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;85(2):244–51

[Clinical trial of the action of a benzodiazepine (Lexotan) on the behavior of the anxious patient in dental outpatient care] Debernardi G, et al. **Minerva Stomatol** 1985 Mar–Apr;34(2):323–8 (Eng. Abstr.) **(Ita)**

[Anxiolytic action of sodium valproate (possible role of gamma-aminobutyric acid in affective disorders)] Raevskii KS, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):574–9 (Eng. Abstr.) **(Rus)**

ANXIETY DISORDERS

Management of specific anxiety disorders in the elderly. Turnbull JM, et al. **Geriatrics** 1985 Aug;40(8):75–82

Emergency treatment of acute psychosis, agitation, and anxiety. Ellison JM. **Hosp Community Psychiatry** 1985 Apr;36(4):351–2

L-5-hydroxytryptophan in the treatment of anxiety disorders. Kahn RS, et al. **J Affective Disord** 1985 Mar–Apr;8(2):197–200

Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam. Ansseau M, et al. **Neuropsychobiology** 1984;12(4):255–9

Clinical pharmacology of benzodiazepines. Rickels K. **Pharmacopsychiatry** 1985 Jan;18(1):156–9

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167–70

New findings in anxiety. A synthesis for clinical practice in 1985. Curtis GC. **Psychiatr Clin North Am** 1985 Mar;8(1):169–75

Generalized anxiety disorder. Hoehn-Saric R, et al. **Psychiatr Clin North Am** 1985 Mar;8(1):73–88 (65 ref.)

Imipramine in the treatment of panic disorder and its complications. Liebowitz MR. **Psychiatr Clin North Am** 1985 Mar;8(1):37–47

APOMORPHINE

Effect of metoclopramide, domperidone and apomorphine on GH secretion in children and adolescents. Massara F, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):451–5

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196–201

Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Grace AA, et al. **Brain Res** 1985 May 6;333(2):285–98

Antagonism of apomorphine-enhanced startle by alpha 1-adrenergic antagonists. Davis M, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):233–41

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269–74

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349–54

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305–8

The supersensitivity of dopaminergic neurons to apomorphine in rats following chronic haloperidol. Vogelsang GD, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):267–9

Reserpine-induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31–8

Inhibitory effects of apomorphine and pergolide on neurogenic vasoconstriction in the hindquarters of the rat. Dupont AG, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):146–51

Effects of discriminant and non-discriminant dopamine antagonists on in vivo accumulation of 3H-N-propyl-norapomorphine in mouse striatum and tuberculum olfactorium. Gulat-Marnay C, et al.

Naunyn Schmiedebergs Arch Pharmacol 1985 Apr;329(2):117–22

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128–34

Effect of chronic haloperidol and quinacrine coadministration on striatal HVA levels and stereotypic behaviors in response to apomorphine in the rat. Deutsch SI, et al. **Neurochem Res** 1985 Apr;10(4):491–8

Antistereotypic effects of cholecystokinin octapeptide (CCK-8), ceruletide and related peptides on apomorphine-induced gnawing in sensitized mice. Zetler G. **Neuropharmacology** 1985 Mar;24(3):251–9

In vivo electrochemical monitoring of apomorphine penetration into the rat brain. Marcenac FM, et al. **Neurosci Lett** 1985 Apr 19; 55(3):305–10

The morphogenesis of stereotyped behavior induced by the dopamine receptor agonist apomorphine in the laboratory rat. Szechtman H, et al. **Neuroscience** 1985 Mar;14(3):783–98

Effect of chronic apomorphine on the development of denervation supersensitivity. Robin M, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):547–51

Effects of selective dopamine receptor agonists in rats trained to discriminate apomorphine from saline. Woolverton WL, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):577–81

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346–52

Increased or decreased locomotor response in rats following repeated administration of apomorphine depends on dosage interval. Castro R, et al. **Psychopharmacology (Berlin)** 1985;85(3):333–9

Influence of cimetidine, ranitidine and imidazole on the behavioral effects of (+/-) N-n-propylnorapomorphine in male rats. Ferrari F, et al. **Psychopharmacology (Berlin)** 1985;85(2):197–200

Increase in plasma ACTH after dopaminergic stimulation in rats. Ježová D, et al. **Psychopharmacology (Berlin)** 1985;85(2):201–3

Effects of apomorphine and haloperidol on 'spontaneous' stereotyped licking behaviour in the Cebus monkey. Korsgaard S, et al. **Psychopharmacology (Berlin)** 1985;85(2):240–3

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204–9

Studies on the stability of 3H-dopamine, 3H-apomorphine and 3H-ADTN: effects of sodium ascorbate and EDTA. Cabbat FS, et al. **Res Commun Chem Pathol Pharmacol** 1985 Mar;47(3):333–43

Circadian variation in the ambulation-increasing effect of apomorphine after repeated administration in mice. Kuribara H, et al. **Yakubutsu Seishin Kodo** 1984 Nov;4(3):231–6

APPETITE

d-Fenfluramine and salbutamol: two drugs causing anorexia through different neurochemical mechanisms. Garattini S, et al. **Int J Obes** 1984; 8 Suppl 1:151–7

The clinical pharmacology of appetite suppressant drugs. Silverstone T, et al. **Int J Obes** 1984;8 Suppl 1:23–33

AROUSAL

Are the anxiogenic effects of yohimbine mediated by its action at benzodiazepine receptors? Pellow S, et al. **Neurosci Lett** 1985 Mar 22; 55(1):5–9

Clinical pharmacology of benzodiazepines. Rickels K. **Pharmacopsychiatry** 1985 Jan;18(1):156–9

1,2-Anellated 1,4-benzodiazepine derivatives--a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174–7

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167–70

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49–55

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731–6

ATTENTION

Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178–93

A limiting factor in the 'normalization' of schizophrenic orienting response dysfunction. Bernstein AS, et al. **Schizophr Bull** 1985;11(2):230–54

ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY

Evaluating drug effectiveness in an office setting for children with attention deficit disorders. Ottinger DR, et al. **Clin Pediatr (Phila)** 1985 May;24(5):245–51

Oral pemoline kinetics in hyperactive children. Sallee F, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):606–9

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227–43

Stimulants and neuroleptics in hyperactive children [letter] Gualtieri CT, et al. **J Am Acad Child Psychiatry** 1985 May;24(3):363–4

Cardiovascular effects of desipramine in children and adolescents with attention deficit disorder. Biederman J, et al. **J Pediatr** 1985 Jun; 106(6):1017–20

Adolescent outcome of hyperactive children treated with stimulants in childhood: a review. Hechtman L. **Psychopharmacol Bull** 1985; 21(2):178–91 (15 ref.)

New drug trials in attention deficit disorder. Rapoport JL, et al. **Psychopharmacol Bull** 1985;21(2):232–6 (16 ref.)

A review of studies of drug treatment efficacy for attention deficit disorder with hyperactivity in adolescents. Varley CK. **Psychopharmacol Bull** 1985;21(2):216–21 (31 ref.)

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222–31

Methylphenidate: rate-dependent drug effects in hyperactive boys. Weber K. **Psychopharmacology (Berlin)** 1985;85(2):231–5

[Urinary 3-methoxy-4-hydroxyphenylglycol sulfate in school children with minimal brain dysfunction syndrome] Wang YF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Feb; 18(1):45–9 (Eng. Abstr.) **(Chi)**

AUTISM, INFANTILE

Vitamin B6, magnesium, and combined B6-Mg: therapeutic effects in childhood autism. Martineau J, et al. **Biol Psychiatry** 1985 May; 20(5):467–78

Serotonin relationships of autistic probands and their first-degree relatives. Kuperman S, et al. **J Am Acad Child Psychiatry** 1985 Mar; 24(2):186–90

AVOIDANCE LEARNING

Direct and indirect behavioral pathways to the social transmission of food avoidance. Galef BG Jr. **Ann NY Acad Sci** 1985;443:203–15

Introduction: physiological mechanisms in conditioned taste aversions. Grill HJ. **Ann NY Acad Sci** 1985;443:67–88

Conditioned food aversions and satiety signals. Kulkosky PJ. **Ann NY Acad Sci** 1985;443:330–47

Conditioned taste aversions: a behavioral index of toxicity. Riley AL, et al. **Ann NY Acad Sci** 1985;443:272–92

Glucocorticoid and other hormonal substrates of conditioned taste aversion. Smotherman WP. **Ann NY Acad Sci** 1985;443:126–44

Interfering with taste aversion learning in rats: the role of associative interference. Cannon DS, et al. **Appetite** 1985 Mar;6(1):1–19

Effects of tifluadom on passive avoidance behaviour in DBA/2 mice. Pavone F, et al. **Behav Brain Res** 1985 May;15(3):177–81

Response of the rat brain beta-endorphin system to novelty: importance of the fornix connection. Netto CA, et al. **Behav Neural Biol** 1985 Jan; 43(1):37–46

Central versus peripheral actions of Leu-enkephalin on acquisition of a one-way active avoidance response in rats. Martinez JL Jr, et al. **Brain Res** 1985 Feb 18;327(1–2):37–43

Aversive effects of subcutaneously injected vasopressin in the rat: independence of the ascending dorsal noradrenergic bundle. Tam FW, et al. **Brain Res** 1985 Jun 24;337(1):133–7

Spontaneous configuring in conditioned flavor aversion. Forbes DT, et al. **J Exp Psychol [Anim Behav]** 1985 Apr;11(2):224–40

Potentiation and overshadowing in preweanling and adult rats. Kucharski D, et al. **J Exp Psychol [Anim Behav]** 1985 Jan;11(1):15–34

2-Amino-4-phosphonobutyric acid selectively blocks two-way avoidance learning in the mouse. Sahai S, et al. **Neurosci Lett** 1985 May 14; 56(2):137–42

Dose-related effects of pentobarbital on the genetic differences seen between paired, Roman high- or low-avoidance rats in a shuttle box. Driscoll P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):435–9

Effects of psychotropic drugs on discrimination conditioning in olfactory bulbectomized rats. Gomita Y, et al. **Pharmacol Biochem Behav** 1985 May;22(5):717–22

Lithium effects on position learning with exploratory and aversive goal-box conditions. Hines G. **Pharmacol Biochem Behav** 1985 May; 22(5):695–8

Intracortical glutamate injection produces helpless-like behavior in the rat. Petty F, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):531–3

Passive avoidance after ibotenic acid and radio frequency lesions in the rat amygdala. Jellestad FK, et al. **Physiol Behav** 1985 Feb; 34(2):299–305

Conditioned taste aversion suppresses induction of delayed–type hypersensitivity immune reactions. Kelley KW, et al. **Physiol Behav** 1985 Feb;34(2):189–93

Target biting associated with a gustatory avoidance response. Wagner GC, et al. **Physiol Behav** 1985 Mar;34(3):465–9

Luteinizing–hormone–releasing hormone modifies retention of passive and active avoidance responses in rats. Mora S, et al. **Psychopharmacology (Berlin)** 1985;85(3):315–8

Anti–aversive role of serotonin in the dorsal periaqueductal grey matter. Schütz MT, et al. **Psychopharmacology (Berlin)** 1985;85(3):340–5

[3,6–disubstituted 1–lupinylquinoxalin–2(1H)–ones of pharmacological interest. Effect on acquisition and modification of a conditioned avoidance response in rats] Sparatore A, et al. **Farmaco [Sci]** 1985 May; 40(5):303–14 (Eng. Abstr.) **(Ita)**

AZEPINES

Differential modulation of gamma–aminobutyric acid receptors by caprolactam derivatives with central nervous system depressant or convulsant activity. Skerritt JH, et al. **Brain Res** 1985 Apr 8; 331(2):225–33

Pharmacological and neurochemical properties of 1,4–diazepines with two annelated heterocycles ('hetrazepines'). Weber KH, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):19–31

The dopamine autoreceptor agonist B–HT 920 markedly stimulates sexual behavior in male rats. Ferrari F, et al. **Experientia** 1985 May 15; 41(5):636–8

I.R. and N.M.R. spectroscopic studies of 1,4–thienodiazepinic drugs. Fernández–Arciniega MA, et al. **Farmaco [Prat]** 1985 Apr; 40(4):124–30

Synthesis and interaction of 5–(substituted–phenyl)–3–methyl–6,7–dihydropyrazolo[4,3–e][1,4]diazepin–8(7H)–ones with benzodiazepine receptors in rat cerebral cortex. Baraldi PG, et al. **J Med Chem** 1985 May;28(5):683–5

The putative dopamine autoreceptor agonist B–HT 920 decreases nigral dopamine cell firing rate and prolactin release in rat. Eriksson E, et al. **Life Sci** 1985 May 13;36(19):1819–27

Effect of cetiedil on platelet aggregation and thromboxane synthesis. Yamaguchi A, et al. **Thromb Res** 1985 Feb 1;37(3):391–400

[Thin–layer densitometric determination of clotiazepam in tablets and blood plasma] Busch M, et al. **Arzneimittelforsch** 1985;35(2):547–51 (Eng. Abstr.) **(Ger)**

[The effect of dilazep on red cell survival] Saito H, et al. **Rinsho Ketsueki** 1985 Jan;26(1):15–9 (Eng. Abstr.) **(Jpn)**

[New derivatives of 7– and 8–member perhydrocyclic compounds. II. Studies on the effect on the central nervous system and circulatory system of new derivatives of perhydro–1,4–oxazepine, perhydro–1,4–diazepine, perhydro–1,4,5–oxadiazepine and perhydro–1,5–oxazocine containing the 2–guanidinoethyl group] Szadowska A, et al. **Acta Pol Pharm** 1985;42(1):55–60 (Eng. Abstr.) **(Pol)**

BEHAVIOR

Neuropharmacologic management of behavior sequelae in head injury: a case report. Haas JF, et al. **Arch Phys Med Rehabil** 1985 Jul; 66(7):472–4

No acute behavioural effects of exposure to styrene: a safe level of exposure? Edling C, et al. **Br J Ind Med** 1985 May;42(5):301–4

On acute and chronic CNS effects of antidepressants in normals: neurophysiological, behavioral and pharmacokinetic studies with pirlindol. Saletu B, et al. **Methods Find Exp Clin Pharmacol** 1985 Mar; 7(3):137–51

[Clinical trial of the action of a benzodiazepine (Lexotan) on the behavior of the anxious patient in dental outpatient care] Debernardi G, et al. **Minerva Stomatol** 1985 Mar–Apr;34(2):323–8 (Eng. Abstr.) **(Ita)**

BEHAVIOR, ANIMAL

The effects of aniracetam on primate behavior and EEG. Schwam E, et al. **Ann NY Acad Sci** 1985;444:482–4

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196–201

Some behavioral effects of early styrene intoxication in experimental animals. Husain R, et al. **Arch Toxicol** 1985 Apr;57(1):53–5

Catecholamine–blocking drugs injected at sites of amine accumulation reverse catecholamine degeneration associated deficits. Willis GL, et al. **Behav Brain Res** 1985 Apr;15(2):101–6

Ethanol preference behaviour and dopamine release in the rat. Schmidt J, et al. **Biomed Biochim Acta** 1984;43(12):1431–4

A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5–HT1 and 5–HT2 receptors. Goodwin GM, et al. **Br J Pharmacol** 1985 Mar;84(3):743–53

Involvement of nigrostriatal dopamine neurons in the contraversive rotational behavior evoked by electrical stimulation of the lateral hypothalamus. Castañeda E, et al. **Brain Res** 1985 Feb 18; 327(1–2):143–51

Enhancement of some 5–HT–dependent behavioural responses following repeated immobilization in rats. Kennett GA, et al. **Brain Res** 1985 Mar 25;330(2):253–63

Amine accumulation in behavioural pathology. Willis GL, et al. **Brain Res** 1985 Jun;356(2):109–32 (302 ref.)

Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behavioural 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):253–6

Long–term behavioral effects of phenobarbital in suckling rats. McBride MC, et al. **Exp Neurol** 1985 Jul;89(1):59–70

Behavioral indications for phenothiazine and benzodiazepine tranquilizers in dogs. Hart BL. **J Am Vet Med Assoc** 1985 Jun 1;186(11):1192–4

Effect of immune complex–forming reactants on catecholamine–modulated behaviors in the rat hypothalamus. Schupf N, et al. **J Neuroimmunol** 1985 Jul;9(1–2):13–27

Characteristics of the cortical and hippocampal EEG power spectra of rabbits during normal behavioral states and after administration of CNS acting drugs. Yamamoto J. **Jpn J Pharmacol** 1985 Mar;37(3):227–34

Effects of bombesin on behavior. Cowan A, et al. **Life Sci** 1985 Jul 15; 37(2):135–45

Beta–endorphin–(10–16) antagonizes behavioral responses elicited by melatonin following injection into the nucleus accumbens of rats. Gaffori O, et al. **Life Sci** 1985 Jul 29;37(4):357–64

Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5–MeODMT or mCPP. Sills MA, et al. **Life Sci** 1985 Jul 1; 36(26):2463–9

Catecholamine–independent behavioral and neurochemical effects of cocaine in rats. Gale K. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:323–32

Psychobiological foundations of behaviors induced by amphetamines. Groves PM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:356–66

The continuity of dopamine receptor antagonism can dictate the long–term behavioural consequences of a mesolimbic infusion of dopamine. Costall B, et al. **Neuropharmacology** 1985 Mar;24(3):193–7

Serotonin and antidepressant drugs antagonize melatonin–induced behavioural changes after injection into the nucleus accumbens of rats. Gaffori O, et al. **Neuropharmacology** 1985 Mar;24(3):237–44

Effects of MET–ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan–Feb;6(1):139–48

Specificity of nucleus accumbens to activities related to cholecystokinin in rats. Katsuura G, et al. **Peptides (Fayetteville)** 1985 Jan–Feb; 6(1):91–6

Altered responses to serotonergic agents in Fawn–Hooded rats. Gudelsky GA, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):489–92

Comparative behavioral effects of CNS cholinesterase inhibitors. Mos DE, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):479–82

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417–51 (238 ref.)

1.2–Anellated 1.4–benzodiazepine derivatives—a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174–7

Postnatal lead exposure and the cholinergic system. Alfano DP, et al. **Physiol Behav** 1985 Mar;34(3):449–55

8th congress of the Polish Pharmacological Society. Symposium II: Pharmacological implications for animal models of mental disorders. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):493–569

Some behavioral effects of microinjections of serotonin and noradrenaline into the limbic structures of the rat brain. Plaźnik A. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):541–54

Neurotropic drugs and brain development: effects on cell replication in vivo and in vitro. Patel AJ. **Prog Clin Biol Res** 1985;163C:301–5

Influence of cimetidine, ranitidine and imidazole on the behavioral effects of (+/–) N–n–propylnorapomorphine in male rats. Ferrari F, et al. **Psychopharmacology (Berlin)** 1985;85(2):197–200

Effects of some dibenzo–azepines on suppressed and nonsuppressed behavior of squirrel monkeys. Spealman RD. **Psychopharmacology (Berlin)** 1985;85(2):129–32

Chronic neuroleptic treatment and mesolimbic dopamine denervation induce behavioural supersensitivity to opiates. Stinus L, et al. **Psychopharmacology (Berlin)** 1985;85(3):323–8

Specific opioid–amphetamine interactions in the caudate putamen. Woo SK, et al. **Psychopharmacology (Berlin)** 1985;85(3):371–6

Behavioral effects of long–term neuroleptic treatment in Cebus monkeys. Casey DE. **Psychopharmacology [Suppl]** 1985;2:211–6

Functional classification of different dopamine receptors. Ungerstedt U, et al. **Psychopharmacology [Suppl]** 1985;2:19–30

An analysis of some behavioural effects of the vibration and noise components of transport in pigs. Stephens DB, et al. **Q J Exp Physiol** 1985 Apr;70(2):211–7

Biogenic amine alterations in limbic brain regions of muricidal rats. Broderick PA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr; 48(1):3-15

[Behavioral pharmacology of amantadine with special references to the effect on abnormal behavior in mice and rats] Fujiwara M, et al. **Nippon Yakurigaku Zasshi** 1985 Apr;85(4):259-74 (Eng. Abstr.) **(Jpn)**

[New derivatives of 7- and 8-member perhydrocyclic compounds. II. Studies on the effect on the central nervous system and circulatory system of new derivatives of perhydro-1,4-oxazepine, perhydro-1,4-diazepine, perhydro-1,4,5-oxadiazepine and perhydro-1,5-oxazocine containing the 2-guanidinoethyl group] Szadowska A, et al. **Acta Pol Pharm** 1985;42(1):55-60 (Eng. Abstr.) **(Pol)**

BENACTYZINE

Comparative effects of aprophen, atropine and benactyzine on central and peripheral cholinoceptors and on acetylcholinesterase. Dawson RM, et al. **Biochem Pharmacol** 1985 May 1;34(9):1577-9

BENZAZEPINES

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665-9

Inhibition of hepatic microsomal drug metabolism by the calcium channel blockers diltiazem and verapamil. Renton KW. **Biochem Pharmacol** 1985 Jul 15;34(14):2549-53

Hemodynamic and pharmacological effects of the converting enzyme inhibitor CGS 14824A in normal volunteers. Schaller MD, et al. **Eur J Clin Pharmacol** 1985;28(3):267-72

Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Creese I, et al. **Eur J Pharmacol** 1985 Feb 12; 109(1):127-8

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349-54

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305-8

Comparative studies of cardiovascular effects of a new dopamine agonist (SK&F 38393A) and dopamine. Tsai CS, et al. **Gen Pharmacol** 1985; 16(2):85-9

Effects of the calcium antagonist, diltiazem on in vitro and in vivo/in vitro bone resorption. Ly SY, et al. **Horm Metab Res** 1985 Mar; 17(3):152-5

Effects of SK&F 82526 and SK&F 83742 on the renal vascular dopamine receptor. Schmidt M, et al. **J Pharmacol** 1985 Jan-Mar;16(1):15-22

Do D 600 and diltiazem interact with serotonin receptors in rabbit vascular tissues? Ohashi M, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):830-5

SCH23390 causes persistent antidopaminergic effects in vivo: evidence for longterm occupation of receptors. Schulz DW, et al. **Life Sci** 1985 May 20;36(20):1941-8

Newer dopamine quinazolones as anti-parkinsonian agents. Kumar P, et al. **Pharmazie** 1985 Apr;40(4):267-8

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346-52

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

BENZODIAZEPINE TRANQUILIZERS

Article-induced' dyscontrol [letter] Gardner DL, et al. **Am J Psychiatry** 1985 Jun;142(6):776

The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. Lauven PM. et al. **Anesthesiology** 1985 Jul;63(1):61-4

A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. Davison K, et al. **Br J Clin Pharmacol** 1985;19 Suppl 1:37S-43S

Pharmacokinetics and pharmacodynamics following single and repeated nightly administrations of loprazolam, a new benzodiazepine hypnotic. McInnes GT, et al. **Br J Clin Pharmacol** 1985 May;19(5):649-56

Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: studies on the olfactory bulbectomized rat model of depression. O'Connor WT, et al. **Br J Clin Pharmacol** 1985; 19 Suppl 1:49S-56S

Brief review of published alprazolam clinical studies. Straw RN. **Br J Clin Pharmacol** 1985;19 Suppl 1:57S-59S (22 ref.)

Drugs in dentistry. Agents for anxiety disorders. Ciancio SG. **Dent Manage** 1985 Jun;25(6):66, 68, 70

Intramuscular bioavailability of chlorazepate as compared to diazepam. Bertler A, et al. **Eur J Clin Pharmacol** 1985;28(2):229-30

Spontaneous and RO 15-1788-induced reversal of subsensitivity to GABA following chronic benzodiazepines. Gonsalves SF, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):163-70

On the spectrophotometric determination of estazolam using Ru(III) ion. Gallo N, et al. **Farmaco [Prat]** 1985 Mar;40(3):77-80

Behavioral indications for phenothiazine and benzodiazepine tranquilizers in dogs. Hart BL. **J Am Vet Med Assoc** 1985 Jun 1;186(11):1192-4

Alprazolam overdose: clinical findings and serum concentrations in two cases. McCormick SR, et al. **J Clin Psychiatry** 1985 Jun;46(6):247-8

Efficiency and cleanliness of ether extraction for benzodiazepines in blood samples treated with aqueous ammonia compared with other methods for the purpose of HPLC assay. Stevens HM. **J Forensic Sci Soc** 1985 Jan-Feb;25(1):67-79

Triazolam, an anomalous benzodiazepine receptor ligand: in vitro characterization of alprazolam and triazolam binding. Clow A, et al. **J Neurochem** 1985 Aug;45(2):621-5

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

Psychological treatment for benzodiazepine dependence [letter] Tyrer P, et al. **Lancet** 1985 May 4;1(8436):1042-3

Acute pharmacokinetic and pharmacodynamic comparison of two different formulations of temazepam. Mattila MJ, et al. **Med Biol** 1985; 63(1):21-7

Benzodiazepines produce contrasting effects on the active membrane properties of an invertebrate neuron. Tan KS, et al. **Neuropharmacology** 1985 Feb;24(2):91-4

The modulation of cortical acetylcholine release by GABA, GABA-like drugs and benzodiazepines in freely moving guinea-pigs. Tanganelli S, et al. **Neuropharmacology** 1985 Apr;24(4):291-9

Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory. Subhan Z, et al. **Neuropsychobiology** 1984;12(4):244-8

gamma-Aminobutyric acid modulation of benzodiazepine receptor binding in vitro does not predict the pharmacologic activity of all benzodiazepine receptor ligands. Chweh AY, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):173-7

Pharmacology of benzodiazepine antagonists. Haefely W. **Pharmacopsychiatry** 1985 Jan;18(1):163-6

Clinical pharmacology of benzodiazepines. Rickels K. **Pharmacopsychiatry** 1985 Jan;18(1):156-9

1.2-Anellated 1.4-benzodiazepine derivatives--a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174-7

The sedative effects of CL 218,872, like those of chlordiazepoxide, are reversed by benzodiazepine antagonists. File SE, et al. **Psychopharmacology (Berlin)** 1985;85(3):295-300

[Alprazolam (Tafil). A new benzodiazepine-with a new action profile?] Rasmussen SB, et al. **Ugeskr Laeger** 1985 Apr 29;147(18):1495-7 **(Dan)**

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[Characteristics of benzodiazepine consumption in patients hospitalized in an internal medicine department] Le Goc I, et al. **Encephale** 1985 Jan-Feb;11(1):1-6 (Eng. Abstr.) **(Fre)**

[Benzodiazepines: pharmacodynamic aspects] Jacqmin P, et al. **J Pharm Belg** 1985 Jan-Feb;40(1):35-54 (74 ref.) (Eng. Abstr.) **(Fre)**

[Clobazam and N-desmethylclobazam. Assay by HPLC. Application to a pharmacokinetic study] Biehler J, et al. **Therapie** 1985 May-Jun; 40(3):167-71 (Eng. Abstr.) **(Fre)**

[Possible disorders after withdrawal of prolonged treatment with benzodiazepines in man (drug addicts excluded)] Lagier G. **Therapie** 1985 Jan-Feb;40(1):51-7 (Eng. Abstr.) **(Fre)**

[Clinical trial of the action of a benzodiazepine (Lexotan) on the behavior of the anxious patient in dental outpatient care] Debernardi G, et al. **Minerva Stomatol** 1985 Mar-Apr;34(2):323-8 (Eng. Abstr.) **(Ita)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

BENZODIAZEPINONES

Effect of H2 receptor- and muscarine receptor antagonists and prostaglandin E1 analog on the gastric mucosal hemodynamics and oxygen sufficiency in rats. Sato N, et al. **Adv Exp Med Biol** 1984; 180:763-71

The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. Lauven PM, et al. **Anesthesiology** 1985 Jul;63(1):61-4

Pharmacokinetics and pharmacodynamics following single and repeated nightly administrations of loprazolam, a new benzodiazepine hypnotic. McInnes GT, et al. **Br J Clin Pharmacol** 1985 May;19(5):649-56

Blockade of the diazepam-induced increase in rat striatal acetylcholine content by the specific benzodiazepine antagonists ethyl-beta-carboline-3-carboxylate and Ro 15-1788. Kolasa K, et al. **Brain Res** 1985 Jun 17;336(2):342-5

Effects of pirenzepine on plasma insulin, glucagon and pancreatic polypeptide levels in normal man. Zaccaria M, et al. **Eur J Clin Pharmacol** 1985;27(6):701-5

The benzodiazepine antagonist Ro 15-1788 reverses the effect of methyl-beta-carboline-3-carboxylate but not of harmaline on cerebellar cGMP and motor performance in mice. Burkard WP, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):241-7

Spontaneous and RO 15-1788-induced reversal of subsensitivity to GABA following chronic benzodiazepines. Gonsalves SF, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):163-70

Kinetics and displacement of [11C]RO 15-1788, a benzodiazepine antagonist, studied in human brain in vivo by positron tomography. Samson Y, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):247-51

Comparative inhibitory effects of pirenzepine and atropine on cholinergic stimulation of exocrine and endocrine rat pancreas. Otsuki M, et al. **Gastroenterology** 1985 Aug;89(2):408-14

Plasma determination of 3-methylclonazepam by capillary gas chromatography. Coassolo P, et al. **J Chromatogr** 1985 Mar 22; 338(2):347-55

1-Azacycloalkyl-1,4-benzodiazepin-2-ones with antianxiety-antidepressant actions. Sugasawa T, et al. **J Med Chem** 1985 Jun;28(6):699-707

'Peripheral-type' binding sites for benzodiazepines in brain: relationship to the convulsant actions of Ro 5-4864. Weissman BA, et al. **J Neurochem** 1985 May;44(5):1494-9

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

The interaction of McN-A-343 with pirenzepine and other selective muscarine receptor antagonists at a prejunctional muscarine receptor. Choo LK, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb; 328(4):430-8

The effects of benzodiazepines on spinal homosynaptic depression. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):301-7

Information processing and benzodiazepines. Kleindienst-Vanderbeke G. **Neuropsychobiology** 1984;12(4):238-43

Clonazepam-induced hyperphagia in nondeprived rats: tests of pharmacological specificity with Ro5-4864, Ro5-3663, Ro15-1788 and CGS 9896. Cooper SJ, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):753-60

NMR analysis of an oligodeoxyribonucleotide-drug adduct: anthramycin-d(ATGCAT). Graves DE, et al. **Prog Clin Biol Res** 1985; 172B:193-205

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[Clobazam and N-desmethylclobazam. Assay by HPLC. Application to a pharmacokinetic study] Biehler J, et al. **Therapie** 1985 May-Jun; 40(3):167-71 (Eng. Abstr.) **(Fre)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

BIOGENIC AMINES

Changes in the brain biogenic monoamines of rats, induced by piracetam and aniracetam. Petkov VD, et al. **Acta Physiol Pharmacol Bulg** 1984; 10(4):6-15

Liquid chromatographic determination of free and conjugated 3-methoxy-4-hydroxyphenylethylene glycol with wide-ranging substances related to monoamine metabolism. Ishikawa K, et al. **Anal Biochem** 1985 Jun;147(2):441-50

Role of the spinal monoaminergic systems in suppression of ejaculation by alpha-methyldopa. Kimura Y, et al. **Andrologia** 1985 Mar-Apr; 17(2):166-71

Biogenic amine/metabolite response during in-flight emergencies. Krahenbuhl GS, et al. **Aviat Space Environ Med** 1985 Jun; 56(6):576-80

Monoamine metabolites: their relationship and lack of relationship to monoaminergic neuronal activity. Commissiong JW. **Biochem Pharmacol** 1985 Apr 15;34(8):1127-31

Effects of intraventricular injections of 6-hydroxydopamine on amine metabolites in rat brain and urine. Edwards DJ, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1255-63

Cerebrospinal fluid (CSF) and brain monoamine metabolites in the developing rat pup. Shaywitz BA, et al. **Brain Res** 1985 Jan; 349(1-2):225-32

Effect of styrene oxide on levels of biogenic amines and activity of monoamine oxidase in different parts of rat brain. Husain R, et al. **Bull Environ Contam Toxicol** 1985 May;34(5):722-9

Pharmacokinetics of oral moclobemide in healthy human subjects and effects on MAO-activity in platelets and excretion of urine monoamine metabolites. Wiesel FA, et al. **Eur J Clin Pharmacol** 1985; 28(1):89-95

Sex differences in long-term gonadectomized rats: monoamine levels and [3H]nitroimipramine binding in brain nuclei. Renner KJ, et al. **Exp Brain Res** 1985;58(1):198-201

Pharmacologic studies of central actions of zopiclone: influence on brain monoamines in rats under stressful condition. Sato K, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Apr;23(4):204-10

New high-performance liquid chromatography system for the separation of biogenic amines as their Dns derivatives. Hayman AR, et al. **J Chromatogr** 1985 Jun 7;325(2):462-6

Modulation by monoamines of somatostatin-sensitive adenylate cyclase on neuronal and glial cells from the mouse brain in primary cultures. Chneiweiss H, et al. **J Neurochem** 1985 Jun;44(6):1825-31

Role of monoamines in experimental spinal cord injury in rats. Relationship between Na+-K+-ATPase and lipid peroxidation. Kurihara M. **J Neurosurg** 1985 May;62(5):743-9

Relationships between drug-induced changes in tetrahydrobiopterin and biogenic amine concentrations in rat brain. Lee EH, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):141-6

Auto-tolerance to the endogenous opioids and sleep. Gillman MA, et al. **Med Hypotheses** 1985 Apr;16(4):393-5

Cardiovascular responses elicited by microinjection of monoamines into mesencephalic nucleus dorsalis raphe in cats. Saxena AK, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):141-5

Mechanisms of the central action of lithium. Sinitskii VN, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):81-8

Biogenic amine alterations in limbic brain regions of muricidal rats. Broderick PA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr; 48(1):3-15

Electrophysiological studies on neuronal transmission in the frog's photosensory pineal organ. The effect of amino acids and biogenic amines. Meissl H, et al. **Vision Res** 1984;24(12):1727-34

[Effect of electroconvulsive shock on brain monoamines] Kuang PG. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Feb; 18(1):41-4 (Eng. Abstr.) **(Chi)**

[A TRH analog (DN-1417). Effects on the levels of monoamines and the metabolites in the various brain regions in rats] Nagai Y, et al. **Nippon Yakurigaku Zasshi** 1985 Apr;85(4):209-20 (Eng. Abstr.) **(Jpn)**

[Changes in the response to the extracellular application of acetylcholine during the intracellular perfusion of isolated neurons with biogenic amines] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985; 280(6):1495-8 **(Rus)**

[Biogenic amine content of brain sections, blood and adrenals of rabbits exposed to vibration and noise] Minasian SM, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):439-45 (Eng. Abstr.) **(Rus)**

BIPOLAR DISORDER

Renal function in 153 manic-depressive patients treated with lithium for more than five years. Løkkegaard H, et al. **Acta Psychiatr Scand** 1985 Apr;71(4):347-55

Plasma lithium level and interepisode functioning in bipolar disorder. Goodnick PJ, et al. **Am J Psychiatry** 1985 Jun;142(6):761-2

Manic depression: a multiple hormone disorder? Skutsch GM. **Biol Psychiatry** 1985 Jun;20(6):662-8

Erythrocyte membrane sodium-potassium and magnesium ATPase in primary affective disorder. Thakar JH, et al. **Biol Psychiatry** 1985 Jul; 20(7):734-40

Methylene blue for MDI [letter] Turner WJ. **Biol Psychiatry** 1985 Jul; 20(7):815

Imipramine metabolism in recurrent depressive episodes. Tollefson G, et al. **J Affective Disord** 1985 Mar-Apr;8(2):183-6

Monoamine oxidase inhibitors in the treatment of atypical depression. Zisook S, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):131-7

Lithium therapy for mania and depression. Murray JB. **J Gen Psychol** 1985 Jan;112(1):5-33

Interdependency of lithium ratio, plasma lithium level and clinical state in patients with affective disorders. Elizur A, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(2):167-72

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

Bipolar disorder and social work practice. Sands RG. **Soc Work Health Care** 1985 Spring;10(3):91-105

[A case of simultaneous treatment of the manic syndrome and granulocytopenia with lithium salts] Greń K, et al. **Psychiatr Pol** 1984 May-Jun;18(3):285-8 **(Pol)**

BLOOD-BRAIN BARRIER

Blood-brain barrier permeability to leucine-enkephalin, D-alanine2-D-leucine5-enkephalin and their N-terminal amino acid (tyrosine). Zlokovic BV, et al. **Brain Res** 1985 Jun 10;336(1):125-32

Role of 5-HT on increased permeability of blood-brain barrier under heat stress. Sharma HS, et al. **Indian J Physiol Pharmacol** 1984 Oct-Dec;

28(4):259-67

[The hemato-encephalic barrier in emotional stress] Belova TI, et al. **Usp Fiziol Nauk** 1985 Apr-Jun;16(2):61-76 (105 ref.) **(Rus)**

BODY IMAGE

Dysmorphophobia [letter] Jenike MA. **Br J Psychiatry** 1985 Mar; 146:326

BRADYKININ

Stimulation of prostacyclin production in isolated rat adipocytes by angiotensin II, vasopressin, and bradykinin: evidence for two separate mechanisms of prostaglandin synthesis. Axelrod L, et al. **Endocrinology** 1985 Jun;116(6):2548-53

BUTYLAMINES

Metabolism of N-nitrodialkylamines. Suzuki E, et al. **IARC Sci Publ** 1984; (57):485-90

BUTYROPHENONE TRANQUILIZERS

Lipids and apolipoproteins in patients treated with major tranquilizers. Sasaki J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):684-7

[Haloperidol decanoate in replacing combinations of antipsychotic agents in the treatment of chronic schizophrenics] Youssef HA. **Acta Psiquiatr Psicol Am Lat** 1984 Dec;30(4):297-304 **(Spa)**

BUTYROPHENONES

Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Shenker A, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):427-9

Pergolide elevation of MHPG sulphate concentration in rat hypothalamus blocked by spiperone and mimicked by other dopamine agonists. Fuller RW, et al. **J Pharm Pharmacol** 1985 Apr;37(4):268-70

A comparison between centrifugation and filtration as a means to separate bound and unbound ligand during 3[H]-spiroperidol binding. Csernansky CA, et al. **J Pharmacol Methods** 1985 Jun;13(3):187-91

Binding of 3H-spiperone to human lymphocytes: a biological marker in schizophrenia? Bondy B, et al. **Psychiatry Res** 1985 May;15(1):41-8

Presynaptic stimulation of dopaminergic CNS structures in sheep as a mechanism of immobilising action of Immobyl (fentanyl + azaperone). Kania BF. **Res Vet Sci** 1985 Mar;38(2):179-83

[Binding of 3H-spiperone in the mouse brain after intraperitoneal injection] Zharkovskiĭ AM, et al. **Biull Eksp Biol Med** 1985 Mar; 99(3):314-5 (Eng. Abstr.) **(Rus)**

CARBAMAZEPINE

Lack of pharmacokinetic interaction of carbamazepine with tranylcypromine [letter] Joffe RT, et al. **Arch Gen Psychiatry** 1985 Jul; 42(7):738

Carbamazepine-induced thrombocytopenia in a young child. Bradley JM, et al. **Clin Pharm** 1985 Mar-Apr;4(2):221-3

The influence of cimetidine on single-dose carbamazepine pharmacokinetics. Dalton MJ, et al. **Epilepsia** 1985 Mar-Apr; 26(2):127-30

A study of some pharmacological actions of carbamazepine and sodium valproate. Mansuri SM, et al. **Indian J Physiol Pharmacol** 1984 Oct-Dec; 28(4):315-8

Bioavailability and central side effects of different carbamazepine tablets. Neuvonen PJ. **Int J Clin Pharmacol Ther Toxicol** 1985 Apr; 23(4):226-32

Differential mediation of the anticonvulsant effects of carbamazepine and diazepam. Weiss SR, et al. **Life Sci** 1985 Jun 24;36(25):2413-9

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

Erythromycin-carbamazepine interaction [letter] Kessler JM. **S Afr Med J** 1985 Jun 29;67(26):1038

Determination of total and free plasma carbamazepine concentrations by enzyme multiplied immunoassay: interference with the 10,11-epoxide metabolite. Contin M, et al. **Ther Drug Monit** 1985;7(1):46-50

Fallacious results from measuring salivary carbamazepine concentrations. Dickinson RG, et al. **Ther Drug Monit** 1985;7(1):41-5

Simultaneous plasma carbamazepine and carbamazepine-epoxide concentrations in pharmacokinetic and bioavailability studies. Hooper WD, et al. **Ther Drug Monit** 1985;7(1):36-40

[Responsibility of the physician in prescribing Tegretol [letter] Kamp JS. **Ned Tijdschr Geneeskd** 1985 Mar 30;129(13):607-8 **(Dut)**

[Tegretol] Benoit P, et al. **Soins Psychiatr** 1985 Feb;(52):I-II **(Fre)**

[Quantitative determination of carbamazepine in tablets by reverse phase HPLC] Mamolo MG, et al. **Boll Chim Farm** 1984 Dec; 123(12):591-9 (Eng. Abstr.) **(Ita)**

[Interaction of carbamacepine and tuberculostatic agents (letter)] Bastús JB. **Med Clin (Barc)** 1985 Apr 6;84(13):542-3 **(Spa)**

[Clinical pharmacology of carbamazepine--a comparison with phenytoin] Bertilsson L, et al. **Lakartidningen** 1985 Apr 10;82(15):1355-60 **(Swe)**

CARBIDOPA

Carbidopa effect on rat brain monoamine oxidase and pineal melatonin. McIntyre IM, et al. **Biol Psychiatry** 1985 Jul;20(7):809-11

CATATONIA

Severe prolonged catatonia with associated flushing reaction responsive to lithium carbonate. Pheterson AD, et al. **J Am Acad Child Psychiatry** 1985 Mar;24(2):235-7

CATECHOL ESTROGENS

Studies on the effects of catecholestrogens on prolactin secretion by cultured normal rat anterior pituitary cells. Lamberts SW, et al. **Endocrinology** 1985 Jun;116(6):2631-6

Effects of short-term exposure to catecholestrogens on serum concentrations of gonadotrophins and metabolism of catecholestrogens in ovariectomized rats. Ball P, et al. **Horm Metab Res** 1985 Apr; 17(4):184-8

CATECHOLAMINES

Catecholamines and contractility of the human myometrium at term: a possible role for prostaglandins. Wikland M, et al. **Acta Physiol Hung** 1985;65(3):331-4

Determinations of catecholamine half-lives and turnover rates in discrete catecholamine nerve terminal systems of the hypothalamus, the preoptic region and the forebrain by quantitative histofluorimetry. Andersson K, et al. **Acta Physiol Scand** 1985 Apr;123(4):411-26

Sub-aggregatory doses of catecholamines prevent prostacyclin-induced inhibition of platelet aggregation. Buttrick PM, et al. **Am Heart J** 1985 Jun;109(6):1258-63

Methodological considerations in the determination of plasma catecholamines by high-performance liquid chromatography with electrochemical detection. Bouloux P, et al. **Ann Clin Biochem** 1985 Mar;22 (Pt 2):194-203

Computer simulations of the conformations of catecholamine derivatives. Hassan M, et al. **Ann NY Acad Sci** 1985;446:185-98

Plasma norepinephrine, epinephrine, and dopamine levels in end-stage renal disease. Effect of hemodialysis. Elias AN, et al. **Arch Intern Med** 1985 Jun;145(6):1013-5

Brain catecholamines and memory modulation: effects of footshock, amygdala implantation, and stimulation. Welsh KA, et al. **Behav Neural Biol** 1985 Mar;43(2):119-31

Response of hepatic ornithine decarboxylase and polyamine concentration to surgical stress in the rat: evidence for a permissive effect of catecholamines on glucocorticoid action. Corti A, et al. **Biochem Biophys Res Commun** 1985 Jun 28;129(3):885-91

The phorbol ester TPA enhances A23187--but not carbachol- and high K+-induced catecholamine secretion from cultured bovine adrenal chromaffin cells. Morita K, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):511-6

Characterization of protein kinase C and its role in catecholamine secretion from bovine adrenal-medullary cells. Brocklehurst KW, et al. **Biochem J** 1985 May 15;228(1):35-42

Declining catecholamine secretion in adrenal medulla on prolonged stimulation with acetylcholine. Bevington A, et al. **Biochem Pharmacol** 1985 May 1;34(9):1497-500

Interaction of phenothiazine drugs with human ceruloplasmin. Relation between activation of catecholamine neurotransmitter oxidation and electron donating ability of phenothiazine drugs. de Mol NJ. **Biochem Pharmacol** 1985 Aug 1;34(15):2605-9

Affinity-dependent cross-linking to neurotoxin sites of the acetylcholine receptor mediated by catechol oxidation. Nickoloff BJ, et al. **Biochemistry** 1985 Feb 12;24(4):999-1007

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

Do catecholamines play a physiologic role in regulating corpus luteum function in the pseudopregnant rabbit? Gadsby JE, et al. **Biol Reprod** 1985 May;32(4):907-15

Hypothalamic epinephrine is released into hypophysial portal blood during stress. Gibbs DM. **Brain Res** 1985 Jun 3;335(2):360-4

Clonidine effects on catecholamine levels and turnover in discrete hypothalamic and extra-hypothalamic areas. Jhanwar-Uniyal M, et al. **Brain Res** 1985 Jun 24;337(1):109-16

Effects of catecholamines on spinal motoneurones and spinal reflex discharges in the isolated spinal cord of the newborn rat. Kitazawa T, et al. **Brain Res** 1985 Mar;351(1):31-6

Place preference conditioning with methylphenidate and nomifensine. Martin-Iverson MT, et al. **Brain Res** 1985 Apr 15;332(1):59-67

Cerebellum plus locus coeruleus in tissue culture: I. Catecholamine histofluorescence and extracellular electrophysiology. Seil FJ, et al. **Brain Res** 1985 Jan;349(1-2):165-70

Intertectal neuronal plasticity in Xenopus laevis: persistence despite catecholamine depletion. Udin SB, et al. **Brain Res** 1985 Mar; 351(1):81–8

Microspectrofluorometric characterization of amine accumulation proximal to lateral hypothalamic lesions. Willis GL, et al. **Brain Res** 1985 May 20;334(2):344–7

Amine accumulation in behavioural pathology. Willis GL, et al. **Brain Res** 1985 Jun;356(2):109–32 (302 ref.)

Ultrastructural evidence of direct synaptic contact of catecholamine terminals with oxytocin–containing neurons in the parvocellular portion of the rat hypothalamic paraventricular nucleus. Yamano M, et al. **Brain Res** 1985 Jun 10;336(1):176–9

Catecholamine innervation of cervical dendrite bundles: possible phrenic nucleus innervation. Bellinger DL, et al. **Brain Res Bull** 1984 Dec; 13(6):701–7

MPTP alters central catecholamine neurons in addition to the nigrostriatal system. Gupta M, et al. **Brain Res Bull** 1984 Dec;13(6):737–42

Effect of delta 9–THC on brain and plasma catecholamine levels as measured by HPLC. Patel V, et al. **Brain Res Bull** 1985 Jan; 14(1):85–90

Plasticity of catecholaminergic neurons in aged rat brain: reinnervation and functional recovery after axotomy. Phelps CJ, et al. **Brain Res Bull** 1984 Dec;13(6):727–36

Early appearance of catecholaminergic neurons in the central nervous system of precocial and altricial avian species. A fluorescence–histochemical study. Guglielmone R, et al. **Cell Tissue Res** 1985;240(2):381–4

Cortisol and catecholamines response to venisection by humans with different blood groups. Locong AH, et al. **Clin Biochem** 1985 Feb; 18(1):67–9

Acetaminophen administration interferes with urinary metanephrine (and catecholamine) determinations [letter] Wilson SP, et al. **Clin Chem** 1985 Jun;31(6):1093–4

Receptor mechanisms in fish chromatophores—VIII. Mediated by beta adrenoceptors, catecholamines always act to disperse pigment in siluroid melanophores. Fujii R, et al. **Comp Biochem Physiol** [C] 1985; 81(1):1–6

Catecholamine hormones and the control of avian salt glands. Wilson JX, et al. **Comp Biochem Physiol** [C] 1985;81(1):77–9

Cardiovascular and catecholamine responses to hypoxemia in chemically sympathectomized fetal lambs. Lewis AB, et al. **Dev Pharmacol Ther** 1985;8(2):129–40

Effect of intravenous ketanserin on plasma catecholamines and renin activity in normal volunteers. Reimann IW, et al. **Eur J Clin Pharmacol** 1985;28(3):273–7

Pharmacological interference with the neurotoxic action of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) on central catecholamine neurons in the mouse. Sundström E, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):293–9

Effects of intracerebroventricular 6–hydroxydopamine on catecholaminergic fibers in the rat hypothalamus. Hwang BH, et al. **Exp Neurol** 1985 May;88(2):336–48

Changes in the size of isolated chromaffin granules in ATP–evoked catecholamine release. Warashina A. **FEBS Lett** 1985 May 6; 184(1):87–9

Hormonal influence on the response of the uterus of the Brazilian marsupial Didelphis albiventris to adrenergic drugs. Rocha LR, et al. **Gen Comp Endocrinol** 1985 May;58(2):179–85

Immunohistochemical demonstration of catecholaminergic cell bodies in the spinal cord of the rat. Preliminary note. Dietl M, et al. **Histochemistry** 1985;82(4):385–9

Effect of phosphodiesterase regulators and catecholamines on motility of isolated pregnant rat uterus. Singh M, et al. **Indian J Exp Biol** 1984 Dec;22(12):645–8

Pharmacologic studies of the central action of zopiclone: effects on locomotor activity and brain monoamines in rats. Liu HJ, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):121–8

Brain catecholamines and the central control of food intake. Stricker EM, et al. **Int J Obes** 1984;8 Suppl 1:39–50 (64 ref.)

Sympathetic activity, plasma renin activity (PRA) and kininogen levels in patients haemodialysed with acetate and bicarbonate. Ksiażek A, et al. **Int Urol Nephrol** 1984;16(4):337–44

Exercise, dobutamine, and combined atropine, norepinephrine, and epinephrine compared. Haidet GC, et al. **J Appl Physiol** 1985 Jun; 58(6):2047–53

The effects of hypoxia on catecholamine dynamics in the rat carotid body. Brokaw JJ, et al. **J Auton Nerv Syst** 1985 May;13(1):35–47

Vasoactive amines modulate actin cables (stress fibers) and surface area in cultured bovine endothelium. Welles SL, et al. **J Cell Physiol** 1985 Jun;123(3):337–42

Simultaneous assay of 3,4–dihydroxyphenylalanine, catecholamines and O–methylated metabolites in human plasma using high–performance liquid chromatography. Ishimitsu T, et al. **J Chromatogr** 1985 Feb 8; 337(2):239–48

Catecholamine secretion as a function of perceived coping self–efficacy. Bandura A, et al. **J Consult Clin Psychol** 1985 Jun;53(3):406–14

Radioreceptor assay for beta–adrenergic receptor–reactive catecholamines in serum samples. Iwo K, et al. **J Lab Clin Med** 1985 Jun; 105(6):711–7

The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3–4):175–81

Direct fluorometric assay of catecholamine secretion from isolated bovine adrenal chromaffin cells. Lelkes PI, et al. **J Neurosci Methods** 1985 May;13(3–4):249–55

An improved technique for extracting catecholamines from body fluids. Macdonald IA, et al. **J Neurosci Methods** 1985 May;13(3–4):239–48

Photoaffinity labelling of MSH receptors on Anolis melanophores: effects of catecholamines, calcium and forskolin. Eberle AN, et al. **J Recept Res** 1985;5(1):59–81

Regional changes in catecholamine content of the pregnant uterus. Arkinstall SJ, et al. **J Reprod Fertil** 1985 Mar;73(2):547–57

Changes in dopamine–beta–hydroxylase, and copper, and catecholamine concentrations in human plasma with physical exercise. Ohno H, et al. **J Sports Med Phys Fitness** 1984 Dec;24(4):315–20

Glucose and insulin infusion directly after cardiac surgery: effects on systemic glucose uptake, catecholamine excretion, O2 consumption, and CO2 production. Nilsson F, et al. **JPEN** 1985 Mar–Apr;9(2):159–64

Effect of 2,4,6–trinitrophenol on catecholamine secretion from perfused bovine adrenal glands. Yamanaka K, et al. **Jpn J Pharmacol** 1985 Jan; 37(1):120–3

Hormonal control of renal potassium excretion. Field MJ, et al. **Kidney Int** 1985 Feb;27(2):379–87 (86 ref.)

The effects of a single acute dose of dexamethasone on monoamine and metabolite levels in rat brain. Rothschild AJ, et al. **Life Sci** 1985 Jul 1;36(26):2491–501

The effects of acute and chronic treatment with triiodothyronine and thyroxine on the hypothalamic and telencephalic catecholamine nerve terminal systems of the hypophysectomized male rat. Chronic treatment modulates catecholamine utilization in discrete catecholamine nerve terminal systems. Andersson K, et al. **Neuroendocrinology** 1985 May; 40(5):398–408

Influences of catecholamines on growth hormone release in female goldfish, Carassius auratus. Chang JP, et al. **Neuroendocrinology** 1985 Jun;40(6):463–70

A combined autoradiographic and immunocytochemical study of 3H–corticosterone target neurons and catecholamine neurons in rat and mouse lower brain stem. Duncan GE, et al. **Neuroendocrinology** 1985 Mar;40(3):262–71

Central and peripheral catecholamine innervation of the rat intermediate and posterior pituitary lobes. Saavedra JM. **Neuroendocrinology** 1985 Apr;40(4):281–4

Comparison of the changes in central catecholamine systems following short– and long–term lithium treatment and the consequences of lithium withdrawal. Ahluwalia P, et al. **Neuropsychobiology** 1984; 12(4):217–23

State of adrenergic and cholinergic systems in schizophrenia patients during psychopharmacotherapy. Krupenina LB, et al. **Neurosci Behav Physiol** 1985 Jan–Feb;15(1):1–8

Morphological evidence that serotonin–immunoreactive neurons in the nucleus dorsomedialis hypothalami could be under catecholaminergic influence. Arezki F, et al. **Neurosci Lett** 1985 May 14;56(2):161–6

Reflex changes in sympatho–adrenal medullary functions in response to various thermal cutaneous stimulations in anesthetized rats. Kurosawa M, et al. **Neurosci Lett** 1985 May 14;56(2):149–54

Effects of gonadal steroids on catecholamine levels in the brain of the oyster toadfish. Pennypacker KR, et al. **Neurosci Lett** 1985 Apr 9; 55(2):203–6

Effects of intravenously administered 6–hydroxydopamine on the content of monoamines in the median eminence and neurointermediate lobe of the rat. Sheward WJ, et al. **Neurosci Lett** 1985 Apr 9;55(2):141–4

Chlordecone interaction with catecholamine binding and uptake in rat brain synaptosomes. Desaiah D. **Neurotoxicology (Little Rock Ar)** 1985 Spring;6(1):159–65

Effect of dialysate sodium on the dopamine, adrenaline and noradrenaline concentration in haemodialysis patients. Ksiażek A, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985;21:225–9

Prostaglandins, catecholamines, and differentiation of the secondary palate. Greene RM, et al. **Prog Clin Biol Res** 1985;163C:277–81

Effects of ketamine on the catecholamine containing cells of the adrenal gland of the lizard Podarcis s. sicula Raf. Varano L, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr;48(1):145–8

Effects of nicotinic an muscarinic stimulation on calcium flux and catecholamine secretion in primary cultures of adrenal medullary cells. Watanabe J. **Tokushima J Exp Med** 1984 Dec;31(3–4):79–84

[Central neurotransmitters and cardiovascular activity] Xia Y. **Sheng Li Ko Hsueh Chin Chan** 1985 Jan;16(1):27–31 (50 ref.) (Ch

[Expression of the adrenergic phenotype by dorsal root ganglion cells of the quail in culture in vitro] Xue ZG, et al. **C R Acad Sci [III]** 1985;300(13):483–8 (Eng. Abstr.) (Fre)

[Concentrations of catecholamines in CSF and plasma, and cardiovascular effects following epidural administration of 2 mg epinephrine] Nakajima

J. **Masui** 1985 Feb;34(2):144-51 (Eng. Abstr.) **(Jpn)**

[Neuro-intestinal peptides and peptide-producing cells--immunohistocytochemistry of catecholamines and opioid peptides in the hamster adrenal medulla] Kobayashi S, et al. **Nippon Heikatsukin Gakkai Zasshi** 1984 Oct;20(5):393-9 **(Jpn)**

[Catecholamine content in the human adrenal gland] Nakada T, et al. **Nippon Hinyokika Gakkai Zasshi** 1985 Feb;76(2):239-43 (Eng. Abstr.) **(Jpn)**

[A study on catecholamine contents of the canine upper urinary tract] Nishimoto T. **Nippon Hinyokika Gakkai Zasshi** 1985 Jan;76(1):56-64 (Eng. Abstr.) **(Jpn)**

[Spatial reorganization of the organelles of catecholamine-synthesizing group A1 neurons during emotional stress] Zhigadlo BA, et al. **Arkh Anat Gistol Embriol** 1985 Feb;88(2):11-6 (Eng. Abstr.) **(Rus)**

[Catecholamine levels in pancreatic tissue after intraperitoneal administration of acetylcholine] Gal'kiv MA, et al. **Fiziol Zh** 1985 Mar-Apr;31(2):230-4 **(Rus)**

[Cardiomyocytes in monolayer culture and the effect on them of catecholamines and hypoxia] Gurevich MI, et al. **Fiziol Zh** 1985 May-Jun;31(3):267-72 (Eng. Abstr.) **(Rus)**

[Biogenic amine content of various parts of the brain under the stimulation of interoceptors of the gastrointestinal tract] Kravets SV, et al. **Fiziol Zh** 1985 Mar-Apr;31(2):216-9 **(Rus)**

[Changes in blood monoamine and 11-hydroxycorticosteroid levels in rats under the action of stress] Ugarova OP. **Fiziol Zh** 1985 Mar-Apr; 31(2):224-7 **(Rus)**

[Effect of gamma-aminobutyric acid, taurine and catecholamines on the synaptic processes in Lorenzini's ampules in Black Sea skates] Akoev GN, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):466-71 (Eng. Abstr.) **(Rus)**

[Cytophotometric study of catecholamines and acetylcholinesterase in neurons of the intramural plexus of the urinary bladder of the cat in controls and animals exposed to experimental conditions] Lapsha VI, et al. **Neirofiziologiia** 1985;17(2):263-70 (Eng. Abstr.) **(Rus)**

CENTRAL NERVOUS SYSTEM AGENTS

Characteristics of the cortical and hippocampal EEG power spectra of rabbits during normal behavioral states and after administration of CNS acting drugs. Yamamoto J. **Jpn J Pharmacol** 1985 Mar;37(3):227-34

Drugs and chemicals that act on the central nervous system: interpretation of experimental evidence. Kellogg CK. **Prog Clin Biol Res** 1985; 163C:147-53 (27 ref.)

CHILD BEHAVIOR DISORDERS

Treatment of an aggressive, compulsive adolescent with sultopride [letter] Bucci L. **Am J Psychiatry** 1985 Jul;142(7):882-3

CHILD DEVELOPMENT DISORDERS

Understanding and treatment of childhood depression. Aylward GP. **J Pediatr** 1985 Jul;107(1):1-9

CHLORAMINES

A possible origin of chemiluminescence in phagocytosing neutrophils. Reaction between chloramines and H2O2. Zgliczyński JM, et al. **Int J Biochem** 1985;17(4):515-9

Generation of free radical intermediates from foreign compounds by neutrophil-derived oxidants. Kalyanaraman B, et al. **J Clin Invest** 1985 May;75(5):1618-22

[In vitro antibacterial activity of chloramide] Farina C, et al. **G Ital Chemioter** 1984 Sep-Dec;31(3):215-8 (Eng. Abstr.) **(Ita)**

CHLORDIAZEPOXIDE

Chlordiazepoxide toxicity in Limbitrol overdose [letter] Goethe JW, et al. **Am J Psychiatry** 1985 Jun;142(6):774

Comparison of limbitrol (chlordiazepoxide/amitriptyline) and amitriptyline alone as a single night-time dose for the treatment of depression with anxiety. James RT, et al. **J Int Med Res** 1985; 13(2):84-7

Brain amines and effects of chlordiazepoxide on motor activity in response to stress. Freeman GB, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):665-70

The effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats. Evenden JL, et al. **Psychopharmacology (Berlin)** 1985;85(3):361-6

The sedative effects of CL 218,872, like those of chlordiazepoxide, are reversed by benzodiazepine antagonists. File SE, et al. **Psychopharmacology (Berlin)** 1985;85(3):295-300

A comparison between chlordiazepoxide and CL 218,872--a synthetic nonbenzodiazepine ligand for benzodiazepine receptors on spontaneous locomotor activity in rats. McElroy JF, et al. **Psychopharmacology (Berlin)** 1985;85(2):224-6

[Effect of stable strontium on spontaneous and drug-induced motor activity in the rat] Escanero JF, et al. **Arch Farmacol Toxicol** 1985 Apr; 11(1):33-9 (Eng. Abstr.) **(Spa)**

P-CHLOROPHENYLALANINE

Decreased serotonin content of embryonic raphe neurons following maternal administration of p-chlorophenylalanine: a quantitative immunocytochemical study. Lauder JM, et al. **Brain Res** 1985 May; 352(1):107-14

CHLORPROMAZINE

Chlorpromazine-associated haemolysis in anorexia nervosa. Van der Weyden MB, et al. **Acta Haematol (Basel)** 1985;73(2):111-3

Comparison of inhibitory actions of chlorpromazine or its 7,8-dihydroxy and 7,8-dioxo-didesmethyl analogs on DA-sensitive adenylate cyclase and calmodulin activation of phosphodiesterase in rat striatum. Palmer GC, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):202-11

Effects of chlorpromazine and its dihydroxy metabolite on calcium movement and electrical activity in superior cervical ganglia. Guzman-Harty M, et al. **Arch Toxicol** 1985 Feb;56(4):272-8

Inhibitory effect of chlorpromazine on bone formation in vivo and in vitro. Komoda T, et al. **Biochem Pharmacol** 1985 Jul 1; 34(13):2389-91

Drug-protein interactions: binding of chlorpromazine to calmodulin, calmodulin fragments, and related calcium binding proteins. Marshak DR, et al. **Biochemistry** 1985 Jan 1;24(1):144-50

Chlorpromazine inhibition of electron transport in Azotobacter vinelandii membranes. Wong TY, et al. **Biochim Biophys Acta** 1985 May 31; 807(3):320-3

The mechanism of intestinal transport of sulfamethoxazole and the effect of chlorpromazine in rat everted intestine. Chung YH, et al. **J Pharmacobiodyn** 1985 Feb;8(2):142-9

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

Effect of chlorpromazine on peritoneal clearances. Indraprasit S, et al. **Nephron** 1985;40(3):341-3

Effect of centrally acting drugs on ethanol detoxification enzymes in distinct rat brain regions. Messiha FS. **Neurobehav Toxicol Teratol** 1985 Mar-Apr;7(2):181-4

Drug interactions and vasoconstrictors used in local anesthetic solutions. Yagiela JA, et al. **Oral Surg Oral Med Oral Pathol** 1985 Jun; 59(6):565-71

Temperature dependent modification of radiosensitivity following hypoxic cytocidal action of chlorpromazine. Shenoy MA, et al. **Radiat Environ Biophys** 1985;24(2):113-7

Thorazine injected; pt. dies: criminal charges. Case in point: people v. Nygren (696 P. 2d 270--CO). Tammelleo AD. **Regan Rep Nurs Law** 1985 May;25(12):2

[Effects of haloperidol, chlorpromazine, metoclopramide and ascorbic acid on adrenergic salivation and lacrimation in mice at an ambient temperature of 30 degrees C] Li BH, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar;6(1):24-6 (Eng. Abstr.) **(Chi)**

[A simple phosphorimetric method for the determination of chlorpromazine] Huang RH, et al. **Yao Hsueh Hsueh Pao** 1984 Aug; 19(8):606-10 (Eng. Abstr.) **(Chi)**

[Biotransformation of Chlorphenethazin (Elroquil, Marophen)] Pfeifer S, et al. **Pharmazie** 1985 Jan;40(1):37-9 (Eng. Abstr.) **(Ger)**

CHLORPROTHIXENE

Determination of chlorprothixene and its sulfoxide metabolite in plasma by high-performance liquid chromatography with ultraviolet and amperometric detection. Brooks MA, et al. **J Chromatogr** 1985 Feb 8;337(2):351-62

Tetracyclic pyridazines as potential psychopharmacological agents. Ross BS, et al. **J Med Chem** 1985 Jul;28(7):870-5

CHOICE BEHAVIOR

The effects of delaying reward on choice preference in rats with hippocampal or selective septal lesions. Rawlins JN, et al. **Behav Brain Res** 1985 May;15(3):191-203

Differential effects of pimozide on response-rate and choice accuracy in a self-stimulation paradigm in mice. Bowers W, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):521-6

CLOMIPRAMINE

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128-34

Role of the serotonin uptake carrier in the neurochemical response to methamphetamine: effects of citalopram and chlorimipramine. Schmidt CJ, et al. **Neurochem Res** 1985 May;10(5):637-48

Clomipramine and imipramine in obsessive-compulsive disorder. Volavka J, et al. **Psychiatry Res** 1985 Jan;14(1):85-93

[Treatment of obsessive compulsive neurosis] Greenberg D, et al. **Harefuah** 1985 Mar 1;108(5):231-5 (Eng. Abstr.) **(Heb)**

COCAINE

Atomizer modification for nasal administration of cocaine and other drugs. Rector FT, et al. **Anesth Analg** 1985 Jul;64(7):739-41

Carl Koller: the man and the drug. McAuley JE. **Br Dent J** 1985 May 11;158(9):339-42

Frequency-related, bidirectional limbic responses to cocaine: comparisons with amphetamine and lidocaine. Lesse H, et al. **Brain Res** 1985 May 27;335(1):21-31

Cocaine increases EEG beta: a replication and extension of Hans Berger's historic experiments. Herning RI, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):470-7

Platelet responsiveness and biosynthesis of thromboxane and prostacyclin in response to in vitro cocaine treatment. Togna G, et al. **Haemostasis** 1985;15(2):100-7

An epidemic of cocaine associated deaths in Utah. Sander R, et al. **J Forensic Sci** 1985 Apr;30(2):478-84

The danger of cocaine [editorial] Pollin W. **JAMA** 1985 Jul 5; 254(1):98

Bromocriptine as treatment of cocaine abuse [letter] Dackis CA, et al. **Lancet** 1985 May 18;1(8438):1151-2

Catecholamine-independent behavioral and neurochemical effects of cocaine in rats. Gale K. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:323-32

Sensitization of rotational behavior produced by a single exposure to cocaine. Guan LC, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):901-3

[A brief review on cocaine] Renggli R. **Schweiz Med Wochenschr** 1985 Mar 30;115(13):426-30 (15 ref.) (Eng. Abstr.) (Ger)

[Fatal cocaine poisoning] Kisser W. **Z Rechtsmed** 1985;94(2):155-8 (Eng. Abstr.) (Ger)

COGNITION

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

Information processing and benzodiazepines. Kleindienst-Vanderbeke G. **Neuropsychobiology** 1984;12(4):238-43

COMPULSIVE BEHAVIOR

Treatment of an aggressive, compulsive adolescent with sultopride [letter] Bucci L. **Am J Psychiatry** 1985 Jul;142(7):882-3

CONDITIONING (PSYCHOLOGY)

Associative conditioning analog selectively increases cAMP levels of tail sensory neurons in Aplysia. Ocorr KA, et al. **Proc Natl Acad Sci USA** 1985 Apr;82(8):2548-52

Anxiolytic drugs and the acquisition of conditioned fear in mice. Sanger DJ, et al. **Psychopharmacology (Berlin)** 1985;85(3):284-8

CONDITIONING, CLASSICAL

Direct and indirect behavioral pathways to the social transmission of food avoidance. Galef BG Jr. **Ann NY Acad Sci** 1985;443:203-15

Introduction: physiological mechanisms in conditioned taste aversions. Grill HJ. **Ann NY Acad Sci** 1985;443:67-88

GABA effect on conditioned reflex responses in teleost. Ivanuš J, et al. **Ann NY Acad Sci** 1985;444:543-6

Conditioned food aversions and satiety signals. Kulkosky PJ. **Ann NY Acad Sci** 1985;443:330-47

Conditioned taste aversions: a behavioral index of toxicity. Riley AL, et al. **Ann NY Acad Sci** 1985;443:272-92

Glucocorticoid and other hormonal substrates of conditioned taste aversion. Smotherman WP. **Ann NY Acad Sci** 1985;443:126-44

Interfering with taste aversion learning in rats: the role of associative interference. Cannon DS, et al. **Appetite** 1985 Mar;6(1):1-19

Potentiation and overshadowing in preweanling and adult rats. Kucharski D, et al. **J Exp Psychol [Anim Behav]** 1985 Jan;11(1):15-34

Conditioned taste aversion suppresses induction of delayed-type hypersensitivity immune reactions. Kelley KW, et al. **Physiol Behav** 1985 Feb;34(2):189-93

CONDITIONING, OPERANT

Arginine vasopressin inoculates against age-related changes in temporal memory. Meck WH, et al. **Ann NY Acad Sci** 1985;444:453-6

Physostigmine reverses memory deficits produced by pretraining electrical stimulation of the dorsal hippocampus in mice. Micheau J, et al. **Behav Brain Res** 1985 Apr;15(2):75-81

Effects of acute oral administration of lithium compounds on multiple schedule performance in rats. Chrislip DW, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):39-42

Differential effects of pimozide on response-rate and choice accuracy in a self-stimulation paradigm in mice. Bowers W, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):521-6

Neuroleptic-induced deficits in operant responding for temperature reinforcement. Ettenberg A, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):761-7

Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. Gramling SE, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):541-5

Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Picker M, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):389-93

Haloperidol and nonreinforcement produce different patterns of response slowing in a food reinforced runway task. Wirtshafter D, et al. **Pharmacol Biochem Behav** 1985 May;22(5):661-3

The effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats. Evenden JL, et al. **Psychopharmacology (Berlin)** 1985;85(3):361-6

Methylphenidate: rate-dependent drug effects in hyperactive boys. Weber K. **Psychopharmacology (Berlin)** 1985;85(2):231-5

CONFLICT (PSYCHOLOGY)

Prenatal stress impairs maternal behavior in a conflict situation and reduces hippocampal benzodiazepine receptors. Fride E, et al. **Life Sci** 1985 Jun 3;36(22):2103-9

CORTICOSTERONE

Pharmacology of the steroid regulation of transmitter choice in cultured rat sympathetic ganglia. McLennan IS, et al. **Aust J Exp Biol Med Sci** 1984 Oct;62 (Pt 5):627-39

Phospholipids, sterol carrier protein2 and adrenal steroidogenesis. Vahouny GV, et al. **Biochim Biophys Acta** 1985 May 17; 834(3):324-30

Effect of fetal decapitation on unbound rat plasma corticosterone concentration at the end of pregnancy. Cohen A, et al. **Biol Neonate** 1985;47(3):163-9

Corticosterone modulation of neurotransmitter receptors in rat hippocampus: a quantitative autoradiographic study. Biegon A, et al. **Brain Res** 1985 Apr 22;332(2):309-14

The development of the glucocorticoid receptor system in the rat limbic brain. I. Ontogeny and autoregulation. Meaney MJ, et al. **Brain Res** 1985 Feb;350(1-2):159-64

The development of the glucocorticoid receptor system in the rat limbic brain. III. Negative-feedback regulation. Sapolsky RM, et al. **Brain Res** 1985 Feb;350(1-2):169-73

Effects of steroid hormones on the neuropil of the hypothalamic paraventricular nucleus of male chickens. Panzica GC, et al. **Cell Tissue Res** 1985;240(1):169-74

Effects of corticotropin-releasing factor (CRF) on aldosterone and 18-hydroxycorticosterone secretion. Maser-Gluth C, et al. **Clin Exp Hypertens [A]** 1984;6(10-11):2097-100

Cytochemical and cytophysiological studies of gonadotropin-releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396-404

Androstenedione or corticosterone treatment during pregnancy alters estrous cycle of adult female offspring in mice. Harvey PW, et al. **Experientia** 1985 Apr 15;41(4):492-4

Effects of chronic changes in dietary electrolytes and acute stress on plasma levels of corticosterone and aldosterone in the duck (Anas platyrhynchos). Klingbeil CK. **Gen Comp Endocrinol** 1985 Apr; 58(1):10-9

Changes in hormone levels in relation to breeding behavior in male bullfrogs (Rana catesbeiana) at the individual and population levels. Mendonça MT, et al. **Gen Comp Endocrinol** 1985 May;58(2):270-9

Inhibition of the ACTH adrenal response to stress by treatment with hydrocortisone, prednisolone and dexamethasone in the rat. Baumann JB, et al. **Horm Res** 1985;21(4):254-60

Alterations in the activities of subcellular fractions marker enzymes in rat liver and brain by hydrocortisone and corticosterone treatment. Garcia MV, et al. **Int J Biochem** 1985;17(2):203-8

The stimulation of lipogenesis in white adipose tissue from fed rats by corticosterone. Minshull M, et al. **Int J Biochem** 1985;17(4):529-32

In vitro metabolism of [3H] corticosterone by mammary glands from lactating rats. Isolation and identification of 21-acyl[3H]corticosterone. Pearlman WH, et al. **J Biol Chem** 1985 May 10;260(9):5296-301

Thymosin fraction 5 causes increased serum corticosterone in rodents in vivo. McGillis JP, et al. **J Immunol** 1985 Jun;134(6):3952-5

Muscarinic receptor subclasses in the chick embryo retina: influence of corticosterone treatment. Gremo F, et al. **J Neurochem** 1985 Aug; 45(2):345-51

Eighteen-deoxyaldosterone and other less polar forms of 18-hydroxycorticosterone as aldosterone precursors in rat adrenals

Cozza EN, et al. **J Steroid Biochem** 1985 May;22(5):665-72

Comparison of the distribution kinetics and metabolism to acid end-products of corticosterone and 11-deoxycorticosterone in BALB/c mice. Marandici A, et al. **J Steroid Biochem** 1985 Apr;22(4):539-45

Dissociation between adrenocorticotropin and corticosterone responses to restraint after previous chronic exposure to stress. Armario A, et al. **Life Sci** 1985 Jun 3;36(22):2085-92

A combined autoradiographic and immunocytochemical study of 3H-corticosterone target neurons and catecholamine neurons in rat and mouse lower brain stem. Duncan GE, et al. **Neuroendocrinology** 1985 Mar;40(3):262-71

ACTH and corticosterone secretion in rats following removal of the neurointermediate lobe of the pituitary gland. Fagin KD, et al. **Neuroendocrinology** 1985 Apr;40(4):352-62

Involvement of the sensory cortex in adrenocortical responses following photic and acoustic stimulation in the rat. Feldman S, et al. **Neurosci Lett** 1985 Apr 9;55(2):249-53

The effect of adrenalectomy and corticosterone on homotypic collateral sprouting of serotonergic fibers in hippocampus. Zhou FC, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):111-6

Effects of emotional stress on the immune system. Miller NE. **Pavlov J Biol Sci** 1985 Apr-Jun;20(2):47-52

Comparative biochemical responses of rats to different stressful stimuli. Odio MR, et al. **Physiol Behav** 1985 Apr;34(4):595-9

Maturation of the diurnal rhythm of corticosterone in female domestic fowl. Webb ML, et al. **Poult Sci** 1985 Apr;64(4):744-50

Increase in plasma ACTH after dopaminergic stimulation in rats. Ježová D, et al. **Psychopharmacology (Berlin)** 1985;85(2):201-3

In vivo effects of glucocorticoids on serum corticosterone levels in rats. Yamada K, et al. **Res Commun Chem Pathol Pharmacol** 1985 Mar; 47(3):441-4

[Appraisal of ultradian components in the ethosecretogram of rat] Shiraishi I. **Hokkaido Igaku Zasshi** 1985 Jan;60(1):66-81 (Eng. Abstr.) **(Jpn)**

[Development of a photoperiod-controllable clean rack for rats: circadian rhythms of water intake and blood corticosterone levels] Torii R, et al. **Jikken Dobutsu** 1985 Jan;34(1):57-62 (Eng. Abstr.) **(Jpn)**

CORTICOTROPIN

The effect of nifedipine on CRF-41 and AVP-induced ACTH release in vitro. Murakami K, et al. **Acta Endocrinol (Copenh)** 1985 May; 109(1):32-6

Opiomelanocorticotropic-like hormones in Vipera aspis pituitary. Uva B, et al. **Acta Histochem (Jena)** 1985;76(1):81-7

Somatostatin inhibition of cyclic AMP accumulation and adrenocorticotropin release from mouse anterior pituitary tumor cells: mode of action and self-regulation. Reisine TD. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:169-77

Distribution of the pro-opiomelanocortin derived peptides, adrenocorticotrope hormone, alpha-melanocyte-stimulating hormone and beta-endorphin (ACTH, alpha-MSH, beta-END) in the rat hypothalamus. Mezey E, et al. **Brain Res** 1985 Mar 4;328(2):341-7

Blood pressure responses to ACTH and adrenaline infusions in dogs. Anderson WP, et al. **Clin Exp Hypertens [A]** 1985;7(4):525-37

Acute and chronic effects of ACTH on thermogenesis and brown adipose tissue in the rat. Rothwell NJ, et al. **Comp Biochem Physiol [A]** 1985; 81(1):99-102

Re-evaluation of 'frontal deafferentation' studies on the regulation of ACTH secretion in the light of CRF immunohistology. Lengvári I, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):3-9

Changes induced in rabbit plasma and aqueous humour by ACTH4-10 and ACTH1-24. Stárka L, et al. **Endocrinol Exp (Bratisl)** 1985 Mar; 19(1):25-8

Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. Young EA, et al. **Endocrinology** 1985 Jul;117(1):23-30

Inhibition of the ACTH adrenal response to stress by treatment with hydrocortisone, prednisolone and dexamethasone in the rat. Baumann JB, et al. **Horm Res** 1985;21(4):254-60

Bacterial lipopolysaccharide induction of leukocyte-derived corticotropin and endorphins. Harbour-McMenamin D, et al. **Infect Immun** 1985 Jun; 48(3):813-7

Lack of renal effects of DOCA, ACTH, spironolactone, and angiotensin II in Squalus acanthias. Churchill PC, et al. **J Exp Zool** 1985 Apr; 234(1):17-22

Dissociation between adrenocorticotropin and corticosterone responses to restraint after previous chronic exposure to stress. Armario A, et al. **Life Sci** 1985 Jun 3;36(22):2085-92

ACTH and corticosterone secretion in rats following removal of the neurointermediate lobe of the pituitary gland. Fagin KD, et al. **Neuroendocrinology** 1985 Apr;40(4):352-62

Development of hypothalamic opioid neurons: a combined immunocytochemical and [3H]thymidine autoradiographic study. Khachaturian H, et al. **Neuropeptides** 1985 Feb;5(4-6):477-80

Changes in releasability of ACTH and beta-endorphin with chronic stress. Young E, et al. **Neuropeptides** 1985 Feb;5(4-6):545-8

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417-51 (238 ref.)

Ultrashort-loop positive feedback of corticotropin (ACTH)-releasing factor to enhance ACTH release in stress. Ono N, et al. **Proc Natl Acad Sci USA** 1985 May;82(10):3528-31

Loss of sensitivity to ACTH of adrenocortical cells isolated from maturing domestic fowl. Carsia RV, et al. **Proc Soc Exp Biol Med** 1985 Jul; 179(3):279-82

Increase in plasma ACTH after dopaminergic stimulation in rats. Ježová D, et al. **Psychopharmacology (Berlin)** 1985;85(2):201-3

ACTH-releasing activity of urotensin I and ovine CRF: interactions with arginine vasotocin, isotocin and arginine vasopressin. Fryer J, et al. **Regul Pept** 1985 May;11(1):11-5

[Corticotropin releasing factor] Conte-Devolx B, et al. **Presse Med** 1985 Mar 30;14(13):737-41 (Eng. Abstr.) **(Fre)**

[Effect of an introductory dose of etomidate, methohexital and midazolam on adrenal cortex function before and after ACTH-stimulation] Börner U, et al. **Dtsch Med Wochenschr** 1985 May 10;110(19):750-2 (Eng. Abstr.) **(Ger)**

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

[Brain blood supply and beta-endorphin and corticotropin content on exposure to thyroliberin] Mirozoian RS, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):318-20 (Eng. Abstr.) **(Rus)**

[Participation of gamma-aminobutyric acid in regulating corticotropin secretion in rats] Mishunina TM, et al. **Fiziol Zh** 1985 May-Jun; 31(3):321-6 (Eng. Abstr.) **(Rus)**

CORTICOTROPIN RELEASING HORMONE

The distribution of corticotrophin-releasing factor immunoreactivity in various ovine tissues. Kawai K, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):433-9

The effect of nifedipine on CRF-41 and AVP-induced ACTH release in vitro. Murakami K, et al. **Acta Endocrinol (Copenh)** 1985 May; 109(1):32-6

Studies on the site of origin and molecular form of the extrahypothalamic corticotrophin-releasing factor (CRF) in rats. Yasuda N, et al. **Acta Endocrinol (Copenh)** 1985 Jun;109(2):145-52

Corticotropin-releasing factor, sauvagine, and urotensin I: effects on blood flow. Lenz HJ, et al. **Am J Physiol** 1985 Jul;249(1 Pt 2):R85-90

Corticotropin-releasing factor inhibits insulin release from perfused rat pancreas. Moltz JH, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 1):E741-3

Corticotropin-releasing factor: a physiologic regulator of adrenal epinephrine secretion. Brown MR, et al. **Brain Res** 1985 Mar 4; 328(2):355-7

Corticotropin-releasing factor (CRF)-immunoreactive neurons in the mammillary body of the rat. Kovács M, et al. **Cell Tissue Res** 1985; 240(2):455-60

The origin and ultrastructural characteristics of corticotropin-releasing factor (CRF)-immunoreactive nerve fibers in the posterior pituitary of the rat. Lengvári I, et al. **Cell Tissue Res** 1985;240(2):467-71

Studies on peptides. CXXIV. Solution synthesis of the hentetracontapeptide amide corresponding to the entire amino acid sequence of human corticotropin releasing factor (hCRF). Fujii N, et al. **Chem Pharm Bull (Tokyo)** 1984 Dec;32(12):4797-805

Studies on peptides. CXXIII. Preparations of nine peptide fragments for the synthesis of human corticotropin releasing factor (hCRF). Fujii N, et al. **Chem Pharm Bull (Tokyo)** 1984 Dec;32(12):4786-96

Effects of corticotropin-releasing factor (CRF) on aldosterone and 18-hydroxycorticosterone secretion. Maser-Gluth C, et al. **Clin Exp Hypertens [A]** 1984;6(10-11):2097-100

Re-evaluation of 'frontal deafferentation' studies on the regulation of ACTH secretion in the light of CRF immunohistology. Lengvári I, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):3-9

Effects and pharmacokinetic properties of the rat/human corticotropin-releasing factor in rhesus monkeys. Schürmeyer TH, et al. **Endocrinology** 1985 Jul;117(1):300-6

Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. Young EA, et al. **Endocrinology** 1985 Jul;117(1):23-30

Relationship between pituitary responses to human corticotropin-releasing factor and thyrotropin-releasing hormone in depressives and normal controls. Holsboer F, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):153-4

Opposite regulation of pro-opiomelanocortin gene transcription by glucocorticoids and CRH. Gagner JP, et al. **Mol Cell Endocrinol** 1985 Apr;40(1):25-32

Co-localization of corticotropin releasing factor and vasopressin mRNA in neurones after adrenalectomy. Wolfson B, et al. **Nature** 1985 May 2-8;315(6014):59-61

Morphometrical analysis of the distribution of corticotrophin releasing factor, glucocorticoid receptor and phenylethanolamine-N-methyltransferase immunoreactive structures in the paraventricular hypothalamic nucleus of the rat. Agnati LF, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):147-52

Anatomical and ontogenetic studies of the human paraventriculo-infundibular corticoliberin system. Bresson JL, et al. **Neuroscience** 1985 Apr;14(4):1077-90

Long-term suspension culture of isolated hypothalamic nuclei of the rat: morphological differentiation and release of substances influencing corticotropin and growth hormone secretion. Gyévai A, et al. **Neuroscience** 1985 Feb;14(2):519-33

Distribution of CRF- and tyrosine hydroxylase-immunoreactive neurons in the brainstem of the domestic fowl (Gallus domesticus). Knigge KM, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):97-101

Ultrashort-loop positive feedback of corticotropin (ACTH)-releasing factor to enhance ACTH release in stress. Ono N, et al. **Proc Natl Acad Sci USA** 1985 May;82(10):3528-31

Interaction of arginine vasopressin and corticotropin releasing factor demonstrated with an improved bioassay. Graf MV, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):303-8

ACTH-releasing activity of urotensin I and ovine CRF: interactions with arginine vasotocin, isotocin and arginine vasopressin. Fryer J, et al. **Regul Pept** 1985 May;11(1):11-5

[Corticotropin releasing factor] Conte-Devolx B, et al. **Presse Med** 1985 Mar 30;14(13):737-41 (Eng. Abstr.) **(Fre)**

DANSYL COMPOUNDS

pH dependence of phosphate transport across the red blood cell membrane after modification by dansyl chloride. Berghout A, et al. **Biochim Biophys Acta** 1985 May 14;815(2):281-6

Binding of N-dansylgalactosamine to the lectin from Erythrina cristagalli as followed by stopped-flow and pressure-jump relaxation kinetics. De Boeck H, et al. **Eur J Biochem** 1985 May 15;149(1):141-5

New high-performance liquid chromatography system for the separation of biogenic amines as their Dns derivatives. Hayman AR, et al. **J Chromatogr** 1985 Jun 7;325(2):462-6

DELUSIONS

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

DEMENTIA

Rational drug treatment of dementia? [editorial] Byrne J, et al. **Br Med J [Clin Res]** 1985 Jun 22;290(6485):1845-6

DEPRESSION

Plasma tryptophan, age and depression. Phipps DA, et al. **Age Ageing** 1985 Mar;14(2):71-5

Biochemical theories of schizophrenia and depression. Hollister LE. **Ann Acad Med Singapore** 1985 Jan;14(1):76-80

Brief review of published alprazolam clinical studies. Straw RN. **Br J Clin Pharmacol** 1985;19 Suppl 1:57S-59S (22 ref.)

DEPRESSIVE DISORDER

Qualitative and quantitative analysis of the action of typical and atypical antidepressants in the experimental animal. Kozlovskaya MM, et al. **Ann Ist Super Sanita** 1984;20(1):73-7

Can lithium carbonate prolong the antidepressant effect of sleep deprivation? [letter] Baxter LR Jr. **Arch Gen Psychiatry** 1985 Jun; 42(6):635

Internight variability of REM latency in major depression: implications for the use of REM latency as a biological correlate. Ansseau M, et al. **Biol Psychiatry** 1985 May;20(5):489-505

Resting metabolic rate is reduced in patients treated with antidepressants. Fernstrom MH, et al. **Biol Psychiatry** 1985 Jun;20(6):692-5

Animal models of depression: parallels and correlates to severe depression in humans. Jesberger JA, et al. **Biol Psychiatry** 1985 Jul; 20(7):764-84

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. Shapira B, et al. **Biol Psychiatry** 1985 May; 20(5):576-9

Platelet monoamine oxidase inhibition by deprenyl and tranylcypromine: implications for clinical use. Simpson GM, et al. **Biol Psychiatry** 1985 Jun;20(6):684-7

Factor analytic derivation of the MHPG/NM ratio: implications for studying the link between physical fitness and depression. Sothmann MS, et al. **Biol Psychiatry** 1985 May;20(5):579-83

Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: studies on the olfactory bulbectomized rat model of depression. O'Connor WT, et al. **Br J Clin Pharmacol** 1985; 19 Suppl 1:49S-56S

Relationship between pituitary responses to human corticotropin-releasing factor and thyrotropin-releasing hormone in depressives and normal controls. Holsboer F, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):153-4

A clinical and pharmacological study of the antidepressant activity of viloxazine in adult and elderly patients. Tosca P, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 May;23(5):270-3

Neuroticism and personality disorder in depression. Davidson J, et al. **J Affective Disord** 1985 Mar-Apr;8(2):177-82

The influence of mania and depression on the pharmacokinetics of lithium. A longitudinal single-case study. Kukopoulos A, et al. **J Affective Disord** 1985 Mar-Apr;8(2):159-66

Plasma nortriptyline and clinical response in depression. Murphy GE, et al. **J Affective Disord** 1985 Mar-Apr;8(2):123-9

Drug response as a predictor of transmission of non-bipolar major depression within families. Prusoff BA, et al. **J Affective Disord** 1985 Mar-Apr;8(2):171-6

Imipramine metabolism in recurrent depressive episodes. Tollefson G, et al. **J Affective Disord** 1985 Mar-Apr;8(2):183-6

Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. Feighner JP, et al. **J Clin Psychiatry** 1985 Jun;46(6):206-9

Trimipramine and maprotiline: antidepressant, anxiolytic, and cardiotoxic comparison. Pecknold JC, et al. **J Clin Psychiatry** 1985 May; 46(5):166-71

Thyroxine binding and TSH in recurrent depressive episodes. Tollefson G, et al. **J Clin Psychiatry** 1985 Jul;46(7):267-72

Peripheral edema associated with trazodone: a report of ten cases. Barnett J, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):161-4

Child and adolescent nortriptyline single dose kinetics predict steady state plasma levels and suggested dose: preliminary data. Geller B, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):154-8

Amitriptyline and hydroxylated metabolite plasma levels in depressed outpatients. Robinson DS, et al. **J Clin Psychopharmacol** 1985 Apr; 5(2):83-8

Monoamine oxidase inhibitors in the treatment of atypical depression. Zisook S, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):131-7

Stress and immunomodulation: the role of depression and neuroendocrine function. Stein M, et al. **J Immunol** 1985 Aug; 135(2 Suppl):827s-833s

Comparison of limbitrol (chlordiazepoxide/amitriptyline) and amitriptyline alone as a single night-time dose for the treatment of depression with anxiety. James RT, et al. **J Int Med Res** 1985; 13(2):84-7

Two cases of obsessive-compulsive disorder with depression responsive to trazodone. Baxter LR Jr. **J Nerv Ment Dis** 1985 Jul;173(7):432-3

Understanding and treatment of childhood depression. Aylward GP. **J Pediatr** 1985 Jul;107(1):1-9

Enhanced signal transduction by adenylate cyclase in platelet membranes of patients showing antidepressant responses to alprazolam: preliminary data. Mooney JJ, et al. **J Psychiatr Res** 1985;19(1):65-75

Cholinomimetic drug RS 86, REM sleep, and depression [letter] Berger M, et al. **Lancet** 1985 Jun 15;1(8442):1385-6

Mianserin versus amitriptyline for depression: a double-blind 6-week trial. Rabkin JG, et al. **Neuropsychobiology** 1984;12(4):224-8

KUSTA (Kurz-Skala Stimmung/Aktivierung): a daily self-rating scale for depressive patients. Wendt G, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):118-22

Studies on the locus coeruleus system in an animal model for antidepressive activity. Kostowski W, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):523-30

The olfactory bulbectomized rat as a model of depression. Leonard BE. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):561-9 (30 ref.)

Trazodone in endogenous depressed patients: a negative report and a critical evaluation of the pertaining literature. Klein HE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(2):173-86

Delta-sleep inducing peptide in cerebrospinal fluid from schizophrenics, depressives and healthy volunteers. Lindström LH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):83-90

The cortisol response to desipramine in endogenous depressives and normal controls: preliminary findings. Asnis GM, et al. **Psychiatry Res** 1985 Mar;14(3):225-33

Elevated plasma homovanillic acid in depressed females with melancholia and psychosis. Devanand DP, et al. **Psychiatry Res** 1985 May; 15(1):1-4

The effect of clorgyline on noradrenergic function. Ross RJ, et al. **Psychopharmacology (Berlin)** 1985;85(2):227-30

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

'Pseudo-allergy': treatment with an MAO inhibitor. Ulwelling W. **Psychosomatics** 1985 Jun;26(6):535-6

A preliminary report on anti-depressant therapy and its effects on hope and immunity. Udelman DL, et al. **Soc Sci Med** 1985; 20(10):1069-72

[Alprazolam (Tafil). A new benzodiazepine-with a new action profile?] Rasmussen SB, et al. **Ugeskr Laeger** 1985 Apr 29;147(18):1495-7 **(Dan)**

[Comparison of various tools for evaluating depression apropos of a study on Athymil 30 mg] Lempérière T, et al. **Ann Med Psychol (Paris)** 1984 Nov;142(9):1206-14 **(Fre)**

[Selective study of sulfate and glucuronide conjugates of urinary MHPG in nervous depression. Peripheral and central influences] Peyrin L, et al. **Encephale** 1985 Jan-Feb;11(1):19-24 (Eng. Abstr.) **(Fre)**

[Depressive states and biological markers] Boyer P. **Rev Prat** 1985 May 11;35(27):1627-32 (Eng. Abstr.) **(Fre)**

[Refractory depressions and their treatment] Jouvent R, et al. **Rev Prat** 1985 May 11;35(27):1647-53 (Eng. Abstr.) **(Fre)**

[Therapeutic strategy in depression] Scotto JC, et al. **Rev Prat** 1985 May 11;35(27):1633-8 (Eng. Abstr.) **(Fre)**

[Treatment of depressive conditions with viloxazine by the general practitioner] Haehn KD. **Fortschr Med** 1985 Apr 18;103(15):408-12 (Eng. Abstr.) **(Ger)**

[Treatment of depressive syndrome with antidepressants] Woggon B, et al. **Med Monatsschr Pharm** 1985 May;8(5):130-6 **(Ger)**

[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**

[Various aspects of the differential therapy of circular depressions] Prokhorova IS. **Zh Nevropatol Psikhiatr** 1985;85(4):570-4 (Eng. Abstr.) **(Rus)**

[Sleep deprivation as a method of treating endogenous depression] Vovin RIa, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):560-5 (Eng. Abstr.) **(Rus)**

DESIPRAMINE

Comparison of the effects of chronic administration of ciclazindol and desipramine on pupillary responses to tyramine, methoxamine and pilocarpine in healthy volunteers. Kerr FA, et al. **Br J Clin Pharmacol** 1985 May;19(5):639-47

Effect of chronic desipramine treatment on adrenoceptor modulation of [3H]dopamine release from rat nucleus accumbens slices. Nurse B, et al. **Brain Res** 1985 May 20;334(2):235-42

Effect of chronic reserpine and desmethylimipramine treatment on CRF-like immunoreactivity of discrete brain areas of rat. Tizabi Y, et al. **Brain Res** 1985 Jun 3;335(2):389-91

Why is amitriptyline much weaker than desipramine at decreasing beta-adrenoceptor numbers? Wise H, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):137-41

Tricyclic antidepressants antagonize prostaglandin (PG) E2-induced contractions of the guinea pig ileum and hypomotility in the mouse. Tayo FM. **Experientia** 1985 Apr 15;41(4):474-6

Interethnic dissociation between debrisoquine and desipramine hydroxylation. Rudorfer MV, et al. **J Clin Psychopharmacol** 1985 Apr; 5(2):89-92

Inhibition of the retrograde axonal transport of acetylcholinesterase by the anti-calmodulin agents amitriptyline and desipramine. Tiberi M, et al. **J Neurobiol** 1985 May;16(3):245-8

Cardiovascular effects of desipramine in children and adolescents with attention deficit disorder. Biederman J, et al. **J Pediatr** 1985 Jun; 106(6):1017-20

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

The effect of prolonged treatment with tricyclic antidepressants on the actions of 5-hydroxytryptamine in the hippocampal slice of the rat. Rowan MJ, et al. **Neuropharmacology** 1985 Feb;24(2):131-7

Drug interactions and vasoconstrictors used in local anesthetic solutions. Yagiela JA, et al. **Oral Surg Oral Med Oral Pathol** 1985 Jun; 59(6):565-71

Studies on the locus coeruleus system in an animal model for antidepressive activity. Kostowski W, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):523-30

The cortisol response to desipramine in endogenous depressives and normal controls: preliminary findings. Asnis GM, et al. **Psychiatry Res** 1985 Mar;14(3):225-33

Dose-dependent growth hormone, prolactin and cortisol stimulation after i.v. administration of desimipramine in human subjects. Laakmann G, et al. **Psychoneuroendocrinology** 1985;10(1):83-93

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

DESOXYCORTICOSTERONE

Effect of hydrocortisone and desoxycorticosterone on some reductases, esterases and synthetases. Tancheva L, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):59-63

Mineralocorticoid regulation of apical cell membrane Na+ and K+ transport of the cortical collecting duct. Sansom SC, et al. **Am J Physiol** 1985 Jun;248(6 Pt 2):F858-68

Lack of renal effects of DOCA, ACTH, spironolactone, and angiotensin II in Squalus acanthias. Churchill PC, et al. **J Exp Zool** 1985 Apr; 234(1):17-22

Sodium-dependent modulation of the renal Na-K-ATPase: influence of mineralocorticoids on the cortical collecting duct. O'Neil RG, et al. **J Membr Biol** 1985;85(2):169-79

Effects of angiotensin or carbachol on sodium intake and excretion in adrenalectomized or deoxycorticosterone-treated rats. Fitzsimons JT, et al. **J Physiol (Lond)** 1985 Feb;359:447-58

Comparison of the distribution kinetics and metabolism to acid end-products of corticosterone and 11-deoxycorticosterone in BALB/c mice. Marandici A, et al. **J Steroid Biochem** 1985 Apr;22(4):539-45

DEXTROAMPHETAMINE

Effects of some motion sickness suppressants on static and dynamic tracking performance. Schroeder DJ, et al. **Aviat Space Environ Med** 1985 Apr;56(4):344-50

Association of the mesencephalic locomotor region with locomotor activity induced by injections of amphetamine into the nucleus accumbens. Brudzyński SM, et al. **Brain Res** 1985 May 13; 334(1):77-84

6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233-41

Nigral reticulata neurons: potentiation of responsiveness to amphetamine with long-term treatment. Kamata K, et al. **Brain Res** 1985 Apr 15; 332(1):188-93

Frequency-related, bidirectional limbic responses to cocaine: comparisons with amphetamine and lidocaine. Lesse H, et al. **Brain Res** 1985 May 27;335(1):21-31

Effects of D- and L-amphetamine on dopamine metabolism and ascorbic acid levels in nucleus accumbens and olfactory tubercle as studied by in vivo differential pulse voltammetry. Louilot A, et al. **Brain Res** 1985 Jun 17;336(2):253-63

An investigation of amphetamine-induced release of 5-HT from rat hippocampal slices. Balfour DJ, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):395-9

Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. Feighner JP, et al. **J Clin Psychiatry** 1985 Jun;46(6):206-9

Amphetamine induced release of endogenous dopamine in vitro is not reduced following pretreatment with reserpine. Niddam R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):123-7

The effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats. Evenden JL, et al. **Psychopharmacology (Berlin)** 1985;85(3):361-6

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

DIAZEPAM

Foot shock-induced decrease of low affinity GABA receptors in the rat brain: antagonism by diazepam. Concas A, et al. **Ann Ist Super Sanita** 1984;20(1):53-6

The influence of cyclobarbital and diazepam on drug metabolism in vitro and their binding to cytochrome P-450. Wierzba W, et al. **Biomed Biochim Acta** 1984;43(12):1425-30

The effects of age and smoking on the plasma protein binding of lignocaine and diazepam. Davis D, et al. **Br J Clin Pharmacol** 1985 Feb; 19(2):261-5

A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. Davison K, et al. **Br J Clin Pharmacol** 1985;19 Suppl 1:37S-43S

Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety. Power KG, et al. **Br Med J [Clin Res]** 1985 Apr 27;290(6477):1246-8

Blockade of the diazepam-induced increase in rat striatal acetylcholine content by the specific benzodiazepine antagonists ethyl-beta-carboline-3-carboxylate and Ro 15-1788. Kolasa K, et al. **Brain Res** 1985 Jun 17;336(2):342-5

Prenatal exposure to diazepam results in enduring reductions in brain receptors and deep slow wave sleep. Livezey GT, et al. **Brain Res** 1985 May 20;334(2):361-5

Pre-natal administration of diazepam improves radial maze learning in mice. Benton D, et al. **Comp Biochem Physiol [C]** 1985;80(2):273-5

Intramuscular bioavailability of chlorazepate as compared to diazepam. Bertler A, et al. **Eur J Clin Pharmacol** 1985;28(2):229-30

Pharmacological evidence that the non-neuronal diazepam binding site in primary cultures of glial cells is associated with a calcium channel. Bender AS, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):287-8

Extraction, separation, and detections of 14C-diazepam and 14C-metabolites from brain tissue of mature and old rats. Komiskey HL, et al. **J Anal Toxicol** 1985 May-Jun;9(3):131-3

Increased sensitivity of the elderly to the central depressant effects of diazepam. Pomara N, et al. **J Clin Psychiatry** 1985 May;46(5):185-7

3-Amino-beta-carboline derivatives and the benzodiazepine receptor. Synthesis of a selective antagonist of the sedative action of diazepam. Dodd RH, et al. **J Med Chem** 1985 Jun;28(6):824-8

Some long-lasting neurochemical effects of prenatal or early postnatal exposure to diazepam. Frieder B, et al. **J Neurochem** 1985 Jul; 45(1):37-42

Solubilization by cosolvents III: Diazepam and benzocaine in binary solvents. Rubino JT, et al. **J Parenter Sci Technol** 1985 May-Jun; 39(3):106-11

Responsibilities of prescribing. Avery JK. **J Tenn Med Assoc** 1985 May; 78(5):297

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

Differential mediation of the anticonvulsant effects of carbamazepine and diazepam. Weiss SR, et al. **Life Sci** 1985 Jun 24;36(25):2413-9

Patterns of diazepam prescribing in primary care: a case control study. Mulvihill MN, et al. **Mt Sinai J Med (NY)** 1985 Apr;52(4):276-80

The effects of benzodiazepines on spinal homosynaptic depression. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):301-7

Evidence that 2-phenylpyrazolo[4,3-c]-quinolin-3(5H)-one antagonises pharmacological, electrophysiological and biochemical effects of diazepam in rats. Santi M, et al. **Neuropharmacology** 1985 Feb; 24(2):99-105

Evidence that tolerance develops to the anxiolytic effect of diazepam in rats. Treit D. **Pharmacol Biochem Behav** 1985 Mar;22(3):383-7

Role of neurotransmitters and teratogens on palate development. Zimmerman EF, et al. **Prog Clin Biol Res** 1985;163C:405-8

The effects of intravenous diazepam and hyoscine upon human memory. Frith CD, et al. **Q J Exp Psychol [A]** 1984 Feb;36(1):133-44

Concentration independent accumulation of diazepam by rat liver slices. Effect of human serum albumin. Blaese U, et al. **Res Commun Chem Pathol Pharmacol** 1985 Feb;47(2):313-6

Generic Valiums clear another hurdle at FDA [news] Sun M. **Science** 1985 Jul 26;229(4711):369

Benzodiazepines inhibit human platelet activation: comparison of the mechanism of antiplatelet actions of flurazepam and diazepam. Romstedt K, et al. **Thromb Res** 1985 May 15;38(4):361-74

[Intravenous sedation before endoscopic interventions. Comparative study of lormetazepam and diazepam in oil] Tolksdorf W, et al. **Fortschr Med** 1985 Mar 7;103(9):249-52 (Eng. Abstr.) **(Ger)**

[Harman-induced changes in the anxiolytic effect of diazepam] Zin'kovskaia LIa, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):21-3 (Eng. Abstr.) **(Rus)**

[Effect of sodium valproate on brain levels of diazepam and N-desmethyldiazepam in the rat] Gómez Luque A, et al. **Arch Farmacol Toxicol** 1985 Apr;11(1):13-8 (Eng. Abstr.) **(Spa)**

DIBENZAZEPINES

Trimipramine and maprotiline: antidepressant, anxiolytic, and cardiotoxic comparison. Pecknold JC, et al. **J Clin Psychiatry** 1985 May; 46(5):166-71

Mianserin versus amitriptyline for depression: a double-blind 6-week trial. Rabkin JG, et al. **Neuropsychobiology** 1984;12(4):224-8

Mianserin [letter] Edwards IR. **NZ Med J** 1985 May 8;98(778):350

Effects of some dibenzo-azepines on suppressed and nonsuppressed behavior of squirrel monkeys. Spealman RD. **Psychopharmacology (Berlin)** 1985;85(2):129-32

Differential alteration of striatal D-1 and D-2 receptors induced by the long-term administration of haloperidol, sulpiride or clozapine to rats. Jenner P, et al. **Psychopharmacology [Suppl]** 1985;2:174-81

[Comparison of various tools for evaluating depression apropos of a study on Athymil 30 mg] Lempérière T, et al. **Ann Med Psychol (Paris)** 1984 Nov;142(9):1206-14 **(Fre)**

[Immunoallergic febrile reaction with hypereosinophilia after ingestion of metapramine (letter)] Gentric A, et al. **Presse Med** 1985 Jun 8; 14(23):1290 **(Fre)**

DIBENZOTHIEPINS

Possible relationship between antimanic effect and activity of zotepine to 5HT1 receptor. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):473-80

Delayed gastric emptying with dothiepin. Woodhouse KW, et al. **Hum Toxicol** 1985 Jan;4(1):67-70

Decreased 5-HT2 but not 5-HT1 receptor binding in cortex of rat after chronic administration of dothiepin. Application of the Woolf plot to analysis of binding parameters. Diggory GL, et al. **Neuropharmacology** 1985 Apr;24(4):275-8

DIBENZOXAZEPINES

Pharmacokinetics of amoxapine and its active metabolites. Calvo B, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Apr;23(4):180-5

Amoxapine-associated acute renal failure [letter] Chu CC, et al. **South Med J** 1985 Jun;78(6):761

DIETHYLAMINES

Dietary phenolics and betel nut extracts as modifiers of N-nitrosation in rat and man. Stich HF, et al. **IARC Sci Publ** 1984;(57):213-22

Metabolism of N-nitrodialkylamines. Suzuki E, et al. **IARC Sci Publ** 1984; (57):485-90

[Gas-chromatographic analysis of beta-diethylaminoethylchloride and beta-diethylaminoethylacetate ether in the air of work areas] Bake MIa. **Gig Tr Prof Zabol** 1985 Feb;(2):54-6 **(Rus)**

DIIODOTYROSINE

[Ultrastructural changes in thyrocytes exposed to the antithyroid preparations betazin and diiodotyrosine] Trunov VI, et al. **Tsitol Genet** 1985 Jan-Feb;19(1):13-7 (Eng. Abstr.) **(Rus)**

DISCRIMINATION (PSYCHOLOGY)

Effects of selective dopamine receptor agonists in rats trained to discriminate apomorphine from saline. Woolverton WL, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):577-81

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

DISCRIMINATION LEARNING

Effects of psychotropic drugs on discrimination conditioning in olfactory bulbectomized rats. Gomita Y, et al. **Pharmacol Biochem Behav** 1985 May;22(5):717-22

DOPA

Simultaneous assay of 3,4-dihydroxyphenylalanine, catecholamines and O-methylated metabolites in human plasma using high-performance liquid chromatography. Ishimitsu T, et al. **J Chromatogr** 1985 Feb 8; 337(2):239-48

[Enzymatic synthesis of 3,4-dihydroxyphenyl-L-alanine by free and immobilized Citrobacter freundii cells] Voivodov KI, et al. **Prikl Biokhim Mikrobiol** 1985 Mar-Apr;21(2):161-6 (Eng. Abstr.) **(Rus)**

DOPAMINE

Catecholamine microfluorometry of nigral perikarya and tyrosine hydroxylase assay in some telencephalic structures of rats exposed to different behavioral situations. Divac I, et al. **Acta Neurobiol Exp (Warsz)** 1984;44(6):262-72

Growth hormone releasing factor (GRF) and dopamine coexist in hypothalamic arcuate neurons. Meister B, et al. **Acta Physiol Scand** 1985 May;124(1):133-6

3H-dopamine clearance from the intravascular compartment of the maternal and fetal rhesus monkey. Phillippe M, et al. **Am J Obstet Gynecol** 1985 Jul 1;152(5):599-601

Clearance of 3H-dopamine from the amniotic fluid in the rhesus monkey. Phillippe M, et al. **Am J Obstet Gynecol** 1985 Jul 1;152(5):601-2

Central effects of angiotensin II and dopamine in sodium-depleted sheep. Huang BS, et al. **Am J Physiol** 1985 May;248(5 Pt 2):R541-8

The renal effects of dopamine [letter] Cramolini GM. **Anesthesiology** 1985 Jun;62(6):844

Physiologic and pharmacologic characterization of a novel group of substantia nigra zona reticulata neurons involved in striatal dopamine regulation. Chan SH. **Ann Acad Med Singapore** 1985 Jan;14(1):153-7

On the role of dopamine receptors in aldosterone secretion. Frisina N, et al. **Ann Endocrinol (Paris)** 1984;45(6):387-91

Mechanisms involved in the release of dopamine from the tuberoinfundibular system in vitro. Amoroso S, et al. **Ann Ist Super Sanita** 1984;20(1):109-11

Effect of dopamine on the threshold of the voltage-dependent ionic channels in the rat brain. Bernardi G, et al. **Ann Ist Super Sanita** 1984; 20(1):1-4

6R-L-erythro-5,6,7,8-tetrahydrobiopterin as a regulator of dopamine and serotonin biosynthesis in the rat brain. Miwa S, et al. **Arch Biochem Biophys** 1985 May 15;239(1):234-41

Asymmetry in the effects of unilateral 6-OHDA lesions on eating and drinking evoked by hypothalamic stimulation. Mittleman G, et al. **Behav Brain Res** 1985 May;15(3):263-7

Catecholamine-blocking drugs injected at sites of amine accumulation reverse catecholamine degeneration associated deficits. Willis GL, et al. **Behav Brain Res** 1985 Apr;15(2):101-6

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665-9

Binding characteristics of the dopamine uptake inhibitor [3H]nomifensine to striatal membranes. Dubocovich ML, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1137-44

BIBLIOGRAPHY

DOPAMINE

Selective increase in dopamine metabolism in the prefrontal cortex by the anxiogenic beta-carboline FG 7142. Tam SY, et al. **Biochem Pharmacol** 1985 May 1;34(9):1595-8

Effect of chronic postnatal hypoxia on dopamine uptake by synaptosomes from striatum of adult rats. Ihle W, et al. **Biomed Biochim Acta** 1985; 44(3):433-7

Dopamine-stimulated fucosylation of brain proteins in vitro is not inhibited by puromycin. Lössner B, et al. **Biomed Biochim Acta** 1985; 44(3):465-73

Ethanol preference behaviour and dopamine release in the rat. Schmidt J, et al. **Biomed Biochim Acta** 1984;43(12):1431-4

Dopamine autoreceptors and the effects of drugs on locomotion and dopamine synthesis. Brown F, et al. **Br J Pharmacol** 1985 Apr; 84(4):853-60

Rapid desensitization of presynaptic dopamine autoreceptors during exposure to exogenous dopamine. Arbilla S, et al. **Brain Res** 1985 Jun 24;337(1):11-7

Subchronic administration of GABAergic agonists elevates [3H]GABA binding and produces tolerance in striatal dopamine catabolism. Beart PM, et al. **Brain Res** 1985 May 27;335(1):169-73

Effects of inhibitors of Na+,K+-ATPase on the membrane potentials and neurotransmitter efflux in rat brain slices. Brosemer RW. **Brain Res** 1985 May 13;334(1):125-37

Association of the mesencephalic locomotor region with locomotor activity induced by injections of amphetamine into the nucleus accumbens. Brudzyński SM, et al **Brain Res** 1985 May 13; 334(1):77-84

Dopaminergic mechanisms in subthalamic nucleus of rat: analysis using horseradish peroxidase and microiontophoresis. Campbell GA, et al. **Brain Res** 1985 May 6;333(2):261-70

Involvement of nigrostriatal dopamine neurons in the contraversive rotational behavior evoked by electrical stimulation of the lateral hypothalamus. Castañeda E, et al. **Brain Res** 1985 Feb 18; 327(1-2):143-51

Excitatory and inhibitory effects of dopamine on synaptic transmission in the rat olfactory cortex slice. Collins GG, et al. **Brain Res** 1985 May 6;333(2):237-45

Topographical analysis of nucleus accumbens sites at which cholecystokinin potentiates dopamine-induced hyperlocomotion in the rat. Crawley JN, et al. **Brain Res** 1985 Jun 3;335(2):337-41

The formation of deaminated metabolites of dopamine in the locus coeruleus depends upon noradrenergic neuronal activity. Curet O, et al. **Brain Res** 1985 Jun 3;335(2):297-301

The hypothalamohypophyseal system in vitro: electrophysiology of the pars intermedia and evidence for both excitatory and inhibitory inputs. Davis MD, et al. **Brain Res** 1985 May 13;334(1):97-104

The prefrontal 'cortex' in the pigeon. Biochemical evidence. Divac I, et al. **Brain Res** 1985 Apr 22;332(2):365-8

Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Grace AA, et al. **Brain Res** 1985 May 6; 333(2):285-98

Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. Grace AA, et al. **Brain Res** 1985 May 6;333(2):271-84

6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233-41

Effects of D- and L-amphetamine on dopamine metabolism and ascorbic acid levels in nucleus accumbens and olfactory tubercle as studied by in vivo differential pulse voltammetry. Louilot A, et al. **Brain Res** 1985 Jun 17;336(2):253-63

Quantification of lesion-induced dopaminergic supersensitivity using the rotational model in the mouse. Mandel RJ, et al. **Brain Res** 1985 Mar 25;330(2):358-63

Effect of chronic desipramine treatment on adrenoceptor modulation of [3H]dopamine release from rat nucleus accumbens slices. Nurse B, et al. **Brain Res** 1985 May 20;334(2):235-42

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Potential changes of frog afferent terminals in response to dopamine. Ryan GP, et al. **Brain Res** 1985 Mar 4;328(2):283-90

Dopamine depletion in a striatal subregion disrupts performance of a skilled motor task in the rat. Sabol KE, et al. **Brain Res** 1985 May 27;335(1):33-43

Spatial distribution of dopamine, methotrexate and antipyrine during continuous intracerebral microperfusion. Sendelbeck SL, et al. **Brain Res** 1985 Mar 4;328(2):251-8

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

Reactive capacity: a sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Spirduso WW, et al. **Brain Res** 1985 May 27;335(1):45-54

On the origin of dopamine and its metabolite in predominantly noradrenergic innervated brain areas. Westerink BH, et al. **Brain Res** 1985 Mar 18;330(1):164-6

Dopamine production by isolated glomeruli and tubules from rat kidneys. Baines AD, et al. **Can J Physiol Pharmacol** 1985 Feb;63(2):155-8

Estradiol increases dopamine turnover in intermediate and posterior pituitary lobes of ovariectomized rats. Saavedra JM, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):397-402

Study of the interrelationship between dopaminergic activity and potassium ion. Matsuda S, et al. **Clin Exp Hypertens [A]** 1984; 6(12):2249-61

Evaluation of the central dopaminergic activity in gestational hyperprolactinaemia by means of the electroretinographic technique. De Luca Brunori I, et al. **Clin Exp Obstet Gynecol** 1985; 12(1-2):13-5

Effect of secretagogues on pancreatic exocrine secretion in the monkey and the dog. Iwatsuki K, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):67-72

Dopamine: receptors and clinical applications. Goldberg LI. **Clin Physiol Biochem** 1985;3(2-3):120-6 (33 ref.)

Norepinephrine alone versus norepinephrine plus low-dose dopamine: enhanced renal blood flow with combination pressor therapy. Schaer GL, et al. **Crit Care Med** 1985 Jun;13(6):492-6

Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215-27

Strain differences in brain biogenic amines concentration in rats with different resistance to emotional stress. Sudakov KV, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):39-45

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

Prolactin metabolic clearance and resistance to dopaminergic suppression in acute uremia. McKenna TM, et al. **Endocrinology** 1985 May; 116(5):2003-7

Rapid effects of hyperprolactinemia on basal prolactin secretion and dopamine turnover in the medial and lateral median eminence. Selmanoff M. **Endocrinology** 1985 May;116(5):1943-52

The effect of dopamine administration on the activity of the renin-angiotensin-aldosterone system in sick preterm infants. Sulyok E, et al. **Eur J Pediatr** 1985 Jan;143(3):191-3

Striatal synaptosomal dopamine synthesis: evidence against direct regulation by an autoreceptor mechanism. Compton DR, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):157-62

Magnesium ions reveal nanomolar potency of dopamine at [3H]spiperone labelled D-2 receptors in rat corpus striatum. De Vries DJ, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):417-9

Dopamine preferentially stimulates postsynaptic alpha 2-adrenoceptors in the femoral vascular bed, but alpha 1-adrenoceptors in the renal vascular bed of the anaesthetised dog. Duval N, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):265-72

Pharmacological changes in dopaminergic systems induced by long-term administration of amantadine. Gianutsos G, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):357-61

Phencyclidine-induced inhibition of rat prolactin secretion: increased portal blood dopamine. Meltzer HY, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):143-6

Electrochemical, pharmacological and electrophysiological evidence of rapid dopamine release and removal in the rat caudate nucleus following electrical stimulation of the median forebrain bundle. Millar J, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):341-8

Role of the dopamine uptake carrier in the neurochemical response to methamphetamine: effects of amfonelic acid. Schmidt CJ, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):73-80

Differences in dopamine- and noradrenaline-induced amylase release from the rat parotid gland. Sundström S, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):355-61

Reduced sensitivity of synaptosomal dopamine autoreceptors following increase in synaptosomal dopamine synthesis. Tissari AH. **Eur J Pharmacol** 1985 Mar 12;109(3):433-4

Number of dopamine neurons predicts prolactin levels in two inbred mouse strains. Sved AF, et al. **Experientia** 1985 May 15;41(5):644-6

Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Hong JS, et al. **Fed Proc** 1985 Jun;44(9):2535-9

Pergolide mesylate inhibits exercise-induced prolactin release in man. De Meirleir K, et al. **Fertil Steril** 1985 Apr;43(4):628-31

Comparative studies of cardiovascular effects of a new dopamine agonist (SK&F 38393A) and dopamine. Tsai CS, et al. **Gen Pharmacol** 1985; 16(2):85-9

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr; 6(2):78-81

Dopamine stimulated increase of GTP levels in the rat retina. Schaeffer JM, et al. **J Biol Chem** 1985 Apr 25;260(8):4555-7

Analysis of the positive inotropic effect of ibopamine in the blood-perfused canine papillary muscle. Kawahara K, et al. **J Cardiovasc Pharmacol** 1985 Mar-Apr;7(2):316-20

BIBLIOGRAPHY

Levels of dopamine and thyrotrophin-releasing hormone in hypophysial stalk blood during an oestrogen-stimulated surge of prolactin in the ovariectomized rat. de Greef WJ, et al. **J Endocrinol** 1985 Apr; 105(1):107-12

Synthesis and central dopaminergic effects of N-(4,6-dimethyl-2-pyridinyl)benzamides. Bouhayat S, et al. **J Med Chem** 1985 May;28(5):555-9

Dopamine sulfoconjugation in the rat brain: regulation by monoamine oxidase. Buu NT. **J Neurochem** 1985 Aug;45(2):470-6

3,4-Dihydroxyphenylethylamine and 5-hydroxytryptamine metabolism in the rat: acidic metabolites in cisternal cerebrospinal fluid before and after giving probenecid. Curzon G, et al. **J Neurochem** 1985 Aug; 45(2):508-13

Neurochemical profile of Lu 19-005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615-22

Evidence that [3H]dopamine is taken up and released from nondopaminergic nerve terminals in the rat substantia nigra in vitro. Kelly E, et al. **J Neurochem** 1985 Jul;45(1):137-44

Dopamine uptake is differentially regulated in rat striatum and nucleus accumbens. Missale C, et al. **J Neurochem** 1985 Jul;45(1):51-6

Preparation and characterization of antisera and monoclonal antibodies to serotonergic and dopaminergic ligands. Flurkey K, et al. **J Neuroimmunol** 1985 May;8(2-3):115-27

Pergolide elevation of MHPG sulphate concentration in rat hypothalamus blocked by spiperone and mimicked by other dopamine agonists. Fuller RW, et al. **J Pharm Pharmacol** 1985 Apr;37(4):268-70

Acute and subchronic effects of MJ-13859, a potential antipsychotic drug, on rat brain dopaminergic function. McMillen BA. **J Pharmacol Exp Ther** 1985 May;233(2):369-75

Role of dopamine in the neurotoxic effects of methamphetamine. Schmidt CJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):539-44

Further studies of dopamine metabolism and function in Tetrahymena. Gundersen RE, et al. **J Protozool** 1985 Feb;32(1):25-3

Benztropine inhibits toxicity of MPTP in mice [letter] Bradbury AJ, et al. **Lancet** 1985 Jun 22;1(8443):1444-5

Dopamine inhibition of anterior pituitary adenylate cyclase is mediated through the high-affinity state of the D2 receptor. Borgundvaag B, et al. **Life Sci** 1985 Jul 29;37(4):379-86

In vivo electrochemical studies of rat striatal dopamine and serotonin release after morphine. Broderick PA. **Life Sci** 1985 Jun 17; 36(24):2269-75

Firing properties of substantia nigra dopaminergic neurons in freely moving rats. Freeman AS, et al. **Life Sci** 1985 May 20; 36(20):1983-94

D2-dopamine receptor-mediated inhibition of cyclic AMP formation in striatal neurons in primary culture. Weiss S, et al. **Mol Pharmacol** 1985 Jun;27(6):595-9

Pharmacology in vivo of the phenylindan derivative, Lu 19-005, a new potent inhibitor of dopamine, noradrenaline and 5-hydroxytryptamine uptake in rat brain. Arnt J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):101-7

Effects of discriminant and non-discriminant dopamine antagonists on in vivo accumulation of 3H-N-propyl-norapomorphine in mouse striatum and tuberculum olfactorium. Gulat-Marnay C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):117-22

Amphetamine induced release of endogenous dopamine in vitro is not reduced following pretreatment with reserpine. Niddam R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):123-7

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128-34

Unexpected potentiation by discriminant benzamide derivatives of stereotyped behaviours elicited by dopamine agonists in mice. Vasse M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):108-16

Comparison of release of endogenous dopamine and gamma-aminobutyric acid from rat caudate synaptosomes. Caudill WL, et al. **Neurochem Res** 1985 Mar;10(3):319-31

Release of endogenous dopamine, 3,4-dihydroxyphenylacetic acid, and amino acid transmitters from rat striatal slices. Flint RS, et al. **Neurochem Res** 1985 Apr;10(4):515-27

The uptake of serotonin and dopamine by homogenates of frozen rat and human brain tissue. Stenström A, et al. **Neurochem Res** 1985 May; 10(5):591-9

Electroacupuncture alters catecholamines in brain regions of rats. Sun AY, et al. **Neurochem Res** 1985 Feb;10(2):251-8

Hypoprolactinemia induced by hypophysectomy and long-term bromocriptine treatment decreases tuberoinfundibular dopaminergic neuronal activity and the responsiveness of these neurons to prolactin. Demarest KT, et al. **Neuroendocrinology** 1985 May;40(5):369-76

Dopamine-induced physical barrier to inhibit prolactin release in mammotrophs disappears during resumption of prolactin secretion. Reifel CW, et al. **Neuroendocrinology** 1985 May;40(5):438-43

Altered pharmacokinetics of L-dopa metabolism [letter] Melamed E, et al. **Neurology** 1985 Jun;35(6):939-41

Activation of muscarinic receptors on striatal synaptosomes increases the release of endogenous dopamine. Bonanno G, et al. **Neuropharmacology** 1985 Mar;24(3):261-4

The continuity of dopamine receptor antagonism can dictate the long-term behavioural consequences of a mesolimbic infusion of dopamine. Costall B, et al. **Neuropharmacology** 1985 Mar;24(3):193-7

Alterations in dopamine metabolism after chronic administration of haloperidol. Possible role of increased autoreceptor sensitivity. Saller CF, et al. **Neuropharmacology** 1985 Feb;24(2):123-9

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer; 9(2):261-82

Dopamine hyperpolarizes and reduces the light responses of rod ON-centre bipolar cells in the retina of the dogfish, Scyliorhinus canicula. Shiells RA, et al. **Neurosci Lett** 1985 Apr 19;55(3):331-6

Alteration of dopamine metabolism in different brain regions of the rabbit by estradiol and tamoxifen. Baksi SN, et al. **Neuroscience** 1985 Apr; 14(4):1053-9

Regulation of dopamine release by impulse flow and by autoreceptors as studied by in vivo voltammetry in the rat striatum. Gonon FG, et al. **Neuroscience** 1985 Mar;14(3):765-74

Effect of haloperidol and sulpiride on dopamine metabolism in nucleus accumbens and olfactory tubercle: a study by in vivo voltammetry. Louilot A, et al. **Neuroscience** 1985 Mar;14(3):775-82

Detection of homovanillic acid in vivo using microcomputer-controlled voltammetry: simultaneous monitoring of rat motor activity and striatal dopamine release. O'Neill RD, et al. **Neuroscience** 1985 Mar; 14(3):753-63

Morphological evidence for a dopaminergic terminal field in the hippocampal formation of young and adult rat. Verney C, et al. **Neuroscience** 1985 Apr;14(4):1039-52

Locomotor response of nialamide pretreated old rats to intraaccumbens dopamine. Cousin KM, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):461-8

Effects of phencyclidine (PCP)-like drugs on turning behavior, 3H-dopamine uptake, and 3H-PCP binding. Johnson KM, et al. **Pharmacol Biochem Behav** 1985 May;22(5):731-5

Suppression of male copulatory behavior by delta 9-THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415-20

Effects of ovariectomy and estrogen replacement on intrastriatal dopamine-elicited postural deviation. Smith RL, et al. **Pharmacol Biochem Behav** 1985 May;22(5):689-93

Dopamine decreases conductance of the electrical junctions between cultured retinal horizontal cells. Lasater EM, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):3025-9

Central inhibitory action of TRH on prolactin secretion in the rat. Ohta H, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):9-12

Neurotropic drugs and brain development: effects on cell replication in vivo and in vitro. Patel AJ. **Prog Clin Biol Res** 1985;163C:301-5

Chronic neuroleptic treatment and mesolimbic dopamine denervation induce behavioural supersensitivity to opiates. Stinus L, et al. **Psychopharmacology (Berlin)** 1985;85(3):323-8

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

Studies on the stability of 3H-dopamine, 3H-apomorphine and 3H-ADTN: effects of sodium ascorbate and EDTA. Cabbat FS, et al. **Res Commun Chem Pathol Pharmacol** 1985 Mar;47(3):333-43

Effects of amfonelic acid, alpha-methyltyrosine, Ro 4-1284 and haloperidol pretreatment on the depletion of striatal dopamine by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. Fuller RW, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr;48(1):17-25

Effect of dopamine and dopamine-receptor blockade on in vitro renin release, tissue renin content and tissue cyclic AMP content in the rat. López GA, et al. **Rev Esp Fisiol** 1985 Mar;41(1):95-100

Inhibitory effects of dopamine and isoprenaline on antral motor activity stimulated by acetylcholine or physostigmine in vitro. Ulvestad A, et al. **Scand J Gastroenterol** 1985 Mar;20(2):243-6

Regional brain dopamine metabolism: a marker for the speed, direction, and posture of moving animals. Freed CR, et al. **Science** 1985 Jul 5; 229(4708):62-5

[Fixed mydriasis in hemorrhagic shock treated with dopamine] Longhi A, et al. **Minerva Anestesiol** 1984 Nov;50(11):551-3 (Eng. Abstr.) **(Ita)**

[Dopamine-induced up-regulation of alpha 2-adrenoceptors in crude synaptic membranes of rat brain] Kohno Y, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):173-83 (Eng. Abstr.) **(Jpn)**

[TRH and its analog (DN-1417). Effects on central dopaminergic system-dependent behaviors in rats and mice] Miyamoto M, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):129-41 (Eng. Abstr.) **(Jpn)**

[Cyclic AMP content of autonomic ganglia as affected by catecholamines] Kniazeva LA, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):348-9 (Eng. Abstr.) **(Rus)**

[Effect of dopamine and its combination with furosemide on urination in the rat] Berkhin EB. **Farmakol Toksikol** 1985 Mar-Apr; 48(2):89-92 (Eng. Abstr.) **(Rus)**

[Effect of dimethoxy dichloro vinyl phosphate and fluorostigmine on the cyclic nucleotide content and dopamine level in the brain nigrostriatal system] Golovko AI, et al. **Farmakol Toksikol** 1985 Mar-Apr; 48(2):46-8 (Eng. Abstr.) **(Rus)**

[Normal values of dopamine, noradrenaline, adrenaline, and 5 hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb; 53(334):49-52 (Eng. Abstr.) **(Spa)**

DOPAMINE BETA-HYDROXYLASE

A monoclonal antibody to dopamine beta-monooxygenase: detection of biosynthetic intermediates. Nolan J, et al. **Arch Biochem Biophys** 1985 Jul;240(1):257-64

3-Phenylpropenes as mechanism-based inhibitors of dopamine beta-hydroxylase: evidence for a radical mechanism. Fitzpatrick PF, et al. **Biochemistry** 1985 Apr 23;24(9):2108-14

Secondary isotope effects and structure-reactivity correlations in the dopamine beta-monooxygenase reaction: evidence for a chemical mechanism. Miller SM, et al. **Biochemistry** 1985 Apr 23; 24(9):2114-27

Immunohistochemical evidence for phenylethanolamine-N-methyltransferase-positive/tyrosine hydroxylase-negative neurones in the retina and the posterior hypothalamus of the rat. Foster GA, et al. **Brain Res** 1985 Mar 18; 330(1):183-8

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

Study on the mechanism of the appearance of noise effects. Okada A, et al. **Eur J Applied Physiol** 1985;53(4):364-7

Sympathetic activity, plasma renin activity (PRA) and kininogen levels in patients haemodialysed with acetate and bicarbonate. Ksiażek A, et al. **Int Urol Nephrol** 1984;16(4):337-44

Dopamine beta-hydroxylase-like immunoreactivity in the rat and cat carotid body: a light and electron microscopic study. Chen IL, et al. **J Neurocytol** 1985 Feb;14(1):131-44

Changes in dopamine-beta-hydroxylase, and copper, and catecholamine concentrations in human plasma with physical exercise. Ohno H, et al. **J Sports Med Phys Fitness** 1984 Dec;24(4):315-20

Dopamine-beta-hydroxylase inhibitors, feeding and locomotor activity: reinstatement of feeding following central norepinephrine. Evans KR, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):535-40

DOXAPRAM

Antagonism of xylazine sedation with yohimbine, 4-aminopyridine, and doxapram in dogs. Hatch RC, et al. **Am J Vet Res** 1985 Feb; 46(2):371-5

Effects of doxapram on body temperature of the rat during radiofrequency irradiation. Jauchem JR, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):1-8

DOXEPIN

Effect of single and repeated doses of activated charcoal on the pharmacokinetics of doxepin. Scheinin M, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Jan;23(1):38-42

ELECTROCONVULSIVE THERAPY

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

Electroconvulsive therapy and schizophrenia. Van Valkenburg C, et al. **Biol Psychiatry** 1985 Jul;20(7):699-700

[Effect of electroconvulsive shock on brain monoamines] Kuang PG. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Feb; 18(1):41-4 (Eng. Abstr.) **(Chi)**

ELECTROENCEPHALOGRAPHY

Effects of fentanyl citrate and droperidol on electroencephalographic findings in dogs. Katherman AE, et al. **Am J Vet Res** 1985 Apr; 46(4):974-6

The effects of aniracetam on primate behavior and EEG. Schwam E, et al. **Ann NY Acad Sci** 1985;444:482-4

Hippocampal-dentate theta disturbance after selective CA1 pyramidal cell damage in the rat. Monmaur P, et al. **Brain Res** 1985 Mar 4; 328(2):301-11

Cocaine increases EEG beta: a replication and extension of Hans Berger's historic experiments. Herning RI, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):470-7

Characteristics of the cortical and hippocampal EEG power spectra of rabbits during normal behavioral states and after administration of CNS acting drugs. Yamamoto J. **Jpn J Pharmacol** 1985 Mar;37(3):227-34

Quantitative electrocortical changes in the rat induced by phencyclidine and other stimulants. Neal H, et al. **Neuropharmacology** 1985 Apr; 24(4):317-23

ELECTROLYTES

Steroids alter ion transport and absorptive capacity in proximal and distal colon. Sellin JH, et al. **Am J Physiol** 1985 Jul;249(1 Pt 1):G113-9

The pharmacological modification of secretory responses. Miller RJ, et al. **Ciba Found Symp** 1985;112:155-74

Effects of chronic changes in dietary electrolytes and acute stress on plasma levels of corticosterone and aldosterone in the duck (Anas platyrhynchos). Klingbeil CK. **Gen Comp Endocrinol** 1985 Apr; 58(1):10-9

Electrolyte transport across the basolateral membrane of the parietal cells. Muallem S, et al. **J Biol Chem** 1985 Jun 10;260(11):6641-53

ELECTROSHOCK

Differential effects of electroconvulsive shock on four models of experimentally-induced aggression in rats. Liou SY, et al. **Jpn J Pharmacol** 1985 Feb;37(2):167-72

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128-34

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

Increased sensitivity to serotonergic agonists after repeated electroconvulsive shock in rats. Wielosz M. **Pharmacol Biochem Behav** 1985 May;22(5):683-7

EMOTIONS

Elevation of mood due to antidepressants [letter] Pearce PL. **JAMA** 1985 Jun 7;253(21):3091-2

A preliminary report on anti-depressant therapy and its effects on hope and immunity. Udelman DL, et al. **Soc Sci Med** 1985; 20(10):1069-72

ENDORPHINS

Maternal and fetal beta-endorphin release in response to the stress of labor and delivery. Kofinas GD, et al. **Am J Obstet Gynecol** 1985 May 1;152(1):56-9

Endogenous opioid immunoreactivity in rat spinal cord following traumatic injury. Faden AI, et al. **Ann Neurol** 1985 Apr; 17(4):386-90

Response of the rat brain beta-endorphin system to novelty: importance of the fornix connection. Netto CA, et al. **Behav Neural Biol** 1985 Jan; 43(1):37-46

Modification of opioid ligand binding in the central and the peripheral nervous system by different buffers. Bourhim N, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):328-33

Ginseng saponin treatment does not alter brain or pituitary levels of beta-endorphin and dynorphin. Ho WK, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):2044-6

Nitrous oxide inhalation does not influence plasma concentrations of beta-endorphin or Met-enkephalin-like immunoreactivity. Evans SF, et al. **Br J Anaesth** 1985 Jun;57(6):624-8

Altered body temperature of rabbits after central injection of beta-endorphin and other peptides. Glyn-Ballinger JR, et al. **Brain Res** 1985 May 6;333(2):366-8

Distribution of the pro-opiomelanocortin derived peptides, adrenocorticotrope hormone, alpha-melanocyte-stimulating hormone and beta-endorphin (ACTH, alpha-MSH, beta-END) in the rat hypothalamus. Mezey E, et al. **Brain Res** 1985 Mar 4;328(2):341-7

Immunohistochemical localization of neurotensin and beta-endorphin in the rat anterior pituitary gland. Miyoshi R, et al. **Brain Res** 1985 Apr 8;331(2):386-8

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Modulation of lordosis behaviour in the female rat by corticotropin releasing factor, beta-endorphin and gonadotropin releasing hormone in the mesencephalic central gray. Sirinathsinghji DJ. **Brain Res** 1985 Jun 10;336(1):45-55

Ultrastructural evidence for beta-endorphin-like immunoreactivity in the nervous system of the rat duodenum. Wolter HJ. **Brain Res** 1985 May 13;334(1):194-9

Homeostatic alterations with major trauma. Arachidonic acid metabolites and endorphins. DeMajo WA. **Can Anaesth Soc J** 1985 May; 32(3 Pt 1):241-2

Occurrence of beta-endorphin-like immunoreactive cells in the neural complex of a protochordate. Pestarino M. **Cell Mol Biol** 1985; 31(1):27-31

Determination of beta-endorphin and beta-lipotropin in human cerebrospinal fluid. Laatikainen TJ, et al. **Clin Chim Acta** 1985 Feb 15;145(3):325-9

Endogenous opioids in marine invertebrates. Piccoli R, et al. **Comp Biochem Physiol** [C] 1985;80(2):237-40

Ovarian immunoreactive beta-endorphin and estrous cycle in the rat. Lolait SJ, et al. **Endocrinology** 1985 Jul;117(1):161-8

Changes in beta-endorphin-like immunoreactivity in pituitary portal blood during the estrous cycle and after ovariectomy in rats. Sarkar DK, et al. **Endocrinology** 1985 May;116(5):2075-9

Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. Young EA, et al. **Endocrinology** 1985 Jul;117(1):23-30

Plasma immunoreactive beta-endorphin and cortisol in the newborn infant after elective caesarean section and after spontaneous labour. Pohjavuori M, et al. **Eur J Obstet Gynecol Reprod Biol** 1985 Feb;19(2):67-74

Isolation and characterization of dipeptidyl peptidase IV from human meconium. Functional role of beta-casomorphins. Caporale C, et al. **FEBS Lett** 1985 May 20;184(2):273-7

The identification and characterization of alpha-N-acetylated beta-endorphin in the human pituitary gland. Smith AI, et al. **FEBS Lett** 1985 Jun 3;185(1):109-11

Endogenous opioid nomenclature: light at the end of the tunnel. Kitchen I. **Gen Pharmacol** 1985;16(2):79-84 (48 ref.)

Beta-endorphin and cold pressor test in the aged. Casale G, et al. **Gerontology** 1985;31(2):101-5

Temporal difference of thyrotropin-releasing hormone in prevention of testicular regression in golden hamsters exposed to short photoperiods: possible involvement of beta-endorphin. Chen HJ, et al. **Horm Res** 1985; 21(3):168-74

Bacterial lipopolysaccharide induction of leukocyte-derived corticotropin and endorphins. Harbour-McMenamin D, et al. **Infect Immun** 1985 Jun; 48(3):813-7

Preparation and properties of tritiated human [Tyr18, Trp27]-beta-endorphin. Hammonds RG Jr, et al. **Int J Pept Protein Res** 1985 Feb;25(2):149-54

Identification of N alpha-acetyl-alpha-endorphin and N alpha-acetyl-gamma-endorphin isolated from the neurointermediate lobe of the rat pituitary gland. Burbach JP, et al. **J Biol Chem** 1985 Jun 10;260(11):6663-9

beta-Casomorphin immunoreactive materials in cows' milk incubated with various bacterial species. Hamel U, et al. **J Dairy Res** 1985 Feb; 52(1):139-48

Opioid peptides of the pituitary and hypothalamus: changes in pregnant and lactating rats. Petraglia F, et al. **J Endocrinol** 1985 May; 105(2):239-45

Plasma beta-endorphin levels after exercise [letter] De Meirleir, et al. **J Endocrinol Invest** 1985 Feb;8(1):89

Preembedding colloidal gold immunostaining of hypothalamic neurons: light and electron microscopic localization of beta-endorphin-immunoreactive perikarya. Lamberts R, et al. **J Histochem Cytochem** 1985 Jun;33(6):499-507

Beta-endorphin-(10-16) antagonizes behavioral responses elicited by melatonin following injection into the nucleus accumbens of rats. Gaffori O, et al. **Life Sci** 1985 Jul 29;37(4):357-64

N alpha-Acetyl-gamma-endorphin is an endogenous non-opioid neuropeptide with biological activity. Wiegant VM, et al. **Life Sci** 1985 Jun 17;36(24):2277-85

Auto-tolerance to the endogenous opioids and sleep. Gillman MA, et al. **Med Hypotheses** 1985 Apr;16(4):393-5

The use of reverse-phase chromatographic procedures coupled with radioimmunoassay in studying regional distribution of beta h-endorphin in the human brain. Pasi A, et al. **Neurobehav Toxicol Teratol** 1985 Mar-Apr;7(2):199-201

Senescent change in tissue weight and immunoreactive beta-endorphin, enkephalin, and vasopressin in eight regions of C57BL/6J mouse brain and pituitary. Rogers J, et al. **Neurobiol Aging** 1985 Spring;6(1):1-9

Postnatal development of beta-endorphin immunoreactivity in the medulla oblongata of rat. Alessi NE, et al. **Neuropeptides** 1985 Feb; 5(4-6):473-6

Separate populations of opioid containing neurons in the guinea-pig intestine. Costa M, et al. **Neuropeptides** 1985 Feb;5(4-6):445-8

Action of neutral metalloendopeptidase ('enkephalinase') on beta-endorphin. Gráf L, et al. **Neuropeptides** 1985 Mar;6(1):13-9

Beta-endorphin processing in pituitary and brain is sensitive to haloperidol stimulation. Ham J, et al. **Neuropeptides** 1985 Feb;5(4-6):497-500

Postnatal development of opioid systems in rat brain. Loughlin SE, et al. **Neuropeptides** 1985 Feb;5(4-6):469-72

Differential modulation of the beta-endorphin and dynorphin systems by serotonergic stimulation in the rat. Majeed NH, et al. **Neuropeptides** 1985 Feb;5(4-6):563-6

A comparison of opioid peptide precursors in guinea pig, rat and bovine striata and guinea pig adrenal. Metters KM, et al. **Neuropeptides** 1985 Feb;5(4-6):521-4

The effect of morphine upon CSF opioids in dogs. Noel MA, et al. **Neuropeptides** 1985 Feb;5(4-6):429-32

Antidepressants and endogenous opioid peptide systems. Przewlocki R, et al. **Neuropeptides** 1985 Feb;5(4-6):575-8

Dermorphin-like immunoreactivity in guinea pig and rat stomach. Tsou K, et al. **Neuropeptides** 1985 Feb;5(4-6):449-52

How is kyotorphin (Tyr-Arg) generated in the brain? Ueda H, et al. **Neuropeptides** 1985 Feb;5(4-6):525-8

Enkephalins and endorphins: activation molecules for the immune system and natural killer activity? Wybran J. **Neuropeptides** 1985 Feb; 5(4-6):371-4

Changes in releasability of ACTH and beta-endorphin with chronic stress. Young E, et al. **Neuropeptides** 1985 Feb;5(4-6):545-8

The effect of surgery on plasma beta-endorphin and methionine-enkephalin. Smith R, et al. **Neurosci Lett** 1985 Mar 22; 55(1):17-21

Acupuncture analgesia [letter] Han JS. **Pain** 1985 Mar;21(3):307-10

Effects of intracranial self-stimulation on brain opioid peptides. Stein EA. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):67-73

Binding characteristics of dermorphin, and [dermorphin1-7]-beta c-endorphin in rat brain membranes. Westphal M, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):149-52

Stress produces opioid-like effects on investigatory behavior. Arnsten AF, et al. **Pharmacol Biochem Behav** 1985 May;22(5):803-9

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417-51 (238 ref.)

The effect of chronic estrogen treatment on immunoreactive beta-endorphin levels in intact female rats. Forman LJ, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):365-72

Glucocorticoid inhibition of immunoreactive beta-endorphin release from the anterior lobe of the rat pituitary: in vitro and in vivo studies. Mueller GP, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):338-47

Endogenous opioid activity in clinical hemorrhagic shock. Shatney CH, et al. **Surg Gynecol Obstet** 1985 Jun;160(6):547-51

[Endogenous opioids] Schulz R, et al. **Tierarztl Prax** 1985;13(1):11-27 (93 ref.) (Eng. Abstr.) **(Ger)**

[Stress and the endogenous opioid system. III. Classification of the opioid system in the process of adaptation] Nieber K, et al. **Z Gesamte Inn Med** 1985 Mar 1;40(5):133-6 (Eng. Abstr.) **(Ger)**

[Stress and the endogenous opioid system. II. Stress, stress models and endogenous opioid peptides] Nieber K, et al. **Z Gesamte Inn Med** 1985 Feb 1;40(3):61-5 (Eng. Abstr.) **(Ger)**

[Endorphins and pregnancy] Stoppelli I, et al. **Minerva Ginecol** 1984 Dec; 36(12):761-6 (Eng. Abstr.) **(Ita)**

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

[Neuro-intestinal peptides and peptide-producing cells--immunohistocytochemistry of catecholamines and opioid peptides in the hamster adrenal medulla] Kobayashi S, et al. **Nippon Heikatsukin Gakkai Zasshi** 1984 Oct;20(5):393-9 **(Jpn)**

[Brain blood supply and beta-endorphin and corticotropin content on exposure to thyroliberin] Mirozoian RS, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):318-20 (Eng. Abstr.) **(Rus)**

[Changes in the opioid peptide content of the adrenals of rats during immobilization stress] Val'dman AV, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):404-6 (Eng. Abstr.) **(Rus)**

[Immunoreactive beta-lipotropin and endorphins are secreted by the isolated alimentary complex of rats] Titov MI, et al. **Dokl Akad Nauk SSSR** 1985;281(2):497-9 **(Rus)**

ENKEPHALIN, LEUCINE

The stimulation of glycogenolysis in isolated hepatocytes by opioid peptides. Leach RP, et al. **Biochem J** 1985 Apr 1;227(1):191-7

The metabolism of neuropeptides. Endopeptidase-24.11 in human synaptic membrane preparations hydrolyses substance P. Matsas R, et al. **Biochem J** 1985 Jun 1;228(2):487-92

Central versus peripheral actions of Leu-enkephalin on acquisition of a one-way active avoidance response in rats. Martinez JL Jr, et al. **Brain Res** 1985 Feb 18;327(1-2):37-43

Blockade of cholinergic receptors in the C1 area abolishes hypertensive response to opiates in the A1 area of the ventrolateral medulla. Punnen S, et al. **Brain Res** 1985 Jun 10;336(1):180-6

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Blood-brain barrier permeability to leucine-enkephalin, D-alanine2-D-leucine5-enkephalin and their N-terminal amino acid (tyrosine). Zlokovic BV, et al. **Brain Res** 1985 Jun 10;336(1):125-32

Effect of hemorrhage on vasopressin, dynorphin A, and leu5-enkephalin in the hypothalamo-pituitary system of the rat. Feuerstein G, et al. **Clin Exp Hypertens** [A] 1984;6(10-11):1973-6

Influence of intracerebroventricular (ICV) GTP-electrolyte infusion on ICV (D-ALA2, D-LEU5) enkephalin (DADL)-induced cardiovascular effects in rats. McDonald WJ, et al. **Clin Exp Hypertens** [A] 1984;

6(10-11):1837-41

Effects of traumatic injury on dynorphin immunoreactivity in spinal cord. Cox BM, et al. **Neuropeptides** 1985 Feb;5(4-6):571-4

Studies in vitro with ICI 174,864, [D-Pen2, D-Pen5]-enkephalin (DPDPE) and [D-Ala2, NMePhe4, Gly-ol]-enkephalin (DAGO). Hirning LD, et al. **Neuropeptides** 1985 Feb;5(4-6):383-6

Localization and quantitation of proenkephalin-derived neuropeptides in the rat hippocampus. Hoffman DW, et al. **Neuropeptides** 1985 Feb; 5(4-6):437-40

Development of hypothalamic opioid neurons: a combined immunocytochemical and [3H]thymidine autoradiographic study. Khachaturian H, et al. **Neuropeptides** 1985 Feb;5(4-6):477-80

Opiate receptor-mediated chemotaxis of human monocytes. Ruff MR, et al. **Neuropeptides** 1985 Feb;5(4-6):363-6

Characterization of a high molecular weight polypeptide from spinal cord with (Leu) enkephalin-immunoreactivity. Wahlström A, et al. **Neuropeptides** 1985 Feb;5(4-6):509-12

Dynorphinergic pathways of Leu-enkephalin production in the rat brain. Zamir N, et al. **Neuropeptides** 1985 Feb;5(4-6):441-4

A study of intracerebroventricular self-administration of leucine or methionine enkephalin by rats in response to intermittent electric shocks. Dib B. **Pain** 1985 May;22(1):49-57

A general procedure for analysis of proenkephalin B derived opioid peptides. Christensson-Nylander I, et al. **Regul Pept** 1985 May; 11(1):65-76

[The nature of cation-binding groups in binding sites for [[3H]Tyr1, D-Ala2, D-Leu5]enkephalin] Zaitsev SV, et al. **Bioorg Khim** 1985 Feb; 11(2):153-61 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, METHIONINE

Protected homocysteine peptides as precursors of labelled methionine peptides. Application in preparation of methionine-enkephalin. Någren K, et al. **Acta Chem Scand [B]** 1985;39(3):157-61

Enzyme-linked immunosorbent assay for Met-enkephalin using unconjugated enkephalin as a solid phase antigen. Takesue Y, et al. **Anal Biochem** 1985 Apr;146(1):35-9

The stimulation of glycogenolysis in isolated hepatocytes by opioid peptides. Leach RP, et al. **Biochem J** 1985 Apr 1;227(1):191-7

Nitrous oxide inhalation does not influence plasma concentrations of beta-endorphin or Met-enkephalin-like immunoreactivity. Evans SF, et al. **Br J Anaesth** 1985 Jun;57(6):624-8

Met-enkephalin-Arg6-Gly7-Leu8 in the organ of Corti: high performance liquid chromatography and immunoelectron microscopy. Eybalin M, et al. **Brain Res** 1985 Apr 8;331(2):389-95

Dopamine receptors regulate Met-enkephalin content in pituitary. George SR, et al. **Brain Res** 1985 May 13;334(1):187-9

Development of methionine-enkephalin in microdissected areas of the rabbit brain. Gingras-Leatherman JL, et al. **Brain Res** 1985 Jun 10; 336(1):73-80

The opioid octapeptide Met5-enkephalin-Arg6-Gly7-Leu8: characterization and distribution in rat spinal cord. Iadarola MJ, et al. **Brain Res** 1985 Mar 18;330(1):127-34

Evidence for the coexistence of acetylcholine and enkephalin in the sympathetic preganglionic neurons of rats. Kondo H, et al. **Brain Res** 1985 Jun 3;335(2):309-14

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Effects of enkephalin and 5-hydroxytryptamine on solitary tract neurones involved in respiration and respiratory reflexes. Sessle BJ, et al. **Brain Res** 1985 Feb 18;327(1-2):221-30

Occurrence of met-enkephalin, met-enkephalin-Arg6-Phe7 and met-enkephalin-Arg6-Gly7-Leu8 in gastrin cells of hog antral mucosa. Jönsson AC. **Cell Tissue Res** 1985;240(2):361-5

Potential role of met-enkephalin in short term regulation of blood pressure in anesthetized rabbits. Rhee HM, et al. **Clin Exp Hypertens [A]** 1984; 6(10-11):2063-7

Methionine enkephalin as a possible neuromodulator of regional cerebral blood flow. Blum K, et al. **Experientia** 1985 Jul 15;41(7):932-3

Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Hong JS, et al. **Fed Proc** 1985 Jun;44(9):2535-9

Evaluation of BW942C, a novel antidiarrheal agent, against enterotoxins of Escherichia coli and Vibrio cholerae. Morgan DR, et al. **Infect Immun** 1985 Jun;48(3):754-8

Methionine-enkephalin inhibits stress-induced increases in noradrenaline turnover in brain regions of rats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Jan;37(1):117-9

Characterization of rat brain opioid receptors by [Tyr-3,5-3H]1, D-Ala2, Leu5-enkephalin binding. Benyhe S, et al. **Neurochem Res** 1985 May; 10(5):627-35

Localization and quantitation of proenkephalin-derived neuropeptides in the rat hippocampus. Hoffman DW, et al. **Neuropeptides** 1985 Feb; 5(4-6):437-40

Release of high molecular weight forms of met5-enkephalin-arg6-gly7-leu8 from rat brain. Lindberg I, et al. **Neuropeptides** 1985 Feb;5(4-6):541-4

Prodynorphin immunoreactivity is located in different neurons than proenkephalin immunoreactivity in the cerebral cortex of rats. McGinty JF. **Neuropeptides** 1985 Feb;5(4-6):465-8

Adrenorphin immunoreactivity in rat brain. Miyata A, et al. **Neuropeptides** 1985 Feb;5(4-6):517-20

Release of synenkephalin from neuronal terminals in vitro. Rossier J, et al. **Neuropeptides** 1985 Feb;5(4-6):549-52

Astrocyte opioid receptors: activation modifies the noradrenaline-evoked increase in 2-[14C]deoxyglucose incorporation into glycogen. Pearce B, et al. **Neurosci Lett** 1985 Apr 9;55(2):157-60

The effect of surgery on plasma beta-endorphin and methionine-enkephalin. Smith R, et al. **Neurosci Lett** 1985 Mar 22; 55(1):17-21

Effect of histamine infusion on circulating methionine-enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289-92

Mesencephalic pathway to the retina exhibits enkephalin-like immunoreactivity. Weiler R. **Neurosci Lett** 1985 Mar 22;55(1):11-6

A study of intracerebroventricular self-administration of leucine or methionine enkephalin by rats in response to intermittent electric shocks. Dib B. **Pain** 1985 May;22(1):49-57

Effects of MET-ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):139-48

Cardiovascular interactions between methionine-enkephalin and substance P in the conscious dog. Sander GE, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):133-7

[Effect of an enkephalin analog on the endocrine system in man] Földes J, et al. **Orv Hetil** 1985 May 12;126(19):1145-8 (Eng. Abstr.) **(Hun)**

ENKEPHALINS

Enkephalin-degrading dipeptidyl carboxypeptidase in guinea pig serum: its properties and action on bioactive peptides. Kase R, et al. **Arch Biochem Biophys** 1985 Jul;240(1):330-6

Enkephalin neurons in the guinea pig proximal colon: an immunocytochemical study using an antiserum to methionine-enkephalin-Arg6-Gly7-Leu8. Kobayashi S, et al. **Arch Histol Jpn** 1985 Feb;48(1):27-44

Enkephalin metabolism and its inhibition. Gros C, et al. **Biochem Soc Trans** 1985 Feb;13(1):47-50

Identification of aminopeptidase M as an enkephalin-inactivating enzyme in rat cerebral membranes. Gros C, et al. **Biochemistry** 1985 Apr 23; 24(9):2179-85

Evidence for synenkephalin-like immunoreactivity in pontobulbar monoaminergic neurons of the cat. Charnay Y, et al. **Brain Res** 1985 May 27;335(1):160-4

Spinal parasympathetic enkephalin fibers: patterns and projections. Romagnano MA, et al. **Brain Res** 1985 May 27;335(1):174-81

An enkephalinergic projection from the hypothalamic paraventricular nucleus to the hypothalamic ventromedial nucleus of the rat: an experimental immunohistochemical study. Yamano M, et al. **Brain Res** 1985 Apr 1;331(1):25-33

Light- and electron-microscopic demonstration of enkephalin-like immunoreactivity in paraganglia of the human urinary bladder. Vaalasti A, et al. **Cell Tissue Res** 1985;239(3):683-7

Quantitation of proenkephalin A messenger RNA in bovine brain, pituitary and adrenal medulla: correlation between mRNA and peptide levels. Pittius CW, et al. **EMBO J** 1985 May;4(5):1257-60

Proenkephalin and prodynorphin related neuropeptides in the cochlea. Hoffman DW, et al. **Hear Res** 1985 Jan;17(1):47-50

Localization of enkephalins in adrenaline cells and the nerves innervating adrenaline cells in rat adrenal medulla. Pelto-Huikko M, et al. **Histochemistry** 1985;82(4):377-83

Selective regulation of carboxypeptidase peptide hormone-processing enzyme during enkephalin biosynthesis in cultured bovine adrenomedullary chromaffin cells. Hook VY, et al. **J Biol Chem** 1985 May 25;260(10):5991-7

Separation of enkephalins from their metabolites and precursor by a single pump gradient high-performance liquid chromatographic method. Hui KS, et al. **J Chromatogr** 1985 Jun 7;325(2):467-72

Immunological characterization of secretory proteins of chromaffin granules: chromogranins A, chromogranins B, and enkephalin-containing peptides. Fischer-Colbrie R, et al. **J Neurochem** 1985 Jun;44(6):1854-61

Characterization of membrane-bound aminopeptidases from rat brain: identification of the enkephalin-degrading aminopeptidase. Hersh LB. **J Neurochem** 1985 May;44(5):1427-35

Changes from enkephalin-like to gastrin/cholecystokinin-like immunoreactivity in snail neurons. Gesser BP, et al. **J Neurosci** 1985 Jun;5(6):1412-7

Nasal delivery of polypeptides I: nasal absorption of enkephalins in rats. Su KS, et al. **J Pharm Sci** 1985 Apr;74(4):394-8

Mu1: a very high affinity subtype of enkephalin binding sites in rat brain. Lutz RA, et al. **Life Sci** 1985 Jun 10;36(23):2233-8

Senescent change in tissue weight and immunoreactive beta-endorphin, enkephalin, and vasopressin in eight regions of C57BL/6J mouse brain and pituitary. Rogers J, et al. **Neurobiol Aging** 1985 Spring;6(1):1-9

Peripheral enkephalin hydrolysis in different animal species: a comparative study. Venturelli F, et al. **Neurochem Res** 1985 Mar;10(3):333-42

Substance P, enkephalins, somatostatin, cholecystokinin, oxytocin, and vasopressin in human spinal cord. Schoenen J, et al. **Neurology** 1985 Jun;35(6):881-90

Influence of acute, subchronic and chronic treatment with neuroleptic (haloperidol) on enkephalins and their precursors in the striatum of rat brain. Blanc D, et al. **Neuropeptides** 1985 Feb;5(4-6):567-70

Studies in vitro with ICI 174,864, [D-Pen2, D-Pen5]-enkephalin (DPDPE) and [D-Ala2, NMePhe4, Gly-ol]-enkephalin (DAGO). Hirning LD, et al. **Neuropeptides** 1985 Feb;5(4-6):383-6

Prodynorphin immunoreactivity is located in different neurons than proenkephalin immunoreactivity in the cerebral cortex of rats. McGinty JF. **Neuropeptides** 1985 Feb;5(4-6):465-8

Partial purification and characterisation of a 31 kDalton putative enkephalin precursor from guinea pig striatum. Metters KM, et al. **Neuropeptides** 1985 Feb;5(4-6):505-8

Identification of high molecular weight enkephalin percursor forms in human cerebrospinal fluid. Nyberg F, et al. **Neuropeptides** 1985 Feb; 5(4-6):537-40

Characterization of a new 23 kDalton enkephalin-containing protein in the bovine adrenal medulla. Patey G, et al. **Neuropeptides** 1985 Feb; 5(4-6):513-6

Release of synenkephalin from neuronal terminals in vitro. Rossier J, et al. **Neuropeptides** 1985 Feb;5(4-6):549-52

Leumorphin in human brain. Suda M, et al. **Neuropeptides** 1985 Feb; 5(4-6):461-4

The comparative distribution of enkephalin, dynorphin and substance P in the human globus pallidus and basal forebrain. Haber SN, et al. **Neuroscience** 1985 Apr;14(4):1011-24

Comparison of substance P and enkephalin distribution in rat brain: an overview using radioimmunocytochemistry. McLean S, et al. **Neuroscience** 1985 Mar;14(3):837-52

Sequence and expression of the rat prodynorphin gene. Civelli O, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4291-5

A general procedure for analysis of proenkephalin B derived opioid peptides. Christensson-Nylander I, et al. **Regul Pept** 1985 May; 11(1):65-76

[Enkephalin-noradrenaline interactions in synaptic transmission] Fan JZ, et al. **Sheng Li Ko Hsueh Chin Chan** 1985 Apr;16(2):158-60 **(Chi)**

[Enkephalins and hormonal-metabolic reactions in experimental stress of differing severity] Lishmanov IuB, et al. **Biull Eksp Biol Med** 1985 Mar; 99(3):269-71 (Eng. Abstr.) **(Rus)**

ENURESIS

[Catecholaminergic activity in children with nocturnal enuresis] Szewczyk L. **Pediatr Pol** 1984 Oct;59(10):841-5 (Eng. Abstr.) **(Pol)**

EPHEDRINE

Bioavailability assessment of a new liquid controlled-release pseudoephedrine product. Graves DA, et al. **Clin Pharm** 1985 Mar-Apr; 4(2):199-203

Aperistalsis of the vas deferens corrected with administration of ephedrine. Tiffany P, et al. **J Urol** 1985 Jun;133(6):1060-1

EPINEPHRINE

Effect of propranolol on post-traumatic hypophosphataemia and catecholamine secretion. Lovén L, et al. **Acta Chir Scand** 1985; 151(3):201-4

Changes in blood level of catecholamines during arterial blood pressure rise induced with sciatic nerve stimulation. Całkosiński I, et al. **Acta Physiol Pol** 1984 Jan-Feb;35(1):47-51

Seasonal changes in blood lipids, adrenaline, noradrenaline, glucose and insulin in Norwegian reindeer. Larsen TS, et al. **Acta Physiol Scand** 1985 May;124(1):53-9

Human platelet alpha 2-adrenergic receptors: effect of Na+ on interaction with the adenylate cyclase system and on epinephrine-stimulated platelet secretion. Limbird LE, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:235-42

Neural and transmitter influence on the capillary diameter in exteriorized frog mesentery. Dietrich HH, et al. **Adv Exp Med Biol** 1984; 180:701-9

Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. Stratton JR, et al. **Am J Cardiol** 1985 Jul 1;56(1):136-9

Intravascular lidocaine toxicity: influence of epinephrine and route of administration. Yagiela JA. **Anesth Prog** 1985 Mar-Apr;32(2):57-61

Effect of amines on fibrinogen synthesis. Roy AK, et al. **Arch Biochem Biophys** 1985 Jun;239(2):364-7

Depletion of adrenal catecholamines alters the amnestic effect of amygdala stimulation. Bennett C, et al. **Behav Brain Res** 1985 Apr;15(2):83-91

Peripheral epinephrine modulates the effects of post-training amygdala stimulation on memory. Liang KC, et al. **Behav Brain Res** 1985 Apr; 15(2):93-100

Stimulation of inositol trisphosphate formation in hepatocytes by vasopressin, adrenaline and angiotensin II and its relationship to changes in cytosolic free Ca2+. Charest R, et al. **Biochem J** 1985 Apr 1; 227(1):79-90

Effects of phorbol esters on alpha 1-adrenergic-mediated and glucagon-mediated actions in isolated rat hepatocytes. García-Sáinz JA, et al. **Biochem J** 1985 May 15;228(1):277-80

Hepatic thiol and glutathione efflux under the influence of vasopressin, phenylephrine and adrenaline. Sies H, et al. **Biochem J** 1985 Mar 1; 226(2):545-9

Effect of methyl palmoxirate, an oral hypoglycemic agent, on epinephrine-induced hyperglycemia in the rat. Tutwiler GF, et al. **Biochem Pharmacol** 1985 Jun 15;34(12):2217-20

The effect of catecholamines and adenosine deaminase on the glucose transport system in rat adipocytes. Gliemann J, et al. **Biochim Biophys Acta** 1985 Jun 30;845(3):373-9

Factor analytic derivation of the MHPG/NM ratio: implications for studying the link between physical fitness and depression. Sothmann MS, et al. **Biol Psychiatry** 1985 May;20(5):579-83

Catecholamine responses to changes in posture during human pregnancy. Whittaker PG, et al. **Br J Obstet Gynaecol** 1985 Jun;92(6):586-92

Corticotropin-releasing factor: a physiologic regulator of adrenal epinephrine secretion. Brown MR, et al. **Brain Res** 1985 Mar 4; 328(2):355-7

Epinephrine- and norepinephrine-evoked potential changes of frog primary afferent terminals: pharmacological characterization of alpha and beta components. Wohlberg CJ, et al. **Brain Res** 1985 Feb 18; 327(1-2):289-301

Acetaminophen administration interferes with urinary metanephrine (and catecholamine) determinations [letter] Wilson SP, et al. **Clin Chem** 1985 Jun;31(6):1093-4

Blood pressure responses to ACTH and adrenaline infusions in dogs. Anderson WP, et al. **Clin Exp Hypertens** [A] 1985;7(4):525-37

Alpha 1-adrenergic responsiveness of young adult and aged rat submandibular cells in vitro. Baum BJ, et al. **Comp Biochem Physiol** [C] 1985;81(1):121-4

Accumulation of intra-arterially administered [3H]adrenaline and [3H]noradrenaline in various tissues of the Atlantic cod, Gadus morhua. Ungell AL. **Comp Biochem Physiol** [C] 1985;81(1):25-8

Regulation of ketogenesis by epinephrine and norepinephrine in the overnight-fasted, conscious dog. Steiner KE, et al. **Diabetes** 1985 May; 34(5):425-32

Plasma glucagon and catecholamines during exhaustive short-term exercise. Näveri H, et al. **Eur J Applied Physiol** 1985;53(4):308-11

Normetanephrine and metanephrine oxidized by both types of monoamine oxidase. Suzuki O, et al. **Experientia** 1985 May 15;41(5):634-6

Enhancement of adrenaline plasma-levels shortens adrenaline half-life. Porta S, et al. **Horm Metab Res** 1985 May;17(5):264-5

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr; 6(2):78-81

Exercise, dobutamine, and combined atropine, norepinephrine, and epinephrine compared. Haidet GC, et al. **J Appl Physiol** 1985 Jun; 58(6):2047-53

Hemodynamic effects of epinephrine: concentration-effect study in humans. Stratton JR, et al. **J Appl Physiol** 1985 Apr;58(4):1199-206

Analysis of USP epinephrine injections for potency, impurities, degradation products, and d-enantiomer by liquid chromatography, using ultraviolet and electrochemical detectors. Kirchhoefer RD, et al. **J Assoc Off Anal Chem** 1985 Mar-Apr;68(2):163-5

Simple and fast analysis of adrenaline and noradrenaline in plasma on microbore high-performance liquid chromatography columns using fluorimetric detection. Kamperman G, et al. **J Chromatogr** 1985 Feb 8;337(2):384-90

High-performance liquid chromatographic analysis of epinephrine enantiomers using a UV detector in series with an optical activity detector. Scott BS, et al. **J Chromatogr** 1985 Feb 20;319(3):419-26

Circadian rhythms of epinephrine and norepinephrine in man. Linsell CR, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1210-5

(-)-Adrenaline-induced, calcium-dependent phosphorylation of proteins in human platelets. Block LH, et al. **J Clin Invest** 1985 May; 75(5):1600-7

Evidence for a beta-adrenoceptor-mediated regulation of human natural killer cells. Hellstrand K, et al. **J Immunol** 1985 Jun;134(6):4095-9

Decrease in hypothalamic epinephrine concentration and other neurochemical changes produced by quinpirole, a dopamine agonist, in rats. Fuller RW, et al. **J Neural Transm** 1985;61(3-4):161-73

Effects of intravenous glucose or epinephrine injection on plasma concentrations of potassium, magnesium and insulin in sheep. Yano H, et al. **J Nutr Sci Vitaminol (Tokyo)** 1984 Dec;30(6):535-40

Review and survey of medicaments used with gingival retraction cords. Donovan TE, et al. **J Prosthet Dent** 1985 Apr;53(4):525-31

Adrenaline, adenosine, and feedback [letter] Böhm M, et al. **Lancet** 1985 May 18;1(8438):1157

Effect of intravenous epinephrine infusion on plasma renin activity in adrenalectomized dogs. Johnson MD. **Life Sci** 1985 Jun 24; 36(25):2403-11

Subsensitive pituitary cyclic AMP response to stress following adrenalectomy is not caused by loss of adrenal epinephrine. Kant GJ, et al. **Life Sci** 1985 Jun 24;36(25):2421-8

Epinephrine and norepinephrine syntheses are regulated by a glucocorticoid receptor-mediated mechanism in the bovine adrenal medulla. Nawata H, et al. **Life Sci** 1985 May 20;36(20):1957-66

The effect of epinephrine and serotonin on hepatic poly(A)+ RNA synthesis. Roy AK, et al. **Life Sci** 1985 Jun 17;36(24):2301-7

Adrenaline and anaphylaxis [letter] Roberts-Thomson P, et al. **Med J Aust** 1985 Jun 24;142(13):708

Excretion of urinary catecholamines and plasma cortisol levels in female nurses on short-rotating shift. Panza G, et al. **Med Lav** 1985 Jan-Feb; 76(1):30-4

Effect of epinephrine on carbohydrate metabolism in exercising dogs. Issekutz B Jr. **Metabolism** 1985 May;34(5):457-64

Plasma catecholamines in arterial and capillary blood. Baumgartner H, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):461-3

Effect of histamine infusion on circulating methionine-enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289-92

Administering epinephrine in an emergency. Gever LN. **Nursing** 1985 Jun;15(6):65

Dissociation of epinephrine's hyperglycemic and anorectic effect. Langhans W, et al. **Physiol Behav** 1985 Mar;34(3):457-63

Airway responses to low concentrations of adrenaline and noradrenaline in normal subjects. Berkin KE, et al. **Q J Exp Physiol** 1985 Apr; 70(2):203-9

Relationship between sleep efficiency and urinary excretion of catecholamines in bed-rested humans. Nishihara K, et al. **Sleep** 1985; 8(2):110-7

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

[Effect of adrenaline and phenylephrine on milk extraction during the mechanical milking of cows] Bernabé J, et al. **Reprod Nutr Dev** 1985; 25(2):379-88 (Eng. Abstr.) **(Fre)**

[Animal experiment studies on the hemodynamic effect of adrenaline following intravenous and endobronchial administration] Hörnchen U, et al. **Anasth Intensivther Notfallmed** 1985 Apr;20(2):84-8 (Eng. Abstr.) **(Ger)**

[Electrocardiographic studies of the modification of cardiac activity in cattle by adrenaline and noradrenaline with and without vagolysis (atropine) and beta-receptor blockade (propranolol)] Mielke H, et al. **Arch Exp Veterinarmed** 1985 Mar;39(2):193-206 (Eng. Abstr.) **(Ger)**

[Concentrations of catecholamines in CSF and plasma, and cardiovascular effects following epidural administration of 2 mg epinephrine] Nakajima J. **Masui** 1985 Feb;34(2):144-51 (Eng. Abstr.) **(Jpn)**

[Urinary excretion of catecholamines in children with functional disorders of the digestive system] Szewczyk L, et al. **Pediatr Pol** 1984 Oct; 59(10):835-9 (Eng. Abstr.) **(Pol)**

[Catecholaminergic activity in children with nocturnal enuresis] Szewczyk L. **Pediatr Pol** 1984 Oct;59(10):841-5 (Eng. Abstr.) **(Pol)**

[Regulation of the cell cycle of B-lymphocytes in mice by substances elevating the levels of intracellular cAMP and cGMP] Ado AD, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):455-8 (Eng. Abstr.) **(Rus)**

[Circadian rhythms of adrenaline and noradrenaline excretion in man in normal conditions and after alcohol intake] Latenkov VP. **Biull Eksp Biol Med** 1985 Mar;99(3):344-6 (Eng. Abstr.) **(Rus)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

[Changes in adrenaline sensitivity during thermal adaptation] Kosenkov NI. **Fiziol Cheloveka** 1984 May-Jun;10(3):478-9 **(Rus)**

[Effect and aftereffect of adrenaline on the respiration of rat liver mitochondria] Babskii AM, et al. **Fiziol Zh** 1985 May-Jun; 31(3):301-6 (Eng. Abstr.) **(Rus)**

[Effect of resection and dissection of the distal portion of the small intestine on the adrenergic inhibition of gastric secretion] Trefilov AB. **Fiziol Zh SSSR** 1985 Feb;71(2):221-5 (Eng. Abstr.) **(Rus)**

[Normal values of dopamine, noradrenaline, adrenaline, and 5-hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb; 53(334):49-52 (Eng. Abstr.) **(Spa)**

[Radioimmunoanalysis of adrenaline and noradrenaline in the normal fetus at term] Martínez Alcalá FO, et al. **Ginecol Obstet Mex** 1983 Oct; 51(318):267-72 (Eng. Abstr.) **(Spa)**

ESCAPE REACTION

Intracortical glutamate injection produces helpless-like behavior in the rat. Petty F, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):531-3

The activation of mice's behavior and reduction of brain beta-adrenergic receptor binding following repeated administration of antidepressant drugs. Nomura S, et al. **Yakubutsu Seishin Kodo** 1984 Nov; 4(3):237-41

ESTRADIOL

The effects of testosterone and estrogen on the pituitary growth hormone response to growth hormone-releasing factor. Wehrenberg WB, et al. **Biol Reprod** 1985 Mar;32(2):369-75

The possible role of 2-hydroxyestradiol in the development of estrogen-induced striatal dopamine receptor hypersensitivity. Clopton JK, et al. **Brain Res** 1985 Apr 29;333(1):1-10

Estradiol benzoate decreases nigral GABAergic activity in male rats. Nicoletti F, et al. **Brain Res** 1985 Apr 15;332(1):179-83

Estradiol increases dopamine turnover in intermediate and posterior pituitary lobes of ovariectomized rats. Saavedra JM, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):397-402

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893-8

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953-9

Hormonal influence on the response of the uterus of the Brazilian marsupial Didelphis albiventris to adrenergic drugs. Rocha LR, et al. **Gen Comp Endocrinol** 1985 May;58(2):179-85

Levels of dopamine and thyrotrophin-releasing hormone in hypophysial stalk blood during an oestrogen-stimulated surge of prolactin in the ovariectomized rat. de Greef WJ, et al. **J Endocrinol** 1985 Apr; 105(1):107-12

Changes in pulsatile LH secretion and the positive and negative feedback actions of oestradiol after administration of a GnRH agonist in the ovariectomized ewe. Fitzgerald BP, et al. **J Reprod Fertil** 1985 Mar; 73(2):433-40

Neurotensin enhances estradiol induced DNA synthesis in immature rat uterus. Mistry A, et al. **Life Sci** 1985 May 27;36(21):2063-7

Progesterone-induced LHRH release in vitro is an estrogen—as well as Ca++- and calmodulin-dependent secretory process. Drouva SV, et al. **Neuroendocrinology** 1985 Apr;40(4):325-31

Alteration of dopamine metabolism in different brain regions of the rabbit by estradiol and tamoxifen. Baksi SN, et al. **Neuroscience** 1985 Apr; 14(4):1053-9

The effect of chronic estrogen treatment on immunoreactive beta-endorphin levels in intact female rats. Forman LJ, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):365-72

[Effect of the administration of thyroxine and estradiol on the morphology of the anterior lobe of the pituitary gland] Szczurek Z, et al. **Patol Pol** 1984 Oct-Dec;35(4):499-507 (Eng. Abstr.) **(Pol)**

ETHOLOGY

Automated measurement of multivariate locomotor behavior in rodents. Sanberg PR, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb; 7(1):87-94

EXPLORATORY BEHAVIOR

Response of the rat brain beta-endorphin system to novelty: importance of the fornix connection. Netto CA, et al. **Behav Neural Biol** 1985 Jan; 43(1):37-46

Sulpiride blocks postsynaptic dopamine receptors in the nucleus accumbens. Morgenstern R, et al. **J Neural Transm** 1985; 61(3-4):151-60

Stress produces opioid-like effects on investigatory behavior. Arnsten AF, et al. **Pharmacol Biochem Behav** 1985 May;22(5):803-9

Increased investigative activity after presynaptic dopaminergic stimulation measured by a fixed-interval recording procedure. Höglund AU, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):403-6

Development of mouse activity, stimulus reactivity, habituation, and response to amphetamine and scopolamine. Alleva E, et al. **Physiol Behav** 1985 Apr;34(4):519-23

Behavioral analysis of the effect of neurotensin injected into the ventral mesencephalon on investigatory and spontaneous motor behavior in the rat. Cador M, et al. **Psychopharmacology (Berlin)** 1985;85(2):187-96

[Effect of stable strontium on spontaneous and drug-induced motor activity in the rat] Escanero JF, et al. **Arch Farmacol Toxicol** 1985 Apr; 11(1):33-9 (Eng. Abstr.) **(Spa)**

EXTINCTION (PSYCHOLOGY)

Haloperidol and nonreinforcement produce different patterns of response slowing in a food reinforced runway task. Wirtshafter D, et al. **Pharmacol Biochem Behav** 1985 May;22(5):661-3

FEAR

Imipramine in the treatment of panic disorder and its complications. Liebowitz MR. **Psychiatr Clin North Am** 1985 Mar;8(1):37–47

Anxiolytic drugs and the acquisition of conditioned fear in mice. Sanger DJ, et al. **Psychopharmacology (Berlin)** 1985;85(3):284–8

FENFLURAMINE

Possible relationships between changes in body weight set–point and stress metabolism after treating rats chronically with D–fenfluramine. Effects of feeding rats acutely with fructose on the metabolism of corticosterone, glucose, fatty acids, glycerol and triacylglycerol. Brindley DN, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1265–71

d–Fenfluramine and salbutamol: two drugs causing anorexia through different neurochemical mechanisms. Garattini S, et al. **Int J Obes** 1984; 8 Suppl 1:151–7

Comparison of the effects of fenfluramine and other anorectic agents in different feeding and drinking paradigms in rats. Rowland NE, et al. **Life Sci** 1985 Jun 17;36(24):2295–300

The effect of previous d–amphetamine treatment on the disposition and lethality of fenfluramine in the rat. Hunsinger RN, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):236–45

[Ponderal Retard] de Longraye J. **Soins** 1985 Feb;(448):III–IV **(Fre)**

FK 33–824

Effect of dopamine receptor stimulation on the inhibition of LH pulsatility by a met–enkephaline (FK 33–824). del Pozo E, et al. **Acta Neurochir (Wien)** 1985;75(1–4):88–90

FLUPHENAZINE

Priapism resulting from fluphenazine hydrochloride treatment reversed by diphenhydramine. Fishbain DA. **Ann Emerg Med** 1985 Jun; 14(6):600–2

The effects of chronic neuroleptic treatment on neurotensin–like immunoreactivity in the rat central nervous system. Goedert M, et al. **Brain Res** 1985 Jun 3;335(2):334–6

Serum neuroleptic levels and clinical outcome in schizophrenic patients treated with fluphenazine decanoate. Brown WA, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):143–7

Double–blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side–effects, dosage and serum levels during a six months' treatment for relapse prevention. Kissling W, et al. **Pharmacopsychiatry** 1985 May;18(3):240–5

Serum and cerebrospinal fluid prolactin patterns during neuroleptic treatment in schizophrenic patients. Rimón R, et al. **Pharmacopsychiatry** 1985 May;18(3):252–4

Effects of thioridazine and fluphenazine on the pituitary, thyroid and adrenal functions in patients with paranoid schizophrenia. Horodnicki JM, et al. **Psychiatr Pol** 1984 May–Jun;18(3):205–11

[Social integration of long–term paraphrenic patients with low–dose depot neuroleptic medication] Lesch OM, et al. **Psychiatr Prax** 1985 Mar; 12(2):63–8 (Eng. Abstr.) **(Ger)**

FLURAZEPAM

GABA and benzodiazepine–induced modification of [14C]L–glutamic acid release from rat spinal cord slices. Vellucci SV, et al. **Brain Res** 1985 Mar 25;330(2):201–7

Benzodiazepines inhibit human platelet activation: comparison of the mechanism of antiplatelet actions of flurazepam and diazepam. Romstedt K, et al. **Thromb Res** 1985 May 15;38(4):361–74

FOOD DEPRIVATION

Effect of feed and water deprivation or force–feeding on plasma prolactin concentration in turkey hens. Zadworny D, et al. **Biol Reprod** 1985 Mar;32(2):241–7

Ontogenetic alterations in the effects of food and/or maternal deprivation on 5–HT, 5–HIAA and 5–HIAA/5–HT ratios. Spear LP, et al. **Brain Res** 1985 Feb;350(1–2):143–57

FSH

Possible site of negative and positive feedback action of oestrogen on gonadotrophin secretion in normal women. Nagahara Y, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):440–4

Long–term, pulsatile, low dose, subcutaneous luteinizing hormone–releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar–Apr;17(2):143–9

Changes in the isoelectric focusing profile of pituitary follicle–stimulating hormone in the developing male rat. Chappel SC, et al. **Biol Reprod** 1985 Apr;32(3):567–73

Dose–dependent inhibition of the preovulatory surges of gonadotropins and prolactin by the antiestrogen CI–628: possible sites of action. De Paolo LV. **Biol Reprod** 1985 May;32(4):745–52

Effect of gonadotropin–releasing hormone antagonists on serum follicle–stimulating hormone and luteinizing hormone under conditions of singular follicle–stimulating hormone secretion. Schwartz NB, et al. **Biol Reprod** 1985 Mar;32(2):391–8

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893–8

Follicle–stimulating hormone induction of Leydig cell maturation. Kerr JB, et al. **Endocrinology** 1985 Jun;116(6):2592–604

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953–9

Release of luteinizing hormone and follicle–stimulating hormone from pituitaries of lactating rats by gonadotropin–releasing hormone and high potassium concentration. Smith MS. **Endocrinology** 1985 May; 116(5):1826–34

Cytochemical and cytophysiological studies of gonadotropin–releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396–404

FSH and LH response to testosterone and gonadotropin–releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter; 10(4):183–7

Effects of short–term exposure to catecholestrogens on serum concentrations of gonadotrophins and metabolism of catecholestrogens in ovariectomized rats. Ball P, et al. **Horm Metab Res** 1985 Apr; 17(4):184–8

Effect of castration and steroid treatment on the release of gonadotropins by the rat pituitary–hypothalamus complex in vitro. Gill MK, et al. **Horm Metab Res** 1985 Mar;17(3):141–6

Hormonal responses to short term fasting in postmenopausal women. Beitins IZ, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1120–6

Heterogeneity of rat FSH by chromatofocusing: studies on serum FSH, hormone released in vitro and metabolic clearance rates of its various forms. Blum WF, et al. **J Endocrinol** 1985 Apr;105(1):29–37

Routine measurement of thyroid hormones and FSH in infertility not worthwhile [letter] Conway DI, et al. **Lancet** 1985 Apr 27; 1(8435):977–8

Differential suppression of follicle–stimulating hormone and luteinizing hormone secretion in vivo by a gonadotropin–releasing hormone antagonist. Grady RR, et al. **Neuroendocrinology** 1985 Mar; 40(3):246–52

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409–11 (Eng. Abstr.) **(Fre)**

GABA

Respiratory depression produced by injection of GABA into the fourth ventricle of the rabbit. Xiang JZ, et al. **Acta Acad Med Wuhan** 1985; 5(1):10–4

Inhibition of anaphylactic histamine release in vitro by GABA. Luzzi S, et al. **Agents Actions** 1985 Apr;16(3–4):160–2

The modulation of acetylcholine release by noradrenaline, GABA and related compounds. Beani L, et al. **Ann Ist Super Sanita** 1984; 20(1):17–9

Selectivity of [3H] GABA uptake and release in cells cultured from the rat cerebellum. Levi G, et al. **Ann Ist Super Sanita** 1984;20(1):39–45

Drugs acting as modulators of neurochemical mechanisms of gabaergic synaptic transmission. Rayevsky KS, et al. **Ann Ist Super Sanita** 1984; 20(1):47–52

GABA effect on conditioned reflex responses in teleost. Ivanuš J, et al. **Ann NY Acad Sci** 1985;444:543–6

Inhibitory effect of GABA on sympathetic neurotransmission in rabbit ear artery. Manzini S, et al. **Arch Int Pharmacodyn Ther** 1985 Jan; 273(1):100–9

Response of the cockroach brain gamma–aminobutyric acid system to isonicotinic acid hydrazide and mercaptopropionic acid. Pandey A, et al. **Biochem Int** 1985 Feb;10(2):213–20

In vivo effects of aminooxyacetic acid and valproic acid on nerve terminal (synaptosomal) GABA levels in discrete brain areas of the rat. Correlation to pharmacological activities. Löscher W, et al. **Biochem Pharmacol** 1985 May 15;34(10):1747–56

gamma–Aminobutyric acid–mediated inhibition at cholinergic synapses formed by cultured retinal neurons. Agardh E, et al. **Brain Res** 1985 Mar 25;330(2):323–8

Subchronic administration of GABAergic agonists elevates [3H]GABA binding and produces tolerance in striatal dopamine catabolism. Beart PM, et al. **Brain Res** 1985 May 27;335(1):169–73

Effects of inhibitors of Na+,K+–ATPase on the membrane potentials and neurotransmitter efflux in rat brain slices. Brosemer RW. **Brain Res** 1985 May 13;334(1):125–37

Effects of glycine and GABA on the ganglion cels of the retina of the skate Raja erinacea. Cohen JL. **Brain Res** 1985 Apr 15; 332(1):169–73

Chemical activation of the mesencephalic locomotor region. Garcia-Rill

E, et al. **Brain Res** 1985 Mar 18;330(1):43-54

Immunohistochemistry of gamma-aminobutyric acid in the cat nucleus tractus solitarius. Maley B, et al. **Brain Res** 1985 Mar 25; 330(2):364-8

Effect of GABA and its antagonists, bicuculline and picrotoxin, on nerve cell discharges of the photosensory pineal organ of the frog, Rana esculenta. Meissl H, et al. **Brain Res** 1985 Apr 15;332(1):39-46

Specific [3H]gamma-aminobutyric acid binding to vestibular membranes of the chick inner ear. Meza G, et al. **Brain Res** 1985 Jun 24; 337(1):179-83

Estradiol benzoate decreases nigral GABAergic activity in male rats. Nicoletti F, et al. **Brain Res** 1985 Apr 15;332(1):179-83

Inhibitory influence of GABA on central serotonergic transmission. Involvement of the habenulo-raphé pathways in the GABAergic inhibition of ascending cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):81-90

Inhibitory influence of GABA on central serotonergic transmission. Raphé nuclei as the neuroanatomical site of the GABAergic inhibition of cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):91-103

The development of the dorsal root potential and the responsiveness of primary afferent fibers to gamma-aminobutyric acid in the spinal cord of rat fetuses. Seno N, et al. **Brain Res** 1985 Jan;349(1-2):11-6

Identified axo-axonic cells are immunoreactive for GABA in the hippocampus and visual cortex of the cat. Somogyi P, et al. **Brain Res** 1985 Apr 15;332(1):143-9

Synthesis of acetylcholine and gamma-aminobutyric acid by dissociated cerebral cortical cells in vitro. Thomas WE. **Brain Res** 1985 Apr 15; 332(1):79-89

GABA and benzodiazepine-induced modification of [14C]L-glutamic acid release from rat spinal cord slices. Vellucci SV, et al. **Brain Res** 1985 Mar 25;330(2):201-7

Neurochemical studies of the nucleus of the solitary tract, dorsal motor nucleus of the vagus and the hypoglossal nucleus in rat: topographical distribution of glutamate uptake, GABA uptake and glutamic acid decarboxylase activity. Simon JR, et al. **Brain Res Bull** 1985 Jan; 14(1):49-53

Interaction of penicillin and pentobarbital with inhibitory synaptic mechanisms in neocortex. Weiss DS, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):301-17

Inhibition of central angiotensin II induced drinking by GABA in the rat. Hutchinson JS, et al. **Clin Exp Hypertens** [A] 1984; 6(10-11):1777-80

Gamma aminobutyric acid (GABA) and hepatic bile flow in the adult rat. Minuk GY, et al. **Clin Invest Med** 1984;7(4):193-7

Comparative actions of GABA and acetylcholine on the Xenopus laevis lateral line. Bobbin RP, et al. **Comp Biochem Physiol** [C] 1985; 80(2):313-8

gamma-Amino butyric-N-acid sensitivity of mouse and human oocytes. Dolci S, et al. **Dev Biol** 1985 May;109(1):242-6

Study of ocular tissue changes, brain GABA and polyamine levels in rats exposed to carbon disulfide. Sefić M, et al. **G Ital Med Lav** 1984 May-Jul;6(3-4):127-9

GABA-ergic system in brain regions of glutamate-lesioned rats. Di Giorgio RM, et al. **Ital J Biochem** 1985 Jan-Feb;34(1):19-28

GABA neurons in the superficial layers of the rat dorsal cochlear nucleus: light and electron microscopic immunocytochemistry. Mugnaini E. **J Comp Neurol** 1985 May 1;235(1):61-81

Orally active and potent inhibitors of gamma-aminobutyric acid uptake. Ali FE, et al. **J Med Chem** 1985 May;28(5):653-60

gamma-Aminobutyric acid: temperature dependence in benzodiazepine receptor binding. Chweh AY, et al. **J Neurochem** 1985 Jul; 45(1):240-3

Modulation of the acetylcholine system in the superior cervical ganglion of rat: effects of GABA and hypoglossal nerve implantation after in vivo GABA treatment. Kása P, et al. **J Neurochem** 1985 May; 44(5):1363-72

A description of the GABAergic neurons and axon terminals in the motor nuclei of the cat thalamus. Kultas-Ilinsky K, et al. **J Neurosci** 1985 May;5(5):1346-69

A specific and sensitive determination of gamma aminobutyric acid in CSF and brain tissue by gas chromatography-mass spectrometry. Schaaf JM, et al. **J Neurosci Methods** 1985 May;13(3-4):257-65

GABAergic inhibition of hypertonic saline-induced vasopressin-dependent hypertension. Brennan TJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):663-71

Evidence for gamma-aminobutyric acid mediation of the sympathetic nerve inhibitory response to vagal afferent stimulation. Humphrey SJ, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):288-97

Possible inhibitory role of endogenous gamma-aminobutyric acid in the nonnicotinic functions of the dog cardiac sympathetic ganglia. Kushiku K, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):810-5

gamma-Aminobutyric-acid- and pentobarbitone-gated chloride currents in internally perfused frog sensory neurones. Akaike N, et al. **J Physiol (Lond)** 1985 Mar;360:367-86

Comparison of the action of baclofen with gamma-aminobutyric acid on rat hippocampal pyramidal cells in vitro. Newberry NR, et al. **J Physiol (Lond)** 1985 Mar;360:161-85

Effects of calcium hopantenate on neurotransmitter receptors in the rat brain. Ogawa N, et al. **Jpn J Pharmacol** 1985 Jan;37(1):45-50

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

The use of 3H-gamma-aminobutyric acid for transport studies with isolated nerve-terminals from rat brain. Halvarsson GB, et al. **Life Sci** 1985 Jul 22;37(3):209-16

Uptake of gamma-aminobutyric acid by human blood platelets: comparison with CNS uptake. Hambley JW, et al. **Life Sci** 1985 May 27;36(21):2053-62

Comparison of the pharmacological and biochemical profiles of valproic acid (VPA) and its cerebral metabolite (2-en-VPA) after oral administration in mice. Keane PE, et al. **Methods Find Exp Clin Pharmacol** 1985 Feb;7(2):83-6

Comparison of release of endogenous dopamine and gamma-aminobutyric acid from rat caudate synaptosomes. Caudill WL, et al. **Neurochem Res** 1985 Mar;10(3):319-31

Cimetidine-induced prolactin release: possible involvement of the GABA-ergic system. Sibilia V, et al. **Neuroendocrinology** 1985 Mar; 40(3):189-92

Chronic valproic acid therapy and synaptic markers of amino acid neurotransmission. Slevin JT, et al. **Neurology** 1985 May; 35(5):728-31

A GABAergic component in homosynaptic depression in the spinal monosynaptic pathway. A requirement for action of benzodiazepines. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):309-16

Inhibitory effect of cholesteryl gamma-aminobutyrate on evoked activity in rat hippocampal slices. Hesse GW, et al. **Neuropharmacology** 1985 Feb;24(2):139-46

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar; 24(3):217-22

The modulation of cortical acetylcholine release by GABA, GABA-like drugs and benzodiazepines in freely moving guinea-pigs. Tanganelli S, et al. **Neuropharmacology** 1985 Apr;24(4):291-9

gamma-Aminobutyric acid modulation of benzodiazepine receptor binding in vitro does not predict the pharmacologic activity of all benzodiazepine receptor ligands. Chweh AY, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):173-7

gamma-Aminobutyric acid enables synaptogenesis in the intact superior cervical ganglion of the adult rat. Dames W, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):159-64

gamma-Aminobutyric acid-induced depression of calcium currents of chick sensory neurons. Deisz RA, et al. **Neurosci Lett** 1985 May 14; 56(2):205-10

gamma-Aminobutyric acid decreases levels of messenger ribonucleic acid encoding prolactin in the rat pituitary. Loeffler JP, et al. **Neurosci Lett** 1985 Jan 7;53(1):121-5

gamma-Aminobutyric acid partly mediates the pentobarbitone depression of synaptic excitation in the guinea-pig olfactory cortex in vitro. Steel L, et al. **Neurosci Lett** 1985 May 1;56(1):33-8

Autoreceptors regulate gamma-[3H]aminobutyric acid release from the guinea pig small intestine. Taniyama K, et al. **Neurosci Lett** 1985 Apr 9;55(2):245-8

Distribution, ontogeny and projections of cholecystokinin-8, vasoactive intestinal polypeptide and gamma-aminobutyrate-containing neuron systems in the rat spinal cord: an immunohistochemical analysis. Fuji K, et al. **Neuroscience** 1985 Mar;14(3):881-94

Effects of octopamine on GABA-ergic transmission in rats. Jagiello-Wójtowicz E, et al. **Pol J Pharmacol Pharm** 1984 Nov-Dec; 36(6):595-601

Influence of GABA mimetics and lithium on biochemical manifestations of striatal dopamine target cell hypersensitivity. Scatton B, et al. **Psychopharmacology [Suppl]** 1985;2:39-45

Actions of GABA and ethylenediamine on CA1 pyramidal neurones of the rat hippocampus. Blaxter TJ, et al. **Q J Exp Physiol** 1985 Jan; 70(1):75-93

Somatostatin and GABA correlate with cervical autonomic nerve activity. Tonoue T, et al. **Regul Pept** 1985 Apr;10(4):299-307

[Pre-synaptic inhibition and pentobarbital] Ohmura Y. **Masui** 1985 Jan; 34(1):2-8 (36 ref.) **(Jpn)**

[Drug activation of GABAergic transmission in the central nervous system: benzodiazepines and GABAergic agonists] Moura D, et al. **Acta Med Port** 1985 Feb;6(2):57-64 (46 ref.) (Eng. Abstr.) **(Por)**

[Action of neurotropic substances on gamma-aminobutyric acid release from brain synaptosomes during K+ depolarization] Maisov NI, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):451-3 (Eng. Abstr.) **(Rus)**

[Participation of gamma-aminobutyric acid in regulating corticotropin secretion in rats] Mishunina TM, et al. **Fiziol Zh** 1985 May-Jun; 31(3):321-6 (Eng. Abstr.) **(Rus)**

[Effects of microinjections of GABA into structures of the medulla oblongata on cardio- and hemodynamics indices] Shapoval LN, et al. **Fiziol Zh** 1985 Mar-Apr;31(2):219-23 **(Rus)**

[Effect of gamma-aminobutyric acid, taurine and catecholamines on the synaptic processes in Lorenzini's ampules in Black Sea skates] Akoev GN, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):466-71 (Eng. Abstr.) **(Rus)**

[Effect of hypothermia on reuptake of neuromediators by synaptosomes] Babiichuk GA, et al. **Ukr Biokhim Zh** 1985 Mar-Apr;57(2):87-9 (Eng. Abstr.) **(Rus)**

GLUCURONIDASE

Assay of beta-glucuronidase in bile following ion-pair extraction of pigments and bile acids. Kurtin WE, et al. **Anal Biochem** 1985 Jun; 147(2):511-6

beta-Glucuronidase activities of intestinal bacteria determined both in vitro and in vivo in gnotobiotic rats. Gadelle D, et al. **Appl Environ Microbiol** 1985 Mar;49(3):682-5

Evaluation and modification of spectrophotometric procedures for analysis of lactate dehydrogenase, beta-glucuronidase and arylsulphatase in human gingival crevicular fluid collected with filter-paper strips. Lamster IB, et al. **Arch Oral Biol** 1985; 30(3):235-42

Glucuronidase activity in Escherichia coli [letter] Nastasi A, et al. **Boll Ist Sieroter Milan** 1982;61(5):441

Human hepatic beta-glucuronidase: an enzyme kinetic study. Ho YC, et al. **Enzyme** 1985;33(1):9-17

Oligosaccharides generated by an endoglucuronidase are intermediates in the intracellular degradation of heparan sulfate proteoglycans. Kjellén L, et al. **J Biol Chem** 1985 Jul 15;260(14):8416-22

Effects of ammonia on processing and secretion of precursor and mature lysosomal enzyme from macrophages of normal and pale ear mice: evidence for two distinct pathways. Brown JA, et al. **J Cell Biol** 1985 Jun;100(6):1894-904

Lactate dehydrogenase, beta-glucuronidase and arylsulfatase activity in gingival crevicular fluid associated with experimental gingivitis in man. Lamster IB, et al. **J Periodontol** 1985 Mar;56(3):139-47

Nucleotide sequence of a regulatory region of the uidA gene in Escherichia coli K12. Blanco C, et al. **MGG** 1985;199(1):101-5

Mutagenicity of beta-glucuronidase in the Ames test. Cerná M. **Mutat Res** 1985 Jul;143(3):169-72

Enzyme histochemistry of the response by naive and sensitised macrophages to phagocytosis of collagen and latex particles. Pugh DI, et al. **Z Mikrosk Anat Forsch** 1985;99(1):14-24

GONADOTROPINS, PITUITARY

Hypothalamic gonadotrophin-releasing hormone and pituitary and plasma FSH and prolactin during photostimulation and photorefractoriness in intact and thyroidectomized starlings (Sturnus vulgaris). Dawson A, et al. **J Endocrinol** 1985 Apr;105(1):71-7

[Effect of veralipride on LH, FSH, and PRL levels and on the climacteric syndrome] De Cecco L, et al. **Rev Fr Gynecol Obstet** 1985 Feb 28; 80(3):152-5 (Eng. Abstr.) **(Fre)**

[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**

GUANETHIDINE

Guanethidine blocks the 2-deoxy-D-glucose-induced hypothalamic noradrenergic drive to hyperglycemia. Storlien LH, et al. **Brain Res** 1985 May 27;335(1):144-7

HABITUATION (PSYCHOPHYSIOLOGY)

Habituation to repeated stress is stressor specific. Kant GJ, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):631-4

HALOPERIDOL

Rapid formation of reduced haloperidol in guinea pigs following haloperidol administration. Korpi ER, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Feb;56(2):94-8

The interpretation of plasma haloperidol concentrations. Kirch DG, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):838-40

Plasma haloperidol levels: clinical response and fancy mathematics [letter] Van Putten T, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):835-8

Ontogeny of striatal unit activity and effects of single or repeated haloperidol administration in rats. Napier TC, et al. **Brain Res** 1985 Apr 29;333(1):35-44

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Effect of duration of haloperidol treatment on DA receptor supersensitization in aging C57BL/6J mice. Randall PK, et al. **Brain Res** 1985 Apr 29;333(1):85-95

Chronic haloperidol does not alter agonist affinity for dopamine receptors in vitro. Meller E, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):389-94

The supersensitivity of dopaminergic neurons to apomorphine in rats following chronic haloperidol. Vogelsang GD, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):267-9

Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Hong JS, et al. **Fed Proc** 1985 Jun;44(9):2535-9

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

Effect of chronic haloperidol and quinacrine coadministration on striatal HVA levels and stereotypic behaviors in response to apomorphine in the rat. Deutsch SI, et al. **Neurochem Res** 1985 Apr;10(4):491-8

Influence of acute, subchronic and chronic treatment with neuroleptic (haloperidol) on enkephalins and their precursors in the striatum of rat brain. Blanc D, et al. **Neuropeptides** 1985 Feb;5(4-6):567-70

Beta-endorphin processing in pituitary and brain is sensitive to haloperidol stimulation. Ham J, et al. **Neuropeptides** 1985 Feb;5(4-6):497-500

Alterations in dopamine metabolism after chronic administration of haloperidol. Possible role of increased autoreceptor sensitivity. Saller CF, et al. **Neuropharmacology** 1985 Feb;24(2):123-9

Effect of haloperidol and sulpiride on dopamine metabolism in nucleus accumbens and olfactory tubercle: a study by in vivo voltammetry. Louilot A, et al. **Neuroscience** 1985 Mar;14(3):775-82

Haloperidol and nonreinforcement produce different patterns of response slowing in a food reinforced runway task. Wirtshafter D, et al. **Pharmacol Biochem Behav** 1985 May;22(5):661-3

Double-blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. Kissling W, et al. **Pharmacopsychiatry** 1985 May;18(3):240-5

Lateral ventricular enlargement and clinical response in schizophrenia. Smith RC, et al. **Psychiatry Res** 1985 Mar;14(3):241-53

Effect of benztropine on the diurnal prolactin responses to haloperidol. Nathan RS, et al. **Psychoneuroendocrinology** 1985;10(1):71-6

Effects of apomorphine and haloperidol on 'spontaneous' stereotyped licking behaviour in the Cebus monkey. Korsgaard S, et al. **Psychopharmacology (Berlin)** 1985;85(2):240-3

Chronic haloperidol during development attenuates dopamine autoreceptor function in striatal and mesolimbic brain regions of young and older adult rats. Scalzo FM, et al. **Psychopharmacology (Berlin)** 1985;85(3):271-6

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

Behavioral effects of long-term neuroleptic treatment in Cebus monkeys. Casey DE. **Psychopharmacology [Suppl]** 1985;2:211-6

Differential alteration of striatal D-1 and D-2 receptors induced by the long-term administration of haloperidol, sulpiride or clozapine to rats. Jenner P, et al. **Psychopharmacology [Suppl]** 1985;2:174-81

[Effects of haloperidol, chlorpromazine, metoclopramide and ascorbic acid on adrenergic salivation and lacrimation in mice at an ambient temperature of 30 degrees C] Li BH, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar;6(1):24-6 (Eng. Abstr.) **(Chi)**

[Bilateral dislocation of mandibular joints induced by haloperidol therapy--a case report] Liu ZZ. **Ssu Chuan I Hsueh Yuan Hsueh Pao** 1985 Mar;16(1):82-3 (Eng. Abstr.) **(Chi)**

[Continuous suppression of methamphetamine-induced supersensitivity by chronic haloperidol administration] Kashihara K, et al. **Seishin Shinkeigaku Zasshi** 1984;86(11):928-32 **(Jpn)**

[Role of serotonin and dopamine receptors in the mechanism of action of haloperidol and pirenperone] Maimets MO, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):15-8 (Eng. Abstr.) **(Rus)**

[Haloperidol decanoate in replacing combinations of antipsychotic agents in the treatment of chronic schizophrenics] Youssef HA. **Acta Psiquiatr Psicol Am Lat** 1984 Dec;30(4):297-304 **(Spa)**

[Malignant syndrome caused by neuroleptics. Rapid response to biperiden in a case of brief development (letter)] Castilla Cortázar A, et al. **Med Clin (Barc)** 1985 Apr 13;84(14):588 **(Spa)**

[Influence of nutritional status on intravenous pharmacokinetics of haloperidol in psychotic patients] Donoso A, et al. **Rev Med Chil** 1984 Aug;112(8):777-83 (Eng. Abstr.) **(Spa)**

HISTAMINE

Alteration of histamine metabolism in the rat brain under influence of various antidepressive treatments. Zawilska J, et al. **Agents Actions** 1985 Apr;16(3-4):105-8

Acetylcholine and histamine interact supra-additively on bronchomotor tone in guinea-pigs in vivo: a possible consequence of the relationship between airways resistance and calibre. Stewart AG, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):33-46

Effect of secretagogues on pancreatic exocrine secretion in the monkey and the dog. Iwatsuki K, et al. **Clin Exp Pharmacol Physiol** 1985 Jan–Feb;12(1):67–72

Involvement of H1– and H2–receptors in triple response to histamine in human volunteers. Patwardhan MD, et al. **Indian J Physiol Pharmacol** 1984 Oct–Dec;28(4):335–7

Vasoactive amines modulate actin cables (stress fibers) and surface area in cultured bovine endothelium. Welles SL, et al. **J Cell Physiol** 1985 Jun;123(3):337–42

Effect of Ni2+ on the multiphasic positive inotropic responses to histamine mediated by H1–receptors in left atria of guinea pigs. Hattori Y, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):188–94

Effect of histamine infusion on circulating methionine–enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289–92

Possible involvement of central adrenergic and histaminergic systems in clonidine–induced inhibition of pinna reflex. Singh PP, et al. **Pharmacol Res Commun** 1985 Mar;17(3):261–9

Chemical mediators and the human heart. Marone G, et al. **Prog Biochem Pharmacol** 1985;20:38–54 (52 ref.)

[The effect of acetylcholine and histamine on blood flow through the abdominal organs] Antal J, et al. **Bratisl Lek Listy** 1985 Mar; 83(3):218–28 (Eng. Abstr.) **(Slo)**

HUNGER

The anorectic effect of satietin is unrelated to carbohydrate metabolism. Gyarmati S, et al. **Physiol Behav** 1985 Feb;34(2):167–70

HYDANTOINS

Synthesis of side chain–protected amino acid phenylthiohydantoins and their use in quantitative solid–phase Edman degradation. Steiman DM, et al. **Anal Biochem** 1985 Feb 15;145(1):91–5

Genetic polymorphism of mephenytoin p(4')–hydroxylation: difference between Orientals and Caucasians. Jurima M, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):483–7

Mephenytoin metabolism in vitro by human liver. Jurima M, et al. **Drug Metab Dispos** 1985 Mar–Apr;13(2):151–5

Isocratic separation of PTH–amino acids at picomole level by reverse–phase HPLC in the presence of sodium dodecylsulfate. Tsunasawa S, et al. **J Biochem (Tokyo)** 1985 Feb;97(2):701–4

Effect of structural modification of the hydantoin ring on anticonvulsant activity. Cortes S, et al. **J Med Chem** 1985 May;28(5):601–6

HYDRAZINES

Blot analyses of glycoconjugates: enzyme–hydrazide—a novel reagent for the detection of aldehydes. Gershoni JM, et al. **Anal Biochem** 1985 Apr; 146(1):59–63

Separation of dansyl hydrazine–derivatized oligosaccharides by liquid chromatography. Hull SR, et al. **Anal Biochem** 1985 Apr; 146(1):143–9

Enhancement of the horseradish peroxidase–catalyzed chemiluminescent oxidation of cyclic diacyl hydrazides by 6–hydroxybenzothiazoles. Thorpe GH, et al. **Anal Biochem** 1985 Feb 15;145(1):96–100

Phosphorus–nitrogen compounds. 26. Phosphaminimides. 2. 2,2'–Phosphinylidenebis(1,1,1–trimethylhydrazinium) iodide inner salts as agents affecting ganglionic transmission. Cates LA, et al. **J Med Chem** 1985 May;28(5):595–7

Effects of rifampicin and phenobarbital on the fate of isoniazid and hydrazine in vivo in rats. Noda A, et al. **Toxicol Lett** 1985 Jun; 25(3):313–7

HYDROXYBUTYRATES

Identification and quantitation of 1,4–butanediol in mammalian tissues: an alternative biosynthetic pathway for gamma–hydroxybutyric acid. Barker SA, et al. **Biochem Pharmacol** 1985 May 15;34(10):1849–52

Natural occurrence of trans–gamma hydroxycrotonic acid in rat brain. Vayer P, et al. **Biochem Pharmacol** 1985 Jul 1;34(13):2401–4

Effects of endogenous sugar acids on the ventromedial hypothalamic nucleus of the rat. Puthuraya KP, et al. **Brain Res** 1985 Apr 15; 332(1):165–8

Plasma levels of glucose, alanine, lactate, and beta–hydroxybutyrate in the unfed spiny dogfish shark (Squalus acanthias) after surgery and following mammalian insulin infusion. deRoos R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):28–43

Effects of propionate and methylmalonate on conversions of acetate, butyrate, and D(–)–3–hydroxybutyrate to fatty acids and carbon dioxide by mammary tissue slices of goats. Emmanuel B, et al. **J Dairy Sci** 1985 Mar;68(3):751–4

The effects of mild congenital methylmercury intoxication on the metabolism of 3–hydroxybutyrate and glucose in the brains of suckling rats. Menon NK, et al. **Neurotoxicology (Little Rock Ar)** 1985 Spring; 6(1):55–61

Ketone kinetics and D–(–)–3–hydroxybutyrate–induced inhibition of feeding in rats. Langhans W, et al. **Physiol Behav** 1985 Apr; 34(4):579–82

Effects of hyperketonemia on mouse embryonic and fetal glucose metabolism in vitro. Horton WE Jr, et al. **Teratology** 1985 Apr; 31(2):227–33

HYDROXYDOPAMINES

Effects of intraventricular injections of 6–hydroxydopamine on amine metabolites in rat brain and urine. Edwards DJ, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1255–63

6–OHDA lesions of the ventral tegmental area block morphine–induced but not amphetamine–induced facilitation of self–stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233–41

Neonatal 6–hydroxydopamine lesion of spinal norepinephrine terminals fails to affect the ontogeny of swimming behavior. Ryan C, et al. **Brain Res** 1985 Jan;349(1–2):258–62

Effect of intracerebroventricular 6–hydroxydopamine (6–HODA) on the angiotensinogen concentration of the brain. Basso N, et al. **Clin Exp Hypertens [A]** 1984;6(10–11):1773–6

Meningeal cells are involved in foliation, lamination, and neurogenesis of the cerebellum: evidence from 6–hydroxydopamine–induced destruction of meningeal cells. Pehlemann FW, et al. **Dev Biol** 1985 Jul;110(1):136–46

Selective destruction of meningeal cells by 6–hydroxydopamine: a tool to study meningeal–neuroepithelial interaction in brain development. Sievers J, et al. **Dev Biol** 1985 Jul;110(1):127–35

Effects of 6–hydroxydopamine–induced catecholamine depletion on shock–precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215–27

Effects of chemical sympathectomy with 6–hydroxydopamine on cardiac output and its distribution in the rat. Nichols AJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):263–8

Effects of intracerebroventricular 6–hydroxydopamine on catecholaminergic fibers in the rat hypothalamus. Hwang BH, et al. **Exp Neurol** 1985 May;88(2):336–48

Cardiovascular effects of intracisternal 6–hydroxydopamine and of subsequent lesions of the ventrolateral medulla coinciding with the A1 group of noradrenaline cells in the rabbit. Elliott JM, et al. **J Auton Nerv Syst** 1985 Feb–Mar;12(2–3):117–30

Rapid changes in synaptic vesicle cytochemistry after depolarization of cultured cholinergic sympathetic neurons. Johnson MI, et al. **J Cell Biol** 1985 Jul;101(1):217–26

Neonatal 6–hydroxydopamine destroys spinal cord noradrenergic axons from the locus coeruleus, but not those from lateral tegmental cell groups. McBride RL, et al. **J Comp Neurol** 1985 May 15; 235(3):375–83

Cardiac postjunctional supersensitivity to beta–agonists after chronic chemical sympathectomy with 6–hydroxydopamine. Chess–Williams RG, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):162–6

6–Hydroxydopamine pretreatment effects on alpha– and beta–adrenergic receptor adaptation to clorgyline. Cohen RM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):158–61

Effects of intravenously administered 6–hydroxydopamine on the content of monoamines in the median eminence and neurointermediate lobe of the rat. Sheward WJ, et al. **Neurosci Lett** 1985 Apr 9;55(2):141–4

Ibotenic acid lesions of the lateral hypothalamus: comparison with 6–hydroxydopamine–induced sensorimotor deficits. Dunnett SB, et al. **Neuroscience** 1985 Feb;14(2):509–18

Supersensitivity to the anticonvulsant and proconvulsant activity of clonidine following noradrenaline depletion induced by 6–hydroxydopamine. Dalton JC, et al. **Psychopharmacology (Berlin)** 1985;85(3):319–22

Differential effects of dopamine D–1 and D–2 agonists and antagonists in 6–hydroxydopamine–lesioned rats. Arnt J. **Psychopharmacology [Suppl]** 1985;2:60–1

HYDROXYINDOLEACETIC ACID

Effects of jejunoileal bypass on food intake, amino acid levels, and indoleamine metabolism in rats. Herlin PM, et al. **Am J Surg** 1985 Jun; 149(6):739–44

Simultaneous determination of homovanillic acid, 3,4–dihydroxyphenylacetic acid and 5–hydroxyindoleacetic acid in brain tissue, using a double–column procedure. Moroji T, et al. **Arzneimittelforsch** 1985;35(2):478–80

Ontogenetic alterations in the effects of food and/or maternal deprivation on 5–HT, 5–HIAA and 5–HIAA/5–HT ratios. Spear LP, et al. **Brain Res** 1985 Feb;350(1–2):143–57

The influence of testosterone in the brain of the male rat on levels of serotonin (5–HT) and hydroxyindole–acetic acid (5–HIAA). Martinez–Conde E, et al. **Comp Biochem Physiol [C]** 1985; 80(2):411–4

The effects of amiflamine on cerebrospinal fluid amine metabolites in the rhesus monkey. Garrick NA, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):1–9

Does brain 5-HIAA indicate serotonin release or monoamine oxidase activity? Wolf WA, et al. **Eur J Pharmacol** 1985 Mar 12, 109(3):381-7

[Normal values of dopamine, noradrenaline, adrenaline, and 5-hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb; 53(334):49-52 (Eng. Abstr.) **(Spa)**

HYDROXYTRYPTOPHAN

Antagonism by lisuride and 8-OH-DPAT of 5-HTP-induced prolongation of the performance of male rat sexual behavior. Ahlenius S, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):379-81

L-5-hydroxytryptophan in the treatment of anxiety disorders. Kahn RS, et al. **J Affective Disord** 1985 Mar-Apr;8(2):197-200

Pharmacology in vivo of the phenylindan derivative, Lu 19-005, a new potent inhibitor of dopamine, noradrenaline and 5-hydroxytryptamine uptake in rat brain. Arnt J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):101-7

HYDROXYZINE

[Atarax] Peutillot JF, et al. **Soins Psychiatr** 1985 Jan;(51):I-II **(Fre)**

HYPOCHONDRIASIS

Modification of disease phobia using a multifaceted exposure program. Tearnan BH, et al. **J Behav Ther Exp Psychiatry** 1985 Mar; 16(1):57-61

IMIPRAMINE

Combined pharmacological and behavioral treatment for agoraphobia. Telch MJ, et al. **Behav Res Ther** 1985;23(3):325-35

Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. Shapira B, et al. **Biol Psychiatry** 1985 May; 20(5):576-9

Regional distribution and elimination kinetics of imipramine in rat brain. Masada M, et al. **Chem Pharm Bull (Tokyo)** 1984 Nov; 32(11):4678-81

Repeated treatment with imipramine decreased the number of [3H]piflutixol binding sites in the rat striatum. Klimek V, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):131-2

Sex differences in long-term gonadectomized rats: monoamine levels and [3H]nitroimipramine binding in brain nuclei. Renner KJ, et al. **Exp Brain Res** 1985;58(1):198-201

Imipramine metabolism in recurrent depressive episodes. Tollefson G, et al. **J Affective Disord** 1985 Mar-Apr;8(2):183-6

Psychophysiological outcome of behavioral and pharmacological treatments of agoraphobia. Michelson L, et al. **J Consult Clin Psychol** 1985 Apr;53(2):229-36

High- and low-affinity binding components for [3H]imipramine in rat cerebral cortex. Conway PG, et al. **J Neurochem** 1985 Jul; 45(1):206-9

Possible artefacts in imipramine binding assays [letter] Reith ME. **J Neurochem** 1985 Aug;45(2):661-3

5-Methoxytryptoline, a competitive endocoid acting at [3H]imipramine recognition sites in human platelets. Segonzac A, et al. **J Neurochem** 1985 Jul;45(1):249-56

The effect of prolonged treatment with tricyclic antidepressants on the actions of 5-hydroxytryptamine in the hippocampal slice of the rat. Rowan MJ, et al. **Neuropharmacology** 1985 Feb;24(2):131-7

Imipramine in the treatment of panic disorder and its complications. Liebowitz MR. **Psychiatr Clin North Am** 1985 Mar;8(1):37-47

3H-Imipramine binding sites in platelets of hospitalized psychiatric patients. Gentsch C, et al. **Psychiatry Res** 1985 Mar;14(3):177-87

Clomipramine and imipramine in obsessive-compulsive disorder. Volavka J, et al. **Psychiatry Res** 1985 Jan;14(1):85-93

Occurrence of myeloid bodies in rats following two-year administration of imipramine hydrochloride. Spaet RH, et al. **Toxicol Pathol** 1983; 11(1):3-11

[Antenatal effect of imipramine on the ontogeny of the imipramine receptors in the cerebral cortex of rats] Pirogova MV, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):35-8 (Eng. Abstr.) **(Rus)**

ISOCARBOXAZID

Monoamine oxidase inhibitors in the treatment of atypical depression. Zisook S, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):131-7

LACTATES

Plasma levels of glucose, alanine, lactate, and beta-hydroxybutyrate in the unfed spiny dogfish shark (Squalus acanthias) after surgery and following mammalian insulin infusion. deRoos R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):28-43

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr; 6(2):78-81

Effect of 1,3-butanediol and short chain acids in sow gestation diets on maternal plasma metabolites and fetal energy storage. Spence CA, et al. **J Anim Sci** 1985 May;60(5):1280-7

Lactate transport through the blood-retinal and the blood-brain barrier in rats. Alm A, et al. **Ophthalmic Res** 1985;17(3):181-4

LEARNING

Interfering with taste aversion learning in rats: the role of associative interference. Cannon DS, et al. **Appetite** 1985 Mar;6(1):1-19

Central action of substance P: possible role in reward. Stäubli U, et al. **Behav Neural Biol** 1985 Jan;43(1):100-8

Pre-natal administration of diazepam improves radial maze learning in mice. Benton D, et al. **Comp Biochem Physiol [C]** 1985;80(2):273-5

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227-43

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer; 9(2):261-82

Learning and memory deficits after lesions of the nucleus basalis magnocellularis: reversal by physostigmine. Murray CL, et al. **Neuroscience** 1985 Apr;14(4):1025-32

The effect of chronic vs. acute injection of vasopressin on animal learning and memory. Hamburger-Bar R, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):23-5

LEVODOPA

Effect of L-DOPA on glucose oxidation and incorporation into glycogen in discrete brain regions of the rat. Barash V, et al. **Brain Res** 1985 Jun 3;335(2):347-9

Altered pharmacokinetics of L-dopa metabolism [letter] Melamed E, et al. **Neurology** 1985 Jun;35(6):939-41

LH

Possible site of negative and positive feedback action of oestrogen on gonadotrophin secretion in normal women. Nagahara Y, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):440-4

Effect of dopamine receptor stimulation on the inhibition of LH pulsatility by a met-enkephaline (FK 33-824). del Pozo E, et al. **Acta Neurochir (Wien)** 1985;75(1-4):88-90

Long-term, pulsatile, low dose, subcutaneous luteinizing hormone-releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar-Apr;17(2):143-9

Control of steroidogenesis in Leydig cells: roles of Ca2+ and lipoxygenase products in LH and LHRH agonist action. Cooke BA, et al. **Ann NY Acad** Sci 1984;438:269-82

Is cAMP the obligatory second messenger in the action of lutropin on Leydig cell steroidogenesis. Themmen AP, et al. **Biochem Biophys Res Commun** 1985 May 16;128(3):1164-72

Dose-dependent inhibition of the preovulatory surges of gonadotropins and prolactin by the antiestrogen CI-628: possible sites of action. De Paolo LV. **Biol Reprod** 1985 May;32(4):745-52

Changes in luteinizing hormone-releasing hormone content of discrete hypothalamic areas associated with spontaneous and induced preovulatory luteinizing hormone surges in the domestic hen. Johnson AL, et al. **Biol Reprod** 1985 May;32(4):813-9

Effect of gonadotropin-releasing hormone antagonists on serum follicle-stimulating hormone and luteinizing hormone under conditions of singular follicle-stimulating hormone secretion. Schwartz NB, et al. **Biol Reprod** 1985 Mar;32(2):391-8

Study of the luteinizing hormone-induced increase of ovarian blood flow during the estrous cycle in the rat. Varga B, et al. **Biol Reprod** 1985 Apr;32(3):480-8

Successful treatment of infertile women with oligomenorrhoea using a combination of an LHRH agonist and exogenous gonadotrophins. Fleming R, et al. **Br J Obstet Gynaecol** 1985 Apr;92(4):369-73

A correlative radioimmunoassay and immunohistochemical study of LHRH-induced LH depletion in the anterior pituitary of male and female neonatal rats in vitro. Watanabe YG, et al. **Cell Tissue Res** 1985; 240(1):95-100

Absence of effect of the peptide PHI-27 on LH release in vitro. Miyake A, et al. **Endocrinol Jpn** 1984 Dec;31(6):821-4

Increased gonadotropin-releasing hormone pulse frequency associated with estrogen-induced luteinizing hormone surges in ovariectomized ewes. Clarke IJ, et al. **Endocrinology** 1985 Jun;116(6):2376-83

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893-8

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953-9

Dynamic characteristics of luteinizing hormone release from perifused sheep anterior pituitary cells stimulated by combined pulsatile and continuous gonadotropin-releasing hormone. McIntosh RP, et al. **Endocrinology** 1985 Jul;117(1):169-79

Neurotransmitters involved in mediating the steroid-dependent suppression of pulsatile luteinizing hormone secretion in anestrous ewes: effects of receptor antagonists. Meyer SL, et al. **Endocrinology** 1985 May;116(5):2054-61

A rise in tonic luteinizing hormone secretion occurs during photoperiod-stimulated sexual maturation of the female ferret. Ryan KD, et al. **Endocrinology** 1985 May;116(5):2013-8

Tunicamycin and neuraminidase effects on luteinizing hormone (LH)-releasing hormone binding and LH release from rat pituitary cells in culture. Schvartz I, et al. **Endocrinology** 1985 Jun;116(6):2341-6

Release of luteinizing hormone and follicle-stimulating hormone from pituitaries of lactating rats by gonadotropin-releasing hormone and high potassium concentration. Smith MS. **Endocrinology** 1985 May;116(5):1826-34

Cytochemical and cytophysiological studies of gonadotropin-releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396-404

FSH and LH response to testosterone and gonadotropin-releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter;10(4):183-7

Seasonal variations in plasma luteinizing hormone and testosterone levels in the European badger Meles meles L. Audy MC, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):445-53

Seasonal variation in pituitary responsiveness to luteinizing hormone-releasing hormone of mallards and canvasbacks. Bluhm CK. **Gen Comp Endocrinol** 1985 Jun;58(3):491-7

Changes in hormone levels in relation to breeding behavior in male bullfrogs (Rana catesbeiana) at the individual and population levels. Mendonça MT, et al. **Gen Comp Endocrinol** 1985 May;58(2):270-9

Short-term changes in plasma levels of hormones during establishment and defense of a breeding territory in male song sparrows, Melospiza melodia. Wingfield JC. **Horm Behav** 1985 Jun;19(2):174-87

Effects of short-term exposure to catecholestrogens on serum concentrations of gonadotrophins and metabolism of catecholestrogens in ovariectomized rats. Ball P, et al. **Horm Metab Res** 1985 Apr;17(4):184-8

Effect of castration and steroid treatment on the release of gonadotropins by the rat pituitary-hypothalamus complex in vitro. Gill MK, et al. **Horm Metab Res** 1985 Mar;17(3):141-6

Prolonged suppression of plasma LH levels in male rats after a single injection of an LH-RH agonist in poly(DL-lactide-co-glycolide) microcapsules. Asch RH, et al. **J Androl** 1985 Mar-Apr;6(2):83-8

Hormonal responses to short term fasting in postmenopausal women. Beitins IZ, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1120-6

Radioimmunoassay of luteinizing hormone in the baboon (Papio hamadryas). Khan SA, et al. **J Med Primatol** 1985;14(3):143-57

GnRH pulse frequency determines LH pulse amplitude by altering the amount of releasable LH in the pituitary glands of ewes. Clarke IJ, et al. **J Reprod Fertil** 1985 Mar;73(2):425-31

Changes in pulsatile LH secretion and the positive and negative feedback actions of oestradiol after administration of a GnRH agonist in the ovariectomized ewe. Fitzgerald BP, et al. **J Reprod Fertil** 1985 Mar;73(2):433-40

Changes in pituitary and ovarian LHRH receptors after active immunization of female rats against LH or LHRH. Popkin RM, et al. **J Reprod Fertil** 1985 Mar;73(2):491-6

Increased gonadotrophin releasing hormone receptors on pituitary gonadotrophs: effect on subsequent LH secretion. Young LS, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):69-78

Diacylglycerols and protein kinase C. Potential amplifying mechanism for Ca2+-mediated gonadotropin-releasing hormone-stimulated luteinizing hormone release. Harris CE, et al. **Mol Pharmacol** 1985 May;27(5):532-6

Pineal melatonin mediates photoperiodic control of pulsatile luteinizing hormone secretion in the ewe. Bittman EL, et al. **Neuroendocrinology** 1985 May;40(5):409-18

Differential suppression of follicle-stimulating hormone and luteinizing hormone secretion in vivo by a gonadotropin-releasing hormone antagonist. Grady RR, et al. **Neuroendocrinology** 1985 Mar;40(3):246-52

Medial preoptic area involvement in norepinephrine-induced suppression of pulsatile luteinizing hormone release in ovariectomized rats. Leipheimer RE, et al. **Neuroendocrinology** 1985 Apr;40(4):345-51

Clinical value of biological activity of serum luteinizing hormone in patients with ovulatory failure. Kuramoto T. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 May;37(5):793-8

Leukotriene C4 as a mediator of luteinizing hormone release from rat anterior pituitary cells. Hulting AL, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3834-8

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[The effects of bromocriptine on anovulatory patients with high LH and euprolactinemia] Mori H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jan 20;61(1):48-55 (Eng. Abstr.) **(Jpn)**

[Biological and immunological characterization of human luteinizing hormone in plasma discharged by LH-RH infusion in normal adult women] Yano M. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 May;37(5):703-12 (Eng. Abstr.) **(Jpn)**

LH-FSH RELEASING HORMONE

Treatment of hypothalamic infertility with pulsatile GN-RH administration. Turla R, et al. **Acta Eur Fertil** 1984 Nov-Dec;15(6):445-8

Successful treatment of anovulatory sterility by use of pulsatile GN-RH application. Wiegand M, et al. **Acta Eur Fertil** 1984 Nov-Dec;15(6):467-8

Success and relapse rate after treatment of cryptorchidism with intranasal LHRH. Schwarz HP, et al. **Acta Paediatr Scand** 1985 Mar;74(2):274-80

Comparison between the steroidogenic responses after pulsatile and continuous administration of gonadotrophin releasing hormone to superfused rat follicles. Hedin L. **Acta Physiol Scand** 1985 Jun;124(2):269-76

Characteristics and bioefficacy of monoclonal antigonadotropin releasing hormone antibody. Gupta SK, et al. **Am J Reprod Immunol Microbiol** 1985 Mar;7(3):104-8

Long-term, pulsatile, low dose, subcutaneous luteinizing hormone-releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar-Apr;17(2):143-9

Control of steroidogenesis in Leydig cells: roles of Ca2+ and lipoxygenase products in LH and LHRH agonist action. Cooke BA, et al. **Ann NY Acad Sci** 1984;438:269-82

Studies on the identification of a LHRH-like peptide in the rat testis. Hedger MP, et al. **Ann NY Acad Sci** 1984;438:371-81

Molecular dynamics and minimum energy conformations of GnRH and analogs. A methodology for computer-aided drug design. Struthers RS, et al. **Ann NY Acad Sci** 1985;439:81-96

GnRH-like factors in the rat testis and human seminal plasma. Swerdloff RS, et al. **Ann NY Acad Sci** 1984;438:382-9

Luteinising hormone releasing hormone for incomplete descent of the testis. Klidjian AM, et al. **Arch Dis Child** 1985 Jun;60(6):568-71

Discrete hypothalamic distribution of luteinizing hormone-releasing hormone (LHRH) content and of LHRH-degrading activity in laying and nonlaying hens. Advis JP, et al. **Biol Reprod** 1985 May;32(4):820-7

Gonadotropin-releasing hormone stimulation of pituitary gonadotrope cells produces an increase in intracellular calcium. Clapper DL, et al. **Biol Reprod** 1985 Mar;32(2):269-78

Changes in luteinizing hormone-releasing hormone content of discrete hypothalamic areas associated with spontaneous and induced preovulatory luteinizing hormone surges in the domestic hen. Johnson AL, et al. **Biol Reprod** 1985 May;32(4):813-9

Effect of gonadotropin-releasing hormone antagonists on serum follicle-stimulating hormone and luteinizing hormone under conditions of singular follicle-stimulating hormone secretion. Schwartz NB, et al. **Biol Reprod** 1985 Mar;32(2):391-8

D-Ala6-des-Gly10-gonadotropin-releasing hormone ethylamide: absence of binding sites and lack of a direct effect in rabbit corpora lutea. Thorson JA, et al. **Biol Reprod** 1985 Mar;32(2):226-31

Biochemical transmethylation of lipids and neuropeptidergic stimulation of pituitary hormone secretion. Prasad C, et al. **Brain Res** 1985 May 13;334(1):41-6

Effects of prostaglandins and luteinizing hormone-releasing hormone on phosphatidic acid-phosphatidylinositol labeling in rat granulosa cells. Minegishi T, et al. **Can J Physiol Pharmacol** 1985 Apr;63(4):320-4

A correlative radioimmunoassay and immunohistochemical study of LHRH-induced LH depletion in the anterior pituitary of male and female neonatal rats in vitro. Watanabe YG, et al. **Cell Tissue Res** 1985;240(1):95-100

The effects of the GnRH agonist, [(imBzl)-D-His6, Pro9-NEt]-GnRH, on the response to stress in rats. Gibson MJ, et al. **Contraception** 1985 Jan;31(1):91-9

Distribution of luteinizing hormone-releasing hormone (LHRH) content and total LHRH-degrading activity (LHRH-DA) in the hypothalamus of the ewe. Advis JP, et al. **Endocrinology** 1985 Jun;116(6):2410-8

A role for extracellular copper in modulating prostaglandin E2 (PGE2) action: facilitation of PGE2 stimulation of the release of gonadotropin-releasing hormone (LHRH) from median eminence explants. Barnea A, et al. **Endocrinology** 1985 Jul;117(1):415-7

D-Trp-6-luteinizing hormone-releasing hormone inhibits hyperprolactinemia in female rats. Debeljuk L, et al. **Endocrinology** 1985 Jun;116(6):2227-31

Prostaglandin E2-induced luteinizing hormone-releasing hormone release involves mobilization of intracellular Ca+2. Ojeda SR, et al. **Endocrinology** 1985 May;116(5):1763-70

Tunicamycin and neuraminidase effects on luteinizing hormone

(LH)-releasing hormone binding and LH release from rat pituitary cells in culture. Schvartz I, et al. **Endocrinology** 1985 Jun;116(6):2341-6

Cytochemical and cytophysiological studies of gonadotropin-releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396-404

Exogenous progesterone for luteal support following gonadotropin-releasing hormone ovulation induction: case report. Berger NG, et al. **Fertil Steril** 1985 Jul;44(1):133-5

Does constant infusion of gonadotropin-releasing hormone agonist lead to greater suppression of gonadal function in man than its intermittent administration? Bhasin S, et al. **Fertil Steril** 1985 Jul;44(1):96-101

Immunoreactive luteinizing hormone-releasing hormone in the seminal plasma and human semen parameters. Izumi S, et al. **Fertil Steril** 1985 Apr;43(4):617-20

Effect on corpus luteum function of luteal phase administration of a potent gonadotropin-releasing hormone analog (nafarelin). Schriock ED, et al. **Fertil Steril** 1985 Jun;43(6):844-50

Seasonal variation in pituitary responsiveness to luteinizing hormone-releasing hormone of mallards and canvasbacks. Bluhm CK. **Gen Comp Endocrinol** 1985 Jun;58(3):491-7

Pimozide modulates the luteinizing hormone-releasing hormone effect on gonadotrophin release in the African catfish, Clarias lazera. de Leeuw R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):120-7

Structure-activity relationships of mammalian, chicken, and salmon gonadotropin releasing hormones in vivo in goldfish. Peter RE, et al. **Gen Comp Endocrinol** 1985 May;58(2):231-42

Seasonal effects of pimozide and des Gly10 [D-Ala6] LH-RH ethylamide on gonadotrophin secretion in goldfish. Sokolowska M, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):472-9

Seasonal changes in luteinizing hormone-releasing hormone concentrations in microdissected brain regions of male rough-skinned newts (Taricha granulosa). Zoeller RT, et al. **Gen Comp Endocrinol** 1985 May;58(2):222-30

Effect of gonadotropin releasing hormone on ventral prostate of rat. Raju VS, et al. **Horm Metab Res** 1985 May;17(5):241-3

Detection of prolactin and LH releasing activity in mid-term human fetal cerebrospinal fluid. Gilmore DP, et al. **Indian J Exp Biol** 1984 Nov;22(11):586-8

Immunological castration by a totally synthetic vaccine: modification of biological properties of LH-RH after conjugation to adjuvant-active muramyl peptide. Carelli C, et al. **Int J Immunopharmacol** 1985;7(2):215-24

Prolonged suppression of plasma LH levels in male rats after a single injection of an LH-RH agonist in poly(DL-lactide-co-glycolide) microcapsules. Asch RH, et al. **J Androl** 1985 Mar-Apr;6(2):83-8

The priming effect of LH-releasing hormone: effects of cold and involvement of new protein synthesis. Curtis A, et al. **J Endocrinol** 1985 May;105(2):163-8

Pituitary and gonadal response to exogenous LH-releasing hormone in the male domestic cat. Goodrowe KL, et al. **J Endocrinol** 1985 May;105(2):175-81

Immunocytochemistry of luteinizing hormone-releasing hormone during spontaneous and thyroxine-induced metamorphosis of bullfrogs. Whalen R, et al. **J Exp Zool** 1985 Apr;234(1):131-44

Improved antagonists of luteinizing hormone-releasing hormone modified in position 7. Hocart SJ, et al. **J Med Chem** 1985 Jul;28(7):967-70

Changes in pituitary and ovarian LHRH receptors after active immunization of female rats against LH or LHRH. Popkin RM, et al. **J Reprod Fertil** 1985 Mar;73(2):491-6

Induction of oestrus and ovulation by means of prostaglandin and gonadoliberin (GnRH) treatment in an old mare barren for two breeding seasons. Penzhorn BL, et al. **J S Afr Vet Assoc** 1985 Mar;56(1):53-4

Changes in plasma steroid levels after single administration of hCG or LHRH agonist analogue in dog and rat. Tremblay Y, et al. **J Steroid Biochem** 1985 Mar;22(3):315-20

Progesterone-induced LHRH release in vitro is an estrogen--as well as Ca++- and calmodulin-dependent secretory process. Drouva SV, et al. **Neuroendocrinology** 1985 Apr;40(4):325-31

Lipoxygenase products of arachidonic acid stimulate LHRH release from rat median eminence. Gerozissis K, et al. **Neuroendocrinology** 1985 Mar;40(3):272-6

Responsiveness of immature versus adult male rat hypothalami to dibutyryl cyclic AMP- and forskolin-induced LHRH release in vitro. Hartter DE, et al. **Neuroendocrinology** 1985 Jun;40(6):476-82

Glutamic acid decarboxylase-containing axons synapse on LHRH neurons in the rat medial preoptic area. Leranth C, et al. **Neuroendocrinology** 1985 Jun;40(6):536-9

Effects of progesterone on hypothalamic and plasma LHRH. Peduto JC, et al. **Neuroendocrinology** 1985 Mar;40(3):238-45

Apparent lack of involvement of cAMP as a mediator of LHRH stimulation of nuclear estrogen receptor activity in the rat anterior pituitary. Singh P, et al. **Neuroendocrinology** 1985 May;40(5):430-7

Shifts in gonadotropin storage in cultured gonadotropes following GnRH stimulation, in vitro. Childs GV. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):103-7

A new antiserum with conformational specificity for LHRH: usefulness for radioimmunoassay and immunocytochemistry. Ellinwood WE, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):45-52

D-Tryptophan-6 analog of luteinizing hormone-releasing hormone as a protective agent against testicular damage caused by cyclophosphamide in baboons. Lewis RW, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):2975-9

Possible negative ultra-short loop feedback of luteinizing hormone releasing hormone (LHRH) in the ovariectomized rat. Bedran de Castro JC, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):132-5

Induction of the self-priming effect of luteinizing hormone releasing hormone during the sexual maturation of the male rat. Nazian SJ. **Proc Soc Exp Biol Med** 1985 Jul;179(3):348-51

Luteinizing-hormone-releasing hormone modifies retention of passive and active avoidance responses in rats. Mora S, et al. **Psychopharmacology (Berlin)** 1985;85(3):315-8

[LHRH stimulates the secretion of an 87 K protein by cultured gonadotrophic cells] Hubert JF, et al. **C R Acad Sci [III]** 1985;300(16):613-6 (Eng. Abstr.) **(Fre)**

[Pulsatile treatment with LH-RH using a portable pump: a new modality for inducing ovulation and treating sterility] Thomas D, et al. **Rev Med Brux** 1985 May;6(5):325-33 (Eng. Abstr.) **(Fre)**

[Treatment of cryptorchism with LHRH nasal spray] Borkenstein M, et al. **Wien Klin Wochenschr** 1985 Apr 26;97(9):414-6 (Eng. Abstr.) **(Ger)**

[Effects of iontophoretically-applied LHRH, TRH, estrogen and clomiphene on thermo-sensitive neurons in the rat hypothalamus] Inagaki K, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Apr;37(4):611-8 (Eng. Abstr.) **(Jpn)**

[Biological and immunological characterization of human luteinizing hormone in plasma discharged by LH-RH infusion in normal adult women] Yano M. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 May;37(5):703-12 (Eng. Abstr.) **(Jpn)**

[Immunohistochemical research on the development of the LHRH system in the development of the rat] Ugriumov MV, et al. **Dokl Akad Nauk SSSR** 1985;280(6):1425-7 **(Rus)**

[Synthetic tripeptide miniluliberin and its biological activity] Babichev VN, et al. **Probl Endokrinol (Mosk)** 1985 Mar-Apr;31(2):47-9 (Eng. Abstr.) **(Rus)**

LIPOTROPIN

Determination of beta-endorphin and beta-lipotropin in human cerebrospinal fluid. Laatikainen TJ, et al. **Clin Chim Acta** 1985 Feb 15;145(3):325-9

[Immunoreactive beta-lipotropin and endorphins are secreted by the isolated alimentary complex of rats] Titov MI, et al. **Dokl Akad Nauk SSSR** 1985;281(2):497-9 **(Rus)**

LITHIUM

Renal function in 153 manic-depressive patients treated with lithium for more than five years. Løkkegaard H, et al. **Acta Psychiatr Scand** 1985 Apr;71(4):347-55

Plasma lithium level and interepisode functioning in bipolar disorder. Goodnick PJ, et al. **Am J Psychiatry** 1985 Jun;142(6):761-2

Lithium-selective polymeric membrane electrodes based on dodecylmethyl-14-crown-4. Kitazawa S, et al. **Analyst** 1985 Mar;110(3):295-9

A novel technique for assessing the sources of dietary sodium. Sanchez-Castillo CP, et al. **Ann Clin Res** 1984;16 Suppl 43:44-8

Can lithium carbonate prolong the antidepressant effect of sleep deprivation? [letter] Baxter LR Jr. **Arch Gen Psychiatry** 1985 Jun;42(6):635

Decreased myeloperoxidase activity of mice polymorphonuclear leukocytes by lithium carbonate treatment. Gómez-Estrada H, et al. **Arch Invest Med (Mex)** 1984 Oct-Dec;15(4):287-91 **(Eng, Spa)**

Automated determinations of K+ and Li+ with a microprocessor-controlled flame photometer [letter] Soltero RA. **Clin Chem** 1985 Jun;31(6):1094

Consensus development summaries. Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health. **Conn Med** 1985 Mar;49(3):157-63

The effect of sulindac on lithium therapy. Furnell MM, et al. **Drug Intell Clin Pharm** 1985 May;19(5):374-6

The effect of lithium carbonate administration on growth in the domestic fowl. Lozanoff S, et al. **Growth** 1985 Spring;49(1):91-104

Lithium-stimulated recovery of granulopoiesis after sublethal irradiation is not mediated via increased levels of colony stimulating factor (CSF). Gallicchio VS, et al. **Int J Radiat Biol** 1985 May;47(5):581-90

The influence of mania and depression on the pharmacokinetics of lithium. A longitudinal single-case study. Kukopoulos A, et al. **J Affective Disord** 1985 Mar-Apr;8(2):159-66

Mania. Diagnosis, state measurement and prediction of treatment response. Secunda SK, et al. **J Affective Disord** 1985 Mar-Apr;8(2):113-21

Severe prolonged catatonia with associated flushing reaction responsive

to lithium carbonate. Pheterson AD, et al. **J Am Acad Child Psychiatry** 1985 Mar;24(2):235-7
Brain glycine levels following lithium toxicity: case report. Stanley M, et al. **J Clin Psychiatry** 1985 Jun;46(6):239
Treatment-resistant catatonic stupor and combined lithium-neuroleptic therapy: a case report. Climo LH. **J Clin Psychopharmacol** 1985 Jun; 5(3):166-70
A pharmacokinetic approach to the study of cell membrane lithium transport in vivo. Mallinger AG, et al. **J Clin Psychopharmacol** 1985 Apr;5(2):78-82
Lithium therapy for mania and depression. Murray JB. **J Gen Psychol** 1985 Jan;112(1):5-33
Na+ (Li+)-proline cotransport in Escherichia coli. Chen CC, et al. **J Membr Biol** 1985;84(2):157-64
The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3-4):175-81
Denervation supersensitivity of the rat pineal to norepinephrine-stimulated [3H]inositide turnover revealed by lithium and a convenient procedure. Zatz M. **J Neurochem** 1985 Jul; 45(1):95-100
Lithium-induced improvement of myotonia: relevance of prostaglandin E1 blockade by lithium [letter] Backon J. **J Neurol Neurosurg Psychiatry** 1985 Jun;48(6):606-7
Familial differences in lithium responsive versus lithium nonresponsive psychoses. Sautter F, et al. **J Psychiatr Res** 1985;19(1):1-8
Poor response when laboratory recommended range for serum lithium is changed [letter] Masterton G, et al. **Lancet** 1985 Apr 27; 1(8435):981
Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health Consensus Development Conference Statement. **Nat Inst Health Consensus Dev Conf Consensus Statement** 1984; 5(4):8 p.
Effects of acute oral administration of lithium compounds on multiple schedule performance in rats. Chrislip DW, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):39-42
Effects of lithium in vitro on noradrenaline-induced cyclic AMP accumulation in rat cortical slices after reserpine-induced supersensitivity. Newman ME, et al. **Neuropharmacology** 1985 Apr; 24(4):353-5
Comparison of the changes in central catecholamine systems following short- and long-term lithium treatment and the consequences of lithium withdrawal. Ahluwalia P, et al. **Neuropsychobiology** 1984; 12(4):217-23
Mechanisms of the central action of lithium. Sinitskii VN, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):81-8
Compliance with outpatient lithium therapy. Connelly CE. **Perspect Psychiatr Care** 1984 Apr-Jun;22(2):44-50
Lithium effects on position learning with exploratory and aversive goal-box conditions. Hines G. **Pharmacol Biochem Behav** 1985 May; 22(5):695-8
Effects of chronic LiCl and RbCl on muricide induced by midbrain raphe lesions in rats. Yamamoto T, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):559-63
How does the patient prefer his lithium treatment? Vestergaard P. **Pharmacopsychiatry** 1985 May;18(3):223-4
Lithiated compounds of biological and oncological interest. Allen EB, et al. **Prog Clin Biol Res** 1985;172B:311-9
Interdependency of lithium ratio, plasma lithium level and clinical state in patients with affective disorders. Elizur A, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(2):167-72
Combined lithium and valproate treatment and subsequent withdrawal: serotonergic mechanism of their interaction in discrete brain regions. Shukla GS. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(2):153-6
Influence of GABA mimetics and lithium on biochemical manifestations of striatal dopamine target cell hypersensitivity. Scatton B, et al. **Psychopharmacology [Suppl]** 1985;2:39-45
Bipolar disorder and social work practice. Sands RG. **Soc Work Health Care** 1985 Spring;10(3):91-105
[Compartmental analysis of 6Li/7Li isotope exchange in equilibrium conditions in mouse plasma] Heurteaux C, et al. **C R Acad Sci [III]** 1985;300(14):529-34 (Eng. Abstr.) **(Fre)**
[Indications and monitoring of lithium treatment] Singer L, et al. **Rev Prat** 1985 May 11;35(27):1657-8, 1661-4 (Eng. Abstr.) **(Fre)**
[Effect of lithium on the proliferation of fibroblasts and tumor cell lines in vitro] Bruchelt G, et al. **Klin Padiatr** 1985 May-Jun; 197(3):249-52 (Eng. Abstr.) **(Ger)**
[Effect of lithium carbonate on the leukocyte count after exposure to ionizing radiation. 2. Influence of lithium carbonate on the leukocyte ratio in peripheral blood] Rose H, et al. **Radiobiol Radiother (Berl)** 1985; 26(1):103-7 (Eng. Abstr.) **(Ger)**
[Effect of lithium carbonate on the leukocyte count after exposure to ionizing radiation. 3. Influence of lithium carbonate on the leukocyte count in peripheral blood following fractionated caudal half-body irradiation] Rose H, et al. **Radiobiol Radiother (Berl)** 1985; 26(1):109-11 (Eng. Abstr.) **(Ger)**
[A case of simultaneous treatment of the manic syndrome and granulocytopenia with lithium salts] Greń K, et al. **Psychiatr Pol** 1984 May-Jun;18(3):285-8 **(Pol)**
[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**
[Lithium salts in the treatment of schizoaffective psychosis] Kopel A. **Psychiatr Pol** 1984 May-Jun;18(3):279-83 **(Pol)**

LORAZEPAM

Aminophylline is an antagonist of lorazepam. Wangler MA, et al. **Anesth Analg** 1985 Aug;64(8):834-6
A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445-51
Clonidine in benzodiazepine withdrawal [letter] Keshavan MS, et al. **Lancet** 1985 Jun 8;1(8441):1325-6
Information processing and benzodiazepines. Kleindienst-Vanderbeke G. **Neuropsychobiology** 1984;12(4):238-43
[Intravenous sedation before endoscopic interventions. Comparative study of lormetazepam and diazepam in oil] Tolksdorf W, et al. **Fortschr Med** 1985 Mar 7;103(9):249-52 (Eng. Abstr.) **(Ger)**

MANIC DISORDER

A controlled clinical trial of L-tryptophan in acute mania. Chouinard G, et al. **Biol Psychiatry** 1985 May;20(5):546-57
The influence of mania and depression on the pharmacokinetics of lithium. A longitudinal single-case study. Kukopoulos A, et al. **J Affective Disord** 1985 Mar-Apr;8(2):159-66
Mania. Diagnosis, state measurement and prediction of treatment response. Secunda SK, et al. **J Affective Disord** 1985 Mar-Apr;8(2):113-21
Comparison of antimanic efficacy of clonidine and verapamil. Giannini AJ, et al. **J Clin Pharmacol** 1985 May-Jun;25(4):307-8

MATERNAL BEHAVIOR

Prenatal stress impairs maternal behavior in a conflict situation and reduces hippocampal benzodiazepine receptors. Fride E, et al. **Life Sci** 1985 Jun 3;36(22):2103-9

MEMORY

Catecholamine microfluorometry of nigral perikarya and tyrosine hydroxylase assay in some telencephalic structures of rats exposed to different behavioral situations. Divac I, et al. **Acta Neurobiol Exp (Warsz)** 1984;44(6):262-72
Mediation of storage and retrieval with two drugs that selectively modulate serotonergic neurotransmission. Altman HJ. **Ann NY Acad Sci** 1985;444:496-8
Lesions in nucleus basalis magnocellularis and medial septal area of rats produce similar memory impairments in appetitive and non-appetitive behavioral tasks. Hepler D, et al. **Ann NY Acad Sci** 1985;444:518-9
Peripheral and central adrenergic influences on brain systems involved in the modulation of memory storage. McGaugh JL. **Ann NY Acad Sci** 1985;444:150-61
Arginine vasopressin inoculates against age-related changes in temporal memory. Meck WH, et al. **Ann NY Acad Sci** 1985;444:453-6
Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178-93
AF64A produces long-term cognitive impairments following infusion into the lateral cerebral ventricles or the dorsal hippocampus: involvement of hippocampal cholinergic processes in learning and memory. Walsh TJ, et al. **Ann NY Acad Sci** 1985;444:538-40
Depletion of adrenal catecholamines alters the amnestic effect of amygdala stimulation. Bennett C, et al. **Behav Brain Res** 1985 Apr;15(2):83-91
Peripheral epinephrine modulates the effects of post-training amygdala stimulation on memory. Liang KC, et al. **Behav Brain Res** 1985 Apr; 15(2):93-100
Physostigmine reverses memory deficits produced by pretraining electrical stimulation of the dorsal hippocampus in mice. Micheau J, et al. **Behav Brain Res** 1985 Apr;15(2):75-81
Effects of tifluadom on passive avoidance behaviour in DBA/2 mice. Pavone F, et al. **Behav Brain Res** 1985 May;15(3):177-81
Brain catecholamines and memory modulation: effects of footshock, amygdala implantation, and stimulation. Welsh KA, et al. **Behav Neural Biol** 1985 Mar;43(2):119-31
Increased sensitivity of the elderly to the central depressant effects of diazepam. Pomara N, et al. **J Clin Psychiatry** 1985 May;46(5):185-7
Interaction of choline and scopolamine in human memory. Mohs RC, et al. **Life Sci** 1985 Jul 15;37(2):193-7
Effects of dietary choline on memory and brain chemistry in aged mice. Mizumori SJ, et al. **Neurobiol Aging** 1985 Spring;6(1):51-6
Learning and memory deficits after lesions of the nucleus basalis

magnocellularis: reversal by physostigmine. Murray CL, et al. **Neuroscience** 1985 Apr;14(4):1025–32

The effect of chronic vs. acute injection of vasopressin on animal learning and memory. Hamburger-Bar R, et al. **Peptides (Fayetteville)** 1985 Jan–Feb;6(1):23–5

Manipulations of 5-HT activity and memory in the rat. Lalonde R, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):377–82

The effects of intravenous diazepam and hyoscine upon human memory. Frith CD, et al. **Q J Exp Psychol [A]** 1984 Feb;36(1):133–44

MEMORY, SHORT-TERM

Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory. Subhan Z, et al. **Neuropsychobiology** 1984;12(4):244–8

MENTAL DISORDERS

1st Czechoslovak Conference on Biological Psychiatry. Karlovy Vary (Karlsbad), September 1983. Abstracts. **Act Nerv Super (Praha)** 1985 Mar;27(1):60–72

26th annual psychopharmacological meeting. Jeseník Spa, January 1984. Proceedings, 2nd part. Abstracts. **Act Nerv Super (Praha)** 1985 Mar; 27(1):26–72

The pharmacokinetization of psychiatry [editorial] Greenblatt DJ. **J Clin Pharmacol** 1985 May–Jun;25(4):239–40

Treatment characteristics of psychiatric programs that correlate with patient community adjustment. Collins JF, et al. **J Clin Psychol** 1985 May;41(3):299–308

Compliance issues in outpatient treatment. Kane JM. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):22S–27S

Behavioral rehabilitation for chronic mental patients. Liberman RP, et al. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):8S–14S

The young adult chronic patient: population overview. Pepper B. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):3S–7S

MAOIs and drug interactions––a proposal for a clearinghouse. Shader RI, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):A17

The chronic patient: issues and concerns. Shader RI, et al. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):1S–2S

Focal neuroleptization: an approach to optimal dosing for initial and continuing therapy. Tupin JP. **J Clin Psychopharmacol** 1985 Jun; 5(3 Suppl):15S–21S

The clinical significance of halopemide, a dopamine-blocker related to the butyrophenones. De Cuyper H, et al. **Neuropsychobiology** 1984; 12(4):211–6

Effects of psychotropic drugs on discrimination conditioning in olfactory bulbectomized rats. Gomita Y, et al. **Pharmacol Biochem Behav** 1985 May;22(5):717–22

Proceedings of the congress of the AGNP. Nuremberg, 1983. Abstracts. **Pharmacopsychiatry** 1985 Jan;18(1):1–177

8th congress of the Polish Pharmacological Society. Symposium II: Pharmacological implications for animal models of mental disorders. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):493–569

3H-Imipramine binding sites in platelets of hospitalized psychiatric patients. Gentsch C, et al. **Psychiatry Res** 1985 Mar;14(3):177–87

Thorazine injected; pt. dies: criminal charges. Case in point: people v. Nygren (696 P. 2d 270––CO). Tammelleo AD. **Regan Rep Nurs Law** 1985 May;25(12):2

[Prescribing psychoactive drugs for children] Bläker F, et al. **Monatsschr Kinderheilkd** 1985 May;133(5):307–9 **(Ger)**

MEPROBAMATE

Meprobamate overdosage. Dennison J, et al. **Hum Toxicol** 1985 Mar; 4(2):215–7

[Responsibility of meprobamate in bone marrow aplasia (letter)] Evreux JC, et al. **Presse Med** 1985 Apr 6;14(14):793 **(Fre)**

METHOTRIMEPRAZINE

[Nozinan] Scottez B, et al. **Soins Psychiatr** 1985 Mar;(53):I–II **(Fre)**

[Clinico-humoral manifestations secondary to treatment with injectable Tisercin] Gheorghe M, et al. **Rev Med Interna [Neurol Psihiatr]** 1985 Jan–Mar;30(1):71–2 **(Rum)**

METHYLPHENIDATE

Place preference conditioning with methylphenidate and nomifensine. Martin-Iverson MT, et al. **Brain Res** 1985 Apr 15;332(1):59–67

Evaluating drug effectiveness in an office setting for children with attention deficit disorders. Ottinger DR, et al. **Clin Pediatr (Phila)** 1985 May;24(5):245–51

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227–43

Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. Feighner JP, et al. **J Clin Psychiatry** 1985 Jun;46(6):206–9

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222–31

Methylphenidate: rate dependent drug effects in hyperactive boys. Weber K. **Psychopharmacology (Berlin)** 1985;85(2):231–5

METHYSERGIDE

Control of suckling and feeding by methysergide in weaning albino rats: a determination of Y-maze preferences. Stoloff ML, et al. **Dev Psychobiol** 1985 May;18(3):273–85

Effects of quipazine and methysergide on play in juvenile rats. Normansell L, et al. **Pharmacol Biochem Behav** 1985 May;22(5):885–7

MOTIVATION

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer; 9(2):261–82

Glutamine-induced alterations in the content of brain amino acid neurotransmitters in rats with different alcohol motivation. Ostrovsky SYu. **Subst Alcohol Actions Misuse** 1984;5(5):247–53

MOTOR ACTIVITY

Activity measures in anorexia nervosa. Falk JR, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):811–4

The effect of methyl parathion on susceptibility of bobwhite quail (Colinus virginianus) to domestic cat predation. Galindo JC, et al. **Behav Neural Biol** 1985 Jan;43(1):21–36

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665–9

Association of the mesencephalic locomotor region with locomotor activity induced by injections of amphetamine into the nucleus accumbens. Brudzyński SM, et al. **Brain Res** 1985 May 13; 334(1):77–84

Quantification of lesion-induced dopaminergic supersensitivity using the rotational model in the mouse. Mandel RJ, et al. **Brain Res** 1985 Mar 25;330(2):358–63

Neonatal 6-hydroxydopamine lesion of spinal norepinephrine terminals fails to affect the ontogeny of swimming behavior. Ryan C, et al. **Brain Res** 1985 Jan;349(1–2):258–62

Inhibition of central angiotensin II induced drinking by GABA in the rat. Hutchinson JS, et al. **Clin Exp Hypertens [A]** 1984; 6(10–11):1777–80

Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215–27

The benzodiazepine antagonist Ro 15-1788 reverses the effect of methyl-beta-carboline-3-carboxylate but not of harmaline on cerebellar cGMP and motor performance in mice. Burkard WP, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):241–7

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349–54

Dysfunction of the midbrain angular complex can accentuate or attenuate circling behaviour in the rat. Starr MS, et al. **Exp Brain Res** 1985; 58(1):45–55

Tricyclic antidepressants antagonize prostaglandin (PG) E2-induced contractions of the guinea pig ileum and hypomotility in the mouse. Tayo FM. **Experientia** 1985 Apr 15;41(4):474–6

Pharmacologic studies of the central action of zopiclone: effects on locomotor activity and brain monoamines in rats. Liu HJ, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):121–8

Sulpiride blocks postsynaptic dopamine receptors in the nucleus accumbens. Morgenstern R, et al. **J Neural Transm** 1985; 61(3–4):151–60

SCH23390 causes persistent antidopaminergic effects in vivo: evidence for longterm occupation of receptors. Schulz DW, et al. **Life Sci** 1985 May 20;36(20):1941–8

Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5-MeODMT or mCPP. Sills MA, et al. **Life Sci** 1985 Jul 1; 36(26):2463–9

Automating the measurement of locomotor activity. Beninger RJ, et al. **Neurobehav Toxicol Teratol** 1985 Jan–Feb;7(1):79–85

Automated measurement of multivariate locomotor behavior in rodents. Sanberg PR, et al. **Neurobehav Toxicol Teratol** 1985 Jan–Feb; 7(1):87–94

Effect of gestational and neonatal styrene exposure on dopamine receptors. Zaidi NF, et al. **Neurobehav Toxicol Teratol** 1985 Jan–Feb;7(1):23–8

Effects of a thyrotropin releasing hormone analogue on locomotor and other motor activity in the rat. Clarke KA, et al. **Neuropeptides** 1985 Apr;6(2):101–12

The effects of neurotensin and [D-Tyr11]-NT on the hyperactivity induced by intra-accumbens administration of a potent dopamine receptor agonist. Jolicoeur FB, et al. **Neuropeptides** 1985 Apr; 6(2):143-56

Evidence that 2-phenylpyrazolo[4,3-c]-quinolin-3(5H)-one antagonises pharmacological, electrophysiological and biochemical effects of diazepam in rats. Santi M, et al. **Neuropharmacology** 1985 Feb; 24(2):99-105

Treatment of rats with the TRH analog MK-771. Down-regulation of TRH receptors and behavioral tolerance. Simasko SM, et al. **Neuropharmacology** 1985 Feb;24(2):157-65

Behavioral interaction of adenosine and trifluoperazine in mice. DeLong RE, et al. **Neurosci Lett** 1985 Jan 7;53(1):101-7

Detection of homovanillic acid in vivo using microcomputer-controlled voltammetry: simultaneous monitoring of rat motor activity and striatal dopamine release. O'Neill RD, et al. **Neuroscience** 1985 Mar; 14(3):753-63

Hypermotility induced by vasoactive intestinal peptide in the rat: its reciprocal action to cholecystokinin octapeptide. Itoh S, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):53-7

Specificity of nucleus accumbens to activities related to cholecystokinins in rats. Katsuura G, et al. **Peptides (Fayetteville)** 1985 Jan-Feb; 6(1):91-6

Locomotor response of nialamide pretreated old rats to intraaccumbens dopamine. Cousin KM, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):461-8

Dopamine-beta-hydroxylase inhibitors, feeding and locomotor activity: reinstatement of feeding following central norepinephrine. Evans KR, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):535-40

Brain amines and effects of chlordiazepoxide on motor activity in response to stress. Freeman GB, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):665-70

Sensitization of rotational behavior produced by a single exposure to cocaine. Guan LC, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):901-3

Effects of phencyclidine (PCP)-like drugs on turning behavior, 3H-dopamine uptake, and 3H-PCP binding. Johnson KM, et al. **Pharmacol Biochem Behav** 1985 May;22(5):731-5

Hypothalamic involvement in the locomotor stimulant or satiety action of thyrotropin-releasing hormone and amphetamine. Shian LR, et al. **Pharmacology** 1985;30(5):259-65

Development of mouse activity, stimulus reactivity, habituation, and response to amphetamine and scopolamine. Alleva E, et al. **Physiol Behav** 1985 Apr;34(4):519-23

Serotonin and schizophrenia: correlations between serotonergic activity and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Behavioral analysis of the effect of neurotensin injected into the ventral mesencephalon on investigatory and spontaneous motor behavior in the rat. Cador M, et al. **Psychopharmacology (Berlin)** 1985;85(2):187-96

Increased or decreased locomotor response in rats following repeated administration of apomorphine depends on dosage interval. Castro R, et al. **Psychopharmacology (Berlin)** 1985;85(3):333-9

A comparison between chlordiazepoxide and CL 218,872--a synthetic nonbenzodiazepine ligand for benzodiazepine receptors on spontaneous locomotor activity in rats. McElroy JF, et al. **Psychopharmacology (Berlin)** 1985;85(2):224-6

The tail suspension test: a new method for screening antidepressants in mice. Steru L, et al. **Psychopharmacology (Berlin)** 1985;85(3):367-70

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

Regional brain dopamine metabolism: a marker for the speed, direction, and posture of moving animals. Freed CR, et al. **Science** 1985 Jul 5; 229(4708):62-5

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

[Appraisal of ultradian components in the ethosecretogram of rat] Shiraishi I. **Hokkaido Igaku Zasshi** 1985 Jan;60(1):66-81 (Eng. Abstr.) **(Jpn)**

[TRH and its analog (DN-1417). Effects on central dopaminergic system-dependent behaviors in rats and mice] Miyamoto M, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):129-41 (Eng. Abstr.) **(Jpn)**

MOTOR SKILLS

Dopamine depletion in a striatal subregion disrupts performance of a skilled motor task in the rat. Sabol KE, et al. **Brain Res** 1985 May 27;335(1):33-43

Sensitivity changes to dopaminergic agents in fine motor control of rhesus monkeys after repeated methamphetamine administration. Ando K, et al. **Pharmacol Biochem Behav** 1985 May;22(5):737-43

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167-70

MSH

Distribution of the pro-opiomelanocortin derived peptides, adrenocorticotrope hormone, alpha-melanocyte-stimulating hormone and beta-endorphin (ACTH, alpha-MSH, beta-END) in the rat hypothalamus. Mezey E, et al. **Brain Res** 1985 Mar 4;328(2):341-7

Cyclic melanotropins. 9. 7-D-Phenylalanine analogues of the active-site sequence. Cody WL, et al. **J Med Chem** 1985 May;28(5):583-8

Photoaffinity labelling of MSH receptors on Anolis melanophores: effects of catecholamines, calcium and forskolin. Eberle AN, et al. **J Recept Res** 1985;5(1):59-81

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417-51 (238 ref.)

NEUROREGULATORS

Catecholamine and opioid receptors, presynaptic inhibition of CNS neurotransmitter release, and adenylate cyclase. Mulder AH, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:273-86

Adenosine, adenylate cyclase, and transmitter release. Phillis JW, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:243-57 (81 ref.)

Neuroendocrinology and the ovulation cycle--advances and review. Schnatz PT. **Adv Psychosom Med** 1985;12:4-24

Psychoendocrinology and the menstrual cycle. Youngs DD, et al. **Adv Psychosom Med** 1985;12:25-34

Delta 1-pyrroline-5-carboxylate dehydrogenase, a possible regulatory enzyme in transmitter glutamic acid metabolism--a preliminary report. Wong PT, et al. **Ann Acad Med Singapore** 1985 Jan;14(1):143-6

Membrane-related effects of atypical antidepressants. Valdman AV, et al. **Ann Ist Super Sanita** 1984;20(1):65-72

Accumulation of inositol phosphates in sympathetic ganglia. Effects of depolarization and of amine and peptide neurotransmitters. Bone EA, et al. **Biochem J** 1985 Apr 1;227(1):263-9

Release of D-[3H]aspartic acid from the rat striatum. Effect of veratridine-evoked depolarization, fronto-parietal cortex ablation, and striatal lesions with kainic acid. Arqueros L, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1217-24

Monoamine metabolites: their relationship and lack of relationship to monoaminergic neuronal activity. Commissiong JW. **Biochem Pharmacol** 1985 Apr 15;34(8):1127-31

Interaction of phenothiazine drugs with human ceruloplasmin. Relation between activation of catecholamine neurotransmitter oxidation and electron donating ability of phenothiazine drugs. de Mol NJ. **Biochem Pharmacol** 1985 Aug 1;34(15):2605-9

Animal models of depression: parallels and correlates to severe depression in humans. Jesberger JA, et al. **Biol Psychiatry** 1985 Jul; 20(7):764-84

The role of substance P as a neurotransmitter in the reflexes of slow time courses in the neonatal rat spinal cord. Akagi H, et al. **Br J Pharmacol** 1985 Mar;84(3):663-73

Electrophysiological evidence that nipecotic acid can be used in vivo as a false transmitter. Lerma J, et al. **Brain Res** 1985 Jun 3; 335(2):377-80

Evidence for genetic influences on neurotransmitter content of identified neurones of Lymnaea stagnalis. Audesirk G, et al. **Comp Biochem Physiol [C]** 1985;81(1):57-60

Motor and behavioural effects induced by putative neurotransmitter injection into the optic lobe of the cuttlefish, Sepia officinalis. Chichery R, et al. **Comp Biochem Physiol [C]** 1985;80(2):415-9

The effects of putative amino acid neurotransmitters on somata isolated from neurons of the locust central nervous system. Giles D, et al. **Comp Biochem Physiol [C]** 1985;80(2):231-6

Neurotransmitter precursors and metabolites in CSF of human neonates. Anderson GM, et al. **Dev Med Child Neurol** 1985 Apr;27(2):207-14

Neurotransmitters involved in mediating the steroid-dependent suppression of pulsatile luteinizing hormone secretion in anestrous ewes: effects of receptor antagonists. Meyer SL, et al. **Endocrinology** 1985 May;116(5):2054-61

Evidence that ATP is involved as a co-transmitter in the hypogastric nerve supplying the seminal vesicle of the guinea-pig. Meldrum LA, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):363-6

Phorbol ester and calcium act synergistically to enhance neurotransmitter release by brain neurons in culture. Zurgil N, et al. **FEBS Lett** 1985 Jun 17;185(2):257-61

Arterial and cardiopulmonary reflexes in the regulation of the neurohumoral drive to the circulation. Bishop VS, et al. **Fed Proc** 1985 May;44(8):2377-81 (31 ref.)

Vasoactive intestinal peptide. Relaxant neurotransmitter in tenia coli of the guinea pig. Grider JR, et al. **Gastroenterology** 1985 Jul; 89(1):36-42

Identification of putative neurotransmitters in the lizard parietal eye. Engbretson GA, et al. **Invest Ophthalmol Vis Sci** 1985 May; 26(5):670-8

Blood pressure control by neurotransmitters in the medulla oblongata and spinal cord. Howe PR. **J Auton Nerv Syst** 1985 Feb-Mar; 12(2-3):95-115

Determination of neurotransmitter amino acids by high-performance liquid chromatography with fluorescence detection. Zecca L, et al. **J Chromatogr** 1985 Feb 8;337(2):391-6

Role of calcium and phosphoinositides in the actions of certain hormones and neurotransmitters. Exton JH. **J Clin Invest** 1985 Jun; 75(6):1753-7 (59 ref.)

Fine structure of peptidergic and catecholaminergic nerve fibers in the anterior cerebral artery and their interrelationship: an immunoelectron microscopic study. Matsuyama T, et al. **J Comp Neurol** 1985 May 8; 235(2):268-76

Immunohistochemical demonstration of some putative neurotransmitters in the lamprey spinal cord and spinal ganglia: 5-hydroxytryptamine-, tachykinin-, and neuropeptide-Y-immunoreactive neurons and fibers. Van Dongen PA, et al. **J Comp Neurol** 1985 Apr 22;234(4):501-22

Insect cardioactive peptides. II. Neurohormonal control of heart activity by two cardioacceleratory peptides in the tobacco hawkmoth, Manduca sexta. Tublitz NJ, et al. **J Exp Biol** 1985 Jan;114:381-95

Distribution of aminergic neurons in the brain of the sterlet, Acipenser ruthenus (Chondrostei, Actinopterygii). Kotrschal K, et al. **J Hirnforsch** 1985;26(1):65-72

Neuropeptides and other mediators in the central nervous system. Bloom FE. **J Immunol** 1985 Aug;135(2 Suppl):743s-745s

Noradrenergic and peptidergic innervation of lymphoid tissue. Felten DL, et al. **J Immunol** 1985 Aug;135(2 Suppl):755s-765s (73 ref.)

Evidence that thymosins and other biologic response modifiers can function as neuroactive immunotransmitters. Hall NR, et al. **J Immunol** 1985 Aug;135(2 Suppl):806s-811s

Cellular interactions at the central and peripheral terminals of primary sensory neurons. Jessell TM. **J Immunol** 1985 Aug; 135(2 Suppl):746s-749s

Modulation of macrophage-mediated tumoricidal activity by neuropeptides and neurohormones. Koff WC, et al. **J Immunol** 1985 Jul;135(1):350-4

Neuroanatomic and neurotransmitter influences on immune function. Roszman TL, et al. **J Immunol** 1985 Aug;135(2 Suppl):769s-772s

Evolutionary origins of neuropeptides, hormones, and receptors: possible applications to immunology. Roth J, et al. **J Immunol** 1985 Aug; 135(2 Suppl):816s-819s

An excitant amino acid projection from the medial prefrontal cortex to the anterior part of nucleus accumbens in the rat. Christie MJ, et al. **J Neurochem** 1985 Aug;45(2):477-82

Composite technique for regional neurochemical studies: measurement of energy and neurotransmitter metabolites in single tissue sample. Djuricic BM, et al. **J Neurochem** 1985 Jun;44(6):1920-4

Some long-lasting neurochemical effects of prenatal or early postnatal exposure to diazepam. Frieder B, et al. **J Neurochem** 1985 Jul; 45(1):37-42

Rat serum contains a developmentally regulated cholinergic inducing activity. Wolinsky EJ, et al. **J Neurosci** 1985 Jun;5(6):1509-12

Expression of noradrenergic and cholinergic traits by sympathetic neurons cultured without serum. Wolinsky EJ, et al. **J Neurosci** 1985 Jun; 5(6):1497-508

Profiles of evoked release along the length of frog motor nerve terminals. D'Alonzo AJ, et al. **J Physiol (Lond)** 1985 Feb;359:235-58

Long-term potentiation of transmitter release induced by repetitive presynaptic activities in bull-frog sympathetic ganglia. Koyano K, et al. **J Physiol (Lond)** 1985 Feb;359:219-33

Burn trauma induces anorexia and aberrations in CNS amine neurotransmitters. Chance WT, et al. **J Trauma** 1985 Jun; 25(6):501-7

Modulation of receptor sensitivity and action potentials by transmitters in vertebrate neurones. Koketsu K. **Jpn J Physiol** 1984;34(6):945-60 (59 ref.)

Proctolin: a potent inhibitor of aminoenkephalinase. Hui KS, et al. **Life Sci** 1985 Jun 17;36(24):2309-15

Tuning in to neurotransmitters [news] Altman J. **Nature** 1985 Jun 13-19; 315(6020):537

Pertussis toxin reverses adenosine inhibition of neuronal glutamate release. Dolphin AC, et al. **Nature** 1985 Jul 11-17;316(6024):148-50

Transport of monoamine and amino acid neurotransmitters by primary astroglial cultures. Hansson E. **Neurochem Res** 1985 May; 10(5):667-75

Selective retrograde labeling in some afferents to the rabbit lateral geniculate nucleus following injections of tritiated neurotransmitter-related compounds. Matute C, et al. **Neurosci Lett** 1985 Jan 7;53(1):9-14

Simultaneous monitoring of voltammetric and ion-selective electrodes in mammalian brain. Nagy G, et al. **Neurosci Lett** 1985 Apr 9; 55(2):119-24

Prolonged non-adrenergic inhibition of cardiac vagal action following sympathetic stimulation: neuromodulation by neuropeptide Y? Potter EK. **Neurosci Lett** 1985 Mar 15;54(2-3):117-21

Effects of chlordecone on neuroendocrine function of female rats. Uphouse L. **Neurotoxicology (Little Rock Ar)** 1985 Spring; 6(1):191-210 (80 ref.)

Sympathetic neuron density differentially regulates transmitter phenotypic expression in culture. Adler JE, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4296-300

N-Acetylaspartylglutamate: possible role as the neurotransmitter of the lateral olfactory tract. Ffrench-Mullen JM, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3897-900

Intraterminal injection of synapsin I or calcium/calmodulin-dependent protein kinase II alters neurotransmitter release at the squid giant synapse. Llinás R, et al. **Proc Natl Acad Sci USA** 1985 May; 82(9):3035-9

Roles for neurotransmitters in development: possible interaction with drugs during the fetal and neonatal periods. Lauder JM. **Prog Clin Biol Res** 1985;163C:375-80

Neurotropic drugs and brain development: effects on cell replication in vivo and in vitro. Patel AJ. **Prog Clin Biol Res** 1985;163C:301-5

Role of neurotransmitters and teratogens on palate development. Zimmerman EF, et al. **Prog Clin Biol Res** 1985;163C:405-8

Biochemical hypotheses of premenstrual tension syndrome. Janowsky DS, et al. **Psychol Med** 1985 Feb;15(1):3-8

Glutamine-induced alterations in the content of brain amino acid neurotransmitters in rats with different alcohol motivation. Ostrovsky SYu. **Subst Alcohol Actions Misuse** 1984;5(5):247-53

Retinal neurotransmission. Pycock CJ. **Surv Ophthalmol** 1985 Mar-Apr; 29(5):335-65

[Central neurotransmitters and cardiovascular activity] Xia Y. **Sheng Li Ko Hsueh Chin Chan** 1985 Jan;16(1):27-31 (50 ref.) **(Chi)**

[Recent advances in research on substance P and related neuropeptides] Kanazawa I. **No To Hattatsu** 1985 Mar;17(2):94-102 (17 ref.) **(Jpn)**

[Neurotransmitters and neuropeptides in schizophrenia] Toru M, et al. **Tanpakushitsu Kakusan Koso** 1984 Dec;29(14):1838-54 (150 ref.) **(Jpn)**

[Regulation of tetanus toxin-inhibited transmitter secretion in the neuromuscular junction in a calcium-free-medium] Kryzhanovskii GN, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):402-9 (Eng. Abstr.) **(Rus)**

[Inherent morphofunctional effects of experimental procedures in studying the mechanism of transmitter release] Nikulin VG, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):373-6 (Eng. Abstr.) **(Rus)**

[Vasoactive hormones and mediators in the mechanism of the development of an aphthous process in the oral mucosa] Rybakov AI, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):424-5 (Eng. Abstr.) **(Rus)**

[Neuroendocrine mechanisms in immunoregulation] Bezedovskii GO, et al. **Fiziol Cheloveka** 1984 Mar-Apr;10(2):224-8 (14 ref.) **(Rus)**

[Neurohumoral regulation of immune homeostasis] Korneva EA, et al. **Fiziol Cheloveka** 1984 Mar-Apr;10(2):179-92 (38 ref.) **(Rus)**

[Distribution and functioning of mediator release sites in the neuromuscular junction of the frog] Zefirov AL. **Neirofiziologiia** 1985; 17(2):152-60 (Eng. Abstr.) **(Rus)**

[Elements of the systems approach in studying the mechanisms of the neurohumoral regulation of immunological processes] Korneva EA. **Vestn Akad Med Nauk SSSR** 1985;(3):63-73 (60 ref.) (Eng. Abstr.) **(Rus)**

[Nervous system regulation of exocrine pancreatic secretion in the chicken] Salido GM, et al. **Rev Esp Fisiol** 1985 Mar;41(1):11-7 (Eng. Abstr.) **(Spa)**

NEUROTENSIN

Immunohistochemical localization of neurotensin in hamster adrenal medulla. Pelto-Huikko M, et al. **Anat Rec** 1985 Apr;211(4):458-64

Dopamine D2 receptors modulate neurotransmitter-regulated calcium ion gates. Memo M, et al. **Ann Ist Super Sanita** 1984;20(1):5-10

Neurotensin degradation by soluble and membrane-associated enzymes from the brain. Emson PC, et al. **Biochem Soc Trans** 1985 Feb; 13(1):53-4

The effects of chronic neuroleptic treatment on neurotensin-like immunoreactivity in the rat central nervous system. Goedert M, et al. **Brain Res** 1985 Jun 3;335(2):334-6

The ontogenetic development of neurotensin-like immunoreactivity and neurotensin receptors in the cat striatum. Goedert M, et al. **Brain Res** 1985 May;352(1):127-31

Immunohistochemical localization of neurotensin and beta-endorphin in the rat anterior pituitary gland. Miyoshi R, et al. **Brain Res** 1985 Apr 8;331(2):386-8

A quantitative, immunochemical demonstration of the postnatal development of neurotensin in the medial preoptic area of the rat. Wolfson B, et al. **Brain Res** 1985 Feb;350(1-2):241-50

Vascular actions of VIP, substance P and neurotensin on the isolated perfused human fetal placenta. de Moura RS, et al. **Contrib Gynecol Obstet** 1985;13:174-5

Changes in neurotensin-like immunoreactivity during menopausal hot flashes. Kronenberg F, et al. **J Clin Endocrinol Metab** 1985 Jun; 60(6):1081-6

Neurotensin enhances estradiol induced DNA synthesis in immature rat uterus. Mistry A, et al. **Life Sci** 1985 May 27;36(21):2063-7

Ultrastructural immunocytochemical studies on CCK-and neurotensin-like immunoreactivity in the nucleus accumbens of the rat. Johansson O, et al. **Med Biol** 1984;62(6):318-22

The effects of neurotensin and [D-Tyr11]-NT on the hyperactivity induced by intra-accumbens administration of a potent dopamine receptor agonist. Jolicoeur FB, et al. **Neuropeptides** 1985 Apr; 6(2):143-56

Release of mast cell mediators, vasoconstriction and edema in the isolated, perfused head of the rat following intracarotid infusion of neurotensin. Rioux F, et al. **Neuropeptides** 1985 Mar;6(1):1–12

Behavioral analysis of the effect of neurotensin injected into the ventral mesencephalon on investigatory and spontaneous motor behavior in the rat. Cador M, et al. **Psychopharmacology (Berlin)** 1985;85(2):187–96

Bombesin, neurotensin and pro-gamma-melanotropin immunoreactants in human milk. Ekman R, et al. **Regul Pept** 1985 Mar; 10(2–3):99–105

[Gastrointestinal hormones and related peptides. V. Neurotensin] Sadowska-Krowicka H, et al. **Postepy Hig Med Dosw** 1984 Jul–Aug; 38(4):535–52 (110 ref.) (Eng. Abstr.) **(Pol)**

[Cyclic AMP content of the blood, brain, stomach, adrenals and duodenum after administration of neurotensin and cholecystokinin] Andreanova MV, et al. **Fiziol Zh SSSR** 1985 Feb;71(2):258–61 **(Rus)**

[Effect of natural neurotensin and its analog on gastric secretion and levels of various peptides in dog blood] Barashkova GM, et al. **Fiziol Zh SSSR** 1985 Feb;71(2):200–5 (Eng. Abstr.) **(Rus)**

NEUROTIC DISORDERS

Neuroticism and personality disorder in depression. Davidson J, et al. **J Affective Disord** 1985 Mar–Apr;8(2):177–82

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731–6

NIALAMIDE

Locomotor response of nialamide pretreated old rats to intraaccumbens dopamine. Cousin KM, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):461–8

NOREPINEPHRINE

Effect of propranolol on post-traumatic hypophosphataemia and catecholamine secretion. Lovén L, et al. **Acta Chir Scand** 1985; 151(3):201–4

Changes in blood level of catecholamines during arterial blood pressure rise induced with sciatic nerve stimulation. Całkosiński I, et al. **Acta Physiol Pol** 1984 Jan–Feb;35(1):47–51

Seasonal changes in blood lipids, adrenaline, noradrenaline, glucose and insulin in Norwegian reindeer. Larsen TS, et al. **Acta Physiol Scand** 1985 May;124(1):53–9

Noradrenergic modulation of cerebral cortical oxidative metabolism. LaManna JC, et al. **Adv Exp Med Biol** 1984;180:211–9

Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. Stratton JR, et al. **Am J Cardiol** 1985 Jul 1;56(1):136–9

Norepinephrine in cochlear microcirculation of guinea pigs. Matsunaga T, et al. **Am J Otolaryngol** 1985 May–Jun;6(3):226–30

Decidua-associated changes in guinea pig uterine blood flow and volume: relation to uterine norepinephrine concentrations. Garris DR, et al. **Anat Rec** 1985 Apr;211(4):410–13

The modulation of acetylcholine release by noradrenaline, GABA and related compounds. Beani L, et al. **Ann Ist Super Sanita** 1984; 20(1):17–9

Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178–93

Selective decrease of hypothalamic noradrenaline by cysteamine. Vécsei L, et al. **Arch Int Pharmacodyn Ther** 1985 Mar;274(1):125–8

Depletion of adrenal catecholamines alters the amnestic effect of amygdala stimulation. Bennett C, et al. **Behav Brain Res** 1985 Apr;15(2):83–91

Studies on the mechanism of inhibition of glucose-stimulated insulin secretion by noradrenaline in rat islets of Langerhans. Morgan NG, et al. **Biochem J** 1985 Mar 1;226(2):571–6

Catecholamine responses to changes in posture during human pregnancy. Whittaker PG, et al. **Br J Obstet Gynaecol** 1985 Jun;92(6):586–92

The formation of deaminated metabolites of dopamine in the locus coeruleus depends upon noradrenergic neuronal activity. Curet O, et al. **Brain Res** 1985 Jun 3;335(2):297–301

The prefrontal 'cortex' in the pigeon. Biochemical evidence. Divac I, et al. **Brain Res** 1985 Apr 22;332(2):363–8

Comparative effects of sciatic nerve stimulation, blood pressure, and morphine on the activity of A5 and A6 pontine noradrenergic neurons. Guyenet PG, et al. **Brain Res** 1985 Feb 18;327(1–2):191–201

Central noradrenergic involvement in yohimbine excitation of acoustic startle: effects of DSP4 and 6-OHDA. Kehne JH, et al. **Brain Res** 1985 Mar 18;330(1):31–41

Neonatal 6-hydroxydopamine lesion of spinal norepinephrine terminals fails to affect the ontogeny of swimming behavior. Ryan C, et al. **Brain Res** 1985 Jan;349(1–2):258–62

The postnatal development of norepinephrine-stimulated cyclic AMP accumulation in rat spinal cord. Simmons K, et al. **Brain Res** 1985 Feb; 350(1–2):306–10

Aversive effects of subcutaneously injected vasopressin in the rat: independence of the ascending dorsal noradrenergic bundle. Tam FW, et al. **Brain Res** 1985 Jun 24;337(1):133–7

Inputs from the A1 noradrenergic region to hypothalamic paraventricular neurons in the rat. Tanaka J, et al. **Brain Res** 1985 Jun 3; 335(2):368–71

Epinephrine- and norepinephrine-evoked potential changes of frog primary afferent terminals: pharmacological characterization of alpha and beta components. Wohlberg CJ, et al. **Brain Res** 1985 Feb 18; 327(1–2):289–301

Mechanisms of supersensitivity to sympathomimetic amines in the chronically denervated heart of the conscious dog. Vatner DE, et al. **Circ Res** 1985 Jul;57(1):55–64

Effect of intracerebroventricular 6-hydroxydopamine (6-HODA) on the angiotensinogen concentration of the brain. Basso N, et al. **Clin Exp Hypertens** [A] 1984;6(10–11):1773–6

Effects of angiotensin II and ACE inhibitors on electrically stimulated noradrenaline release from superfused rat brain slices. Schacht U. **Clin Exp Hypertens** [A] 1984;6(10–11):1847–51

Accumulation of intra-arterially administered [3H]adrenaline and [3H]noradrenaline in various tissues of the Atlantic cod, Gadus morhua. Ungell AL. **Comp Biochem Physiol** [C] 1985;81(1):25–8

Norepinephrine alone versus norepinephrine plus low-dose dopamine: enhanced renal blood flow with combination pressor therapy. Schaer GL, et al. **Crit Care Med** 1985 Jun;13(6):492–6

Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215–27

Regulation of ketogenesis by epinephrine and norepinephrine in the overnight-fasted, conscious dog. Steiner KE, et al. **Diabetes** 1985 May; 34(5):425–32

Strain differences in brain biogenic amines concentration in rats with different resistance to emotional stress. Sudakov KV, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):39–45

Plasma glucagon and catecholamines during exhaustive short-term exercise. Näveri H, et al. **Eur J Applied Physiol** 1985;53(4):308–11

Differences in dopamine- and noradrenaline-induced amylase release from the rat parotid gland. Sundström S, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):355–61

Response of phasically firing paraventricular neurons to A1 noradrenergic region stimulation and its attenuation by adrenoceptor antagonists. Tanaka J, et al. **Exp Neurol** 1985 Jun;88(3):714–25

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr; 6(2):78–81

Heat acclimation: role of norepinephrine in the anterior hypothalamus. Christman JV, et al. **J Appl Physiol** 1985 Jun;58(6):1923–8

Exercise, dobutamine, and combined atropine, norepinephrine, and epinephrine compared. Haidet GC, et al. **J Appl Physiol** 1985 Jun; 58(6):2047–53

Cardiovascular effects of intracisternal 6-hydroxydopamine and of subsequent lesions of the ventrolateral medulla coinciding with the Al group of noradrenaline cells in the rabbit. Elliott JM, et al. **J Auton Nerv Syst** 1985 Feb–Mar;12(2–3):117–30

Role of central nervous system monoamines in cardiopulmonary effects of Althesin in rabbit and man. Quail AW, et al. **J Auton Nerv Syst** 1985 Feb–Mar;12(2–3):159–74

Ambient temperature modulates the differentiated cardiorespiratory pattern generated by the central noradrenergic system, most likely via alterations of thyrotropin-releasing hormone (TRH) activity. Riedel W. **J Auton Nerv Syst** 1985 Feb–Mar;12(2–3):145–57

Central nervous system 5-hydroxytryptamine and noradrenaline specificity of ear vascular and ventilation reflexes in thermoregulating rabbits. White SW, et al. **J Auton Nerv Syst** 1985 Feb–Mar; 12(2–3):131–44

Rapid changes in synaptic vesicle cytochemistry after depolarization of cultured cholinergic sympathetic neurons. Johnson MI, et al. **J Cell Biol** 1985 Jul;101(1):217–26

Pial artery responses to norepinephrine potentiated by endothelium removal. Sercombe R, et al. **J Cereb Blood Flow Metab** 1985 Jun; 5(2):312–7

Simultaneous assay of 3,4-dihydroxyphenylethylene glycol and norepinephrine in human plasma by high-performance liquid chromatography with electrochemical detection. Howes LG, et al. **J Chromatogr** 1985 Mar 22;338(2):401–3

Simple and fast analysis of adrenaline and noradrenaline in plasma on microbore high-performance liquid chromatography columns using fluorimetric detection. Kamperman G, et al. **J Chromatogr** 1985 Feb 8;337(2):384–90

Circadian rhythms of epinephrine and norepinephrine in man. Linsell CR, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1210–5

Modulation of calcium channels by norepinephrine in internally dialyzed avian sensory neurons. Forscher P, et al. **J Gen Physiol** 1985 May; 85(5):743–63

Effect of norepinephrine on swelling-induced potassium transport in duck red cells. Evidence against a volume-regulatory decrease under physiological conditions. Haas M, et al. **J Gen Physiol** 1985 May; 85(5):649–67

BIBLIOGRAPHY

Norepinephrine as a possible transmitter involved in synaptic transmission in frog taste organs and Ca dependence of its release. Nagahama S, et al. **J Gen Physiol** 1985 Mar;85(3):431-42

Pressor responsiveness to norepinephrine in rabbits with adrenal perturbations. Siripaisarnpipat S, et al. **J Hypertens** 1985 Feb; 3(1):89-96

Neurochemical profile of Lu 19-005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615-22

Assessment of noradrenaline and 5-hydroxytryptamine uptake in intact rat brain. Wyllie MG, et al. **J Neurochem** 1985 Aug;45(2):456-60

Denervation supersensitivity of the rat pineal to norepinephrine-stimulated [3H]inositide turnover revealed by lithium and a convenient procedure. Zatz M. **J Neurochem** 1985 Jul; 45(1):95-100

Dopamine beta-hydroxylase-like immunoreactivity in the rat and cat carotid body: a light and electron microscopic study. Chen IL, et al. **J Neurocytol** 1985 Feb;14(1):131-44

Effect of immune complex-forming reactants on catecholamine-modulated behaviors in the rat hypothalamus. Schupf N, et al. **J Neuroimmunol** 1985 Jul;9(1-2):13-27

Measurement of noradrenaline synthesis in rat hippocampal synaptosomes using HPLC with ECD. Birch PJ, et al. **J Neurosci Methods** 1985 May; 13(3-4):231-8

A technique for the microinjection of macromolecules into viable chromaffin cells in culture. Kenigsberg RL, et al. **J Neurosci Methods** 1985 Apr;13(2):103-18

Inhibition by 5,6-dihydroxy-2-dimethylaminotetralin (M7) of noradrenergic neurotransmission in the rabbit hypothalamus: role of alpha-2 adrenoceptors and of dopamine receptors. Galzin AM, et al. **J Pharmacol Exp Ther** 1985 May;233(2):459-65

Adrenergic and possible nonadrenergic sources of adenosine 5'-triphosphate release from nerve varicosities isolated from ileal myenteric plexus. Al-Humayyd M, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):796-800

Inhibitory effects of norepinephrine, methoxamine and phenylephrine on renin release from rat kidney cortical slices. Matsumura Y, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):782-7

Chronic thyroxine treatment of rats down-regulates the noradrenergic cyclic AMP generating system in cerebral cortex. Schmidt BH, et al. **J Pharmacol Exp Ther** 1985 May;233(2):466-72

Demonstration of an alpha adrenoceptor-mediated inotropic effect of norepinephrine in human atria. Skomedal T, et al. **J Pharmacol Exp Ther** 1985 May;233(2):441-6

Reduction of the cyclic adenosine 3',5'-monophosphate response to catecholamines in rat brain slices after repeated restraint stress. Stone EA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):382-8

Noradrenaline hyperpolarization and depolarization in cat vesical parasympathetic neurones. Akasu T, et al. **J Physiol (Lond)** 1985 Apr; 361:165-84

Efflux of 5-hydroxytryptamine and noradrenaline into spinal cord superfusates during stimulation of the rat medulla. Hammond DL, et al. **J Physiol (Lond)** 1985 Feb;359:151-62

Methionine-enkephalin inhibits stress-induced increases in noradrenaline turnover in brain regions of rats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Jan;37(1):117-9

Inhibition of locus coeruleus neuronal activity by beta-phenylethylamine. Lundberg PA, et al. **Life Sci** 1985 May 13;36(19):1889-96

Epinephrine and norepinephrine syntheses are regulated by a glucocorticoid receptor-mediated mechanism in the bovine adrenal medulla. Nawata H, et al. **Life Sci** 1985 May 20;36(20):1957-66

Norepinephrine-dependent and independent mechanisms of persistent effects of amphetamine in rat cerebellum. Sorensen SM, et al. **Life Sci** 1985 Jun 24;36(25):2383-9

Enhancement of the pressor response to norepinephrine by angiotensin in the conscious rabbit. Weber MA, et al. **Life Sci** 1985 May 20; 36(20):1897-907

Excretion of urinary catecholamines and plasma cortisol levels in female nurses on short-rotating shift. Panza G, et al. **Med Lav** 1985 Jan-Feb; 76(1):30-4

Pharmacology in vivo of the phenylindan derivative, Lu 19-005, a new potent inhibitor of dopamine, noradrenaline and 5-hydroxytryptamine uptake in rat brain. Arnt J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):101-7

Plasma catecholamines in arterial and capillary blood. Baumgartner H, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):461-3

Effects of clorgyline and (-)deprenyl on the deamination of normetanephrine and noradrenaline in strips and homogenates of the canine saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):396-400

Influence of MAO A and MAO B on the inactivation of noradrenaline in the saphenous vein of the dog. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):401-6

Cardiac glycosides, calcium and the release of neurotransmitter from peripheral noradrenergic nerves. Tan CM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Mar;329(1):1-8

Electroacupuncture alters catecholamines in brain regions of rats. Sun AY, et al. **Neurochem Res** 1985 Feb;10(2):251-8

Medial preoptic area involvement in norepinephrine-induced suppression of pulsatile luteinizing hormone release in ovariectomized rats. Leipheimer RE, et al. **Neuroendocrinology** 1985 Apr;40(4):345-51

Effects of lithium in vitro on noradrenaline-induced cyclic AMP accumulation in rat cortical slices after reserpine-induced supersensitivity. Newman ME, et al. **Neuropharmacology** 1985 Apr; 24(4):353-5

Stress and brain noradrenaline: a review. Glavin GB. **Neurosci Biobehav Rev** 1985 Summer;9(2):233-43 (81 ref.)

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer; 9(2):261-82

Temporal relationship between noradrenaline release in the central amygdala and plasma noradrenaline secretion in rats and tree shrews. Dietl H. **Neurosci Lett** 1985 Mar 22;55(1):41-6

Astrocyte opioid receptors: activation modifies the noradrenaline-evoked increase in 2-[14C]deoxyglucose incorporation into glycogen. Pearce B, et al. **Neurosci Lett** 1985 Apr 9;55(2):157-60

Effect of histamine infusion on circulating methionine-enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289-92

Relative pre- and postjunctional roles of noradrenaline and adenosine 5'-triphosphate as neurotransmitters of the sympathetic nerves of guinea-pig and mouse vas deferens. Stjärne L, et al. **Neuroscience** 1985 Mar;14(3):929-46

alpha 1- and beta-adrenergic receptors are co-regulated during both noradrenergic denervation and hyperinnervation. Sutin J, et al. **Neuroscience** 1985 Apr;14(4):973-80

Dopamine-beta-hydroxylase inhibitors, feeding and locomotor activity: reinstatement of feeding following central norepinephrine. Evans KR, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):535-40

Effect of a low sodium medium, ouabain and noradrenaline on relaxation of the myocardium of the perfused rabbit heart. Fišer B, et al. **Physiol Bohemoslov** 1985;34(1):77-84

The influence of prazosin on E. coli lipopolysaccharide-induced fever and noradrenaline hyperthermia. Matuszek M, et al. **Pol J Pharmacol Pharm** 1984 Nov-Dec;36(6):585-93

Some behavioral effects of microinjections of serotonin and noradrenaline into the limbic structures of the rat brain. Płaźnik A. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):541-54

The effects of lesions of the locus coeruleus and treatment with drugs affecting brain noradrenergic neurotransmission on dominant-subordinate behavior in rats competing for water. Plewako M, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):555-60

The role of the central noradrenaline system in regulating neuronal plasticity in the developing neocortex. Kasamatsu T. **Prog Clin Biol Res** 1985;163C:369-73

Hypophysectomy disturbs the noradrenergic feeding system of the paraventricular nucleus. Roland CR, et al. **Psychoneuroendocrinology** 1985;10(1):109-20

Supersensitivity to the anticonvulsant and proconvulsant activity of clonidine following noradrenaline depletion induced by 6-hydroxydopamine. Dalton JC, et al. **Psychopharmacology (Berlin)** 1985;85(3):319-22

The effect of clorgyline on noradrenergic function. Ross RJ, et al. **Psychopharmacology (Berlin)** 1985;85(2):227-30

Airway responses to low concentrations of adrenaline and noradrenaline in normal subjects. Berkin KE, et al. **Q J Exp Physiol** 1985 Apr; 70(2):203-9

Relationship between sleep efficiency and urinary excretion of catecholamines in bed-rested humans. Nishihara K, et al. **Sleep** 1985; 8(2):110-7

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

[Enkephalin-noradrenaline interactions in synaptic transmission] Fan JZ, et al. **Sheng Li Ko Hsueh Chin Chan** 1985 Apr;16(2):158-60 (Chi)

[Electrocardiographic studies of the modification of cardiac activity in cattle by adrenaline and noradrenaline with and without vagolysis (atropine) and beta-receptor blockade (propranolol)] Mielke H, et al. **Arch Exp Veterinarmed** 1985 Mar;39(2):193-206 (Eng. Abstr.) (Ger)

[Direct observation on microcirculation of cochlea. I. Effects of ADP and norepinephrine injections upon blood flow of radiating arteriole in guinea pigs] Fuzisaki Y, et al. **Nippon Jibiinkoka Gakkai Kaiho** 1985 Feb;88(2):128-37 (Eng. Abstr.) (Jpn)

[Urinary excretion of catecholamines in children with functional disorders of the digestive system] Szewczyk L, et al. **Pediatr Pol** 1984 Oct; 59(10):835-9 (Eng. Abstr.) (Pol)

[Catecholaminergic activity in children with nocturnal enuresis] Szewczyk L. **Pediatr Pol** 1984 Oct;59(10):841-5 (Eng. Abstr.) (Pol)

[Cyclic AMP content of autonomic ganglia as affected by catecholamines] Kniazeva LA, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):348-9 (Eng. Abstr.) (Rus)

[Circadian rhythms of adrenaline and noradrenaline excretion in man in normal conditions and after alcohol intake] Latenkov VP. **Biull Eksp Biol Med** 1985 Mar;99(3):344-6 (Eng. Abstr.) **(Rus)**

[Reactivity of the coronary vessels and adrenergic action] Lysenko LT, et al. **Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR** 1985; 8(1):82-8 **(Rus)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

[Effect of hypothermia on reuptake of neuromediators by synaptosomes] Babiichuk GA, et al. **Ukr Biokhim Zh** 1985 Mar-Apr;57(2):87-9 (Eng. Abstr.) **(Rus)**

[Normal values of dopamine, noradrenaline, adrenaline, and 5-hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb; 53(334):49-52 (Eng. Abstr.) **(Spa)**

[Radioimmunoanalysis of adrenaline and noradrenaline in the normal fetus at term] Martínez Alcalá FO, et al. **Ginecol Obstet Mex** 1983 Oct; 51(318):267-72 (Eng. Abstr.) **(Spa)**

NORMETANEPHRINE

Normetanephrine and metanephrine oxidized by both types of monoamine oxidase. Suzuki O, et al. **Experientia** 1985 May 15;41(5):634-6

Effects of clorgyline and (-)deprenyl on the deamination of normetanephrine and noradrenaline in strips and homogenates of the canine saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):396-400

NORTRIPTYLINE

Monitoring plasma concentration of nortriptyline. Methodological, pharmakokinetic and clinical aspects. Kragh-Sørensen P. **Dan Med Bull** 1985 Mar;32(1):29-53

Plasma nortriptyline and clinical response in depression. Murphy GE, et al. **J Affective Disord** 1985 Mar-Apr;8(2):123-9

Child and adolescent nortriptyline single dose kinetics predict steady state plasma levels and suggested dose: preliminary data. Geller B, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):154-8

Structural analysis of the epitope recognized by a monoclonal antibody directed against tricyclic antidepressants. Marullo S, et al. **J Immunol** 1985 Jul;135(1):471-7

OBSESSIVE-COMPULSIVE DISORDER

Two cases of obsessive-compulsive disorder with depression responsive to trazodone. Baxter LR Jr. **J Nerv Ment Dis** 1985 Jul;173(7):432-3

Obsessive-compulsive disorder. Insel TR. **Psychiatr Clin North Am** 1985 Mar;8(1):105-17 (85 ref.)

Clomipramine and imipramine in obsessive-compulsive disorder. Volavka J, et al. **Psychiatry Res** 1985 Jan;14(1):85-93

[Treatment of obsessive compulsive neurosis] Greenberg D, et al. **Harefuah** 1985 Mar 1;108(5):231-5 (Eng. Abstr.) **(Heb)**

ORGANIC MENTAL DISORDERS, SUBSTANCE-INDUCED

Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. Goldberg E. **Schizophr Bull** 1985;11(2):255-63

Tardive dysmentia : further comments. Jones BD. **Schizophr Bull** 1985; 11(2):187-9

OXAZEPAM

Protein binding of oxazepam and its glucuronide conjugates to human albumin. Boudinot FD, et al. **Biochem Pharmacol** 1985 Jun 15; 34(12):2115-21

Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam. Ansseau M, et al. **Neuropsychobiology** 1984;12(4):255-9

PARASYMPATHOMIMETICS

The mechanism by which adenosine and cholinergic agents reduce contractility in rat myocardium. Correlation with cyclic adenosine monophosphate and receptor densities. Linden J, et al. **Circ Res** 1985 May;56(5):728-35

Comparative inhibitory effects of pirenzepine and atropine on cholinergic stimulation of exocrine and endocrine rat pancreas. Otsuki M, et al. **Gastroenterology** 1985 Aug;89(2):408-14

Cholinomimetic drug RS 86, REM sleep, and depression [letter] Berger M, et al. **Lancet** 1985 Jun 15;1(8442):1385-6

Allosteric interactions between muscarinic agonist binding sites and effector sites demonstrated by the use of bisquaternary pyridinium oximes. Kloog Y, et al. **Life Sci** 1985 Jun 3;36(22):2127-36

Cholinergic stimulation of pancreatic amylase release and muscarinic receptors: effect of ionophore A23187. Larose L, et al. **Life Sci** 1985 Jul 22;37(3):255-61

Food and water intake of broiler chicks as affected by intracerebroventricular injections of cholinomimetics. Denbow DM, et al. **Poult Sci** 1985 May;64(5):991-4

Effects of nicotinic an muscarinic stimulation on calcium flux and catecholamine secretion in primary cultures of adrenal medullary cells. Watanabe J. **Tokushima J Exp Med** 1984 Dec;31(3-4):79-84

[Comparative sensitivity of the m-cholinoreceptors in various sites to cholinotropic agents] Angelova LA. **Farmakol Toksikol** 1985 Mar-Apr; 48(2):115-20 **(Rus)**

PARGYLINE

The metabolic fate of pargyline in rat liver microsomes. Weli AM, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1993-8

Localization in rat brain of binding sites for parkinsonian toxin MPTP: similarities with [3H]pargyline binding to monoamine oxidase. Rainbow TC, et al. **Brain Res** 1985 Mar 25;330(2):337-42

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222-31

PEMOLINE

Oral pemoline kinetics in hyperactive children. Sallee F, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):606-9

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222-31

PENTOBARBITAL

Interaction of penicillin and pentobarbital with inhibitory synaptic mechanisms in neocortex. Weiss DS, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):301-17

Blood versus bone marrow pentobarbital concentrations. Winek CL, et al. **Forensic Sci Int** 1985 Jan;27(1):15-24

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

gamma-Aminobutyric-acid- and pentobarbitone-gated chloride currents in internally perfused frog sensory neurones. Akaike N, et al. **J Physiol (Lond)** 1985 Mar;360:367-86

Effect of pentobarbital dependence on adenylate cyclase activity and calmodulin levels in rat cerebral cortex. Piascik MT, et al. **Life Sci** 1985 Jul 8;37(1):55-62

gamma-Aminobutyric acid partly mediates the pentobarbitone depression of synaptic excitation in the guinea-pig olfactory cortex in vitro. Steel L, et al. **Neurosci Lett** 1985 May 1;56(1):33-8

Barbiturate-enhanced paired-pulse depression in neonatal rats. Wilson DA, et al. **Neurosci Lett** 1985 May 14;56(2):101-6

Dose-related effects of pentobarbital on the genetic differences seen between paired, Roman high- or low-avoidance rats in a shuttle box. Driscoll P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):435-9

Involvement of the serotonergic system in the prolongation of pentobarbital sleeping time produced by prostaglandin D2. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):365-70

[Pre-synaptic inhibition and pentobarbital] Ohmura Y. **Masui** 1985 Jan; 34(1):2-8 (36 ref.) **(Jpn)**

PEPTIDES

Isolation from calf brain of a polypeptide fraction affecting aminoacylation of tRNA. Brzuszkiewicz-Żarnowska H, et al. **Acta Biochim Pol** 1984; 31(4):397-400

Corticotropin-releasing factor, sauvagine, and urotensin I: effects on blood flow. Lenz HJ, et al. **Am J Physiol** 1985 Jul;249(1 Pt 2):R85-90

Synthesis of side chain-protected amino acid phenylthiohydantoins and their use in quantitative solid-phase Edman degradation. Steiman DM, et al. **Anal Biochem** 1985 Feb 15;145(1):91-5

LHRH-like substance in the rat testis. Arimura A, et al. **Ann NY Acad Sci** 1984;438:390-3

Beta-endorphin, Met-enkephalin, and calcitonin in human semen: evidence for a possible role in human sperm motility. Fraioli F, et al. **Ann NY Acad Sci** 1984;438:365-70

Studies on the identification of a LHRH-like peptide in the rat testis. Hedger MP, et al. **Ann NY Acad Sci** 1984;438:371-81

GnRH-like factors in the rat testis and human seminal plasma. Swerdloff RS, et al. **Ann NY Acad Sci** 1984;438:382-9

Vascular, plasma membrane aminopeptidase M. Metabolism of vasoactive peptides. Palmieri FE, et al. **Biochem Pharmacol** 1985 Jul 1; 34(13):2309-17

Poly(DL-proline), a synthetic polypeptide behaving as an ion channel across bilayer membranes. De Santis P, et al. **Biophys Chem** 1985 Mar; 21(3-4):211-5

Peptide homologs, isosteres, and isomers: a general approach to structure-activity relationships. Goodman M. **Biopolymers** 1985 Jan;

24(1):137-55

Substance K excites dopaminergic and non-dopaminergic neurons in rat substantia nigra. Innis RB, et al. **Brain Res** 1985 Jun 3;335(2):381-3

Vasoactive intestinal peptide and PHI stimulate somatostatin release from rat cerebral cortical and diencephalic cells in dispersed cell culture. Tapia-Arancibia L, et al. **Brain Res** 1985 Jun 10;336(1):67-72

Proopiomelanocortin peptide immunocytochemistry in rhesus monkey brain. Khachaturian H, et al. **Brain Res Bull** 1984 Dec; 13(6):785-800

Localization of somatostatin-, bombesin-, and serotonin-like immunoreactivity in the lung of the fetal rhesus monkey. Dayer AM, et al. **Cell Tissue Res** 1985;239(3):621-5

Studies on peptides. CXXIII. Preparations of nine peptide fragments for the synthesis of human corticotropin releasing factor (hCRF). Fujii N, et al. **Chem Pharm Bull (Tokyo)** 1984 Dec;32(12):4786-96

Electrophysiological studies of peptide actions on the excitability of cultured nerve and pituitary cells. Barker JL, et al. **Clin Exp Hypertens** [A] 1984;6(10-11):1701-16 (32 ref.)

Proximal tubular hydrolysis and transport of small peptides. Carone FA, et al. **Contrib Nephrol** 1984;42:1-9

Absence of effect of the peptide PHI-27 on LH release in vitro. Miyake A, et al. **Endocrinol Jpn** 1984 Dec;31(6):821-4

Mouse salivary glands secrete a glucagon-degrading enzyme, not glucagon. Baldissera FG, et al. **Endocrinology** 1985 Jul;117(1):84-7

Selective regulation of carboxypeptidase peptide hormone-processing enzyme during enkephalin biosynthesis in cultured bovine adrenomedullary chromaffin cells. Hook VY, et al. **J Biol Chem** 1985 May 25;260(10):5991-7

Multiple forms of somatostatin-like immunoreactivity in the hypothalamus and amygdala of the rat: selective localization of somatostatin-28 in the median eminence. Pierotti AR, et al. **J Endocrinol** 1985 Jun; 105(3):383-9

Inhibition of sodium transport in frog skin and iodination of tyrosine in vitro by a peptide of renal origin. Fregly MJ, et al. **Klin Wochenschr** 1985;63 Suppl 3:102-6

Effects of bombesin on behavior. Cowan A, et al. **Life Sci** 1985 Jul 15; 37(2):135-45

Effect of bombesin on feeding behavior. Gibbs J. **Life Sci** 1985 Jul 15; 37(2):147-53

Bombesin evoked acetylcholine release from the guinea pig antrum Kantoh M, et al. **Life Sci** 1985 Jun 24;36(25):2445-52

Centrally-mediated bombesin effects on gastrointestinal motility. Porreca F, et al. **Life Sci** 1985 Jul 15;37(2):125-34

Central nervous system action of bombesin to inhibit gastric acid secretion. Tache Y, et al. **Life Sci** 1985 Jul 15;37(2):115-23 (43 ref.)

Characterization of a high molecular weight polypeptide from spinal cord with (Leu) enkephalin-immunoreactivity. Wahlström A, et al. **Neuropeptides** 1985 Feb;5(4-6):509-12

Cholecystokinin and bombesin suppress operant responding for food reward. Babcock AM, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):893-5

Biochemistry of peptide-secreting neurons. White JD, et al. **Physiol Rev** 1985 Jul;65(3):553-606 (313 ref.)

Cerebrospinal fluid cholecystokinin, bombesin and somatostatin in schizophrenia and normals. Gerner RH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):73-82

Physiological neuroendocrinology of peptides, steroids and other hormones in cerebrospinal fluid. Kee DB Jr, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):55-72 (131 ref.)

Distribution and vasomotor effects of peptide HI (PHI) in feline cerebral blood vessels in vitro and in situ. Edvinsson L, et al. **Regul Pept** 1985 Apr;10(4):345-56

Bombesin, neurotensin and pro-gamma-melanotropin immunoreactants in human milk. Ekman R, et al. **Regul Pept** 1985 Mar; 10(2-3):99-105

ACTH-releasing activity of urotensin I and ovine CRF: interactions with arginine vasotocin, isotocin and arginine vasopressin. Fryer J, et al. **Regul Pept** 1985 May;11(1):11-5

Effects of secretagogues on membrane potential and input resistance of pancreatic acinar cells of sheep. Katoh K, et al. **Res Vet Sci** 1985 Mar; 38(2):250-1

Effects of somatostatin-14 and somatostatin-28 on plasma hormonal and gastric secretory responses to cephalic and gastrointestinal stimulation in man. Konturek SJ, et al. **Scand J Gastroenterol** 1985 Jan; 20(1):31-8

[Effect of peptides on thermoregulation] He ZA. **Sheng Li Ko Hsueh Chin Chan** 1985 Jan;16(1):36-40 (33 ref.) **(Chi)**

[Stress and the endogenous opioid system. II. Stress, stress models and endogenous opioid peptides] Nieber K, et al. **Z Gesamte Inn Med** 1985 Feb 1;40(3):61-5 (Eng. Abstr.) **(Ger)**

PERSONALITY DISORDERS

Axis II personality disorders: diagnostic and treatment issues. Widiger TA, et al. **Hosp Community Psychiatry** 1985 Jun;36(6):619-27

Neuroticism and personality disorder in depression. Davidson J, et al. **J Affective Disord** 1985 Mar-Apr;8(2):177-82

PHENCYCLIDINE

Phencyclidine-induced inhibition of rat prolactin secretion: increased portal blood dopamine. Meltzer HY, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):143-6

Acute and chronic phencyclidine administration changes serotonin receptors in rat brain. Nabeshima T, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):129-30

Hemoperfusion of phencyclidine in the dog. Allen WR, et al. **Int J Artif Organs** 1985 Mar;8(2):101-4

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

Local anesthetic properties of opioids and phencyclidines: interaction with the voltage-dependent, batrachotoxin binding site in sodium channels. Creveling CR, et al. **Neuropeptides** 1985 Feb;5(4-6):253-6

Quantitative electrocortical changes in the rat induced by phencyclidine and other stimulants. Neal H, et al. **Neuropharmacology** 1985 Apr; 24(4):317-23

Effects of phencyclidine (PCP)-like drugs on turning behavior, 3H-dopamine uptake, and 3H-PCP binding. Johnson KM, et al. **Pharmacol Biochem Behav** 1985 May;22(5):731-5

PHENELZINE

Formation of beta-phenylethylamine from the antidepressant, beta-phenylethylhydrazine. Dyck LE, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1925-9

Drug interactions and vasoconstrictors used in local anesthetic solutions. Yagiela JA, et al. **Oral Surg Oral Med Oral Pathol** 1985 Jun; 59(6):565-71

'Pseudo-allergy': treatment with an MAO inhibitor. Ulwelling W. **Psychosomatics** 1985 Jun;26(6):535-6

PHENETHYLAMINES

Thermodynamics of agonist and antagonist binding to the alpha 1-adrenoceptor studied using [125I]BE 2254. Adams A, et al. **Biochem Biophys Res Commun** 1985 Apr 30;128(2):816-23

Formation of beta-phenylethylamine from the antidepressant, beta-phenylethylhydrazine. Dyck LE, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1925-9

Platelet monoamine oxidase inhibition by deprenyl and tranylcypromine: implications for clinical use. Simpson GM, et al. **Biol Psychiatry** 1985 Jun;20(6):684-7

The effects of amiflamine on cerebrospinal fluid amine metabolites in the rhesus monkey. Garrick NA, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):1-9

Selective inhibition of MAO-A but not MAO-B activity increases rat pineal melatonin. Oxenkrug GF, et al. **J Neural Transm** 1985; 61(3-4):265-70

m-Octopamine: normal occurrence with p-octopamine in mammalian sympathetic nerves. Ibrahim KE, et al. **J Neurochem** 1985 Jun; 44(6):1862-7

Inhibition of locus coeruleus neuronal activity by beta-phenylethylamine. Lundberg PA, et al. **Life Sci** 1985 May 13;36(19):1889-96

Effects of clorgyline and (-)deprenyl on the deamination of normetanephrine and noradrenaline in strips and homogenates of the canine saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):396-400

Cold-restraint stress and urinary endogenous beta-phenylethylamine excretion in rats. Snoddy AM, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):497-500

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222-31

PHENOBARBITAL

Monoclonal antibody directed isolation and amino-terminal sequence analysis of phenobarbital induced rat liver cytochromes P-450. Friedman FK, et al. **Biochem Biophys Res Commun** 1985 Jun 28; 129(3):926-33

Comparison of kidney, lung and liver coumarin 7-hydroxylases in phenobarbital pretreated DBA/2J and C57BL/6J mice. Kaipainen P, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1987-91

Induction of cytochrome P-450 by phenobarbital is mediated at the level of transcription. Pike SF, et al. **Biochem Pharmacol** 1985 Jul 15; 34(14):2489-94

Ultrastructural and immunohistochemical studies on non-ciliated cells of the tracheal epithelium of normal, phenobarbital-treated and 3-methylcholanthrene-treated mice. Ishimura K, et al. **Cell Tissue Res** 1985;240(2):501-4

Effect of peritoneal dialysis on serum concentrations of three drugs commonly used in pediatric patients. Chow-Tung E, et al. **Dev Pharmacol Ther** 1985;8(2):85-95

Diphenylbarbituric acid: its effects on neuromuscular and spinal cord function in the cat. Zavadil AP 3d, et al. **Epilepsia** 1985 Mar-Apr; 26(2):158-66

Long-term behavioral effects of phenobarbital in suckling rats. McBride MC, et al. **Exp Neurol** 1985 Jul;89(1):59-70

Response of meiotic chromosomes of mice to phenobarbitone. Subramanyam S, et al. **Indian J Exp Biol** 1984 Dec;22(12):666-9

On the mechanism of the inactivation of the major phenobarbital-inducible isozyme of rat liver cytochrome P-450 by chloramphenicol. Halpert JR, et al. **J Biol Chem** 1985 Jul 15; 260(14):8397-403

Gene structure of a major form of phenobarbital-inducible cytochrome P-450 in rat liver. Suwa Y, et al. **J Biol Chem** 1985 Jul 5; 260(13):7980-4

Kinetics of drug action in disease states. XIII. Effect of dialyzable component(s) of uremic blood on phenobarbital concentrations in rats at onset of loss of righting reflex. Hisaoka M, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):180-3

Effect of centrally acting drugs on ethanol detoxification enzymes in distinct rat brain regions. Messiha FS. **Neurobehav Toxicol Teratol** 1985 Mar-Apr;7(2):181-4

Stereological analysis of smooth endoplasmic reticulum and peroxisome proliferation in hepatocytes from neonatal and adult mice after phenobarbital administration. Kanai K, et al. **Okajimas Folia Anat Jpn** 1984 Dec;61(5):327-35

Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Picker M, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):389-93

The time course of [3H]PteGlu uptake and its incorporation into pteroylpolyglutamates in liver of phenobarbitone treated rats. Formiggini G, et al. **Pharmacol Res Commun** 1985 Feb;17(2):123-8

Biopharmaceutical investigation of rectal suppositories. Part 2(1): Pharmaceutical and biological availability of phenobarbital and phenobarbital-sodium. Minkov E, et al. **Pharmazie** 1985 Apr; 40(4):257-9

Neonatal phenobarbital imprinting of hepatic microsomal enzymes in adult rats: modulation by neonatal testosterone presence. Bagley DM, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):227-35

Inducible aldehyde dehydrogenases from rat liver cytosol. Simpson VJ, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):193-203

Reduction of ochratoxin A toxicity in mice treated with phenylalanine and phenobarbital. Moroi K, et al. **Toxicol Lett** 1985 Apr;25(1):1-5

Effects of rifampicin and phenobarbital on the fate of isoniazid and hydrazine in vivo in rats. Noda A, et al. **Toxicol Lett** 1985 Jun; 25(3):313-7

[Pharmacokinetics of injectable phenobarbital in the premature infant. Study of a new lyophilized form] Kossmann JC, et al. **Arch Fr Pediatr** 1985 Apr;42(4):317-20 (Eng. Abstr.) **(Fre)**

[Value of a charcoal column of our design for hemoperfusion in the treatment of experimental barbiturate poisoning] Bakula S, et al. **Pol Tyg Lek** 1985 Feb 25;40(8):217-9 (Eng. Abstr.) **(Pol)**

[Comparative study of zixoryn and phenobarbital as enzyme inducers of the liver mono-oxygenase system] Loginov AS, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):437-40 (Eng. Abstr.) **(Rus)**

[Immunomorphological study of cytochrome P-450PB induction in the liver of rat embryos and pregnant females after phenobarbital administration] Popova NV, et al. **Biull Eksp Biol Med** 1985 Mar; 99(3):366-8 (Eng. Abstr.) **(Rus)**

[Nomogram for phenobarbital dosage in children (letter)] Armijo JA, et al. **An Esp Pediatr** 1985 Apr 15;22(5):418-21 **(Spa)**

PHENOTHIAZINE TRANQUILIZERS

Lipids and apolipoproteins in patients treated with major tranquilizers. Sasaki J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):684-7

Behavioral indications for phenothiazine and benzodiazepine tranquilizers in dogs. Hart BL. **J Am Vet Med Assoc** 1985 Jun 1;186(11):1192-4

[Ecto-ATPases in leukocytes and its modification by drugs] Hehl EM, et al. **Allerg Immunol (Leipz)** 1985;31(1):17-23 (Eng. Abstr.) **(Ger)**

[Biotransformation of Chlorphenethazin (Elroquil, Marophen)] Pfeifer S, et al. **Pharmazie** 1985 Jan;40(1):37-9 (Eng. Abstr.) **(Ger)**

[Clinico-humoral manifestations secondary to treatment with injectable Tisercin] Gheorghe M, et al. **Rev Med Interna [Neurol Psihiatr]** 1985 Jan-Mar;30(1):71-2 **(Rum)**

PHENOTHIAZINES

Interaction of phenothiazine drugs with human ceruloplasmin. Relation between activation of catecholamine neurotransmitter oxidation and electron donating ability of phenothiazine drugs. de Mol NJ. **Biochem Pharmacol** 1985 Aug 1;34(15):2605-9

Reciprocal effects of phenothiazines and naphthalene sulfonamides on the external ATP-dependent permeability change in Chinese hamster ovary cells. Kitagawa T, et al. **Biochim Biophys Acta** 1985 Apr 26; 815(1):25-32

Selective effects of CAPP1-calmodulin on its target proteins. Newton D, et al. **Biochim Biophys Acta** 1985 Jun 30;845(3):533-9

Cimetidine inhibition of ethmozine metabolism. Biollaz J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):665-8

Pharmacokinetics of dixyrazine: low bioavailability, improved by food intake. Liedholm H, et al. **Drug Nutr Interact** 1985;3(2):87-92

The involvement of nucleosomes in Giemsa staining of chromosomes. A new hypothesis on the banding mechanism. van Duijn P, et al. **Histochemistry** 1985;82(4):363-76

Assessment of the potential pharmacokinetic interaction between digoxin and ethmozine. MacFarland RT, et al. **J Clin Pharmacol** 1985 Mar; 25(2):138-43

A versatile and simple method for staining nervous tissue using Giemsa dye. Iñiguez C, et al. **J Neurosci Methods** 1985 Mar;13(1):77-86

Application of Azure C for the extractive spectrophotometric determination of microgram amounts of penicillin. Gowda AT, et al. **J Pharmacol Methods** 1985 Jun;13(3):275-80

[Interaction of oxygen anion radicals with eye melanins and ommochromes] Lapina VA, et al. **Dokl Akad Nauk SSSR** 1985; 280(6):1463-5 **(Rus)**

PHENOXYBENZAMINE

Influence of intracerebroventricular phenoxybenzamine on the renal action of intracerebroventricular morphine. Kook YJ, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):289-98

PHENYLALANINE

Identification of peptides containing tryptophan, tyrosine, and phenylalanine using photodiode-array spectrophotometry. Yang CY, et al. **Anal Biochem** 1985 Feb 15;145(1):67-72

L-Phenylalanine and L-tyrosine catabolism by selected Streptomyces species. Pometto AL 3d, et al. **Appl Environ Microbiol** 1985 Mar; 49(3):727-9

Abilities of some tryptophan and phenylalanine derivatives to inhibit gastric acid secretion. Magous R, et al. **Biochim Biophys Acta** 1985 May 30;845(2):158-62

The effect of the intracellular sodium level on the activity of amino acid transport systems L and A in SV40 3T3 cells. Petronini PG, et al. **Biochim Biophys Acta** 1985 May 28;815(3):361-8

Clues from Xanthomonas campestris about the evolution of aromatic biosynthesis and its regulation. Whitaker RJ, et al. **J Mol Evol** 1984-85; 21(2):139-49

The effect of phenylalanine on intracellular pH and sodium activity in proximal convoluted tubule cells of the frog kidney. Messner G, et al. **Pflugers Arch** 1985 May;404(2):145-9

Reduction of ochratoxin A toxicity in mice treated with phenylalanine and phenobarbital. Moroi K, et al. **Toxicol Lett** 1985 Apr;25(1):1-5

PHENYLPROPANOLAMINE

Determination of phenylpropanolamine hydrochloride and acetaminophen in pharmaceutical preparations by Raman spectroscopy. King TH, et al. **J Pharm Sci** 1985 Apr;74(4):443-7

Effects of reserpine and adrenal demedullation on brown adipose tissue thermogenesis induced by dl-phenylpropanolamine. Wellman PJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Feb;47(2):211-20

Vascular effects of phenylpropanolamine on human nasal mucosa. Bende M, et al. **Rhinology** 1985 Mar;23(1):43-8

PHENYTOIN

Effects of ibuprofen on the disposition kinetics of phenytoin in pregnant rats. Cleveland PA, et al. **Biopharm Drug Dispos** 1985 Apr-Jun; 6(2):167-76

Audit of a monitoring service for free phenytoin. Peterson GM, et al. **Br J Clin Pharmacol** 1985 May;19(5):693-7

Effect of phenytoin on intracellular calcium and intracellular protein changes during pentylenetetrazole-induced bursting activity in snail neurons. Sugaya E, et al. **Brain Res** 1985 Feb 18;327(1-2):161-8

A theoretical and an in vitro experimental model for estimation of drug transfer through the human placenta. Mor L, et al. **Contrib Gynecol Obstet** 1985;13:155-7

Phenytoin clearance by continuous ambulatory peritoneal dialysis. Hays DP, et al. **Drug Intell Clin Pharm** 1985 Jun;19(6):429-31

Effects of phenytoin administration on vestibular function in the rat. Mameli O, et al. **Epilepsia** 1985 May-Jun;26(3):262-7

The effects of phenytoin on serum and organ concentrations of zinc and copper in cat. Palm R, et al. **Epilepsia** 1985 Mar-Apr;26(2):184-8

A rapid method for separation and estimation of free phenytoin in serum. Ahmad SN, et al. **Indian J Exp Biol** 1984 Nov;22(11):605-7

Phenytoin bioavailability assessed by steady state serum concentrations. Halkin H, et al. **Isr J Med Sci** 1985 Apr;21(4):327-30

Phenytoin pharmacokinetics in therapeutic plasmapheresis. Nasca TJ, et al. **J Clin Pharmacol** 1985 May-Jun;25(4):302-4

The use of a monosaccharide linkage group in a heterologous solid-phase enzyme immunoassay for phenytoin. Hinds JA, et al. **J Immunol Methods** 1985 Jun 25;80(2):239-53

Expanding physician duties and patients rights in wrongful life: Harbeson

v. Parke-Davis, Inc. Skolnick M. **Med Law** 1985;4(3):283-98

Mutagenic potential of anticonvulsant diphyenylhydantoin (DPH) on human lymphocytes in vitro. Maurya AK, et al. **Methods Find Exp Clin Pharmacol** 1985 Mar;7(3):109-12

Preparation of a phenytoin beta-cyclodextrin complex and evaluation of a suspension and a tablet dosage form prepared from the complex. Hegde RP, et al. **Pharm Acta Helv** 1985;60(2):53-7

Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Picker M, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):389-93

Phenytoin and trimethadione: pharmacokinetics, embryotoxicity, and maternal toxicity. Khera KS. **Prog Clin Biol Res** 1985;163C:317-22

Phenytoin teratogenicity and effects on embryonic and maternal folate metabolism. Hansen DK, et al. **Teratology** 1985 Jun;31(3):363-71

The water, DNA, collagen and noncollagen protein contents in embryos after maternal administration of a teratogenic dose of phenytoin. Hicks HE, et al. **Toxicol Lett** 1985 Apr;25(1):41-6

[Study on phenytoin-selective electrode] Yao SZ, et al. **Yao Hsueh Hsueh Pao** 1984 Jun;19(6):455-60 (Eng. Abstr.) **(Chi)**

[Effects of diphenylhydantoin on thyroid function] Giroud M, et al. **Therapie** 1985 Mar-Apr;40(2):119-22 (Eng. Abstr.) **(Fre)**

[Experimental study of the effects of diphenylhydantoins and estrogens in rats. I. Microbiological aspects of changes in the gingival flora of rats treated with diphenylhydantoins] Bascones A, et al. **Rev Esp Estomatol** 1984 May-Jun;32(3):147-54 **(Spa)**

[Clinical pharmacology of carbamazepine--a comparison with phenytoin] Bertilsson L, et al. **Lakartidningen** 1985 Apr 10;82(15):1355-60 **(Swe)**

PHOBIC DISORDERS

Agoraphobia. Horn TL. **Am Fam Physician** 1985 Jul;32(1):165-73

Combined pharmacological and behavioral treatment for agoraphobia. Telch MJ, et al. **Behav Res Ther** 1985;23(3):325-35

Dysmorphophobia [letter] Jenike MA. **Br J Psychiatry** 1985 Mar; 146:326

Agoraphobia. Pyke JM, et al. **Can Nurse** 1985 Jun;81(6):18-21

Modification of disease phobia using a multifaceted exposure program. Tearnan BH, et al. **J Behav Ther Exp Psychiatry** 1985 Mar; 16(1):57-61

Catecholamine secretion as a function of perceived coping self-efficacy. Bandura A, et al. **J Consult Clin Psychol** 1985 Jun;53(3):406-14

Psychophysiological outcome of behavioral and pharmacological treatments of agoraphobia. Michelson L, et al. **J Consult Clin Psychol** 1985 Apr;53(2):229-36

[Agoraphobia] Pyke JM, et al. **Infirm Can** 1985 Jun;27(6):24-7 **(Fre)**

PHYSOSTIGMINE

Antagonism of physostigmine induced lethality by a combination of scopolamine and methscopolamine. Janowsky DS, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Feb;56(2):154-7

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196-201

Physostigmine reverses memory deficits produced by pretraining electrical stimulation of the dorsal hippocampus in mice. Micheau J, et al. **Behav Brain Res** 1985 Apr;15(2):75-81

Physostigmine effects on serotonin uptake in human blood platelets. Rausch JL, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):91-6

Determination of physostigmine in plasma and brain by HPLC. Somani SM, et al. **J Anal Toxicol** 1985 Mar-Apr;9(2):71-5

Plasma physostigmine concentrations after oral administration [letter] Sharpless NS, et al. **Lancet** 1985 Jun 15;1(8442):1397-8

Inhibitory effects of dopamine and isoprenaline on antral motor activity stimulated by acetylcholine or physostigmine in vitro. Ulvestad A, et al. **Scand J Gastroenterol** 1985 Mar;20(2):243-6

[The acute toxicity of eserine, VX and paraoxon for the establishment of a mathematical model for extrapolation to humans] Leblic C, et al. **Arch Belg** 1984;Suppl:226-42 (Eng. Abstr.) **(Fre)**

[Stabilization of physostigmine salicylate injection solutions] Trose D, et al. **Pharmazie** 1985 Feb;40(2):124-6 (Eng. Abstr.) **(Ger)**

PILOCARPINE

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196-201

Prevention of intraocular pressure elevation following neodymium-YAG laser posterior capsulotomy. Richter CU, et al. **Arch Ophthalmol** 1985 Jul;103(7):912-5

Comparison of the effects of chronic administration of ciclazindol and desipramine on pupillary responses to tyramine, methoxamine and pilocarpine in healthy volunteers. Kerr FA, et al. **Br J Clin Pharmacol** 1985 May;19(5):639-47

[The stability of pilocarpine hydrochloride in eyedrops] Porst H, et al. **Pharmazie** 1985 Jan;40(1):23-9 (Eng. Abstr.) **(Ger)**

PITUITARY HORMONE RELEASING HORMONES

Gonadotropin releasing hormone stimulates the formation of inositol phosphates in rat anterior pituitary tissue. Schrey MP. **Biochem J** 1985 Mar 1;226(2):563-9

Modulation of lordosis behaviour in the female rat by corticotropin releasing factor, beta-endorphin and gonadotropin releasing hormone in the mesencephalic central gray. Sirinathsinghji DJ. **Brain Res** 1985 Jun 10;336(1):45-55

Mechanisms of gonadotropin-releasing hormone and prostaglandin action on luteal cells. Leung PC. **Can J Physiol Pharmacol** 1985 Mar; 63(3):249-56 (79 ref.)

Increased gonadotropin-releasing hormone pulse frequency associated with estrogen-induced luteinizing hormone surges in ovariectomized ewes. Clarke IJ, et al. **Endocrinology** 1985 Jun;116(6):2376-83

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893-8

The frequency of gonadotropin-releasing hormone stimulation determines the number of pituitary gonadotropin-releasing hormone receptors. Katt JA, et al. **Endocrinology** 1985 May;116(5):2113-5

Release of luteinizing hormone and follicle-stimulating hormone from pituitaries of lactating rats by gonadotropin-releasing hormone and high potassium concentration. Smith MS. **Endocrinology** 1985 May; 116(5):1826-34

FSH and LH response to testosterone and gonadotropin-releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter; 10(4):183-7

Influence of the frequency of gonadotropin-releasing hormone (GnRH) administration on ovulatory responses in women with anovulation. Bringer J, et al. **Fertil Steril** 1985 Jul;44(1):42-8

Structure-activity relationships of mammalian, chicken, and salmon gonadotropin releasing hormones in vivo in goldfish. Peter RE, et al. **Gen Comp Endocrinol** 1985 May;58(2):231-42

Successful pregnancy following ovulation induction with pulsatile GnRH. O'Herlihy C, et al. **Ir Med J** 1985 May;78(5):133-4, 136

Hypothalamic gonadotrophin-releasing hormone and pituitary and plasma FSH and prolactin during photostimulation and photorefractoriness in intact and thyroidectomized starlings (Sturnus vulgaris). Dawson A, et al. **J Endocrinol** 1985 Apr;105(1):71-7

Diacylglycerols and protein kinase C. Potential amplifying mechanism for Ca2+-mediated gonadotropin-releasing hormone-stimulated luteinizing hormone release. Harris CE, et al. **Mol Pharmacol** 1985 May; 27(5):532-6

Differential suppression of follicle-stimulating hormone and luteinizing hormone secretion in vivo by a gonadotropin-releasing hormone antagonist. Grady RR, et al. **Neuroendocrinology** 1985 Mar; 40(3):246-52

[Pulsatile administration of gonadoliberin by subcutaneous route in the induction of ovulation (letter)] Fenichel P, et al. **Presse Med** 1985 Apr 13;14(15):846 **(Fre)**

[The effect of blood serum on GnRH-loaded multilayer liposomes: proof of a correlation between their size and the inclusion stability of the peptide hormones] Schäfer H, et al. **Pharmazie** 1985 Feb;40(2):131-2 **(Ger)**

PITUITARY HORMONES, ANTERIOR

Ketanserin without effects on basal anterior pituitary hormone secretion in healthy subjects. Gordin A, et al. **J Endocrinol Invest** 1985 Feb; 8(1):73-5

Idiopathic premature ovarian failure. A clinical and biochemical study. Naidoo C, et al. **S Afr Med J** 1985 Jul 20;68(2):91-4

PROGESTERONE

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

Phorbol ester regulation of rat granulosa cell prostaglandin and progesterone accumulation. Kawai Y, et al. **Endocrinology** 1985 Jun; 116(6):2320-6

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953-9

Exogenous progesterone for luteal support following gonadotropin-releasing hormone ovulation induction: case report. Berger NG, et al. **Fertil Steril** 1985 Jul;44(1):133-5

Hormonal influence on the response of the uterus of the Brazilian marsupial Didelphis albiventris to adrenergic drugs. Rocha LR, et al. **Gen Comp Endocrinol** 1985 May;58(2):179-85

Progesterone-induced LHRH release in vitro is an estrogen--as well as Ca++- and calmodulin-dependent secretory process. Drouva SV, et al. **Neuroendocrinology** 1985 Apr;40(4):325-31

Effects of progesterone on hypothalamic and plasma LHRH. Peduto JC, et al. **Neuroendocrinology** 1985 Mar;40(3):238-45

PROLACTIN

Age-related changes in prolactin and growth hormone release from pituitary glands in vitro. Hall TR, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):479-84

Plasma prolactin in the rat during suckling without prior separation from pups. Mattheij JA, et al. **Acta Endocrinol (Copenh)** 1985 Apr; 108(4):468-74

Temporary increase in the circulating prolactin levels during and after consecutive administration of bromocriptine-mesilate (CB-154) in female mice. Mori T, et al. **Acta Endocrinol (Copenh)** 1985 Jun; 109(2):208-13

Neuro-endocrine effects of isotheoline. Zhelyazkov D, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):53-8

Serum concentrations of thyroxine, 3,5,3'-triiodothyronine, thyrotropin, and prolactin in dogs before and after thyrotropin-releasing hormone administration. Kaufman J, et al. **Am J Vet Res** 1985 Feb; 46(2):486-92

Dopamine D2 receptors modulate neurotransmitter-regulated calcium ion gates. Memo M, et al. **Ann Ist Super Sanita** 1984;20(1):5-10

Effect of prolactin and bromocriptine administration on testicular metabolism in albino rats. Dhananjaya Reddy Y, et al. **Arch Int Physiol Biochim** 1985 May;93(1):19-23

Dose-dependent inhibition of the preovulatory surges of gonadotropins and prolactin by the antiestrogen CI-628: possible sites of action. De Paolo LV. **Biol Reprod** 1985 May;32(4):745-52

The proestrous surge of prolactin enhances sexual receptivity in the rat. Witcher JA, et al. **Biol Reprod** 1985 May;32(4):834-9

Effect of feed and water deprivation or force-feeding on plasma prolactin concentration in turkey hens. Zadworny D, et al. **Biol Reprod** 1985 Mar;32(2):241-7

Intolerance of bromocriptine: is metergoline a satisfactory alternative? Casson IF, et al. **Br Med J [Clin Res]** 1985 Jun 15; 290(6484):1783-4

Effects of prostaglandin F2 alpha on prolactin secretion in the fowl. Hall TR, et al. **Br Poult Sci** 1985 Apr;26(2):239-45

The effect of long-term diethylstilbestrol treatment or hyperprolactinemia on the response of the tuberoinfundibular dopamine neurons to elevated prolactin. Morgan WW, et al. **Brain Res** 1985 Jun 3;335(2):330-3

Evaluation of the central dopaminergic activity in gestational hyperprolactinaemia by means of the electroretinographic technique. De Luca Brunori I, et al. **Clin Exp Obstet Gynecol** 1985; 12(1-2):13-5

p-Tyramine, a natural amine, inhibits prolactin release in vivo. Becú-Villalobos D, et al. **Endocrinology** 1985 May;116(5):2044-8

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

D-Trp-6-luteinizing hormone-releasing hormone inhibits hyperprolactinemia in female rats. Debeljuk L, et al. **Endocrinology** 1985 Jun;116(6):2227-31

5-Hydroxyeicosatetraenoic acid increases prolactin release from rat anterior pituitary cells. Koike K, et al. **Endocrinology** 1985 May; 116(5):1813-7

Studies on the effects of catecholestrogens on prolactin secretion by cultured normal rat anterior pituitary cells. Lamberts SW, et al. **Endocrinology** 1985 Jun;116(6):2631-6

Prolactin metabolic clearance and resistance to dopaminergic suppression in acute uremia. McKenna TM, et al. **Endocrinology** 1985 May; 116(5):2003-7

Rapid effects of hyperprolactinemia on basal prolactin secretion and dopamine turnover in the medial and lateral median eminence. Selmanoff M. **Endocrinology** 1985 May;116(5):1943-52

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

Phencyclidine-induced inhibition of rat prolactin secretion: increased portal blood dopamine. Meltzer HY, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):143-6

Inhibition by antiserum to vasoactive intestinal polypeptide (VIP) of prolactin secretion induced by serotonin in the rat. Ohta H, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):409-12

Number of dopamine neurons predicts prolactin levels in two inbred mouse strains. Sved AF, et al. **Experientia** 1985 May 15;41(5):644-6

Pergolide mesylate inhibits exercise-induced prolactin release in man. De Meirleir K, et al. **Fertil Steril** 1985 Apr;43(4):628-31

Hyperprolactinaemia and testosterone production. Observations in 2 men on long-term dialysis. Stegmayr B, et al. **Horm Res** 1985; 21(4):224-8

Chronic treatment with 2-alpha-bromocriptine in women with the hyperprolactinemic syndrome. Eshel A, et al. **Int J Fertil** 1984; 29(4):247-53

Effects of induced hypoprolactinemia on testicular function during gonadal maturation in the rat. Suescun MO, et al. **J Androl** 1985 Mar-Apr;6(2):77-82

Levels of dopamine and thyrotrophin-releasing hormone in hypophysial stalk blood during an oestrogen-stimulated surge of prolactin in the ovariectomized rat. de Greef WJ, et al. **J Endocrinol** 1985 Apr; 105(1):107-12

Possible role of prolactin in the inhibitory effect of testosterone on the hypothalamic-pituitary-testicular axis in the rat. Tresguerres JA, et al. **J Endocrinol** 1985 Jun;105(3):423-7

The putative dopamine autoreceptor agonist B-HT 920 decreases nigral dopamine cell firing rate and prolactin release in rat. Eriksson E, et al. **Life Sci** 1985 May 13;36(19):1819-27

The mechanism of action of cyproheptadine on prolactin release by cultured anterior pituitary cells. Lamberts SW, et al. **Life Sci** 1985 Jun 10;36(23):2257-62

Adrenalectomy does not prevent the hyperprolactinemic, induced sexual behavior deficits in CDF male rats. Shrenker P, et al. **Life Sci** 1985 May 13;36(19):1881-8

Calcium mobilization potentiates prolactin release induced by protein kinase C activators. Koike K, et al. **Mol Cell Endocrinol** 1985 May; 40(2-3):137-43

Hypoprolactinemia induced by hypophysectomy and long-term bromocriptine treatment decreases tuberoinfundibular dopaminergic neuronal activity and the responsiveness of these neurons to prolactin. Demarest KT, et al. **Neuroendocrinology** 1985 May;40(5):369-76

Dopamine-induced physical barrier to inhibit prolactin release in mammotrophs disappears during resumption of prolactin secretion. Reifel CW, et al. **Neuroendocrinology** 1985 May;40(5):438-43

Cimetidine-induced prolactin release: possible involvement of the GABA-ergic system. Sibilia V, et al. **Neuroendocrinology** 1985 Mar; 40(3):189-92

gamma-Aminobutyric acid decreases levels of messenger ribonucleic acid encoding prolactin in the rat pituitary. Loeffler JP, et al. **Neurosci Lett** 1985 Jan 7;53(1):121-5

Serum and cerebrospinal fluid prolactin patterns during neuroleptic treatment in schizophrenic patients. Rimón R, et al. **Pharmacopsychiatry** 1985 May;18(3):252-4

Cyproheptadine stimulated prolactin release in the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Poult Sci** 1985 May; 64(5):1038-40

Central inhibitory action of TRH on prolactin secretion in the rat. Ohta H, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):9-12

Dose-dependent growth hormone, prolactin and cortisol stimulation after i.v. administration of desimipramine in human subjects. Laakmann G, et al. **Psychoneuroendocrinology** 1985;10(1):83-93

Effect of benztropine on the diurnal prolactin responses to haloperidol. Nathan RS, et al. **Psychoneuroendocrinology** 1985;10(1):71-6

Behavior therapy, pimozide treatment and prolactin secretion in anorexia nervosa. Weizman A, et al. **Psychother Psychosom** 1985;43(3):136-40

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[The mechanism of induction of ovulation by bromocriptine in euprolactinemic anovulation--the role of occult hyperprolactinemia in anovulation] Mori H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jan 20;61(1):38-47 (Eng. Abstr.) **(Jpn)**

[The effects of bromocriptine on anovulatory patients with high LH and euprolactinemia] Mori H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jan 20;61(1):48-55 (Eng. Abstr.) **(Jpn)**

[Specific proteases which degrade prolactin in the mammary glands; subcellular localization and inhibitory analysis] Marinchenko GV. **Biokhimiia** 1985 Feb;50(2):200-10 (Eng. Abstr.) **(Rus)**

[Lactation and re-induction of lactation] Vargas W. **GEN** 1983 Jan-Jun; 37(1-2):16-28 **(Spa)**

PROMETHAZINE

Effects of some motion sickness suppressants on static and dynamic tracking performance. Schroeder DJ, et al. **Aviat Space Environ Med** 1985 Apr;56(4):344-50

Changes in the disposition of promethazine during multiple dosing in the rabbit. Taylor G, et al. **J Pharm Pharmacol** 1985 Apr;37(4):243-7

[Attempted suicide with barbiturate after glue sniffing] Sami HO, et al. **Orv Hetil** 1985 Mar 31;126(13):781-3 (Eng. Abstr.) **(Hun)**

PROPANEDIOLS

Propylene glycol-induced heparin resistance during nitroglycerin infusion. Col J, et al. **Am Heart J** 1985 Jul;110(1 Pt 1):171-3

Solubilization by cosolvents I: organic solutes in propylene glycol-water mixtures. Yalkowsky SH, et al. **J Pharm Sci** 1985 Apr;74(4):416-21

PROPERICIAZINE

Measurement of propericiazine in plasma by capillary gas chromatography and selected ion monitoring detection. De Leenheer AP, et al. **Biomed Mass Spectrom** 1985 Jan;12(1):25-9

PROPRANOLOL

Effect of propranolol on post-traumatic hypophosphataemia and catecholamine secretion. Lovén L, et al. **Acta Chir Scand** 1985; 151(3):201-4

Perturbations of sarcolemmal and microsomal enzymes by amphiphilic lipids and drugs. Weglicki WB, et al. **Adv Myocardiol** 1985;6:127-36

Effects of cardioselective and nonselective beta-adrenergic blockade on the performance of highly trained runners. Anderson RL, et al. **Am J Cardiol** 1985 Apr 26;55(10):149D-154D

Effect of selective and nonselective beta-adrenoceptor blockade on thermoregulation during prolonged exercise in heat. Gordon NF. **Am J Cardiol** 1985 Apr 26;55(10):74D-78D

Cardiovascular and pharmacokinetic consequences of combined administration of verapamil and propranolol in dogs. Hamann SR, et al. **Am J Cardiol** 1985 Jul 1;56(1):147-56

Effects of intravenous infusion of esmolol and propranolol on biventricular performance at rest and during exercise as assessed by quantitative radionuclide angiography. Iskandrian AS, et al. **Am J Cardiol** 1985 May 1;55(11):1287-92

Beta blockade in the compensation for bed-rest cardiovascular deconditioning: physiologic and pharmacologic observations. Sandler H, et al. **Am J Cardiol** 1985 Apr 26;55(10):114D-119D

Exercise training during long-term beta-blockade treatment in healthy subjects. Savin WM, et al. **Am J Cardiol** 1985 Apr 26; 55(10):101D-109D

Cardiorespiratory alterations consequent to endurance exercise training during chronic beta-adrenergic blockade with atenolol and propranolol. Wilmore JH, et al. **Am J Cardiol** 1985 Apr 26;55(10):142D-148D

Acute response to submaximal and maximal exercise consequent to beta-adrenergic blockade: implications for the prescription of exercise. Wilmore JH, et al. **Am J Cardiol** 1985 Apr 26;55(10):135D-141D

Effects of aspirin and propranolol alone and in combination on hemostatic determinants in the healthy cat. Allen DG, et al. **Am J Vet Res** 1985 Mar;46(3):660-3

Effect of propranolol on human spermatozoal in vitro hamster ova penetration. Chan SY, et al. **Arch Androl** 1984;12 Suppl:79-82

Renin response to captopril in conscious dogs pretreated with indomethacin or propranolol. Kamijo T, et al. **Arch Int Pharmacodyn Ther** 1985 Mar;274(1):56-64

Modification of propranolol binding to alpha-1-acid glycoprotein by serum albumin. Chauvelot-Moachon L, et al. **Biochem Pharmacol** 1985 May 1;34(9):1591-4

Reduced hepatic uptake of propranolol in rats with acute renal failure. Hori R, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2679-83

Adrenergic ligand binding in human serum. Sager G, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2812-5

Semi-empirical conformational analysis of propranolol interacting with dipalmitoylphosphatidylcholine. Brasseur R, et al. **Biochim Biophys Acta** 1985 May 28;815(3):341-50

Penbutolol and propranolol: a comparison of their effects on antipyrine clearance in man. Bax ND, et al. **Br J Clin Pharmacol** 1985 May; 19(5):593-6

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445-51

The effects of propranolol and digoxin on the acute vascular responses to frusemide in normal man. Johnston GD, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):417-21

Pre-dosing plasma concentrations and beta-adrenoceptor blocking effects during repeated once daily dosing with 160 mg sustained-release propranolol (Inderal LA) and 16/260 oxprenolol Oros to healthy volunteers. Moppert J, et al. **Br J Clin Pharmacol** 1985; 19 Suppl 2:197S-201S

Comparative effects of adimolol, labetalol and propranolol on heart rate and blood pressure in man. Riddell JG, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):405-10

Ethnic differences in human lymphocytic cyclic AMP production after isoprenaline stimulation and propranolol blockade. Venter CP, et al. **Br J Clin Pharmacol** 1985 Feb;19(2):187-90

Enhancement of the antiaggregatory activity of prostacyclin by propranolol in human platelets. Callahan KS, et al. **Circulation** 1985 Jun;71(6):1237-46

Propranolol: pooled Michaelis-Menten parameters and the effect of input rate on bioavailability. Wagner JG. **Clin Pharmacol Ther** 1985 May; 37(5):481-7

Quantitative account of propranolol metabolism in urine of normal man. Walle T, et al. **Drug Metab Dispos** 1985 Mar-Apr;13(2):204-9

Comparative beta-adrenoceptor blocking effect and pharmacokinetics of bucindolol and propranolol in man. Maury M, et al. **Eur J Clin Pharmacol** 1985;27(6):649-56

Effects of propranolol during pregnancy and development of rats. II. Adverse effects on development. Schoenfeld N, et al. **Eur J Pediatr** 1985 Jan;143(3):194-5

The contribution of vasopressin and angiotensin to the maintenance of blood pressure after autonomic blockade. Hiwatari M, et al. **Hypertension** 1985 Jul-Aug;7(4):547-53

Lack of influence of aluminum hydroxide on the bioavailability and beta-adrenoceptor blocking activity of propranolol. Hong CY, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 May;23(5):244-6

Impairment of isoniazid clearance by propranolol. Santoso B. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):134-6

Comparative pharmacokinetics of intravenous propranolol in black and white volunteers [letter] Venter CP, et al. **J Cardiovasc Pharmacol** 1985 Mar-Apr;7(2):409-10

Augmentation by propranolol of growth hormone-releasing hormone-(1-44)-NH2-induced growth hormone release in normal short and normal children. Chihara K, et al. **J Clin Endocrinol Metab** 1985 Aug;61(2):229-33

Plasma concentration-response relationships of two formulations of propranolol. DeLeve LD, et al. **J Clin Pharmacol** 1985 Apr; 25(3):182-6

Synthesis of 4'-hydroxypropranolol sulfate, a major non-beta-blocking propranolol metabolite in man. Oatis JE Jr, et al. **J Med Chem** 1985 Jun;28(6):822-4

Effect of the sialylation state of alpha 1-acid glycoprotein on propranolol binding. Primozic S, et al. **J Pharm Sci** 1985 Apr;74(4):473-5

Reduced extraction of l-propranolol by perfused rat liver in the presence of uremic blood. Terao N, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):277-84

Effect of chronic treatment of propranolol on lipid metabolism in spontaneously hypertensive rats (SHR). Tonooka M, et al. **Jpn J Pharmacol** 1985 Apr;37(4):335-44

Competitive binding of quinidine, propranolol, and 4-OH-propranolol to human plasma very low-density (VLDL) and low-density (LDL) lipoproteins. Ho Ngoc-Ta Trung A, et al. **Pharm Acta Helv** 1985; 60(4):106-9

The effects of d-propranolol and captopril on post-ischaemic acute renal failure in rats. Ishigami M, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985;21:843-8

[Effect of the central action of propranolol on coronary circulation in dogs] Xie BZ, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar; 6(1):33-6 (Eng. Abstr.) **(Chi)**

[Electrocardiographic studies of the modification of cardiac activity in cattle by adrenaline and noradrenaline with and without vagolysis (atropine) and beta-receptor blockade (propranolol)] Mielke H, et al. **Arch Exp Veterinarmed** 1985 Mar;39(2):193-206 (Eng. Abstr.) **(Ger)**

[The anticonvulsant action of propranolol in pentylenetetrazole-induced convulsions] Lasek R, et al. **Pharmazie** 1985 Apr;40(4):271-2 **(Ger)**

PROSTAGLANDINS

Catecholamines and contractility of the human myometrium at term: a possible role for prostaglandins. Wikland M, et al. **Acta Physiol Hung** 1985;65(3):331-4

Effects of prostaglandins on vasoconstrictor action in isolated renal arterioles. Edwards RM. **Am J Physiol** 1985 Jun; 248(6 Pt 2):F779-84

Carbon tetrachloride-induced eicosanoid synthesis and enzyme release from rat peritoneal leucocytes. Lynch TJ, et al. **Biochem Pharmacol** 1985 May 1;34(9):1515-22

Modulatory effects of prostaglandin D2, E2 and F2 alpha on the postsynaptic actions of inhibitory and excitatory amino acids in cerebellar Purkinje cell dendrites in vitro. Kimura H, et al. **Brain Res** 1985 Mar 25;330(2):235-44

Mechanisms of gonadotropin-releasing hormone and prostaglandin action on luteal cells. Leung PC. **Can J Physiol Pharmacol** 1985 Mar; 63(3):249-56 (79 ref.)

Phorbol ester regulation of rat granulosa cell prostaglandin and progesterone accumulation. Kawai Y, et al. **Endocrinology** 1985 Jun; 116(6):2320-6

Effect of verapamil & lignocaine on prostaglandin induced contractions in isolated rat uterus. Kothekar V, et al. **Indian J Med Res** 1985 Jan; 81:79-82

Role of calcium in prostaglandin induced contractile activity in rat uterus. Reddy G, et al. **Indian J Med Res** 1984 Oct;80:491-3

Beclobrinic acid--a new hypolipidemic agent--inhibits in vitro human platelet activation by blocking prostaglandin synthesis. Anwer K, et al. **Life Sci** 1985 Jul 8;37(1):63-70

Prostaglandins, catecholamines, and differentiation of the secondary palate. Greene RM, et al. **Prog Clin Biol Res** 1985;163C:277-81

Evidence against prostaglandin-mediation of somatostatin-inhibition of gastric secretions. Albinus M, et al. **Regul Pept** 1985 Mar; 10(2-3):259-66

[Physiological and pharmacological actions of prostaglandins and related substances on the endocrine system] Kasai Y, et al. **Nippon Rinsho** 1985 Mar;43(3):507-13 (38 ref.) **(Jpn)**

PSYCHIATRIC STATUS RATING SCALES

Mania. Diagnosis, state measurement and prediction of treatment response. Secunda SK, et al. **J Affective Disord** 1985 Mar-Apr;8(2):113-21

KUSTA (Kurz-Skala Stimmung/Aktivierung): a daily self-rating scale for depressive patients. Wendt G, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):118-22

[Comparison of various tools for evaluating depression apropos of a study on Athymil 30 mg] Lempérière T, et al. **Ann Med Psychol (Paris)** 1984 Nov;142(9):1206-14 **(Fre)**

PSYCHIATRY

Data-based psychiatric consultation: applying mainframe computer capability to consultation. Popkin MK, et al. **Gen Hosp Psychiatry** 1985 Apr;7(2):109-12

PSYCHOLOGICAL TESTS

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

PSYCHOMOTOR AGITATION

Emergency treatment of acute psychosis, agitation, and anxiety. Ellison JM. **Hosp Community Psychiatry** 1985 Apr;36(4):351-2

PSYCHOMOTOR PERFORMANCE

Effects of some motion sickness suppressants on static and dynamic tracking performance. Schroeder DJ, et al. **Aviat Space Environ Med** 1985 Apr;56(4):344-50

Evaluation of antimotion sickness drug side effects on performance. Wood CD, et al. **Aviat Space Environ Med** 1985 Apr;56(4):310-6

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445-51

Increased sensitivity of the elderly to the central depressant effects of diazepam. Pomara N, et al. **J Clin Psychiatry** 1985 May;46(5):185-7

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

Ibotenic acid lesions of the lateral hypothalamus: comparison with 6-hydroxydopamine-induced sensorimotor deficits. Dunnett SB, et al. **Neuroscience** 1985 Feb;14(2):509-18

PSYCHOPHARMACOLOGY

Fifth Italo-Soviet symposium on neuropsychopharmacology. Proceedings, Florence, November 25-26, 1983. **Ann Ist Super Sanita** 1984;20(1):1-122

Automating the measurement of locomotor activity. Beninger RJ, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):79-85

Automated measurement of multivariate locomotor behavior in rodents. Sanberg PR, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb; 7(1):87-94

Proceedings of the congress of the AGNP. Nuremberg, 1983. Abstracts. **Pharmacopsychiatry** 1985 Jan;18(1):1-177

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204-9

PSYCHOPHYSIOLOGIC DISORDERS

Psychoendocrinology and the menstrual cycle. Youngs DD, et al. **Adv Psychosom Med** 1985;12:25-34

[Auto-erythrocyte sensitization] Inbal A, et al. **Harefuah** 1984 Dec 16; 107(12):385-7 (Eng. Abstr.) **(Heb)**

[Urinary excretion of catecholamines in children with functional disorders of the digestive system] Szewczyk L, et al. **Pediatr Pol** 1984 Oct; 59(10):835-9 (Eng. Abstr.) **(Pol)**

PSYCHOSES, SUBSTANCE-INDUCED

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

[Is the combination of amphetamine and chloroquine the cause of unexpected psychological symptoms?] **Lakartidningen** 1985 May 22; 82(21):1962 **(Swe)**

PSYCHOTHERAPY

Psychological treatment for benzodiazepine dependence [letter] Tyrer P, et al. **Lancet** 1985 May 4;1(8436):1042-3

PSYCHOTIC DISORDERS

Clinical characteristics of hospitalized psychotic patients who refuse antipsychotic drug therapy. Zito JM, et al. **Am J Psychiatry** 1985 Jul; 142(7):822-6

Antipsychotic and prophylactic effects of acetazolamide (Diamox) on atypical psychosis. Inoue H, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):425-36

Emergency treatment of acute psychosis, agitation, and anxiety. Ellison JM. **Hosp Community Psychiatry** 1985 Apr;36(4):351-2

Familial differences in lithium responsive versus lithium nonresponsive psychoses. Sautter F, et al. **J Psychiatr Res** 1985;19(1):1-8

Acutely psychotic patients: a treatment approach. Wagemaker H, et al. **South Med J** 1985 Jul;78(7):833-7

[Classification of chronic psychoses types I and II and platelet serotonin levels. Apropos of 38 cases] Boudjema F, et al. **Encephale** 1985 Jan-Feb; 11(1):39-42 (Eng. Abstr.) **(Fre)**

[Lithium salts in the treatment of schizoaffective psychosis] Kopel A. **Psychiatr Pol** 1984 May-Jun;18(3):279-83 **(Pol)**

[Influence of nutritional status on intravenous pharmacokinetics of haloperidol in psychotic patients] Donoso A, et al. **Rev Med Chil** 1984 Aug;112(8):777-83 (Eng. Abstr.) **(Spa)**

QUINIDINE

Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers. Relationship to potassium and cycle length. Roden DM, et al. **Circ Res** 1985 Jun; 56(6):857-67

Kinetics and electrocardiographic changes after oral 3-OH-quinidine in healthy subjects. Vožeh S, et al. **Clin Pharmacol Ther** 1985 May; 37(5):575-81

Pharmacokinetics and pharmacodynamics of quinidine and its metabolite, quinidine-N-oxide, in beagle dogs. Rakhit A, et al. **Eur J Drug Metab Pharmacokinet** 1984 Oct-Dec;9(4):315-24

Elimination kinetic of high polar metabolites pool of quinidine from human serum. Camsonne R, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Feb;23(2):74-5

Quinidine-digoxin interaction: are the pharmacokinetics of both drugs altered? Rameis H. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar; 23(3):145-53

Competitive binding of quinidine, propranolol, and 4-OH-propranolol to human plasma very low-density (VLDL) and low-density (LDL) lipoproteins. Ho Ngoc-Ta Trung A, et al. **Pharm Acta Helv** 1985; 60(4):106-9

REACTION TIME

Reactive capacity: a sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Spirduso WW, et al. **Brain Res** 1985 May 27;335(1):45-54

RECEPTORS, ADRENERGIC

Peripheral and central adrenergic influences on brain systems involved in the modulation of memory storage. McGaugh JL. **Ann NY Acad Sci** 1985;444:150-61

Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178-93

Effect of chronic desipramine treatment on adrenoceptor modulation of [3H]dopamine release from rat nucleus accumbens slices. Nurse B, et al. **Brain Res** 1985 May 20;334(2):235-42

Beta 1 and beta 2 adrenergic receptors: their role in the regulation of paradoxical sleep in the rat. Lanfumey L, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):558-67

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar; 24(3):217-22

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

[Role of hypothalamic adrenoreactive structures in regulating the protective reaction to plasmin] Kalishevskaia TM, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):418-21 (Eng. Abstr.) **(Rus)**

RECEPTORS, ADRENERGIC, ALPHA

Human platelet alpha 2-adrenergic receptors: effect of Na + on interaction with the adenylate cyclase system and on epinephrine-stimulated platelet secretion. Limbird LE, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:235-42

Catecholamine and opioid receptors, presynaptic inhibition of CNS neurotransmitter release, and adenylate cyclase. Mulder AH, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:273-86

Alpha 2-adrenoceptor antagonism of vasopressin-induced changes in sodium excretion. Smyth DD, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 2):F767-72

Thermodynamics of agonist and antagonist binding to the alpha 1-adrenoceptor studied using [125I]BE 2254. Adams A, et al. **Biochem Biophys Res Commun** 1985 Apr 30;128(2):816-23

Comparison of postnatal changes in alpha 1-adrenoceptor binding and adrenergic stimulation of phosphoinositide hydrolysis in rat cerebral cortex. Schoepp DD, et al. **Biochem Pharmacol** 1985 Aug 1; 34(15):2705-11

Platelet alpha-2-adrenergic dysfunction in negative symptom schizophrenia: a preliminary study. Rosen J, et al. **Biol Psychiatry** 1985 May;20(5):539-45

Acetylcholine release from rat atria can be regulated through an alpha 1-adrenergic receptor. Wetzel GT, et al. **Circ Res** 1985 May; 56(5):763-6

Alpha 1-adrenergic responsiveness of young adult and aged rat submandibular cells in vitro. Baum BJ, et al. **Comp Biochem Physiol** [C] 1985;81(1):121-4

Trials of serotonin, substance P and alpha 2-adrenergic receptor effects on the equine large colon. Sellers AF, et al. **Cornell Vet** 1985 Apr; 75(2):319-23

Evidence for alpha 1-adrenergic stimulatory control of in vitro release of immunoreactive thyrotropin-releasing hormone from rat median eminence: in vivo corroboration. Tapia-Arancibia L, et al. **Endocrinology** 1985 Jun;116(6):2314-9

Dopamine preferentially stimulates postsynaptic alpha 2-adrenoceptors in the femoral vascular bed, but alpha 1-adrenoceptors in the renal vascular bed of the anaesthetised dog. Duval N, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):265-72

Inhibition by 5,6-dihydroxy-2-dimethylaminotetralin (M7) of noradrenergic neurotransmission in the rabbit hypothalamus: role of alpha-2 adrenoceptors and of dopamine receptors. Galzin AM, et al. **J Pharmacol Exp Ther** 1985 May;233(2):459-65

Demonstration of an alpha adrenoceptor-mediated inotropic effect of norepinephrine in human atria. Skomedal T, et al. **J Pharmacol Exp Ther** 1985 May;233(2):441-6

Modulation of a transient outward current in serotonergic neurones by alpha 1-adrenoceptors. Aghajanian GK. **Nature** 1985 Jun 6-12; 315(6019):501-3

6-Hydroxydopamine pretreatment effects on alpha- and beta-adrenergic receptor adaptation to clorgyline. Cohen RM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):158-61

alpha 1- and beta-adrenergic receptors are co-regulated during both noradrenergic denervation and hyperinnervation. Sutin J, et al. **Neuroscience** 1985 Apr;14(4):973-80

[Dopamine-induced up-regulation of alpha 2-adrenoceptors in crude synaptic membranes of rat brain] Kohno Y, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):173-83 (Eng. Abstr.) **(Jpn)**

RECEPTORS, ADRENERGIC, BETA

Increase in serotonin2 receptor density in rat cerebral cortex slices by stimulation of beta-adrenergic receptors. Scott JA, et al. **Biochem Pharmacol** 1985 May 1;34(9):1585-8

Mechanisms of supersensitivity to sympathomimetic amines in the chronically denervated heart of the conscious dog. Vatner DE, et al. **Circ Res** 1985 Jul;57(1):55-64

Receptor mechanisms in fish chromatophores--VIII. Mediated by beta adrenoceptors, catecholamines always act to disperse pigment in siluroid melanophores. Fujii R, et al. **Comp Biochem Physiol** [C] 1985; 81(1):1-6

Why is amitriptyline much weaker than desipramine at decreasing beta-adrenoceptor numbers? Wise H, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):137-41

The effect of age on beta-adrenergic function in man: a review. Ebstein RP, et al. **Isr J Med Sci** 1985 Mar;21(3):302-11

Evidence for a beta-adrenoceptor-mediated regulation of human natural killer cells. Hellstrand K, et al. **J Immunol** 1985 Jun;134(6):4095-9

Radioreceptor assay for beta-adrenergic receptor-reactive catecholamines in serum samples. Iwo K, et al. **J Lab Clin Med** 1985 Jun; 105(6):711-7

Effects of clenbuterol and antidepressant drugs on beta adrenergic receptor/N-protein coupling in the cerebral cortex of the rat. O'Donnell JM, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):30-6

Chronic thyroxine treatment of rats down-regulates the noradrenergic cyclic AMP generating system in cerebral cortex. Schmidt BH, et al. **J Pharmacol Exp Ther** 1985 May;233(2):466-72

Effects of beta-adrenoceptor antagonist administration on beta 2-adrenoceptor density in human lymphocytes. The role of the 'intrinsic sympathomimetic activity'. Brodde OE, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):417-22

6-Hydroxydopamine pretreatment effects on alpha- and beta-adrenergic receptor adaptation to clorgyline. Cohen RM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):158-61

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

alpha 1- and beta-adrenergic receptors are co-regulated during both noradrenergic denervation and hyperinnervation. Sutin J, et al. **Neuroscience** 1985 Apr;14(4):973-80

The activation of mice's behavior and reduction of brain beta-adrenergic receptor binding following repeated administration of antidepressant drugs. Nomura S, et al. **Yakubutsu Seishin Kodo** 1984 Nov; 4(3):237-41

RECEPTORS, CHOLINERGIC

Comparative effects of aprophen, atropine and benactyzine on central and peripheral cholinoceptors and on acetylcholinesterase. Dawson RM, et al. **Biochem Pharmacol** 1985 May 1;34(9):1577-9

Affinity-dependent cross-linking to neurotoxin sites of the acetylcholine receptor mediated by catechol oxidation. Nickoloff BJ, et al. **Biochemistry** 1985 Feb 12;24(4):999-1007

Blockade of cholinergic receptors in the C1 area abolishes hypertensive response to opiates in the A1 area of the ventrolateral medulla. Punnen S, et al. **Brain Res** 1985 Jun 10;336(1):180-6

Cholinergic-muscarinic receptors do not mediate growth hormone release in response to baclofen, a gamma-aminobutyric acid agonist, in humans. Coiro V, et al. **Horm Metab Res** 1985 May;17(5):260-1

High-affinity binding of [3H]acetylcholine to muscarinic cholinergic receptors. Kellar KJ, et al. **J Neurosci** 1985 Jun;5(6):1577-82

[Effect of RNAse inhibitors and activators on acetylcholine interaction with the cholinoreceptor in a tissue extract] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985;281(2):500-2 **(Rus)**

[Possible participation of slow Na+--Ca++ channels in realizing cholinergic effects on the cardiac pacemaker] Sukhova GS, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):506-9 (Eng. Abstr.) **(Rus)**

RECEPTORS, DOPAMINE

Effect of metoclopramide, domperidone and apomorphine on GH secretion in children and adolescents. Massara F, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):451-5

Effect of dopamine receptor stimulation on the inhibition of LH pulsatility by a met-enkephaline (FK 33-824). del Pozo E, et al. **Acta Neurochir (Wien)** 1985;75(1-4):88-90

Age-related changes in rat brain dopaminergic receptors. Petkov VV, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):16-27

On the role of dopamine receptors in aldosterone secretion. Frisina N, et al. **Ann Endocrinol (Paris)** 1984;45(6):387-91

Dopamine D2 receptors modulate neurotransmitter-regulated calcium ion gates. Memo M, et al. **Ann Ist Super Sanita** 1984;20(1):5-10

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665-9

Dopamine autoreceptors and the effects of drugs on locomotion and dopamine synthesis. Brown F, et al. **Br J Pharmacol** 1985 Apr; 84(4):853-60

Rapid desensitization of presynaptic dopamine autoreceptors during exposure to exogenous dopamine. Arbilla S, et al. **Brain Res** 1985 Jun 24;337(1):11-7

The possible role of 2-hydroxyestradiol in the development of estrogen-induced striatal dopamine receptor hypersensitivity. Clopton JK, et al. **Brain Res** 1985 Apr 29;333(1):1-10

Effects of pertussis toxin on D2-dopamine receptor in rat striatum: evidence for coupling of Ni regulatory protein with D2-receptor. Fujita N, et al. **Brain Res** 1985 May 6;333(2):231-6

Dopamine receptors regulate Met-enkephalin content in pituitary. George SR, et al. **Brain Res** 1985 May 13;334(1):187-9

Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Grace AA, et al. **Brain Res** 1985 May 6; 333(2):285-98

Effect of duration of haloperidol treatment on DA receptor supersensitization in aging C57BL/6J mice. Randall PK, et al. **Brain Res** 1985 Apr 29;333(1):85-95

Regional sensitivity of neuroleptic receptors to sub-acute soman intoxication. Valdes JJ, et al. **Brain Res Bull** 1985 Feb;14(2):117-21

Dopamine: receptors and clinical applications. Goldberg LI. **Clin Physiol Biochem** 1985;3(2-3):120-6 (33 ref.)

An investigation of amphetamine-induced release of 5-HT from rat hippocampal slices. Balfour DJ, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):395-9

Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behavioural 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):253-6

Striatal synaptosomal dopamine synthesis: evidence against direct regulation by an autoreceptor mechanism. Compton DR, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):157-62

Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Creese I, et al. **Eur J Pharmacol** 1985 Feb 12; 109(1):127-8

Magnesium ions reveal nanomolar potency of dopamine at [3H]spiperone labelled D-2 receptors in rat corpus striatum. De Vries DJ, et al.

Eur J Pharmacol 1985 Mar 12;109(3):417-9

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

N-methyl,N-propargyl-2-aminotetralins:novel dopamine agonists with monoamine oxidase inhibiting properties. Hazelhoff B, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):229-40

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349-54

Chronic haloperidol does not alter agonist affinity for dopamine receptors in vitro. Meller E, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):389-94

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305-8

Dopamine receptor subtypes: in vivo biochemical evidence for functional interaction. Saller CF, et al. **Eur J Pharmacol** 1985 Feb 26; 109(2):297-300

Reduced sensitivity of synaptosomal dopamine autoreceptors following increase in synaptosomal dopamine synthesis. Tissari AH. **Eur J Pharmacol** 1985 Mar 12;109(3):433-4

The supersensitivity of dopaminergic neurons to apomorphine in rats following chronic haloperidol. Vogelsang GD, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):267-9

The dopamine autoreceptor agonist B-HT 920 markedly stimulates sexual behavior in male rats. Ferrari F, et al. **Experientia** 1985 May 15; 41(5):636-8

Resolution of 5,6-dihydroxy-2-(N,N-di-n-propylamino)tetralin in relation to the structural and stereochemical requirements for centrally acting dopamine agonists. Grol CJ, et al. **J Med Chem** 1985 May; 28(5):679-83

Sulpiride blocks postsynaptic dopamine receptors in the nucleus accumbens. Morgenstern R, et al. **J Neural Transm** 1985; 61(3-4):151-60

Effects of SK&F 82526 and SK&F 83742 on the renal vascular dopamine receptor. Schmidt M, et al. **J Pharmacol** 1985 Jan-Mar;16(1):15-22

Computer imaging and analysis of dopamine (D2) and serotonin (S2) binding sites in rat basal ganglia or neocortex labeled by [3H]spiroperidol. Altar CA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):527-38

Inhibition by 5,6-dihydroxy-2-dimethylaminotetralin (M7) of noradrenergic neurotransmission in the rabbit hypothalamus: role of alpha-2 adrenoceptors and of dopamine receptors. Galzin AM, et al. **J Pharmacol Exp Ther** 1985 May;233(2):459-65

Acute and subchronic effects of MJ-13859, a potential antipsychotic drug, on rat brain dopaminergic function. McMillen BA. **J Pharmacol Exp Ther** 1985 May;233(2):369-75

Inactivation of D1 and D2 dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vivo: selective protection by neuroleptics. Meller E, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):656-62

D-2 dopamine receptors in aging mouse striatum: determination of high- and low-affinity agonist binding sites. Severson JA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):361-8

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

Dopamine inhibition of anterior pituitary adenylate cyclase is mediated through the high-affinity state of the D2 receptor. Borgundvaag B, et al. **Life Sci** 1985 Jul 29;37(4):379-86

Reserpine-induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31-8

The putative dopamine autoreceptor agonist B-HT 920 decreases nigral dopamine cell firing rate and prolactin release in rat. Eriksson E, et al. **Life Sci** 1985 May 13;36(19):1819-27

Dopamine receptor antagonists inhibit the natriuretic response to atrial natriuretic factor (ANF). Marin-Grez M, et al. **Life Sci** 1985 Jun 3; 36(22):2171-6

SCH23390 causes persistent antidopaminergic effects in vivo: evidence for longterm occupation of receptors. Schulz DW, et al. **Life Sci** 1985 May 20;36(20):1941-8

D2-dopamine receptor-mediated inhibition of cyclic AMP formation in striatal neurons in primary culture. Weiss S, et al. **Mol Pharmacol** 1985 Jun;27(6):595-9

Unexpected potentiation by discriminant benzamide derivatives of stereotyped behaviours elicited by dopamine agonists in mice. Vasse M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):108-16

Effect of gestational and neonatal styrene exposure on dopamine receptors. Zaidi NF, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):23-8

The effects of neurotensin and [D-Tyr11]-NT on the hyperactivity induced by intra-accumbens administration of a potent dopamine receptor agonist. Jolicoeur FB, et al. **Neuropeptides** 1985 Apr; 6(2):143-56

The continuity of dopamine receptor antagonism can dictate the long-term behavioural consequences of a mesolimbic infusion of dopamine. Costall B, et al. **Neuropharmacology** 1985 Mar;24(3):193-7

Striatal topography of D-2 receptors correlates with indexes of cholinergic neuron localization. Joyce JN, et al. **Neurosci Lett** 1985 Jan 7;53(1):127-31

Lack of effect of intranigral administration of a dopamine analogue, (+/-)-3-(3-hydroxyphenyl)-N,n-propylpiperidine [(+/-)-3-PPP], on nigrostriatal dopamine neurones. Kelly E, et al. **Neurosci Lett** 1985 May 1;56(1):57-62

Regulation of dopamine release by impulse flow and by autoreceptors as studied by in vivo voltammetry in the rat striatum. Gonon FG, et al. **Neuroscience** 1985 Mar;14(3):765-74

Increased investigative activity after presynaptic dopaminergic stimulation measured by a fixed-interval recording procedure. Höglund AU, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):403-6

Effect of chronic apomorphine on the development of denervation supersensitivity. Robin M, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):547-51

Effects of selective dopamine receptor agonists in rats trained to discriminate apomorphine from saline. Woolverton WL, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):577-81

Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. Farde L, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3863-7

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346-52

Characterization of the bupropion cue in the rat: lack of evidence for a dopaminergic mechanism. Blitzer RD, et al. **Psychopharmacology (Berlin)** 1985;85(2):173-7

Chronic haloperidol during development attenuates dopamine autoreceptor function in striatal and mesolimbic brain regions of young and older adult rats. Scalzo FM, et al. **Psychopharmacology (Berlin)** 1985;85(3):271-6

Differential effects of dopamine D-1 and D-2 agonists and antagonists in 6-hydroxydopamine-lesioned rats. Arnt J. **Psychopharmacology [Suppl]** 1985;2:60-1

Intermittent treatment with droperidol, a short-acting neuroleptic, increases behavioral dopamine receptor sensitivity. Belmaker RH, et al. **Psychopharmacology [Suppl]** 1985;2:194-9

Pharmacological differentiation of dopamine D-1 and D-2 antagonists after single and repeated administration. Christensen AV, et al. **Psychopharmacology [Suppl]** 1985;2:182-90

Receptor-binding profiles of neuroleptics. Hyttel J, et al. **Psychopharmacology [Suppl]** 1985;2:9-18

Differential alteration of striatal D-1 and D-2 receptors induced by the long-term administration of haloperidol, sulpiride or clozapine to rats. Jenner P, et al. **Psychopharmacology [Suppl]** 1985;2:174-81

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

Influence of GABA mimetics and lithium on biochemical manifestations of striatal dopamine target cell hypersensitivity. Scatton B, et al. **Psychopharmacology [Suppl]** 1985;2:39-45

Functional classification of different dopamine receptors. Ungerstedt U, et al. **Psychopharmacology [Suppl]** 1985;2:19-30

Effect of dopamine and dopamine-receptor blockade on in vitro renin release, tissue renin content and tissue cyclic AMP content in the rat. López GA, et al. **Rev Esp Fisiol** 1985 Mar;41(1):95-100

[Continuous suppression of methamphetamine-induced supersensitivity by chronic haloperidol administration] Kashihara K, et al. **Seishin Shinkeigaku Zasshi** 1984;86(11):928-32 **(Jpn)**

[Role of serotonin and dopamine receptors in the mechanism of action of haloperidol and pirenperone] Maimets MO, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):15-8 (Eng. Abstr.) **(Rus)**

RECEPTORS, DRUG

Synthesis and structure-activity studies on excitatory amino acids structurally related to ibotenic acid. Krogsgaard-Larsen P, et al. **J Med Chem** 1985 May;28(5):673-9

RECEPTORS, ENDOGENOUS SUBSTANCES

Adenosine, adenylate cyclase, and transmitter release. Phillis JW, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:243-57 (81 ref.)

Endocrine-mediated parallel changes in hepatic glucocorticoid and prolactin receptors. Dave JR, et al. **Biochim Biophys Acta** 1985 May 30;845(2):276-82

Regulation of infant and developing rat testicular gonadotropin and prolactin receptors and steroidogenesis by treatments with human chorionic gonadotropin, gonadotropin-releasing hormone analogs, bromocriptine, prolactin, and estrogen. Huhtaniemi IT, et al. **Biol Reprod** 1985 May;32(4):721-32

Somatostatin-14 and somatostatin-28 pretreatment down-regulate somatostatin-14 receptors and have biphasic effects on forskolin-stimulated cyclic adenosine, 3',5'-monophosphate synthesis and adrenocorticotropin secretion in mouse anterior pituitary tumor cells. Heisler S, et al. **Endocrinology** 1985 Jul;117(1):217-25

The frequency of gonadotropin-releasing hormone stimulation determines the number of pituitary gonadotropin-releasing hormone receptors. Katt JA, et al. **Endocrinology** 1985 May;116(5):2113-5

Tunicamycin and neuraminidase effects on luteinizing hormone (LH)-releasing hormone binding and LH release from rat pituitary cells in culture. Schvartz I, et al. **Endocrinology** 1985 Jun;116(6):2341-6

Interaction of growth hormone-releasing factor (GRF) and 14 GRF analogs with vasoactive intestinal peptide (VIP) receptors of rat pancreas. Discovery of (N-Ac-Tyr1,D-Phe2)-GRF(1-29)-NH2 as a VIP antagonist. Waelbroeck M, et al. **Endocrinology** 1985 Jun;116(6):2643-9

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

3,5,3'-Triiodothyronine receptors and thyroxine 5'-monodeiodinating activity in thyroid hormone-insensitive amphibia. Galton VA. **Gen Comp Endocrinol** 1985 Mar;57(3):465-71

A unique control mechanism in the regulation of insulin secretion. Secretagogue-induced somatostatin receptor recruitment. Draznin B, et al. **J Clin Invest** 1985 May;75(5):1510-6

Neuropeptides and their receptors: a psychosomatic network. Pert CB, et al. **J Immunol** 1985 Aug;135(2 Suppl):820s-826s

Evolutionary origins of neuropeptides, hormones, and receptors: possible applications to immunology. Roth J, et al. **J Immunol** 1985 Aug;135(2 Suppl):816s-819s

Localization of somatostatin receptors in secretion vesicles in anterior pituitary cells and pancreatic islets. Draznin B, et al. **J Recept Res** 1985;5(1):83-103

Photoaffinity labelling of MSH receptors on Anolis melanophores: effects of catecholamines, calcium and forskolin. Eberle AN, et al. **J Recept Res** 1985;5(1):59-81

Changes in pituitary and ovarian LHRH receptors after active immunization of female rats against LH or LHRH. Popkin RM, et al. **J Reprod Fertil** 1985 Mar;73(2):491-6

Newborn and immature rat testes contain gonadotropin-releasing hormone (GnRH) receptors, and their testosterone production is stimulated by a GnRH agonist in vitro. Huhtaniemi IT, et al. **Mol Cell Endocrinol** 1985 Apr;40(1):41-4

Receptor-mediated degradation of human growth hormone in rat adipocytes and cultured human lymphocytes (IM-9). Weyer B, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):85-92

Increased gonadotrophin releasing hormone receptors on pituitary gonadotrophs: effect on subsequent LH secretion. Young LS, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):69-78

Treatment of rats with the TRH analog MK-771. Down-regulation of TRH receptors and behavioral tolerance. Simasko SM, et al. **Neuropharmacology** 1985 Feb;24(2):157-65

Products of cholecystokinin (CCK)-octapeptide proteolysis interact with central CCK receptors. Steardo L, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):319-25

Somatostatin analogs: correlation of receptor affinity with inhibition of cyclic AMP formation in pancreatic acinar cells. Taparel D, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):109-14

Up-regulation of thyrotropin-releasing hormone (TRH) receptors in rat spinal cord after codepletion of serotonin and TRH. Ogawa N, et al. **Regul Pept** 1985 Mar;10(2-3):85-90

RECEPTORS, ENDORPHIN

Catecholamine and opioid receptors, presynaptic inhibition of CNS neurotransmitter release, and adenylate cyclase. Mulder AH, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:273-86

Effects of tifluadom on passive avoidance behaviour in DBA/2 mice. Pavone F, et al. **Behav Brain Res** 1985 May;15(3):177-81

Modification of opioid ligand binding in the central and the peripheral nervous system by different buffers. Bourhim N, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):328-33

Central nervous system opiate and 5-hydroxytryptamine influences on baroreflex control of the coronary circulation. Moore PG, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):185-94

Mu1: a very high affinity subtype of enkephalin binding sites in rat brain. Lutz RA, et al. **Life Sci** 1985 Jun 10;36(23):2233-8

Characterization of rat brain opioid receptors by [Tyr-3,5-3H]1, D-Ala2, Leu5-enkephalin binding. Benyhe S, et al. **Neurochem Res** 1985 May;10(5):627-35

Studies in vitro with ICI 174,864, [D-Pen2, D-Pen5]-enkephalin (DPDPE) and [D-Ala2, NMePhe4, Gly-ol]-enkephalin (DAGO). Hirning LD, et al. **Neuropeptides** 1985 Feb;5(4-6):383-6

Postnatal development of opioid systems in rat brain. Loughlin SE, et al. **Neuropeptides** 1985 Feb;5(4-6):469-72

The interaction of the two isomers of the opioid benzodiazepine tifluadom with mu-, delta-, and kappa-binding sites and their analgesic and intestinal effects in rats. Petrillo P, et al. **Neuropeptides** 1985 Feb;5(4-6):403-6

Opiate receptor-mediated chemotaxis of human monocytes. Ruff MR, et al. **Neuropeptides** 1985 Feb;5(4-6):363-6

Opiate and histamine H1 receptors are present on some substance P-containing dorsal root ganglion cells. Ninkovic M, et al. **Neurosci Lett** 1985 Jan 7;53(1):133-7

Astrocyte opioid receptors: activation modifies the noradrenaline-evoked increase in 2-[14C]deoxyglucose incorporation into glycogen. Pearce B, et al. **Neurosci Lett** 1985 Apr 9;55(2):157-60

Acupuncture analgesia [letter] Han JS. **Pain** 1985 Mar;21(3):307-10

Binding characteristics of dermorphin, and [dermorphin1-7]-beta c-endorphin in rat brain membranes. Westphal M, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):149-52

[The nature of cation-binding groups in binding sites for [[3H]Tyr1, D-Ala2, D-Leu5]enkephalin] Zaitsev SV, et al. **Bioorg Khim** 1985 Feb;11(2):153-61 (Eng. Abstr.) **(Rus)**

RECEPTORS, GABA-BENZODIAZEPINE

Foot shock-induced decrease of low affinity GABA receptors in the rat brain: antagonism by diazepam. Concas A, et al. **Ann Ist Super Sanita** 1984;20(1):53-6

Central effects of nicotinamide and inosine which are not mediated through benzodiazepine receptors. Bold JM, et al. **Br J Pharmacol** 1985 Mar;84(3):689-96

Prenatal exposure to diazepam results in enduring reductions in brain receptors and deep slow wave sleep. Livezey GT, et al. **Brain Res** 1985 May 20;334(2):361-5

Specific [3H]gamma-aminobutyric acid binding to vestibular membranes of the chick inner ear. Meza G, et al. **Brain Res** 1985 Jun 24;337(1):179-83

Differential modulation of gamma-aminobutyric acid receptors by caprolactam derivatives with central nervous system depressant or convulsant activity. Skerritt JH, et al. **Brain Res** 1985 Apr 8;331(2):225-33

Heterogeneity of brain benzodiazepine receptors: effects of physiological conditions. Lippa AS, et al. **Brain Res Bull** 1985 Feb;14(2):189-95

Pharmacological evidence that the non-neuronal diazepam binding site in primary cultures of glial cells is associated with a calcium channel. Bender AS, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):287-8

Benzodiazepine receptor photoaffinity labeling: correlation of function with binding. Gibbs TT, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):171-80

Spontaneous and RO 15-1788-induced reversal of subsensitivity to GABA following chronic benzodiazepines. Gonsalves SF, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):163-70

Synthesis and interaction of 5-(substituted-phenyl)-3-methyl-6,7-dihydropyrazolo[4,3-e][1,4]diazepin-8(7H)-ones with benzodiazepine receptors in rat cerebral cortex. Baraldi PG, et al. **J Med Chem** 1985 May;28(5):683-5

3-Amino-beta-carboline derivatives and the benzodiazepine receptor. Synthesis of a selective antagonist of the sedative action of diazepam. Dodd RH, et al. **J Med Chem** 1985 Jun;28(6):824-8

gamma-Aminobutyric acid: temperature dependence in benzodiazepine receptor binding. Chweh AY, et al. **J Neurochem** 1985 Jul;45(1):240-3

Triazolam, an anomalous benzodiazepine receptor ligand: in vitro characterization of alprazolam and triazolam binding. Clow A, et al. **J Neurochem** 1985 Aug;45(2):621-5

Differential degradation of different benzodiazepine binding proteins by incubation of membranes from cerebellum or hippocampus with trypsin. Eichinger A, et al. **J Neurochem** 1985 Jul;45(1):219-26

Radiation inactivation studies of the benzodiazepine/gamma-aminobutyric acid/chloride ionophore receptor complex. Schwartz RD, et al. **J Neurochem** 1985 Jul;45(1):108-15

'Peripheral-type' binding sites for benzodiazepines in brain: relationship to the convulsant actions of Ro 5-4864. Weissman BA, et al. **J Neurochem** 1985 May;44(5):1494-9

Effects of acute and chronic treatment on the pro- and anti-convulsant actions of CL 218, 872, PK 8165 and PK 9084, putative ligands for the benzodiazepine receptor. File SE, et al. **J Pharm Pharmacol** 1985 Apr;37(4):252-6

Daily rhythms of benzodiazepine receptor numbers in frontal lobe and cerebellum of the rat. Brennan MJ, et al. **Life Sci** 1985 Jun 17;36(24):2333-7

Prenatal stress impairs maternal behavior in a conflict situation and reduces hippocampal benzodiazepine receptors. Fride E, et al. **Life Sci** 1985 Jun 3;36(22):2103-9

Reduction of GABAB receptor binding induced by climbing fiber degeneration in the rat cerebellum. Kato K, et al. **Life Sci** 1985 Jul 22;37(3):279-88

The effects of benzodiazepines on spinal homosynaptic depression. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):301-7

The influence of bicarbonate ions on the GABA-mimetic activity of ethylenediamine. Hill DR. **Neuropharmacology** 1985 Feb;24(2):147-55

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar; 24(3):217-22

gamma-Aminobutyric acid modulation of benzodiazepine receptor binding in vitro does not predict the pharmacologic activity of all benzodiazepine receptor ligands. Chweh AY, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):173-7

Are the anxiogenic effects of yohimbine mediated by its action at benzodiazepine receptors? Pellow S, et al. **Neurosci Lett** 1985 Mar 22; 55(1):5-9

Autoreceptors regulate gamma-[3H]aminobutyric acid release from the guinea pig small intestine. Taniyama K, et al. **Neurosci Lett** 1985 Apr 9;55(2):245-8

On the location of gamma-aminobutyrate and benzodiazepine receptors in the cerebellum of the normal C3H and Lurcher mutant mouse. Fry JP, et al. **Neuroscience** 1985 Apr;14(4):1091-101

Pharmacology of benzodiazepine antagonists. Haefely W. **Pharmacopsychiatry** 1985 Jan;18(1):163-6

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167-70

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: punished barpressing. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;85(2):244-51

RECEPTORS, SEROTONIN

Increase in serotonin2 receptor density in rat cerebral cortex slices by stimulation of beta-adrenergic receptors. Scott JA, et al. **Biochem Pharmacol** 1985 May 1;34(9):1585-8

Tryptamine-induced vasoconstrictor responses in rat caudal arteries are mediated predominantly via 5-hydroxytryptamine receptors. Bradley PB, et al. **Br J Pharmacol** 1985 Apr;84(4):919-25

A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT1 and 5-HT2 receptors. Goodwin GM, et al. **Br J Pharmacol** 1985 Mar;84(3):743-53

Serotonin release in human cerebral cortex and its modulation via serotonin receptors. Schlicker E, et al. **Brain Res** 1985 Apr 8; 331(2):337-41

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

A molecular theory of recognition and activation at a 5-HT receptor based on a quantum chemical approach to structure activity relationships. Osman R, et al. **Clin Physiol Biochem** 1985;3(2-3):80-8

Acute and chronic phencyclidine administration changes serotonin receptors in rat brain. Nabeshima T, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):129-30

Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Shenker A, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):427-9

The enteric neural receptor for 5-hydroxytryptamine. Gershon MD, et al. **Experientia** 1985 Jul 15;41(7):863-8

Evidence that phospholipid turnover is the signal transducing system coupled to serotonin-S2 receptor sites. de Chaffoy de Courcelles D, et al. **J Biol Chem** 1985 Jun 25;260(12):7603-8

5-Hydroxytryptamine stimulates inositol phosphate production in a cell-free system from blowfly salivary glands. Evidence for a role of GTP in coupling receptor activation to phosphoinositide breakdown. Litosch I, et al. **J Biol Chem** 1985 May 10;260(9):5464-71

Bioactive conformation of 1-arylpiperazines at central serotonin receptors. Huff JR, et al. **J Med Chem** 1985 Jul;28(7):945-8

Cardiovascular effects in the Sprague-Dawley rat of 8-hydroxy-2(di-N-propylamino) tetralin, a selective 5-hydroxytryptamine receptor agonist. Gradin K, et al. **J Pharm Pharmacol** 1985 Apr;37(4):263-5

Computer imaging and analysis of dopamine (D2) and serotonin (S2) binding sites in rat basal ganglia or neocortex labeled by [3H]spiroperidol. Altar CA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):527-38

5-Hydroxytryptamine receptor in isolated rabbit aorta: characterization with tryptamine analogs. Clancy BM, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):761-9

5-Hydroxytryptamine-stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: pharmacological characterization and effects of antidepressants. Kendall DA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):473-9

Do D 600 and diltiazem interact with serotonin receptors in rabbit vascular tissues? Ohashi M, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):830-5

Receptor-binding properties in vitro and in vivo of ritanserin: A very potent and long acting serotonin-S2 antagonist. Leysen JE, et al. **Mol Pharmacol** 1985 Jun;27(6):600-11

Decreased 5-HT2 but not 5-HT1 receptor binding in cortex of rat after chronic administration of dothiepin. Application of the Woolf plot to analysis of binding parameters. Diggory GL, et al. **Neuropharmacology** 1985 Apr;24(4):275-8

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

[Central serotonin receptors] Fillion G. **Pathol Biol (Paris)** 1985 Apr; 33(4):221-6 (56 ref.) **(Fre)**

[Structure of the binding center of the serotonin S2 receptor] Kats MM. **Biol Nauki** 1985;(3):19-24 (Eng. Abstr.) **(Rus)**

[pH changes in the matrix of serotonin organelles of stimulated thrombocytes] Kozlov VK, et al. **Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR** 1985; 8(1):77-82 (Eng. Abstr.) **(Rus)**

[Role of serotonin and dopamine receptors in the mechanism of action of haloperidol and pirenperone] Maimets MO, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):15-8 (Eng. Abstr.) **(Rus)**

REFLEX

Anterior hypothalamic lesions impair reflex bradycardia selectively in rats. Miyajima E, et al. **Am J Physiol** 1985 Jun;248(6 Pt 2):H937-44

The role of substance P as a neurotransmitter in the reflexes of slow time courses in the neonatal rat spinal cord. Akagi H, et al. **Br J Pharmacol** 1985 Mar;84(3):663-73

Attenuation of the reflex pressor response to muscular contraction by a substance P antagonist. Kaufman MP, et al. **Brain Res** 1985 Apr 29; 333(1):182-4

Effects of catecholamines on spinal motoneurones and spinal reflex discharges in the isolated spinal cord of the newborn rat. Kitazawa T, et al. **Brain Res** 1985 Mar;351(1):31-6

Effects of enkephalin and 5-hydroxytryptamine on solitary tract neurones involved in respiration and respiratory reflexes. Sessle BJ, et al. **Brain Res** 1985 Feb 18;327(1-2):221-30

Arterial and cardiopulmonary reflexes in the regulation of the neurohumoral drive to the circulation. Bishop VS, et al. **Fed Proc** 1985 May;44(8):2377-81 (31 ref.)

Central nervous system opiate and 5-hydroxytryptamine influences on baroreflex control of the coronary circulation. Moore PG, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):185-94

Central nervous system 5-hydroxytryptamine and noradrenaline specificity of ear vascular and ventilation reflexes in thermoregulating rabbits. White SW, et al. **J Auton Nerv Syst** 1985 Feb-Mar; 12(2-3):131-44

Kinetics of drug action in disease states. XIII. Effect of dialyzable component(s) of uremic blood on phenobarbital concentrations in rats at onset of loss of righting reflex. Hisaoka M, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):180-3

Reflex changes in sympatho-adrenal medullary functions in response to various thermal cutaneous stimulations in anesthetized rats. Kurosawa M, et al. **Neurosci Lett** 1985 May 14;56(2):149-54

Effects of glutamate, substance P and eledoisin-related peptide on solitary tract neurones involved in respiration and respiratory reflexes. Henry JL, et al. **Neuroscience** 1985 Mar;14(3):863-73

Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. Gramling SE, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):541-5

Possible involvement of central adrenergic and histaminergic systems in clonidine-induced inhibition of pinna reflex. Singh PP, et al. **Pharmacol Res Commun** 1985 Mar;17(3):261-9

[Role of hypothalamic adrenoreactive structures in regulating the protective reaction to plasmin] Kalishevskaia TM, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):418-21 (Eng. Abstr.) **(Rus)**

[Analysis of the factors affecting cardiac output in exclusion of the sino-carotid reflexogenic area] Osadchiĭ LI, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):500-5 (Eng. Abstr.) **(Rus)**

RESERPINE

Effects of reserpine and isoproterenol on elemental distribution in submandibular gland of rat. Müller RM, et al. **Acta Physiol Scand** 1985 Apr;123(4):383-91

The chronically reserpinized rat: decreased glycolytic activity in the submandibular gland. Bardoń A, et al. **Biochem Med** 1985 Feb; 33(1):99-103

Effect of chronic reserpine and desmethylimipramine treatment on CRF-like immunoreactivity of discrete brain areas of rat. Tizabi Y, et al. **Brain Res** 1985 Jun 3;335(2):389-91

Catecholamine hormones and the control of avian salt glands. Wilson JX, et al. **Comp Biochem Physiol [C]** 1985;81(1):77-9

Reserpine toxicosis in a horse. Lloyd KC, et al. **J Am Vet Med Assoc** 1985 May 1;186(9):980-1

Reserpine-induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31-8

Amphetamine induced release of endogenous dopamine in vitro is not

best copy available

reduced following pretreatment with reserpine. Niddam R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):123-7

Effects of lithium in vitro on noradrenaline-induced cyclic AMP accumulation in rat cortical slices after reserpine-induced supersensitivity. Newman ME, et al. **Neuropharmacology** 1985 Apr; 24(4):353-5

Developmental status of sympathetic innervation in relation to calcium accumulation by submandibular gland following reserpine, surgical sympathectomy or cyclocytidine. Schneyer CA, et al. **Proc Soc Exp Biol Med** 1985 Jun;179(2):143-6

Effects of reserpine and adrenal demedullation on brown adipose tissue thermogenesis induced by dl-phenylpropanolamine. Wellman PJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Feb;47(2):211-20

RUBIDIUM

Stimulus-secretion coupling of parathyroid hormone release: studies of 45Ca and 86Rb fluxes. Wallfelt C, et al. **Acta Physiol Scand** 1985 Jun; 124(2):239-45

Occlusion of Rb+ by detergent-solubilized (Na+ + K+)-ATPase from shark salt glands. Esmann M. **Biochim Biophys Acta** 1985 May 14; 815(2):196-202

Effects of chronic LiCl and RbCl on muricide induced by midbrain raphe lesions in rats. Yamamoto T, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):559-63

SCHIZOPHRENIA

Differential response to amphetamine in schizophrenia. Cesarec Z, et al. **Acta Psychiatr Scand** 1985 May;71(5):523-38

Biochemical theories of schizophrenia and depression. Hollister LE. **Ann Acad Med Singapore** 1985 Jan;14(1):76-80

Creatine phosphokinase and schizophrenia in Singapore. Tsoi WF, et al. **Ann Acad Med Singapore** 1985 Jan;14(1):84-6

The interpretation of plasma haloperidol concentrations. Kirch DG, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):838-40

Plasma haloperidol levels: clinical response and fancy mathematics [letter] Van Putten T, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):835-8

Ceruletide for schizophrenia: a double-blind study. Mattes JA, et al. **Biol Psychiatry** 1985 May;20(5):533-8

Platelet alpha-2-adrenergic dysfunction in negative symptom schizophrenia: a preliminary study. Rosen J, et al. **Biol Psychiatry** 1985 May;20(5):539-45

Electroconvulsive therapy and schizophrenia. Van Valkenburg C, et al. **Biol Psychiatry** 1985 Jul;20(7):699-700

Schizophrenia with good and poor outcome. I: Early clinical features, response to neuroleptics and signs of organic dysfunction. Kolakowska T, et al. **Br J Psychiatry** 1985 Mar;146:229-39

Schizophrenia with good and poor outcome. II: Cerebral ventricular size and its clinical significance. Williams AO, et al. **Br J Psychiatry** 1985 Mar;146:239-46

Lipids and apolipoproteins in patients treated with major tranquilizers. Sasaki J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):684-7

Bioavailability of oral and intramuscular molindone hydrochloride in schizophrenic patients. Zetin M, et al. **Clin Ther** 1985;7(2):169-75

Platelet monoamine-oxidase activity in schizophrenia. Relation to genetic load of the illness and treatment with antipsychotic drugs. Kemali D, et al. **Encephale** 1985 Jan-Feb;11(1):31-4

Abnormal phosphatidylinositol-cycle of platelet membrane in schizophrenia--a preliminary study. Kaiya H, et al. **Folia Psychiatr Neurol Jpn** 1984;38(4):437-44

Positron emission tomography in schizophrenic patients with and without neuroleptic medication. DeLisi LE, et al. **J Cereb Blood Flow Metab** 1985 Jun;5(2):201-6

Drugs and the quality of life: the patient's point of view. Diamond R. **J Clin Psychiatry** 1985 May;46(5 Pt 2):29-35

Serum neuroleptic levels and clinical outcome in schizophrenic patients treated with fluphenazine decanoate. Brown WA, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):143-7

Problems in classification of schizophrenics as neuroleptic responders and nonresponders. Csernansky JG, et al. **J Nerv Ment Dis** 1985 Jun; 173(6):325-31 (93 ref.)

Lower CSF level of dynorphin(1-8) immunoreactivity in schizophrenic patients. Zhang AZ, et al. **Neuropeptides** 1985 Feb;5(4-6):553-6

State of adrenergic and cholinergic systems in schizophrenia patients during psychopharmacotherapy. Krupenina LB, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):1-8

One-year outcome of schizophrenic patients--the interaction of chronicity and neuroleptic treatment. Gaebel W, et al. **Pharmacopsychiatry** 1985 May;18(3):235-9

Double-blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. Kissling W, et al. **Pharmacopsychiatry** 1985 May;18(3):240-5

Serum and cerebrospinal fluid prolactin patterns during neuroleptic treatment in schizophrenic patients. Rimón R, et al. **Pharmacopsychiatry** 1985 May;18(3):252-4

Cerebrospinal fluid cholecystokinin, bombesin and somatostatin in schizophrenia and normals. Gerner RH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):73-82

Delta-sleep inducing peptide in cerebrospinal fluid from schizophrenics, depressives and healthy volunteers. Lindström LH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):83-90

Binding of 3H-spiperone to human lymphocytes: a biological marker in schizophrenia? Bondy B, et al. **Psychiatry Res** 1985 May;15(1):41-8

Serotonin and schizophrenia: correlations between serotonergic activity and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Lateral ventricular enlargement and clinical response in schizophrenia. Smith RC, et al. **Psychiatry Res** 1985 Mar;14(3):241-53

Amphetamine response and relapse risk after depot neuroleptic discontinuation. Angrist B, et al. **Psychopharmacology (Berlin)** 1985; 85(3):277-83

A limiting factor in the 'normalization' of schizophrenic orienting response dysfunction. Bernstein AS, et al. **Schizophr Bull** 1985;11(2):230-54

Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. Goldberg E. **Schizophr Bull** 1985;11(2):255-63

[Treatment of schizophrenia without symptoms with viloxazine (letter)] Kornhuber HH, et al. **Dtsch Med Wochenschr** 1985 Apr 26; 110(17):698 **(Ger)**

[Social integration of long-term paraphrenic patients with low-dose depot neuroleptic medication] Lesch OM, et al. **Psychiatr Prax** 1985 Mar; 12(2):63-8 (Eng. Abstr.) **(Ger)**

[Neurotransmitters and neuropeptides in schizophrenia] Toru M, et al. **Tanpakushitsu Kakusan Koso** 1984 Dec;29(14):1838-54 (150 ref.) **(Jpn)**

[Asymmetry of cholinesterase activity in cortical centers of human cerebral hemispheres] Kononenko VS, et al. **Fiziol Zh** 1985 Mar-Apr; 31(2):134-8 (Eng. Abstr.) **(Rus)**

SCHIZOPHRENIA, CATATONIC

Treatment-resistant catatonic stupor and combined lithium-neuroleptic therapy: a case report. Climo LH. **J Clin Psychopharmacol** 1985 Jun; 5(3):166-70

SCHIZOPHRENIA, PARANOID

Effects of thioridazine and fluphenazine on the pituitary, thyroid and adrenal functions in patients with paranoid schizophrenia. Horodnicki JM, et al. **Psychiatr Pol** 1984 May-Jun;18(3):205-11

[Haloperidol decanoate in replacing combinations of antipsychotic agents in the treatment of chronic schizophrenics] Yousef HA. **Acta Psiquiatr Psicol Am Lat** 1984 Dec;30(4):297-304 **(Spa)**

SELF STIMULATION

6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233-41

Comparison of deficits in electrical self-stimulation after ibotenic acid lesion of the lateral hypothalamus and the medial prefrontal cortex. Nassif S, et al. **Brain Res** 1985 Apr 22;332(2):247-57

Lateral hypothalamic self-stimulation persists in rats after destruction of lateral hypothalamic neurons by kainic acid or ibotenic acid. Sprick U, et al. **Neurosci Lett** 1985 May 14;56(2):211-6

Effects of intracranial self-stimulation on brain opioid peptides. Stein EA. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):67-73

Differential effects of pimozide on response-rate and choice accuracy in a self-stimulation paradigm in mice. Bowers W, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):521-6

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

SEROTONIN

Patency of saphenous veins used for aortocoronary bypass grafting: effects of platelet-derived mediators. Chiavarelli M, et al. **Adv Prostaglandin Thromboxane Leukotriene Res** 1985;13:311-4

The effect of stimulation and blocking of histamine H2 receptors on the turnover of the serotonin in different parts of the alimentary tract and the brain of the rat. Skrzydło-Radomańska B, et al. **Agents Actions** 1985 Apr;16(3-4):183-6

An immunohistochemical study of serotonin development in the opossum cerebellum. Bishop GA, et al. **Anat Embryol (Berl)** 1985; 171(3):325-38

Mediation of storage and retrieval with two drugs that selectively modulate serotonergic neurotransmission. Altman HJ. **Ann NY Acad Sci** 1985;444:496-8

6R-L-erythro-5,6,7,8-tetrahydrobiopterin as a regulator of dopamine and serotonin biosynthesis in the rat brain. Miwa S, et al. **Arch Biochem Biophys** 1985 May 15;239(1):234-41

Effect of amines on fibrinogen synthesis. Roy AK, et al. **Arch Biochem Biophys** 1985 Jun;239(2):364-7

Influence of chronic stellectomy on reactivity to serotonin in the dog external carotid bed. Mena MA, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):110-6

Human prostatic endocrine-paracrine (APUD) cells. Distributional analysis with a comparison of serotonin and neuron-specific enolase immunoreactivity and silver stains. di Sant'Agnese PA, et al. **Arch Pathol Lab Med** 1985 Jul;109(7):607-12

Differential release of serotonin without comparable histamine under diverse conditions in the rat mast cell. Theoharides TC, et al. **Biochem Pharmacol** 1985 May 1;34(9):1389-98

Endogenous platelet serotonin release monitored during aggregation by means of a new electrochemical technique. Marcenac F, et al. **Biochim Biophys Acta** 1985 Jul 5;840(3):377-82

The distribution and origin of serotonin immunoreactivity in the rat cerebellum. Bishop GA, et al. **Brain Res** 1985 Apr 8;331(2):195-207

Differential responses of serotonergic and non-serotonergic neurons in nucleus raphe magnus to systemic morphine in rats. Chiang CY, et al. **Brain Res** 1985 Jun 24;337(1):146-50

Ontogenetic development of serotoninergic neurons in the brain of a teleost, the three-spined stickleback. An immunohistochemical analysis. Ekström P, et al. **Brain Res** 1985 Jan;349(1-2):209-24

Serotonin depolarizes type A and C primary afferents: an intracellular study in bullfrog dorsal root ganglion. Holz GG, et al. **Brain Res** 1985 Feb 18;327(1-2):71-9

Enhancement of some 5-HT-dependent behavioural responses following repeated immobilization in rats. Kennett GA, et al. **Brain Res** 1985 Mar 25;330(2):253-63

Decreased serotonin content of embryonic raphe neurons following maternal administration of p-chlorophenylalanine: a quantitative immunocytochemical study. Lauder JM, et al. **Brain Res** 1985 May;352(1):107-14

Inhibitory influence of GABA on central serotonergic transmission. Raphe nuclei as the neuroanatomical site of the GABAergic inhibition of cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):91-103

Inhibitory influence of GABA on central serotonergic transmission. Involvement of the habenulo-raphe pathways in the GABAergic inhibition of ascending cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):81-90

Serotonin release in human cerebral cortex and its modulation via serotonin receptors. Schlicker E, et al. **Brain Res** 1985 Apr 8;331(2):337-41

Effects of enkephalin and 5-hydroxytryptamine on solitary tract neurones involved in respiration and respiratory reflexes. Sessle BJ, et al. **Brain Res** 1985 Feb 18;327(1-2):221-30

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

Ontogenetic alterations in the effects of food and/or maternal deprivation on 5-HT, 5-HIAA and 5-HIAA/5-HT ratios. Spear LP, et al. **Brain Res** 1985 Feb;350(1-2):143-57

Characterization of sodium-dependent, high-affinity serotonin uptake in rat spinal cord synaptosomes. Stauderman KA, et al. **Brain Res** 1985 Mar 18;330(1):11-20

Denervation supersensitivity to 5-hydroxytryptamine in the rat spinal cord is not due to the absence of 5-hydroxytryptamine. Tremblay LE, et al. **Brain Res** 1985 Mar 18;330(1):174-7

Immunocytochemical and radioautographic study of serotonin projections to cerebral ventricles of perinatal rats. Ugrumov MV, et al. **Brain Res** 1985 Feb;350(1-2):225-30

A comparison of the effects of serotonin, substance P and thyrotropin-releasing hormone on excitability of rat spinal motoneurons in vivo. White SR. **Brain Res** 1985 May 27;335(1):63-70

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

Postnatal development of serotonin in adrenal medullary cells. Holzwarth MA, et al. **Brain Res Bull** 1985 Jan;14(1):15-23

Localization of somatostatin-, bombesin-, and serotonin-like immunoreactivity in the lung of the fetal rhesus monkey. Dayer AM, et al. **Cell Tissue Res** 1985;239(3):621-5

Immunocytochemical demonstration of neuropeptides and serotonin in the tapeworm Diphyllobothrium dendriticum. Gustafsson MK, et al. **Cell Tissue Res** 1985;240(2):255-60

Immunocytochemical localization of serotonin in the brain and pituitary gland of the platyfish, Xiphophorus maculatus. Margolis-Kazan H, et al. **Cell Tissue Res** 1985;240(2):311-4

Unsaturated 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholines (unsaturated platelet-activating factor): aggregation of human platelets after incubation with indomethacin, creatinephosphate/creatinephosphokinase, xylocain and hirudine, and serotonin release after incubation with indomethacin. Korth R, et al. **Chem Phys Lipids** 1985 Jan;36(3):209-14

Removal of the endothelium potentiates canine large coronary artery constrictor responses to 5-hydroxytryptamine in vivo. Lamping KG, et al. **Circ Res** 1985 Jul;57(1):46-54

Liquid chromatography of serotonin and adenine nucleotides in blood platelets, illustrated by evaluation of functional integrity of platelet preparations. Ingebretsen OC, et al. **Clin Chem** 1985 May;31(5):695-8

Further studies on the effects of adrenal steroids in the active transport of serotonin into rat platelets. Lee PH, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):43-50

Intraplatelet serotonin (I5HT) in children with the hemolytic uremic syndrome. Edefonti A, et al. **Clin Nephrol** 1985 Apr;23(4):207-11

A molecular theory of recognition and activation at a 5-HT receptor based on a quantum chemical approach to structure activity relationships. Osman R, et al. **Clin Physiol Biochem** 1985;3(2-3):80-8

The influence of testosterone in the brain of the male rat on levels of serotonin (5-HT) and hydroxyindole-acetic acid (5-HIAA). Martinez-Conde E, et al. **Comp Biochem Physiol** [C] 1985;80(2):411-4

The uptake and metabolism of 5-hydroxytryptamine by tissue slices of the cestode Hymenolepis diminuta. Webb RA. **Comp Biochem Physiol** [C] 1985;80(2):305-12

Trials of serotonin, substance P and alpha 2-adrenergic receptor effects on the equine large colon. Sellers AF, et al. **Cornell Vet** 1985 Apr;75(2):319-23

Scheduled feeding and 24-hour rhythms of N-acetylserotonin and melatonin in rats. Ho AK, et al. **Endocrinology** 1985 May;116(5):1858-62

Serotonergic elements of the mammalian pituitary. Payette RF, et al. **Endocrinology** 1985 May;116(5):1933-42

An investigation of amphetamine-induced release of 5-HT from rat hippocampal slices. Balfour DJ, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):395-9

Age-related changes in 5HT uptake and [3H]imipramine binding sites in rat cerebral cortex. Brunello N, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):393-4

Inhibition by antiserum to vasoactive intestinal polypeptide (VIP) of prolactin secretion induced by serotonin in the rat. Ohta H, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):409-12

Physostigmine effects on serotonin uptake in human blood platelets. Rausch JL, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):91-6

Does brain 5-HIAA indicate serotonin release or monoamine oxidase activity? Wolf WA, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):381-7

Activity of serotonin-containing neurons in nucleus raphe magnus in freely moving cats. Fornal C, et al. **Exp Neurol** 1985 Jun;88(3):590-608

The enteric neural receptor for 5-hydroxytryptamine. Gershon MD, et al. **Experientia** 1985 Jul 15;41(7):863-8

Effect of various excitatory agonists on the secretion of 5-hydroxytryptamine from permeabilised human platelets induced by Ca2+ in the presence or absence of GTP. Knight DE, et al. **FEBS Lett** 1985 Apr 22;183(2):417-22

Endothelial serotonin uptake and mediation of prostanoid secretion and stress fiber formation. Shepro D, et al. **Fed Proc** 1985 Jul;44(10):2616-9

Evidence for negative feedback control of the release of [3H]serotonin from superfused mouse cerebellum slices induced by electrical field stimulation. Figueroa HR, et al. **Gen Pharmacol** 1985;16(2):103-8

Subcellular localization of serotonin immunoreactivity in rat enterochromaffin cells. Nilsson O, et al. **Histochemistry** 1985;82(4):351-5

Immunohistological studies of masked indoleamine cells in the area postrema of the rat. Nishida K, et al. **Histochemistry** 1985;82(2):101-6

Role of 5-HT on increased permeability of blood-brain barrier under heat stress. Sharma HS, et al. **Indian J Physiol Pharmacol** 1984 Oct-Dec;28(4):259-67

Cloned mouse mast cells and normal mouse peritoneal mast cells. Determination of serotonin content and ability to synthesize serotonin in vitro. Weitzman G, et al. **Int Arch Allergy Appl Immunol** 1985;77(1-2):189-91

Pharmacologic studies of the central action of zopiclone: effects on locomotor activity and brain monoamines in rats. Liu HJ, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):121-8

Effects of pinealectomy on regional brain serotonin metabolism. Aldegunde M, et al. **Int J Neurosci** 1985 Apr;26(1-2):9-13

d-Fenfluramine and salbutamol: two drugs causing anorexia through different neurochemical mechanisms. Garattini S, et al. **Int J Obes** 1984;8 Suppl 1:151-7

Two novel agents affecting eating through an action on monoaminergic systems. Roncucci R, et al. **Int J Obes** 1984;8 Suppl 1:103-17

Serotonin relationships of autistic probands and their first-degree relatives. Kuperman S, et al. **J Am Acad Child Psychiatry** 1985 Mar;24(2):186-90

Central nervous system opiate and 5-hydroxytryptamine influences on baroreflex control of the coronary circulation. Moore PG, et al. **J Auton Nerv Syst** 1985 Feb–Mar;12(2–3):185–94

Role of central nervous system monoamines in cardiopulmonary effects of Althesin in rabbit and man. Quail AW, et al. **J Auton Nerv Syst** 1985 Feb–Mar;12(2–3):159–74

Central nervous system 5–hydroxytryptamine and noradrenaline specificity of ear vascular and ventilation reflexes in thermoregulating rabbits. White SW, et al. **J Auton Nerv Syst** 1985 Feb–Mar; 12(2–3):131–44

Evidence that phospholipid turnover is the signal transducing system coupled to serotonin–S2 receptor sites. de Chaffoy de Courcelles D, et al. **J Biol Chem** 1985 Jun 25;260(12):7603–8

Thrombin induces serotonin secretion and aggregation independently of inositol phospholipids hydrolysis and protein phosphorylation in human platelets permeabilized with saponin. Lapetina EG, et al. **J Biol Chem** 1985 Jun 10;260(11):7078–83

5–Hydroxytryptamine stimulates inositol phosphate production in a cell–free system from blowfly salivary glands. Evidence for a role of GTP in coupling receptor activation to phosphoinositide breakdown. Litosch I, et al. **J Biol Chem** 1985 May 10;260(9):5464–71

Vasoactive amines modulate actin cables (stress fibers) and surface area in cultured bovine endothelium. Welles SL, et al. **J Cell Physiol** 1985 Jun;123(3):337–42

Nimodipine has an inhibitory action on neurotransmitter release from human cerebral arteries. Porter JD, et al. **J Cereb Blood Flow Metab** 1985 Jun;5(2):338–42

Localization of serotonin immunoreactivity in the opossum cerebellum. Bishop GA, et al. **J Comp Neurol** 1985 May 15;235(3):301–21

Possible target neurons of 5–hydroxytryptamine fibers in the lamprey spinal cord: immunohistochemistry combined with intracellular staining with Lucifer yellow. Van Dongen PA, et al. **J Comp Neurol** 1985 Apr 22;234(4):523–35

Serotoninlike immunoreactivity in the cestode Hymenolepis diminuta. Webb RA, et al. **J Comp Neurol** 1985 Apr 22;234(4):431–40

Ultrastructural analysis of central serotoninergic neurons immunolabeled by silver–gold–intensified diaminobenzidine chromogen. Completion of immunocytochemistry with X–ray microanalysis. Liposits Z, et al. **J Histochem Cytochem** 1985 Jun;33(6):604–10

Sprouting and functional regeneration of an identified serotonergic neuron following axotomy. Murphy AD, et al. **J Neurobiol** 1985 Mar; 16(2):137–51

3,4–Dihydroxyphenylethylamine and 5–hydroxytryptamine metabolism in the rat: acidic metabolites in cisternal cerebrospinal fluid before and after giving probenecid. Curzon G, et al. **J Neurochem** 1985 Aug; 45(2):508–13

Neurochemical profile of Lu 19–005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615–22

Tryptamine concentrations in areas of 5–hydroxytryptamine terminal innervation after electrolytic lesions of midbrain raphe nuclei. Juorio AV, et al. **J Neurochem** 1985 Aug;45(2):422–6

Assessment of noradrenaline and 5–hydroxytryptamine uptake in intact rat brain. Wyllie MG, et al. **J Neurochem** 1985 Aug;45(2):456–60

Localization of 5–hydroxytryptamine to neurons and endoneurial mast cells in rat sensory ganglia. Kai–Kai MA, et al. **J Neurocytol** 1985 Feb; 14(1):63–78

Preparation and characterization of antisera and monoclonal antibodies to serotonergic and dopaminergic ligands. Flurkey K, et al. **J Neuroimmunol** 1985 May;8(2–3):115–27

Effect of prostaglandin F2 alpha on brain and stomach 5–hydroxytryptamine. Sanyal AK, et al. **J Pharm Pharmacol** 1985 Apr; 37(4):274–5

5–Hydroxytryptamine–stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: pharmacological characterization and effects of antidepressants. Kendall DA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):473–9

Efflux of 5–hydroxytryptamine and noradrenaline into spinal cord superfusates during stimulation of the rat medulla. Hammond DL, et al. **J Physiol (Lond)** 1985 Feb;359:151–62

A calcium–dependent reversible permeability increase in microvessels in frog brain, induced by serotonin. Olesen SP. **J Physiol (Lond)** 1985 Apr;361:103–13

In vivo electrochemical studies of rat striatal dopamine and serotonin release after morphine. Broderick PA. **Life Sci** 1985 Jun 17; 36(24):2269–75

Differential effects of isoproterenol injections on the levels of pineal N–acetyltransferase, serum N–acetylserotonin and melatonin. Ho AK, et al. **Life Sci** 1985 Jun 3;36(22):2137–43

Differential regulation of the brain and gut immunoreactive dynorphin by the serotonin system. Majeed NH, et al. **Life Sci** 1985 Jul 29; 37(4):339–43

The effect of epinephrine and serotonin on hepatic poly(A)+ RNA synthesis. Roy AK, et al. **Life Sci** 1985 Jun 17;36(24):2301–7

Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5–MeODMT or mCPP. Sills MA, et al. **Life Sci** 1985 Jul 1; 36(26):2463–9

Modulation of a transient outward current in serotonergic neurones by alpha 1–adrenoceptors. Aghajanian GK. **Nature** 1985 Jun 6–12; 315(6019):501–3

The depolarizing action of 5–hydroxytryptamine on rabbit vagal primary afferent and sympathetic neurones and its selective blockade by MDL 72222. Azami J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb; 328(4):423–9

Effect of triamterene on 5–hydroxytryptamine biosynthesis in different brain areas. Steinberg P, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Mar;329(1):42–4

Role of the serotonin uptake carrier in the neurochemical response to methamphetamine: effects of citalopram and chlorimipramine. Schmidt CJ, et al. **Neurochem Res** 1985 May;10(5):637–48

The uptake of serotonin and dopamine by homogenates of frozen rat and human brain tissue. Stenström A, et al. **Neurochem Res** 1985 May; 10(5):591–9

Opiate regulation of mesolimbic serotonin release: in vivo semiderivative electrochemical analyses. Broderick PA. **Neuropeptides** 1985 Feb; 5(4–6):587–90

Differential modulation of the beta–endorphin and dynorphin systems by serotonergic stimulation in the rat. Majeed NH, et al. **Neuropeptides** 1985 Feb;5(4–6):563–6

Serotonin and antidepressant drugs antagonize melatonin–induced behavioural changes after injection into the nucleus accumbens of rats. Gaffori O, et al. **Neuropharmacology** 1985 Mar;24(3):237–44

Down–regulation of beta–adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5–HT neurones but not 5–HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279–83

The effect of prolonged treatment with tricyclic antidepressants on the actions of 5–hydroxytryptamine in the hippocampal slice of the rat. Rowan MJ, et al. **Neuropharmacology** 1985 Feb;24(2):131–7

Morphological evidence that serotonin–immunoreactive neurons in the nucleus dorsomedialis hypothalami could be under catecholaminergic influence. Arezki F, et al. **Neurosci Lett** 1985 May 14;56(2):161–6

Immunohistochemical and biochemical detection of serotonin in the guinea pig celiac–superior mesenteric plexus. Ma RC, et al. **Neurosci Lett** 1985 May 14;56(2):107–12

Membrane responses and changes in cAMP levels in Aplysia sensory neurons produced by serotonin, tryptamine, FMRFamide and small cardioactive peptideB (SCPB). Ocorr KA, et al. **Neurosci Lett** 1985 Apr 9;55(2):113–8

The effect of adrenalectomy and corticosterone on homotypic collateral sprouting of serotonergic fibers in hippocampus. Zhou FC, et al. **Neurosci Lett** 1985 Mar 15;54(2–3):111–6

Distribution of serotonergic neurons and processes in the lamprey spinal cord. Harris–Warrick RM, et al. **Neuroscience** 1985 Apr; 14(4):1127–40

A serotonin–containing pathway from the area postrema to the parabrachial nucleus in the rat. Lança AJ, et al. **Neuroscience** 1985 Apr; 14(4):1117–26

Serotonergic terminals in the neural sheath of the blowfly nervous system: electron microscopical immunocytochemistry and 5,7–dihydroxytryptamine labelling. Nässel DR, et al. **Neuroscience** 1985 May;15(1):293–307

Altered responses to serotonergic agents in Fawn–Hooded rats. Gudelsky GA, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):489–92

Involvement of the serotonergic system in the prolongation of pentobarbital sleeping time produced by prostaglandin D2. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):365–70

The effects produced by prostaglandin D2 on serotonin turnover and release and tryptophan uptake. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):371–5

Manipulations of 5–HT activity and memory in the rat. Lalonde R, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):377–82

Effects of quipazine and methysergide on play in juvenile rats. Normansell L, et al. **Pharmacol Biochem Behav** 1985 May;22(5):885–7

Suppression of male copulatory behavior by delta 9–THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415–20

Increased sensitivity to serotonergic agonists after repeated electroconvulsive shock in rats. Wielosz M. **Pharmacol Biochem Behav** 1985 May;22(5):683–7

Some behavioral effects of microinjections of serotonin and noradrenaline into the limbic structures of the rat brain. Plaźnik A. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):541–54

Serotonergic control of experimental aggression. Valzelli L, et al. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):495–503

Combined lithium and valproate treatment and subsequent withdrawal: serotonergic mechanism of their interaction in discrete brain regions. Shukla GS. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(2):153–6

Serotonin and schizophrenia: correlations between serotonergic activity and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Anti-aversive role of serotonin in the dorsal periaqueductal grey matter. Schütz MT, et al. **Psychopharmacology (Berlin)** 1985;85(3):340-5

Inhibition of platelet function by contrast media: iopamidol and ioxaglate versus iothalamate. Work in progress. Rao AK, et al. **Radiology** 1985 Aug;156(2):311-3

Up-regulation of thyrotropin-releasing hormone (TRH) receptors in rat spinal cord after codepletion of serotonin and TRH. Ogawa N, et al. **Regul Pept** 1985 Mar;10(2-3):85-90

High-performance liquid chromatographic assay of serotonin in human plasma. Marasini B, et al. **Ric Clin Lab** 1985 Jan-Mar;15(1):63-9

The effects of vagal nerve stimulation on endoluminal release of serotonin and substance P into the feline small intestine. Grønstad KO, et al. **Scand J Gastroenterol** 1985 Mar;20(2):163-9

High-affinity uptake of serotonin into immunocytochemically identified astrocytes. Kimelberg HK, et al. **Science** 1985 May 17; 228(4701):889-91

Diurnal rhythms of N-acetylserotonin and serotonin in cerebrospinal fluid of monkeys. Taylor PA, et al. **Science** 1985 May 17;228(4701):900

Serotonin-induced platelet aggregation in whole blood and the effects of ketanserin and mepyramine. Bevan J, et al. **Thromb Res** 1985 Apr 15;38(2):189-94

Platelet-mediated vascular permeability in the rat: a predominant role for 5-hydroxytryptamine. De Clerck F, et al. **Thromb Res** 1985 May 15;38(4):321-39

[Stimulatory control by oxytocin (or an analog peptide) of the pituitary intermediate lobe in rabbits. Inhibitory role of serotonin] Schimchowitsch S, et al. **C R Acad Sci [III]** 1985;300(7):283-6 (Eng. Abstr.) **(Fre)**

[Classification of chronic psychoses types I and II and platelet serotonin levels. Apropos of 38 cases] Boudjema F, et al. **Encephale** 1985 Jan-Feb; 11(1):39-42 (Eng. Abstr.) **(Fre)**

[Central serotonin receptors] Fillion G. **Pathol Biol (Paris)** 1985 Apr; 33(4):221-6 (56 ref.) **(Fre)**

[Preliminary observations on the distribution of serotoninergic and cerebellar-projecting neurons of the raphe nuclei of the brain stem] De Leo F, et al. **Boll Soc Ital Biol Sper** 1985 Feb 28;61(2):229-33 (Eng. Abstr.) **(Ita)**

[Structure of the binding center of the serotonin S2 receptor] Kats MM. **Biol Nauki** 1985;(3):19-24 (Eng. Abstr.) **(Rus)**

[pH changes in the matrix of serotonin organelles of stimulated thrombocytes] Kozlov VK, et al. **Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR** 1985; 8(1):77-82 (Eng. Abstr.) **(Rus)**

[Effect of cold on the brain serotonin system and the corticosteroid level of the blood in different strains of mice] Koriakina LA, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):422-7 (Eng. Abstr.) **(Rus)**

SEX BEHAVIOR, ANIMAL

The proestrous surge of prolactin enhances sexual receptivity in the rat. Witcher JA, et al. **Biol Reprod** 1985 May;32(4):834-9

Modulation of lordosis behaviour in the female rat by corticotropin releasing factor, beta-endorphin and gonadotropin releasing hormone in the mesencephalic central gray. Sirinathsinghji DJ. **Brain Res** 1985 Jun 10;336(1):45-55

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

Antagonism by lisuride and 8-OH-DPAT of 5-HTP-induced prolongation of the performance of male rat sexual behavior. Ahlenius S, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):379-81

The dopamine autoreceptor agonist B-HT 920 markedly stimulates sexual behavior in male rats. Ferrari F, et al. **Experientia** 1985 May 15; 41(5):636-8

Changes in hormone levels in relation to breeding behavior in male bullfrogs (Rana catesbeiana) at the individual and population levels. Mendonça MT, et al. **Gen Comp Endocrinol** 1985 May;58(2):270-9

Adrenalectomy does not prevent the hyperprolactinemic, induced sexual behavior deficits in CDF male rats. Shrenker P, et al. **Life Sci** 1985 May 13;36(19):1881-8

Neuroendocrine regulation of seasonal reproductive activity in the male golden hamster. Steger RW, et al. **Neurosci Biobehav Rev** 1985 Summer; 9(2):191-201

Potentiative action of alpha- and beta-adrenergic receptor stimulation in inducing lordosis behavior. Fernández-Guasti A, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):613-7

Serotonin antagonist pirenperone inhibits sexual behavior in the male rat: attenuation by quipazine. Mendelson SD, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):565-71

Suppression of male copulatory behavior by delta 9-THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415-20

SHARED PARANOID DISORDER

A relapsing folie à trois. Fernando FP, et al. **Br J Psychiatry** 1985 Mar; 146:315-6

SLEEP

Effects of doxylamine and acetaminophen on postoperative sleep. Smith GM, et al. **Clin Pharmacol Ther** 1985 May;37(5):549-57

Beta 1 and beta 2 adrenergic receptors: their role in the regulation of paradoxical sleep in the rat. Lanfumey L, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):558-67

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

Effects of exhaustive submaximal exercise on cardiovascular function during sleep. Bunnell DE, et al. **J Appl Physiol** 1985 Jun; 58(6):1909-13

Auto-tolerance to the endogenous opioids and sleep. Gillman MA, et al. **Med Hypotheses** 1985 Apr;16(4):393-5

Effects of acute and chronic treatment with amitryptyline on the sleep-wake activity of rats. Obál F Jr, et al. **Neuropharmacology** 1985 Mar;24(3):223-9

p-Chloroamphetamine: effect on sleep and respiration in the rat. DeMesquita S. **Pharmacol Biochem Behav** 1985 May;22(5):889-91

Involvement of the serotonergic system in the prolongation of pentobarbital sleeping time produced by prostaglandin D2. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):365-70

SLEEP DEPRIVATION

Can lithium carbonate prolong the antidepressant effect of sleep deprivation? [letter] Baxter LR Jr. **Arch Gen Psychiatry** 1985 Jun; 42(6):635

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

[Sleep deprivation as a method of treating endogenous depression] Vovin RIa, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):560-5 (Eng. Abstr.) **(Rus)**

SLEEP, REM

Internight variability of REM latency in major depression: implications for the use of REM latency as a biological correlate. Ansseau M, et al. **Biol Psychiatry** 1985 May;20(5):489-505

Cholinomimetic drug RS 86, REM sleep, and depression [letter] Berger M, et al. **Lancet** 1985 Jun 15;1(8442):1385-6

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

SLEEP STAGES

Prenatal exposure to diazepam results in enduring reductions in brain receptors and deep slow wave sleep. Livezey GT, et al. **Brain Res** 1985 May 20;334(2):361-5

Relationship between sleep efficiency and urinary excretion of catecholamines in bed-rested humans. Nishihara K, et al. **Sleep** 1985; 8(2):110-7

SOCIAL ADJUSTMENT

Treatment characteristics of psychiatric programs that correlate with patient community adjustment. Collins JF, et al. **J Clin Psychol** 1985 May;41(3):299-308

[Social integration of long-term paraphrenic patients with low-dose depot neuroleptic medication] Lesch OM, et al. **Psychiatr Prax** 1985 Mar; 12(2):63-8 (Eng. Abstr.) **(Ger)**

SODIUM

Human platelet alpha 2-adrenergic receptors: effect of Na^+ on interaction with the adenylate cyclase system and on epinephrine-stimulated platelet secretion. Limbird LE, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:235-42

Studies on role of calmodulin in Ca^{2+} regulation of rabbit ileal Na and Cl transport. Donowitz M, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 1):G726-40

Central effects of angiotensin II and dopamine in sodium-depleted sheep. Huang BS, et al. **Am J Physiol** 1985 May;248(5 Pt 2):R541-8

Mineralocorticoid regulation of apical cell membrane Na^+ and K^+ transport of the cortical collecting duct. Sansom SC, et al. **Am J Physiol** 1985 Jun;248(6 Pt 2):F858-68

A novel technique for assessing the sources of dietary sodium. Sanchez-Castillo CP, et al. **Ann Clin Res** 1984;16 Suppl 43:44-8

Inhibition of Na^+/Ca^{2+} exchange in pituitary plasma membrane vesicles by analogues of amiloride. Kaczorowski GJ, et al. **Biochemistry** 1985 Mar 12;24(6):1394–403

Coupling of a loop diuretic-sensitive Na+ influx with the net loop diuretic-sensitive K+ efflux in mouse NIH 3T3 cells. Panet R, et al. **Biochim Biophys Acta** 1985 Jun 27;816(2):278–82

The effect of the intracellular sodium level on the activity of amino acid transport systems L and A in SV40 3T3 cells. Petronini PG, et al. **Biochim Biophys Acta** 1985 May 28;815(3):361–8

Characterization of sodium-dependent, high-affinity serotonin uptake in rat spinal cord synaptosomes. Stauderman KA, et al. **Brain Res** 1985 Mar 18;330(1):11–20

Study of the interrelationship between dopaminergic activity and potassium ion. Matsuda S, et al. **Clin Exp Hypertens [A]** 1984; 6(12):2249–61

The influence of the membrane sodium pump activity on the ability of human peripheral blood lymphocytes to form early rosettes with SRBC. Witkowski J. **Immunology** 1985 Jun;55(2):339–45

Localization of potassium and sodium fluxes in the rat lens. Reszelbach R, et al. **Invest Ophthalmol Vis Sci** 1985 Jul;26(7):945–52

Evidence for tyrosyl residues at the Na+ site on the intestinal Na+/glucose cotransporter. Peerce BE, et al. **J Biol Chem** 1985 May 25;260(10):6026–31

Na+ (Li+)-proline cotransport in Escherichia coli. Chen CC, et al. **J Membr Biol** 1985;84(2):157–64

Sodium-dependent modulation of the renal Na-K-ATPase: influence of mineralocorticoids on the cortical collecting duct. O'Neil RG, et al. **J Membr Biol** 1985;85(2):169–79

Influence of lead ions on cation permeability in human red cell ghosts. Simons TJ. **J Membr Biol** 1985;84(1):61–71

GABAergic inhibition of hypertonic saline-induced vasopressin-dependent hypertension. Brennan TJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):663–71

Effects of angiotensin or carbachol on sodium intake and excretion in adrenalectomized or deoxycorticosterone-treated rats. Fitzsimons JT, et al. **J Physiol (Lond)** 1985 Feb;359:447–58

Cation activation of the pig kidney sodium pump: transmembrane allosteric effects of sodium. Karlish SJ, et al. **J Physiol (Lond)** 1985 Feb;359:119–49

Inhibition of sodium transport in frog skin and iodination of tyrosine in vitro by a peptide of renal origin. Fregly MJ, et al. **Klin Wochenschr** 1985;63 Suppl 3:102–6

The relation of sodium transport to blood pressure in the adrenalectomized rat. Friedman SM. **Klin Wochenschr** 1985;63 Suppl 3:55–8

Modulation of erythrocyte Na transport pathway(s) by excess Na intake. Dagher G, et al. **Life Sci** 1985 Jul 22;37(3):243–53

Intracellular Ca indicator Quin-2 inhibits Ca2+ inflow via Na/Ca exchange in squid axon. Allen TJ, et al. **Nature** 1985 Jun 27–Jul 3; 315(6022):755–6

The effect of phenylalanine on intracellular pH and sodium activity in proximal convoluted tubule cells of the frog kidney. Messner G, et al. **Pflugers Arch** 1985 May;404(2):145–9

Behaviour of chemically modified sodium channels in frog nerve supports a three-state model of inactivation. Schmidtmayer J. **Pflugers Arch** 1985 May;404(1):21–8

Effect of a low sodium medium, ouabain and noradrenaline on relaxation of the myocardium of the perfused rabbit heart. Fišer B, et al. **Physiol Bohemoslov** 1985;34(1):77–84

Effect of dialysate sodium on the dopamine, adrenaline and noradrenaline concentration in haemodialysis patients. Ksiażek A, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985;21:225–9

Study of the ionic basis of visual transduction in vertebrate retinal rods. Yau KW, et al. **Prog Clin Biol Res** 1985;176:21–31 (36 ref.)

[Possible participation of slow Na+--Ca++ channels in realizing cholinergic effects on the cardiac pacemaker] Sukhova GS, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):506–9 (Eng. Abstr.) **(Rus)**

SOMATOSTATIN

Somatostatin inhibition of cyclic AMP accumulation and adrenocorticotropin release from mouse anterior pituitary tumor cells: mode of action and self-regulation. Reisine TD. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:169–77

Cholecystokinin potently releases somatostatin from canine fundic mucosal cells in short-term culture. Soll AH, et al. **Am J Physiol** 1985 May;248(5 Pt 1):G569–73

The somatostatin-28 convertase of rat brain cortex generates both somatostatin-14 and somatostatin-28. Gluschankof P, et al. **Biochem Biophys Res Commun** 1985 May 16;128(3):1051–7

Effect of somatostatin on the proliferation of mouse spleen lymphocytes in vitro. Pawlikowski M, et al. **Biochem Biophys Res Commun** 1985 May 31;129(1):52–5

Difference in dose-response curves for glucose-induced insulin and somatostatin release in rat pancreas. Dettori-Gera C, et al. **Biochim Biophys Acta** 1985 May 8;839(3):281–6

The biological activity of duck 'big' somatostatin on chicken adipose tissue. Di Scala-Guenot D, et al. **Biochim Biophys Acta** 1985 May 30; 845(2):261–4

Immunocytochemical localization of somatostatin and cholecystokinin in the cat visual cortex. Demeulemeester H, et al. **Brain Res** 1985 Apr 22;332(2):361–4

Immunocytochemical localization of somatostatin-28 in the rat hypothalamus. Guy J, et al. **Brain Res** 1985 Mar 25;330(2):283–9

Thyroid hormones reversibly suppress somatostatin secretion and immunoreactivity in cultured neocortical cells. Peterfreund RA, et al. **Brain Res** 1985 Mar 4;328(2):259–70

The effects of neurotensin, vasoactive intestinal polypeptide and other neuropeptides on the secretion of somatostatin from cerebral cortical cells. Robbins RJ, et al. **Brain Res** 1985 Apr 15;332(1):161–4

Vasoactive intestinal peptide and PHI stimulate somatostatin release from rat cerebral cortical and diencephalic cells in dispersed cell culture. Tapia-Arancibia L, et al. **Brain Res** 1985 Jun 10;336(1):67–72

Comparison of somatostatin-28 and somatostatin-14 clearance by the perfused rat liver. Seno M, et al. **Can J Physiol Pharmacol** 1985 Jan; 63(1):62–7

Tissue-specific posttranslational processing of pre-prosomatostatin encoded by a metallothionein-somatostatin fusion gene in transgenic mice. Low MJ, et al. **Cell** 1985 May;41(1):211–9

Localization of somatostatin-, bombesin-, and serotonin-like immunoreactivity in the lung of the fetal rhesus monkey. Dayer AM, et al. **Cell Tissue Res** 1985;239(3):621–5

Somatostatin-14 modulates postprandial glucose levels and release of gastrointestinal and pancreatic hormones. O'Shaughnessy DJ, et al. **Digestion** 1985;31(4):234–42

Characterization of tissue and releasable molecular forms of somatostatin-28[1–12]-like immunoreactivity in rat median eminence. Charpenet G, et al. **Endocrinology** 1985 May;116(5):1863–8

Somatostatin-14 and somatostatin-28 pretreatment down-regulate somatostatin-14 receptors and have biphasic effects on forskolin-stimulated cyclic adenosine, 3',5'-monophosphate synthesis and adrenocorticotropin secretion in mouse anterior pituitary tumor cells. Heisler S, et al. **Endocrinology** 1985 Jul;117(1):217–25

Forskolin, an activator of adenylate cyclase, stimulates pancreatic insulin, glucagon, and somatostatin release in the dog: studies in vitro. Hermansen K. **Endocrinology** 1985 Jun;116(5):2251–8

Somatostatin secretion from the isolated perfused dog ileum. Hermansen K. **Endocrinology** 1985 Jul;117(1):287–91

Cysteamine induces a loss of tissue somatostatin-28 when measured as somatostatin-28(15–28)-like immunoreactivity but not when assessed as somatostatin-28(1–14)-like immunoreactivity: evidence for the importance of the disulfide bond for cysteamine action. Patel YC, et al. **Endocrinology** 1985 May;116(5):1699–702

Mouse hypothalamic somatostatin release: roles of calcium and calmodulin. Richardson S, et al. **Endocrinology** 1985 Jul; 117(1):369–75

Hepatic metabolism of somatostatin-14 and somatostatin-28: immunochemical characterization of the metabolic fragments and comparison of cleavage sites. Ruggere MD, et al. **Endocrinology** 1985 Jul;117(1):88–96

Antiserum to rat growth hormone (GH)-releasing factor suppresses but does not abolish antisomatostatin-induced GH release in the rat. Thomas CR, et al. **Endocrinology** 1985 Jun;116(6):2174–8

Immunoreactive and biologically active somatostatin in human and sheep milk. Werner H, et al. **Eur J Biochem** 1985 Apr 15;148(2):353–7

Pituitary growth hormone and hypothalamic somatostatin in young female rats versus old constant estrous female rats. Forman LJ, et al. **Experientia** 1985 May 15;41(5):653–4

Effect of long acting somatostatin-analogue, SMS 201 995, on gut hormone secretion in normal subjects. Kraenzlin ME, et al. **Experientia** 1985 Jun 15;41(6):738–40

Neurobiological actions of cysteamine. Brown M, et al. **Fed Proc** 1985 Jun;44(9):2556–60

Regulatory peptides (glucagon, somatostatin, substance P, and VIP) in the brain and gastrointestinal tract of Ambystoma mexicanum. Conlon JM, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):150–8

Is somatostatin a humoral regulator of the endocrine pancreas and gastric acid secretion in man? Loud FB, et al. **Gut** 1985 May;26(5):445–9

Differential changes in calcitonin, somatostatin and gastrin/cholecystokinin-like immunoreactivities in rat thyroid parafollicular cells during ontogeny. Larsson LI. **Histochemistry** 1985; 82(2):121–30

Different effects of prostaglandin E1, E2 and D2 on pancreatic somatostatin release. Nishi S, et al. **Horm Metab Res** 1984 Dec; 16 Suppl 1:114–8

Effect of long and short photoperiod and/or pinealectomy on immunoreactive somatostatin in the Syrian hamster. Webb SM, et al. **Horm Metab Res** 1985 Feb;17(2):107–8

Z-DNA in the rat somatostatin gene. Hayes TE, et al. **J Biol Chem** 1985 Jul 5;260(13):8145–56

In situ hybridization of putative somatostatin mRNA within hypothalamus of the rat using synthetic oligonucleotide probes. Arentzen R, et al. **J Cell Biochem** 1985;27(4):415–22

A unique control mechanism in the regulation of insulin secretion. Secretagogue-induced somatostatin receptor recruitment. Draznin B, et al. **J Clin Invest** 1985 May;75(5):1510-6

Effects of cysteamine and antibody to somatostatin on islet cell function in vitro. Evidence that intracellular somatostatin deficiency augments insulin and glucagon secretion. Patel YC, et al. **J Clin Invest** 1985 Apr; 75(4):1249-55

Multiple forms of somatostatin-like immunoreactivity in the hypothalamus and amygdala of the rat: selective localization of somatostatin-28 in the median eminence. Pierotti AR, et al. **J Endocrinol** 1985 Jun; 105(3):383-9

Modulation of lymphocyte function by sensory neuropeptides. Payan DG, et al. **J Immunol** 1985 Aug;135(2 Suppl):783s-786s

Modulation by monoamines of somatostatin-sensitive adenylate cyclase on neuronal and glial cells from the mouse brain in primary cultures. Chneiweiss H, et al. **J Neurochem** 1985 Jun;44(6):1825-31

Localization of somatostatin receptors in secretion vesicles in anterior pituitary cells and pancreatic islets. Draznin B, et al. **J Recept Res** 1985; 5(1):83-103

Effect of a cyclic hexapeptide analog (L363,586) of somatostatin on the function of pancreas grafts in dogs. Liu T, et al. **J Surg Res** 1985 Jul; 39(1):39-45

Somatostatin: hormonal and therapeutic roles [editorial] **Lancet** 1985 Jul 13;2(8446):77-8

Different effects of three kinds of somatostatin (15-28, 1-14, 1-28) on rabbit's platelet aggregation. Fuse I, et al. **Life Sci** 1985 May 27; 36(21):2047-52

Somatostatin antagonist analogue stimulates growth in rats. Spencer GS, et al. **Life Sci** 1985 Jul 8;37(1):27-30

Effect of a selective octapeptide analogue of somatostatin on renal water excretion in the dog. Mountokalakis T, et al. **Metabolism** 1985 May; 34(5):408-9

Somatostatin release from the median eminence of unanesthetized rats: lack of correlation with pharmacologically suppressed growth hormone secretion. Fukata J, et al. **Neuroendocrinology** 1985 Mar; 40(3):193-200

The binding of somatostatin to rat synaptosomal membranes: effects of detergent solubilisation and of bacitracin. Weightman DR, et al. **Neuropeptides** 1985 Mar;6(1):83-92

Rat brain membranes possess two high-affinity binding sites for [3H]somatostatin. Weightman DR, et al. **Neurosci Lett** 1985 Apr 9; 55(2):161-6

Long-term suspension culture of isolated hypothalamic nuclei of the rat: morphological differentiation and release of substances influencing corticotropin and growth hormone secretion. Gyévai A, et al. **Neuroscience** 1985 Feb;14(2):519-33

The somatostatin systems of the guinea-pig brainstem. Taber-Pierce E, et al. **Neuroscience** 1985 May;15(1):215-35

Immunohistochemical studies of substance P, cholecystokinin-octapeptide and somatostatin in dorsal root ganglia of the rat. Tuchscherer MM, et al. **Neuroscience** 1985 Feb;14(2):593-605

Effects of MET-ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):139-48

Somatostatin analogs: correlation of receptor affinity with inhibition of cyclic AMP formation in pancreatic acinar cells. Taparel D, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):109-14

Human pancreatic polypeptide and somatostatin in chronic renal failure. Lugari R, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985; 21:614-7

Cerebrospinal fluid cholecystokinin, bombesin and somatostatin in schizophrenia and normals. Gerner RH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):73-82

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

Evidence against prostaglandin-mediation of somatostatin-inhibition of gastric secretions. Albinus M, et al. **Regul Pept** 1985 Mar; 10(2-3):259-66

Somatostatin and GABA correlate with cervical autonomic nerve activity. Tonoue T, et al. **Regul Pept** 1985 Apr;10(4):299-307

Effects of somatostatin-14 and somatostatin-28 on plasma hormonal and gastric secretory responses to cephalic and gastrointestinal stimulation in man. Konturek SJ, et al. **Scand J Gastroenterol** 1985 Jan; 20(1):31-8

Effect of somatostatin on bethanechol-stimulated gastric pepsin secretion in gastric fistula dogs. Ladegaard L, et al. **Scand J Gastroenterol** 1985 Jan;20(1):87-91

Effects of substance P and somatostatin on taurocholate-stabilized and CCK- or secretin-induced choleresis in the anesthetized dog. Magnusson I, et al. **Scand J Gastroenterol** 1984 Nov;19(8):1007-14

The microvasculature of the small-intestinal mucosa of the rat: quantification of hemodynamic effects of topically applied cimetidine, ranitidine, somatostatin, and vasopressin. Neff M, et al. **Scand J Gastroenterol [Suppl]** 1985;112:6-11

High plasma levels of immunoreactive somatostatin in transgenic mice expressing a metallothionein-somatostatin fusion gene. Low MJ, et al. **Trans Assoc Am Physicians** 1984;97:205-9

[Somastostatin in domestic fowl] Baldissera FG, et al. **Riv Biol** 1985 Spring;78(1):123-8 (Eng. Abstr.) **(Ita)**

[Effect of somatostatin on the neurosecretory cells of the hypothalamic paraventricular nucleus and argentaffin cells of the antral part of the rat stomach] Kotel'nikova VI, et al. **Fiziol Zh SSSR** 1985 Feb; 71(2):206-12 (Eng. Abstr.) **(Rus)**

SOMATOTROPIN RELEASING HORMONE

Human pancreatic tumor GH-releasing factor. Thorner MO, et al. **Acta Neurochir (Wien)** 1985;75(1-4):72-80

Growth hormone releasing factor (GRF) and dopamine coexist in hypothalamic arcuate neurons. Meister B, et al. **Acta Physiol Scand** 1985 May;124(1):133-6

Physiological studies with somatocrinin, a growth hormone-releasing factor. Wehrenberg WB, et al. **Annu Rev Pharmacol Toxicol** 1985; 25:463-83 (98 ref.)

The effects of testosterone and estrogen on the pituitary growth hormone response to growth hormone-releasing factor. Wehrenberg WB, et al. **Biol Reprod** 1985 Mar;32(2):369-75

Plasma growth hormone secretion during constant growth hormone-releasing factor infusion. Takano K, et al. **Endocrinol Jpn** 1984 Dec;31(6):681-5

Pituitary response of growth hormone release in administration of hpGRF-44 to pregnant rats. Uchida N, et al. **Endocrinol Jpn** 1984 Dec; 31(6):831-5

Effects of intraventricular growth hormone-releasing factor on growth hormone release: further evidence for ultrashort loop feedback. Lumpkin MD, et al. **Endocrinology** 1985 May;116(5):2070-4

Dose-response characteristics of various peptides with growth hormone-releasing activity in the unanesthetized male rat. McCormick GF, et al. **Endocrinology** 1985 Jul;117(1):97-105

Antiserum to rat growth hormone (GH)-releasing factor suppresses but does not abolish antisomatostatin-induced GH release in the rat. Thomas CR, et al. **Endocrinology** 1985 Jun;116(6):2174-8

Interaction of growth hormone-releasing factor (GRF) and 14 GRF analogs with vasoactive intestinal peptide (VIP) receptors of rat pancreas. Discovery of (N-Ac-Tyr1,D-Phe2)-GRF(1-29)-NH2 as a VIP antagonist. Waelbroeck M, et al. **Endocrinology** 1985 Jun; 116(6):2643-9

Interaction between human pancreatic growth hormone releasing factor (hpGRF) and thyrotropin releasing hormone (TRH) on growth hormone secretion in domestic fowl. Harvey S, et al. **Horm Metab Res** 1985 Feb;17(2):113-4

Augmentation by propranolol of growth hormone-releasing hormone-(1-44)-NH2-induced growth hormone release in normal short and normal children. Chihara K, et al. **J Clin Endocrinol Metab** 1985 Aug;61(2):229-33

Growth hormone responses to continuous infusions of growth hormone-releasing hormone. Gelato MC, et al. **J Clin Endocrinol Metab** 1985 Aug;61(2):223-8

Effect of different growth hormone-releasing factors on the concentrations of growth hormone, insulin and metabolites in the plasma of sheep maintained in positive and negative energy balance. Hart IC, et al. **J Endocrinol** 1985 Apr;105(1):113-9

Effect of intravenous bovine growth hormone or human pancreatic growth hormone-releasing factor on milk production and plasma hormones and metabolites in sheep. Hart IC, et al. **J Endocrinol** 1985 May;105(2):189-96

GnRH pulse frequency determines LH pulse amplitude by altering the amount of releasable LH in the pituitary glands of ewes. Clarke IJ, et al. **J Reprod Fertil** 1985 Mar;73(2):425-31

Changes in pulsatile LH secretion and the positive and negative feedback actions of oestradiol after administration of a GnRH agonist in the ovariectomized ewe. Fitzgerald BP, et al. **J Reprod Fertil** 1985 Mar; 73(2):433-40

Radioimmunoassay for human growth hormone-releasing factor (hGRF 1-40): comparison of plasma immunoreactive GRF after intravenous and subcutaneous administration to rats. Rafferty B, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):19-25

Expression of human growth hormone-releasing factor in transgenic mice results in increased somatic growth. Hammer RE, et al. **Nature** 1985 May 30-Jun 5;315(6018):413-6

Modification of basal and GRF-stimulated cyclic AMP levels and growth hormone release by phospholipid metabolic enzyme inhibitors. Cronin MJ, et al. **Neuroendocrinology** 1985 Apr;40(4):332-8

Long-term suspension culture of isolated hypothalamic nuclei of the rat: morphological differentiation and release of substances influencing corticotropin and growth hormone secretion. Gyévai A, et al. **Neuroscience** 1985 Feb;14(2):519-33

Growth hormone releasing hormone and growth hormone: genetic studies in familial growth hormone deficiency. Rogol AD, et al. **Pediatr Res** 1985 May;19(5):489-92

Levels of human and rat hypothalamic growth hormone-releasing factor as determined by specific radioimmunoassay systems. Audhya T, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):2970-4

SPATIAL BEHAVIOR

Place preference conditioning with methylphenidate and nomifensine. Martin-Iverson MT, et al. **Brain Res** 1985 Apr 15;332(1):59-67

STARTLE REACTION

Central noradrenergic involvement in yohimbine excitation of acoustic startle: effects of DSP4 and 6-OHDA. Kehne JH, et al. **Brain Res** 1985 Mar 18;330(1):31-41

Antagonism of apomorphine-enhanced startle by alpha 1-adrenergic antagonists. Davis M, et al. **Eur J Pharmacol** 1985 Feb 5; 108(3):233-41

STEREOTYPED BEHAVIOR

Effect of duration of haloperidol treatment on DA receptor supersensitization in aging C57BL/6J mice. Randall PK, et al. **Brain Res** 1985 Apr 29;333(1):85-95

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305-8

Opposite effects of sulpiride and metoclopramide on amphetamine-induced stereotypy. Robertson A, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):81-9

Unexpected potentiation by discriminant benzamide derivatives of stereotyped behaviours elicited by dopamine agonists in mice. Vasse M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):108-16

Effect of gestational and neonatal styrene exposure on dopamine receptors. Zaidi NF, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):23-8

Effect of chronic haloperidol and quinacrine coadministration on striatal HVA levels and stereotypic behaviors in response to apomorphine in the rat. Deutsch SI, et al. **Neurochem Res** 1985 Apr;10(4):491-8

Antistereotypic effects of cholecystokinin octapeptide (CCK-8), ceruletide and related peptides on apomorphine-induced gnawing in sensitized mice. Zetler G. **Neuropharmacology** 1985 Mar;24(3):251-9

The morphogenesis of stereotyped behavior induced by the dopamine receptor agonist apomorphine in the laboratory rat. Szechtman H, et al. **Neuroscience** 1985 Mar;14(3):783-98

Serotonin and schizophrenia: correlations between serotonergic activity and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346-52

Effects of apomorphine and haloperidol on 'spontaneous' stereotyped licking behaviour in the Cebus monkey. Korsgaard S, et al. **Psychopharmacology (Berlin)** 1985;85(2):240-3

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204-9

Differential effects of dopamine D-1 and D-2 agonists and antagonists in 6-hydroxydopamine-lesioned rats. Arnt J. **Psychopharmacology [Suppl]** 1985;2:60-1

Intermittent treatment with droperidol, a short-acting neuroleptic, increases behavioral dopamine receptor sensitivity. Belmaker RH, et al. **Psychopharmacology [Suppl]** 1985;2:194-9

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

[TRH and its analog (DN-1417). Effects on central dopaminergic system-dependent behaviors in rats and mice] Miyamoto M, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):129-41 (Eng. Abstr.) **(Jpn)**

[Continuous suppression of methamphetamine-induced supersensitivity by chronic haloperidol administration] Kashihara K, et al. **Seishin Shinkeigaku Zasshi** 1984;86(11):928-32 **(Jpn)**

STRESS, PSYCHOLOGICAL

Interaction of chemical and psychogenic stress: biochemical response to repeated 'conditioned fear' and chronic carbon disulphide poisoning. Beneš V, et al. **Act Nerv Super (Praha)** 1985 Mar;27(1):23-5

Effects of psychological stress on male reproduction: a review. McGrady AV. **Arch Androl** 1984;13(1):1-7

Enhancement of some 5-HT-dependent behavioural responses following repeated immobilization in rats. Kennett GA, et al. **Brain Res** 1985 Mar 25;330(2):253-63

Platelet activation and secretion associated with emotional stress. Levine SP, et al. **Circulation** 1985 Jun;71(6):1129-34

Exercise and stress reduction. Rosch PJ. **Compr Ther** 1985 Apr; 11(4):10-5

Stress and immunomodulation: the role of depression and neuroendocrine function. Stein M, et al. **J Immunol** 1985 Aug; 135(2 Suppl):827s-833s

Reduction of the cyclic adenosine 3',5'-monophosphate response to catecholamines in rat brain slices after repeated restraint stress. Stone EA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):382-8

Methionine-enkephalin inhibits stress-induced increases in noradrenaline turnover in brain regions of rats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Jan;37(1):117-9

Psychic distress and the immune response. Tecoma ES, et al. **Life Sci** 1985 May 13;36(19):1799-812 (58 ref.)

Effects of emotional stress on the immune system. Miller NE. **Pavlov J Biol Sci** 1985 Apr-Jun;20(2):47-52

Brain amines and effects of chlordiazepoxide on motor activity in response to stress. Freeman GB, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):665-70

Habituation to repeated stress is stressor specific. Kant GJ, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):631-4

A psychophysiological field study of stress at Three Mile Island. Gatchel RJ, et al. **Psychophysiology** 1985 Mar;22(2):175-81

[Spatial reorganization of the organelles of catecholamine-synthesizing group A1 neurons during emotional stress] Zhigadlo BA, et al. **Arkh Anat Gistol Embriol** 1985 Feb;88(2):11-6 (Eng. Abstr.) **(Rus)**

[The state of brain mitochondrial membranes in stress and its correction with drugs] Kresiun VI. **Biofizika** 1985 Mar-Apr;30(2):306-8 (Eng. Abstr.) **(Rus)**

[Changes in the substance P content of the blood and hypothalamus during experimental emotional stress] Iumatov EA, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):397-9 (Eng. Abstr.) **(Rus)**

[Changes in the opioid peptide content of the adrenals of rats during immobilization stress] Val'dman AV, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):404-6 (Eng. Abstr.) **(Rus)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

[Changes in blood monoamine and 11-hydroxycorticosteroid levels in rats under the action of stress] Ugarova OP. **Fiziol Zh** 1985 Mar-Apr; 31(2):224-7 **(Rus)**

[The hemato-encephalic barrier in emotional stress] Belova TI, et al. **Usp Fiziol Nauk** 1985 Apr-Jun;16(2):61-76 (105 ref.) **(Rus)**

[Effect of an alimentary factor on the activity of the sympathetic-adrenal system in workers performing stressful work] Khotimchenko SA, et al. **Vopr Pitan** 1985 Mar-Apr;(2):36-9 **(Rus)**

SUBSTANCE P

Central action of substance P: possible role in reward. Stäubli U, et al. **Behav Neural Biol** 1985 Jan;43(1):100-8

The metabolism of neuropeptides. Endopeptidase-24.11 in human synaptic membrane preparations hydrolyses substance P. Matsas R, et al. **Biochem J** 1985 Jun 1;228(2):487-92

The role of substance P as a neurotransmitter in the reflexes of slow time courses in the neonatal rat spinal cord. Akagi H, et al. **Br J Pharmacol** 1985 Mar;84(3):663-73

The effect of a conditioning lesion on the regeneration rate of peripheral nerve axons containing substance P. Bisby MA, et al. **Brain Res** 1985 Jun 17;336(2):201-6

Substance P depolarizes nerve terminals in an autonomic ganglion. Dryer SE, et al. **Brain Res** 1985 Jun 10;336(1):190-4

Attenuation of the reflex pressor response to muscular contraction by a substance P antagonist. Kaufman MP, et al. **Brain Res** 1985 Apr 29; 333(1):182-4

Synaptic interaction between catecholaminergic neurons and substance P-immunoreactive axons in the caudal part of the nucleus of the solitary tract of the rat: demonstration by the electron microscopic mirror technique. Kubota Y, et al. **Brain Res** 1985 Apr 29;333(1):188-92

Coexistence of calcitonin gene-related peptide and substance P-like peptide in single cells of the trigeminal ganglion of the rat: immunohistochemical analysis. Lee Y, et al. **Brain Res** 1985 Mar 18; 330(1):194-6

Substance P mechanisms of the spinal cord related to vasomotor tone in the spontaneously hypertensive rat. Takano Y, et al. **Brain Res** 1985 May 13;334(1):105-16

Reduction of [3H]substance P binding in the intermediolateral cell column after sympathectomy. Takano Y, et al. **Brain Res** 1985 Apr 29; 333(1):193-6

Sciatic nerve transection produces death of dorsal root ganglion cells and reversible loss of substance P in spinal cord. Tessler A, et al. **Brain Res** 1985 Apr 22;332(2):209-18

The acute and chronic effects of capsaicin on slow excitatory transmission in rat dorsal horn. Urbán L, et al. **Brain Res** 1985 Mar 25; 330(2):390-6

Release of substance P from peripheral nerve terminals following electrical stimulation of the sciatic nerve. White DM, et al. **Brain Res** 1985 Jun 10;336(1):27-31

A comparison of the effects of serotonin, substance P and thyrotropin-releasing hormone on excitability of rat spinal motoneurons in vivo. White SR. **Brain Res** 1985 May 27;335(1):63-70

Ontogeny of substance P-containing fibers in the taste buds and the surrounding epithelium. I. Light microscopic analysis. Yamasaki H, et al. **Brain Res** 1985 Feb;350(1-2):301-5

A presynaptic site of action of substance P and vasoactive intestinal polypeptide on myenteric neurons. Yau WM, et al. **Brain Res** 1985 Mar 25;330(2):382-5

Vascular actions of VIP, substance P and neurotensin on the isolated perfused human fetal placenta. de Moura RS, et al. **Contrib Gynecol Obstet** 1985;13:174-5

Trials of serotonin, substance P and alpha 2-adrenergic receptor effects on the equine large colon. Sellers AF, et al. **Cornell Vet** 1985 Apr; 75(2):319-23

Sympathectomy enhances the substance P-mediated breakdown of the blood-aqueous barrier in response to infrared irradiation of the rabbit iris. Bynke G, et al. **Experientia** 1985 Apr 15;41(4):488-9

Substance P-like immunoreactivity in the frog dorsal root ganglia. Kemali M, et al. **Experientia** 1985 Apr 15;41(4):481-2

Regulatory peptides (glucagon, somatostatin, substance P, and VIP) in the brain and gastrointestinal tract of Ambystoma mexicanum. Conlon JM, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):150-8

Vasoactive effects of substance P on isolated rabbit pulmonary artery. Tanaka DT, et al. **J Appl Physiol** 1985 Apr;58(4):1291-7

The role of substance P in arterial chemoreflex control of ventilation. Gallagher PJ, et al. **J Auton Nerv Syst** 1985 Feb-Mar; 12(2-3):195-210

Spinal cord substance P mediates bicuculline-induced activation of cardiovascular responses from the ventral medulla. Keeler JR, et al. **J Auton Nerv Syst** 1985 May;13(1):19-33

Origin of small primary afferent substance P-immunoreactive nerve fibers in the guinea-pig heart. Urban L, et al. **J Auton Nerv Syst** 1985 Apr; 12(4):321-31

Effect of substance P and other tachykinins on arterial pressure in guinea-pigs. Hancock JC, et al. **J Auton Pharmacol** 1985 Mar; 5(1):25-30

Modulation of lymphocyte function by sensory neuropeptides. Payan DG, et al. **J Immunol** 1985 Aug;135(2 Suppl):783s-786s

Substance P in human plasma is degraded by dipeptidyl peptidase IV, not by cholinesterase. Nausch I, et al. **J Neurochem** 1985 May; 44(5):1354-7

Autoradiographic localization and characterization of spinal cord substance P binding sites: high densities in sensory, autonomic, phrenic, and Onuf's motor nuclei. Charlton CG, et al. **J Neurosci** 1985 Jun; 5(6):1653-61

Cardiovascular effects of spinal cord substance P: studies with a stable receptor agonist. Keeler JR, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):755-60

Blockade of slow excitatory post-synaptic potential by substance P antagonists in guinea-pig sympathetic ganglia. Konishi S, et al. **J Physiol (Lond)** 1985 Apr;361:115-30

Substance P raises neuronal membrane excitability by reducing inward rectification. Stanfield PR, et al. **Nature** 1985 Jun 6-12; 315(6019):498-501

Substance P enteric neurons mediate non-cholinergic transmission to the circular muscle of the guinea-pig intestine. Costa M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):446-53

Substance P action on phosphoinositides in guinea-pig intestinal muscle: a possible transduction mechanism? Holzer P, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Mar;329(1):50-5

Substance P, enkephalins, somatostatin, cholecystokinin, oxytocin, and vasopressin in human spinal cord. Schoenen J, et al. **Neurology** 1985 Jun;35(6):881-90

Immunocytochemical localization of glutamic acid decarboxylase and substance P in the lateral cervical nucleus: a light and electron microscopic study in the cat. Blomqvist A, et al. **Neurosci Lett** 1985 May 14;56(2):229-33

Effects of substance P antagonists on the atropine-sensitive and atropine-resistant responses of guinea-pig ileum to substance P. Chahl LA. **Neurosci Lett** 1985 Mar 22;55(1):35-40

Binding sites for [3H]substance P on neurons of cultured rat spinal cord and brain stem: an autoradiographic study. Hösli E, et al. **Neurosci Lett** 1985 May 14;56(2):199-203

Opiate and histamine H1 receptors are present on some substance P-containing dorsal root ganglion cells. Ninkovic M, et al. **Neurosci Lett** 1985 Jan 7;53(1):133-7

Substance P concentrations in human cerebrospinal fluid vary inversely with age. Tam PK, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):327-32

The comparative distribution of enkephalin, dynorphin and substance P in the human globus pallidus and basal forebrain. Haber SN, et al. **Neuroscience** 1985 Apr;14(4):1011-24

Effects of glutamate, substance P and eledoisin-related peptide on solitary tract neurones involved in respiration and respiratory reflexes. Henry JL, et al. **Neuroscience** 1985 Mar;14(3):863-73

Comparison of substance P and enkephalin distribution in rat brain: an overview using radioimmunocytochemistry. McLean S, et al. **Neuroscience** 1985 Mar;14(3):837-52

Immunohistochemical studies of substance P, cholecystokinin-octapeptide and somatostatin in dorsal root ganglia of the rat. Tuchscherer MM, et al. **Neuroscience** 1985 Feb;14(2):593-605

Effects of MET-ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):139-48

Cardiovascular interactions between methionine-enkephalin and substance P in the conscious dog. Sander GE, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):133-7

Sympathetic neuron density differentially regulates transmitter phenotypic expression in culture. Adler JE, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4296-300

Identification of substance P precursor forms in human brain tissue. Nyberg F, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3921-4

The effects of vagal nerve stimulation on endoluminal release of serotonin and substance P into the feline small intestine. Grønstad KO, et al. **Scand J Gastroenterol** 1985 Mar;20(2):163-9

Effects of substance P and somatostatin on taurocholate-stabilized and CCK- or secretin-induced choleresis in the anesthetized dog. Magnusson I, et al. **Scand J Gastroenterol** 1984 Nov;19(8):1007-14

Immunohistochemical demonstration of nociceptors in the ligamentous structures of the lumbar spine. Korkala O, et al. **Spine** 1985 Mar; 10(2):156-7

[Recent advances in research on substance P and related neuropeptides] Kanazawa I. **No To Hattatsu** 1985 Mar;17(2):94-102 (17 ref.) **(Jpn)**

[Changes in the substance P content of the blood and hypothalamus during experimental emotional stress] Iumatov EA, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):397-9 (Eng. Abstr.) **(Rus)**

SUBSTANCE USE DISORDERS

[Attempted suicide with barbiturate after glue sniffing] Sami HO, et al. **Orv Hetil** 1985 Mar 31;126(13):781-3 (Eng. Abstr.) **(Hun)**

SUCKING BEHAVIOR

Plasma prolactin in the rat during suckling without prior separation from pups. Mattheij JA, et al. **Acta Endocrinol (Copenh)** 1985 Apr; 108(4):468-74

Control of suckling and feeding by methysergide in weaning albino rats: a determination of Y-maze preferences. Stoloff ML, et al. **Dev Psychobiol** 1985 May;18(3):273-85

SYMPATHOMIMETICS

In vitro studies on the pharmacological properties of diacetolol, the major metabolite of acebutolol in man. Borchard U, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):4-17

Adrenergic ligand binding in human serum. Sager G, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2812-5

Comparison of postnatal changes in alpha 1-adrenoceptor binding and adrenergic stimulation of phosphoinositide hydrolysis in rat cerebral cortex. Schoepp DD, et al. **Biochem Pharmacol** 1985 Aug 1; 34(15):2705-11

The effect of glucagon and adrenergic agonists on intracellular pH of isolated rat hepatocytes. Deutsch CJ, et al. **J Biol Chem** 1985 Jun 10; 260(11):6808-10

Effects of beta-adrenoceptor antagonist administration on beta 2-adrenoceptor density in human lymphocytes. The role of the 'intrinsic sympathomimetic activity'. Brodde OE, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):417-22

[Heptaminol adenosine phosphate and the premenstrual syndrome] Anglade JP. **Rev Fr Gynecol Obstet** 1985 Mar;80(4):245-7 (Eng. Abstr.) **(Fre)**

SYNAPTIC RECEPTORS

Effects of long-term drug treatments on the sensitivity of presynaptic receptors regulating neurotransmitter release. Raiteri M, et al. **Ann Ist Super Sanita** 1984;20(1):57-64

Corticosterone modulation of neurotransmitter receptors in rat hippocampus: a quantitative autoradiographic study. Biegon A, et al. **Brain Res** 1985 Apr 22;332(2):309-14

The ontogenetic development of neurotensin-like immunoreactivity and neurotensin receptors in the cat striatum. Goedert M, et al. **Brain Res** 1985 May;352(1):127-31

Age-related changes in 5HT uptake and [3H]imipramine binding sites in rat cerebral cortex. Brunello N, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):393-4

Possible relationship between antimanic effect and activity of zotepine to 5HT1 receptor. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):473-80

Ibotenic acid analogues. Synthesis, molecular flexibility, and in vitro activity of agonists and antagonists at central glutamic acid receptors. Lauridsen J, et al. **J Med Chem** 1985 May;28(5):668-72

High- and low-affinity binding components for [3H]imipramine in rat cerebral cortex. Conway PG, et al. **J Neurochem** 1985 Jul; 45(1):206-9

5-Methoxytryptoline, a competitive endocoid acting at [3H]imipramine recognition sites in human platelets. Segonzac A, et al. **J Neurochem** 1985 Jul;45(1):249-56

Pharmacological characterization of postsynaptic receptors for excitatory amino acids in Purkinje cell dendrites in the guinea pig cerebellum. Kimura H, et al. **J Pharmacobiodyn** 1985 Feb;8(2):119-27

Cardiovascular effects of spinal cord substance P: studies with a stable receptor agonist. Keeler JR, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):755-60

Effects of calcium hopantenate on neurotransmitter receptors in the rat brain. Ogawa N, et al. **Jpn J Pharmacol** 1985 Jan;37(1):45-50

Modulation of receptor sensitivity and action potentials by transmitters in vertebrate neurones. Koketsu K. **Jpn J Physiol** 1984;34(6):945-60 (59 ref.)

3H-Imipramine binding sites in platelets of hospitalized psychiatric patients. Gentsch C, et al. **Psychiatry Res** 1985 Mar;14(3):177-87

[Antenatal effect of imipramine on the ontogeny of the imipramine receptors in the cerebral cortex of rats] Pirogova MV, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):35-8 (Eng. Abstr.) **(Rus)**

TERRITORIALITY

Short-term changes in plasma levels of hormones during establishment and defense of a breeding territory in male song sparrows, Melospiza melodia. Wingfield JC. **Horm Behav** 1985 Jun;19(2):174-87

TESTOSTERONE

Neuro-endocrine effects of isotheoline. Zhelyazkov D, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):53-8

Long-term, pulsatile, low dose, subcutaneous luteinizing hormone-releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar-Apr;17(2):143-9

Regulation of infant and developing rat testicular gonadotropin and prolactin receptors and steroidogenesis by treatments with human chorionic gonadotropin, gonadotropin-releasing hormone analogs, bromocriptine, prolactin, and estrogen. Huhtaniemi IT, et al. **Biol Reprod** 1985 May;32(4):721-32

The effects of testosterone and estrogen on the pituitary growth hormone response to growth hormone-releasing factor. Wehrenberg WB, et al. **Biol Reprod** 1985 Mar;32(2):369-75

Effects of steroid hormones on the neuropil of the hypothalamic paraventricular nucleus of male chickens. Panzica GC, et al. **Cell Tissue Res** 1985;240(1):169-74

The influence of testosterone in the brain of the male rat on levels of serotonin (5-HT) and hydroxyindole-acetic acid (5-HIAA). Martinez-Conde E, et al. **Comp Biochem Physiol [C]** 1985; 80(2):411-4

The role of calcium/phospholipid-dependent protein kinase in Leydig cell steroidogenesis. Lin T. **Endocrinology** 1985 Jul;117(1):119-26

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

FSH and LH response to testosterone and gonadotropin-releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter; 10(4):183-7

Seasonal variations in plasma luteinizing hormone and testosterone levels in the European badger Meles meles L. Audy MC, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):445-53

Seasonal changes in plasma testosterone, thyroxine, and cortisol levels in wild rabbits (Oryctolagus cuniculus algirus) of Zembra island. Ben Saad M, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):383-8

Annual and diurnal cycles in plasma testosterone and thyroxine in the male green sea turtle Chelonia mydas. Licht P, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):335-44

Effect of temperature and darkness on testosterone concentration in the testes of intact frogs (Rana esculenta) treated with gonadotrophin-releasing hormone analog (HOE 766). Pierantoni R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):128-30

Short-term changes in plasma levels of hormones during establishment and defense of a breeding territory in male song sparrows, Melospiza melodia. Wingfield JC. **Horm Behav** 1985 Jun;19(2):174-87

Hyperprolactinaemia and testosterone production. Observations in 2 men on long-term dialysis. Stegmayr B, et al. **Horm Res** 1985; 21(4):224-8

Possible role of prolactin in the inhibitory effect of testosterone on the hypothalamic-pituitary-testicular axis in the rat. Tresguerres JA, et al. **J Endocrinol** 1985 Jun;105(3):423-7

Newborn and immature rat testes contain gonadotropin-releasing hormone (GnRH) receptors, and their testosterone production is stimulated by a GnRH agonist in vitro. Huhtaniemi IT, et al. **Mol Cell Endocrinol** 1985 Apr;40(1):41-4

Influence of perinatal androgen on the sexually dimorphic distribution of tyrosine hydroxylase-immunoreactive cells and fibers in the anteroventral periventricular nucleus of the rat. Simerly RB, et al. **Neuroendocrinology** 1985 Jun;40(6):501-10

Suppression of male copulatory behavior by delta 9-THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415-20

Neonatal phenobarbital imprinting of hepatic microsomal enzymes in adult rats: modulation by neonatal testosterone presence. Bagley DM, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):227-35

THIORIDAZINE

Effects of thioridazine and fluphenazine on the pituitary, thyroid and adrenal functions in patients with paranoid schizophrenia. Horodnicki JM, et al. **Psychiatr Pol** 1984 May-Jun;18(3):205-11

Lateral ventricular enlargement and clinical response in schizophrenia. Smith RC, et al. **Psychiatry Res** 1985 Mar;14(3):241-53

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204-9

THIOTHIXENE

Acute thiothixene overdose. Kemal M, et al. **J Anal Toxicol** 1985 Mar-Apr;9(2):94-5

Treatment-resistant catatonic stupor and combined lithium-neuroleptic therapy: a case report. Climo LH. **J Clin Psychopharmacol** 1985 Jun; 5(3):166-70

THYROID HORMONES

Thyroid hormones reversibly suppress somatostatin secretion and immunoreactivity in cultured neocortical cells. Peterfreund RA, et al. **Brain Res** 1985 Mar 4;328(2):259-70

Modulatory effect of thyroid hormones on uptake of phosphate and other solutes across luminal brush border membrane of kidney cortex. Yusufi AN, et al. **Endocrinology** 1985 Jun;116(6):2438-49

3,5,3'-Triiodothyronine receptors and thyroxine 5'-monodeiodinating activity in thyroid hormone-insensitive amphibia. Galton VA. **Gen Comp Endocrinol** 1985 Mar;57(3):465-71

Relationship of the menstrual cycle and thyroid hormones to whole-body protein turnover in women. Garrel DR, et al. **Hum Nutr Clin Nutr** 1985 Jan;39(1):29-37

Changes in cardiac function following administration of thyroid hormones in thyroidectomised rats: assessment using the isolated working rat heart preparation. Brooks I, et al. **J Cardiovasc Pharmacol** 1985 Mar-Apr; 7(2):290-6

Routine measurement of thyroid hormones and FSH in infertility not worthwhile [letter] Conway DI, et al. **Lancet** 1985 Apr 27; 1(8435):977-8

Correlation between thyroid function and nephron loss. Giordano C, et al. **Life Support Syst** 1985 Jan-Mar;3(1):41-3

Thyroid gland volume and serum concentrations of thyroid hormones in chronic renal failure. Hegedüs L, et al. **Nephron** 1985;40(2):171-4

[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**

[Hormones of the thyroid gland and pancreas in lethally irradiated rats] Ahlersová E, et al. **Bratisl Lek Listy** 1985 Apr;83(4):433-9 (Eng. Abstr.) **(Slo)**

[The thyroid and amiodarone (I). Changes in peripheral thyroid hormones caused by prolonged treatment with amiodarone] Gómez JM, et al. **Med Clin (Barc)** 1985 Mar 16;84(10):381-3 (Eng. Abstr.) **(Spa)**

THYROTROPIN

Serum concentrations of thyroxine, 3,5,3'-triiodothyronine, thyrotropin, and prolactin in dogs before and after thyrotropin-releasing hormone administration. Kaufman J, et al. **Am J Vet Res** 1985 Feb; 46(2):486-92

Sensitive immunoradiometric assay (IRMA) for serum thyrotropin may be insufficient to make the thyrotropin-releasing-factor test unnecessary [letter] Rodriquez-Espinosa J, et al. **Clin Chem** 1985 Jun; 31(6):1081-2

Intranasal thyrotrophin releasing hormone is a potent stimulus for TSH release in man (comparison with intravenous and oral TRH). Staub JJ, et al. **Clin Endocrinol (Oxf)** 1985 Apr;22(4):567-72

Functional specificity of gonadotropin and thyrotropin in Fundulus heteroclitus. Brown CL, et al. **Gen Comp Endocrinol** 1985 May; 58(2):252-8

Administration of low doses of TSH result in a rapid increase in the metabolic rate of young lambs. Lynch MA, et al. **Horm Metab Res** 1985 Mar;17(3):136-40

Thyroxine binding and TSH in recurrent depressive episodes. Tollefson G, et al. **J Clin Psychiatry** 1985 Jul;46(7):267-72

Hypothalamo-pituitary regulation of thyrotrophin secretion in chronically catheterized Brattleboro rats. Wolf BA, et al. **J Endocrinol** 1985 May; 105(2):277-83

Photoperiodic regulation of thyroid responsiveness to TSH in Fundulus heteroclitus. Grau EG, et al. **J Exp Zool** 1985 May;234(2):199-205

Effects of TSH on iodination in rat thyroid follicles studied by autoradiography. Ofverholm T, et al. **Mol Cell Endocrinol** 1985 Apr; 40(1):1-7

Acute effect of triiodothyronine on the dynamics of thyrotropin release from superfused anterior pituitary cells. Shiota K, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):79-84

Oxytocin attenuates TRH-induced TSH release from rat pituitary cells. Frawley LS, et al. **Neuroendocrinology** 1985 Mar;40(3):201-4

Role of the sympathetic nervous system in the control of thyroid compensatory growth of normal and hypophysectomized rats. Romeo HE, et al. **Neuroendocrinology** 1985 Apr;40(4):309-15

THYROXINE

Plasma growth hormone and thyroxine levels in the chronically catheterised pig foetus and the effect of thyrotrophin releasing hormone. Macdonald AA, et al. **Acta Endocrinol (Copenh)** 1985 May; 109(1):126-9

Effect of thyroxine on hepatic glucose-6-phosphatase activity and glycogen content of toad (Bufo melanostictus) and Lata fish (Ophicephalus punctatus) at different stages of life. Paul AK, et al. **Acta Physiol Hung** 1985;65(3):233-8

Effect of propylthiouracil dose on serum thyroxine, growth, and weaning in young rats. Blake HH, et al. **Am J Physiol** 1985 May; 248(5 Pt 2):R524-30

Transport of thyroxine bound to human prealbumin into rat liver. Pardridge WM, et al. **Am J Physiol** 1985 May;248(5 Pt 1):G545-50

Serum concentrations of thyroxine, 3,5,3'-triiodothyronine, thyrotropin, and prolactin in dogs before and after thyrotropin-releasing hormone administration. Kaufman J, et al. **Am J Vet Res** 1985 Feb; 46(2):486-92

Effects of D- and L-thyroxine on the glucocorticoid binding capacity of adult rat liver. Naito K, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):447-52

Regulation of NAD- and NADP-linked isocitrate dehydrogenase by thyroxine in the brain and liver of female rats of various ages. Yadav RN. **Biochem Med** 1985 Jun;33(3):312-9

In vitro synthesis of thyroxine in a low molecular weight polypeptide fragment from human thyroglobulin. Lejeune PJ, et al. **Biochimie** 1985 Feb;67(2):199-203

Least squares calculation of the standard curve for the EMIT manual thyroxin assay [letter] Johnson D Jr, et al. **Clin Chem** 1985 Jul; 31(7):1247

Differences between measurements of free thyroxin in serum from siliconized and nonsiliconized tubes are influenced by analyte concentration [letter] Ordóñez-Llanos J, et al. **Clin Chem** 1985 Jul; 31(7):1249-50

The production and characterisation of a monoclonal antibody to thyroxine. Mpoko CN, et al. **Clin Chim Acta** 1985 Mar 15; 146(2-3):215-22

The effect of in vivo glucose administration on human erythrocyte Ca2+-ATPase activity and on enzyme responsiveness in vitro to thyroid hormone and calmodulin. Davis FB, et al. **Diabetes** 1985 Jul; 34(7):639-46

Seasonal changes in plasma testosterone, thyroxine, and cortisol levels in wild rabbits (Oryctolagus cuniculus algirus) of Zembra island. Ben Saad M, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):383-8

3,5,3'-Triiodothyronine receptors and thyroxine 5'-monodeiodinating activity in thyroid hormone-insensitive amphibia. Galton VA. **Gen Comp Endocrinol** 1985 Mar;57(3):465-71

Thyroid hormone binding in serum of 15 vertebrate species: isolation of thyroxine-binding globulin and prealbumin analogs. Larsson M, et al. **Gen Comp Endocrinol** 1985 Jun;58(3):360-75

Annual and diurnal cycles in plasma testosterone and thyroxine in the male green sea turtle Chelonia mydas. Licht P, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):335-44

Thyroxine binding and TSH in recurrent depressive episodes. Tollefson G, et al. **J Clin Psychiatry** 1985 Jul;46(7):267-72

Immunocytochemistry of luteinizing hormone-releasing hormone during spontaneous and thyroxine-induced metamorphosis of bullfrogs. Whalen R, et al. **J Exp Zool** 1985 Apr;234(1):131-44

Effect of breast-feeding vs formula-feeding on circulating thyroxine levels in premature infants. Oberkotter LV, et al. **J Pediatr** 1985 May; 106(5):822-5

Chronic thyroxine treatment of rats down-regulates the noradrenergic cyclic AMP generating system in cerebral cortex. Schmidt BH, et al. **J Pharmacol Exp Ther** 1985 May;233(2):466-72

Lead poisoning and euthyroid hyperthyroxinaemia [letter] Tiwari I, et al. **Lancet** 1985 Jun 29;1(8444):1508-9

Photoperiodic and light spectral conditions which inhibit circulating concentrations of thyroxine in the male hamster. Vaughan MK, et al. **Life Sci** 1985 Jun 10;36(23):2183-8

The effects of acute and chronic treatment with triiodothyronine and thyroxine on the hypothalamic and telencephalic catecholamine nerve terminal systems of the hypophysectomized male rat. Chronic treatment modulates catecholamine utilization in discrete catecholamine nerve terminal systems. Andersson K, et al. **Neuroendocrinology** 1985 May; 40(5):398-408

Role of thyroxine in the postnatal development of rat hepatic tryptophan oxygenase and ornithine aminotransferase. Vandewater LJ, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):83-9

[Automated recording of precision profiles for the radioimmunological determination of T4 using a pocket calculator of the HP-41 CV type] Ditu M, et al. **Ann Endocrinol (Paris)** 1984;45(6):393-6 (Eng. Abstr.) **(Fre)**

[Lugol's solution and thyroid gland activity in cattle. Determination of the total thyroxine in blood plasma as a method for evaluating thyroid gland activity] Braun U, et al. **Tierarztl Prax** 1985;Suppl 1:33-40 (Eng. Abstr.) **(Ger)**

[Evaluation of free thyroxine radioimmunoassays for assessing thyroid function in hypoproteinemia] Matsumura K, et al. **Kaku Igaku** 1985 Apr;22(4):511-20 (Eng. Abstr.) **(Jpn)**

[Effect of the administration of thyroxine and estradiol on the morphology of the anterior lobe of the pituitary gland] Szczurek Z, et al. **Patol Pol** 1984 Oct-Dec;35(4):499-507 (Eng. Abstr.) **(Pol)**

TIME PERCEPTION

Arginine vasopressin inoculates against age-related changes in temporal memory. Meck WH, et al. **Ann NY Acad Sci** 1985;444:453-6

Cannabis, atropine, and temporal information processing. Hicks RE, et al. **Neuropsychobiology** 1984;12(4):229-37

TRANQUILIZING AGENTS

1st Czechoslovak Conference on Biological Psychiatry. Karlovy Vary (Karlsbad), September 1983. Abstracts. **Act Nerv Super (Praha)** 1985 Mar;27(1):60-72

Sex differences in the use of alcohol and tranquilizers: testing a role convergence hypothesis. Bell R, et al. **Am J Drug Alcohol Abuse** 1984; 10(4):551-61

Chlordiazepoxide toxicity in Limbitrol overdose [letter] Goethe JW, et al. **Am J Psychiatry** 1985 Jun;142(6):774

Some neurochemical effects of a new antianxiety agent centazolone. Laxmi CV, et al. **Indian J Exp Biol** 1984 Dec;22(12):649-52

Determination of cyclobenzaprine in plasma and urine using capillary gas chromatography with nitrogen-selective detection. Constanzer ML, et al. **J Chromatogr** 1985 May 3;339(2):414-8

Serotonin antagonist pirenperone inhibits sexual behavior in the male rat: attenuation by quipazine. Mendelson SD, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):565-71

[Practical advice concerning the immobilization of wild and zoo animals] Wiesner H, et al. **Tierarztl Prax** 1985;13(1):113-27 (Eng. Abstr.) **(Ger)**

TRANQUILIZING AGENTS, MAJOR

Clinical characteristics of hospitalized psychotic patients who refuse antipsychotic drug therapy. Zito JM, et al. **Am J Psychiatry** 1985 Jul; 142(7):822-6

Prolonged pharmacologic activity of neuroleptics [letter] Campbell A, et al. **Arch Gen Psychiatry** 1985 Jun;42(6):637

Selection of neuroleptic dosage [letter] Teicher MH, et al. **Arch Gen Psychiatry** 1985 Jun;42(6):636-7

Schizophrenia with good and poor outcome. I: Early clinical features, response to neuroleptics and signs of organic dysfunction. Kolakowska T, et al. **Br J Psychiatry** 1985 Mar;146:229-39

Platelet monoamine-oxidase activity in schizophrenia. Relation to genetic load of the illness and treatment with antipsychotic drugs. Kemali D, et al. **Encephale** 1985 Jan-Feb;11(1):31-4

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Creese I, et al. **Eur J Pharmacol** 1985 Feb 12; 109(1):127-8

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

Repeated treatment with imipramine decreased the number of [3H]piflutixol binding sites in the rat striatum. Klimek V, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):131-2

Possible relationship between antimanic effect and activity of zotepine to 5HT1 receptor. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):473-80

Pharmacokinetics and initial distribution of a new neuroleptic agent picobenzide (M-14012-4). Calvo MV, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 May;23(5):233-7

Stimulants and neuroleptics in hyperactive children [letter] Gualtieri CT, et al. **J Am Acad Child Psychiatry** 1985 May;24(3):363-4

Neuroleptic bioequivalency: tablet versus concentrate. Fann WE, et al. **J Clin Pharmacol** 1985 May-Jun;25(4):305-6

Drugs and the quality of life: the patient's point of view. Diamond R.

J Clin Psychiatry 1985 May;46(5 Pt 2):29-35

Compliance issues in outpatient treatment. Kane JM. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):22S-27S

Focal neuroleptization: an approach to optimal dosing for initial and continuing therapy. Tupin JP. **J Clin Psychopharmacol** 1985 Jun; 5(3 Suppl):15S-21S

Synthesis and neuroleptic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles. Strupczewski JT, et al. **J Med Chem** 1985 Jun;28(6):761-9

Problems in classification of schizophrenics as neuroleptic responders and nonresponders. Csernansky JG, et al. **J Nerv Ment Dis** 1985 Jun; 173(6):325-31 (93 ref.)

Inactivation of D1 and D2 dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vivo: selective protection by neuroleptics. Meller E, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):656-62

Mental health dilemmas. Parts of a whole. Lacey R. **Nurs Times** 1985 May 1-7;81(18):27-8

Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. Gramling SE, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):541-5

One-year outcome of schizophrenic patients--the interaction of chronicity and neuroleptic treatment. Gaebel W, et al. **Pharmacopsychiatry** 1985 May;18(3):235-9

1.2-Anellated 1.4-benzodiazepine derivatives--a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174-7

Amphetamine response and relapse risk after depot neuroleptic discontinuation. Angrist B, et al. **Psychopharmacology (Berlin)** 1985; 85(3):277-83

Chronic neuroleptic treatment and mesolimbic dopamine denervation induce behavioural supersensitivity to opiates. Stinus L, et al. **Psychopharmacology (Berlin)** 1985;85(3):323-8

Pharmacological differentiation of dopamine D-1 and D-2 antagonists after single and repeated administration. Christensen AV, et al. **Psychopharmacology [Suppl]** 1985;2:182-90

Receptor-binding profiles of neuroleptics. Hyttel J, et al. **Psychopharmacology [Suppl]** 1985;2:9-18

Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. Goldberg E. **Schizophr Bull** 1985;11(2):255-63

Tardive dysmentia : further comments. Jones BD. **Schizophr Bull** 1985; 11(2):187-9

Acutely psychotic patients: a treatment approach. Wagemaker H, et al. **South Med J** 1985 Jul;78(7):833-7

[Benzonitrile and structural analogs. Action of para-aminobenzonitrile on the central nervous system] Cheav SL, et al. **Ann Pharm Fr** 1984; 42(4):367-78 (Eng. Abstr.) **(Fre)**

[Adsorption of cationic amphiphilic drugs to antacids and adsorbents. 3. Adsorption of tricyclic antidepressive agents and neuroleptics in relation to their colloid chemical properties] Thomas K, et al. **Pharm Acta Helv** 1985;60(2):39-47 (Eng. Abstr.) **(Ger)**

[The effect of psychopharmacologic agents on the passive transport of Ca2+ induced by vanadate in human erythrocytes] Pogády J, et al. **Bratisl Lek Listy** 1985 Apr;83(4):345-52 (Eng. Abstr.) **(Slo)**

TRANQUILIZING AGENTS, MINOR

The relationship between buspirone bioavailability and dose in healthy subjects. Gammans RE, et al. **Biopharm Drug Dispos** 1985 Apr-Jun; 6(2):139-45

Rapid gas chromatographic assay for monitoring valnoctamide in plasma. Bialer M, et al. **J Chromatogr** 1985 Feb 8;337(2):408-11

1-Azacycloalkyl-1,4-benzodiazepin-2-ones with antianxiety-antidepressant actions. Sugasawa T, et al. **J Med Chem** 1985 Jun;28(6):699-707

Effects of acute and chronic treatment on the pro- and anti-convulsant actions of CL 218, 872, PK 8165 and PK 9084, putative ligands for the benzodiazepine receptor. File SE, et al. **J Pharm Pharmacol** 1985 Apr;37(4):252-6

Animal models for the study of anti-anxiety agents: a review. Treit D. **Neurosci Biobehav Rev** 1985 Summer;9(2):203-22

Evidence that tolerance develops to the anxiolytic effect of diazepam in rats. Treit D. **Pharmacol Biochem Behav** 1985 Mar;22(3):383-7

The sedative effects of CL 218,872, like those of chlordiazepoxide, are reversed by benzodiazepine antagonists. File SE, et al. **Psychopharmacology (Berlin)** 1985;85(3):295-300

A comparison between chlordiazepoxide and CL 218,872--a synthetic nonbenzodiazepine ligand for benzodiazepine receptors on spontaneous locomotor activity in rats. McElroy JF, et al. **Psychopharmacology (Berlin)** 1985;85(2):224-6

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: punished barpressing. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;85(2):244-51

Anxiolytic drugs and the acquisition of conditioned fear in mice. Sanger DJ, et al. **Psychopharmacology (Berlin)** 1985;85(3):284-8

[Thiophene as a structural element in physiologically active substances. 15. Thiophene analogs of an anxiolytic acting 1,2,4-triazolo[4,3-b]pyridazine] Binder D, et al. **Arch Pharm (Weinheim)** 1985 Mar;318(3):243-9 (Eng. Abstr.) **(Ger)**

[Anxiolytic action of sodium valproate (possible role of gamma-aminobutyric acid in affective disorders)] Raevskii KS, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):574-9 (Eng. Abstr.) **(Rus)**

TRANYLCYPROMINE

Lack of pharmacokinetic interaction of carbamazepine with tranylcypromine [letter] Joffe RT, et al. **Arch Gen Psychiatry** 1985 Jul; 42(7):738

Platelet monoamine oxidase inhibition by deprenyl and tranylcypromine: implications for clinical use. Simpson GM, et al. **Biol Psychiatry** 1985 Jun;20(6):684-7

TRIFLUOPERAZINE

Sites of interaction of calmodulin with trifluoperazine and glucagon. Steiner RF, et al. **Arch Biochem Biophys** 1985 Jul;240(1):297-311

Behavioral interaction of adenosine and trifluoperazine in mice. DeLong RE, et al. **Neurosci Lett** 1985 Jan 7;53(1):101-7

Evidence that a Ca2+ chelator and a calmodulin blocker interfere with the structure of inter-Sertoli junctions. Franchi E, et al. **Tissue Cell** 1985;17(1):13-25

The effect of trifluoperazine (Stellazine) on Hymenolepis diminuta in vitro. Brandford White CJ, et al. **Z Parasitenkd** 1985;71(3):365-72

TRYPTAMINES

Increased protective effect of cystamine and mexamine against radiation after activation of the haemopoiesis by dextran sulphate in mice. Vacek A, et al. **Acta Radiol [Oncol]** 1985 Mar-Apr;24(2):193-8

In vitro pigment formation from tryptamine. Role of indole-3-acetaldehyde. Das PK, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2663-7

Tryptamine-induced vasoconstrictor responses in rat caudal arteries are mediated predominantly via 5-hydroxytryptamine receptors. Bradley PB, et al. **Br J Pharmacol** 1985 Apr;84(4):919-25

Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Shenker A, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):427-9

Indoleamine-sensitive adenylate cyclase in rabbit retina: characterization and distribution. Blazynski C, et al. **J Neurochem** 1985 Aug; 45(2):440-7

Tryptamine concentrations in areas of 5-hydroxytryptamine terminal innervation after electrolytic lesions of midbrain raphe nuclei. Juorio AV, et al. **J Neurochem** 1985 Aug;45(2):422-6

5-Hydroxytryptamine receptor in isolated rabbit aorta: characterization with tryptamine analogs. Clancy BM, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):761-9

Membrane responses and changes in cAMP levels in Aplysia sensory neurons produced by serotonin, tryptamine, FMRFamide and small cardioactive peptideB (SCPB). Ocorr KA, et al. **Neurosci Lett** 1985 Apr 9;55(2):113-8

TRYPTOPHAN

Plasma tryptophan, age and depression. Phipps DA, et al. **Age Ageing** 1985 Mar;14(2):71-5

An amino-terminal tryptophan derivative which is refractory to Edman degradation. Mahoney WC. **Anal Biochem** 1985 Jun;147(2):331-5

Spectrophotometric estimation of protein concentration in the presence of tryptophan modified by 2-hydroxy-5-nitrobenzyl bromide. Malin EL, et al. **Anal Biochem** 1985 Feb 1;144(2):356-61

Identification of peptides containing tryptophan, tyrosine, and phenylalanine using photodiode-array spectrophotometry. Yang CY, et al. **Anal Biochem** 1985 Feb 15;145(1):67-72

Energy transfer from tryptophan residues to pyridoxal 5'-phosphate at the active site of ribulose-1,5-bisphosphate carboxylase/oxygenase. Verma NC, et al. **Biochem Biophys Res Commun** 1985 May 31; 129(1):256-61

Effect of tryptophan metabolites on the activities of rat liver pyridoxal kinase and pyridoxamine 5-phosphate oxidase in vitro. Takeuchi F, et al. **Biochem J** 1985 Apr 15;227(2):537-44

Analysis and identification of aromatic signals in the proton magnetic resonance spectrum of the kringle 4 fragment from human plasminogen. De Marco A, et al. **Biochemistry** 1985 Jan 29;24(3):748-53

Protein structural changes accompanying formation of enzymatic transition states: tryptophan environment in ground-state and transition-state analogue complexes of adenosine deaminase. Kurz LC, et al. **Biochemistry** 1985 Mar 12;24(6):1342-6

In vitro characterization of hybrid promoters and altered tryptophan operon promoters. Russell DR, et al. **Biochemistry** 1985 Mar 12; 24(6):1410-7

Effect of tryptophan derivatives on the phase properties of bilayers. Jain

MK, et al. **Biochim Biophys Acta** 1985 Jun 11;816(1):153-62

Abilities of some tryptophan and phenylalanine derivatives to inhibit gastric acid secretion. Magous R, et al. **Biochim Biophys Acta** 1985 May 30;845(2):153-62

A controlled clinical trial of L-tryptophan in acute mania. Chouinard G, et al. **Biol Psychiatry** 1985 May;20(5):546-57

Effect of alkylation of tryptophan residues on the enzymatic and pharmacological properties of snake venom phospholipase A2. Condrea E, et al. **Can J Physiol Pharmacol** 1985 Apr;63(4):331-9

Tryptophan content of serum albumin. Kaldy MS, et al. **Comp Biochem Physiol [B]** 1985;80(4):743-5

The microbial metabolism of tryptophan in rats fed a diet containing 7.5% saccharin in a two-generation protocol. Sims J, et al. **Food Chem Toxicol** 1985 Apr-May;23(4-5):437-44

Nucleotide sequence of the Bacillus subtilis tryptophan operon. Henner DJ, et al. **Gene** 1985;34(2-3):169-77

Nutritive value of D-tryptophan for the growing pig. Arentson BE, et al. **J Anim Sci** 1985 Feb;60(2):474-9

Xanthurenic acid 8-O-beta-D-glucoside, a novel tryptophan metabolite in eye-color mutants of Drosophila melanogaster. Ferré J, et al. **J Biol Chem** 1985 Jun 25;260(12):7509-14

Analysis of the requirements for transcription pausing in the tryptophan operon. Fisher RF, et al. **J Mol Biol** 1985 Apr 5;182(3):397-409

Clues from Xanthomonas campestris about the evolution of aromatic biosynthesis and its regulation. Whitaker RJ, et al. **J Mol Evol** 1984-85; 21(2):139-49

The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3-4):175-81

Variables influencing the effect of a meal on brain tryptophan. Sarna GS, et al. **J Neurochem** 1985 May;44(5):1575-80

Lowering of plasma free tryptophan in normal and portacaval shunt dogs. Miyai M, et al. **J Surg Res** 1985 Jul;39(1):8-15

Ontogenetic studies on tryptophan transport into plasma membrane vesicles derived from rat brain synaptosomes: effect of thyroid hormones. Herrero E, et al. **Neurochem Res** 1985 May;10(5):579-89

The effects produced by prostaglandin D2 on serotonin turnover and release and tryptophan uptake. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):371-5

UGA is read as tryptophan in Mycoplasma capricolum. Yamao F, et al. **Proc Natl Acad Sci USA** 1985 Apr;82(8):2306-9

Fluorescence properties of insulin analogs with tryptophan substitutions. Wang ZZ. **Sci Sin [B]** 1985 Mar;28(3):264-72

TRYPTOPHAN HYDROXYLASE

Effect of clonidine on the activity of tryptophan hydroxylase from rat brainstem following in vivo or in vitro treatment. Weekley LB, et al. **Biochem Pharmacol** 1985 May 1;34(9):1549-57

Tryptophan 5-hydroxylase. Rapid purification from whole rat brain and production of a specific antiserum. Cash CD, et al. **Eur J Biochem** 1985 Jun 3;149(2):239-45

Regulation of 3-indoleacetic acid production in Pseudomonas syringae pv. savastanoi. Purification and properties of tryptophan 2-monooxygenase. Hutcheson SW, et al. **J Biol Chem** 1985 May 25; 260(10):6281-7

TYROSINE

Identification of peptides containing tryptophan, tyrosine, and phenylalanine using photodiode-array spectrophotometry. Yang CY, et al. **Anal Biochem** 1985 Feb 15;145(1):67-72

L-Phenylalanine and L-tyrosine catabolism by selected Streptomyces species. Pometto AL 3d, et al. **Appl Environ Microbiol** 1985 Mar; 49(3):727-9

Chemiluminescence in L-tyrosine-H2O2-horseradish peroxidase system: possible formation of tyrosine cation radical. Ushijima Y, et al. **Biochem Biophys Res Commun** 1985 Apr 30;128(2):936-41

Analysis and identification of aromatic signals in the proton magnetic resonance spectrum of the kringle 4 fragment from human plasminogen. De Marco A, et al. **Biochemistry** 1985 Jan 29;24(3):748-53

Formation of radiation-induced cross-links between thymine and tyrosine: possible model for cross-linking of DNA and proteins by ionizing radiation. Simic MG, et al. **Biochemistry** 1985 Jan 1;24(1):233-6

Enzymatic and nonenzymatic dehydration reactions of L-arogenate. Zamir LO, et al. **Biochemistry** 1985 Mar 26;24(7):1607-12

Elastase-cathepsin G inhibitors eglin b and eglin c differ by a single Tyr——His substitution. A micro-method for the identification of amino-acid substitution. Chang JY, et al. **Biol Chem Hoppe Seyler** 1985 Mar;366(3):281-6

Properties of the aminotyrosine derivatives of calmodulin. Steiner RF, et al. **Biopolymers** 1985 Mar;24(3):547-63

Inhibition of tyrosine hydroxylation in tissue slices of the rat striatum by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Hirata Y, et al. **Brain Res** 1985 Jun 24;337(1):193-6

Blood-brain barrier permeability to leucine-enkephalin, D-alanine2-D-leucine5-enkephalin and their N-terminal amino acid (tyrosine). Zlokovic BV, et al. **Brain Res** 1985 Jun 10;336(1):125-32

Hapten-specific T-cell response to azobenzenearsonate-N-acetyl-L-tyrosine in the Lewis rat. IV. Rat dendritic cells present soluble and insoluble azobenzenearsonate conjugates to T cells. Amsden A, et al. **Cell Immunol** 1985 Jul; 93(2):447-58

Bone cell phosphotyrosine phosphatase: characterization and regulation by calcitropic hormones. Puzas JE, et al. **Endocrinology** 1985 Jun; 116(6):2463-8

Tyrosine-311 of a beta chain is the essential residue specifically modified by 4-chloro-7-nitrobenzofurazan in bovine heart mitochondrial ATPase. Sutton R, et al. **Eur J Biochem** 1985 May 2;148(3):551-4

Clostridium pasteurianum glutamine synthetase mechanism. Evidence for active site tyrosine residues. Krishnan IS, et al. **FEBS Lett** 1985 Jun 17;185(2):267-71

Species variation in the tyrosine sulfation of mammalian gastrins. Andersen BN. **Gen Comp Endocrinol** 1985 Apr;58(1):44-50

Biosynthesis of chlortetracycline: Part I—oxidative metabolism of L-tyrosine by Streptomyces aureofaciens and its relation to the biosynthesis of chlortetracycline. Maladkar NK. **Hindustan Antibiot Bull** 1984 Aug-Nov;26(3-4):81-95

Structural studies of mitochondrial coupling factor 1 using tyrosine fluorescence. Fernández-Belda F, et al. **Int J Biochem** 1985; 17(2):223-8

Tyrosine sulfation of yolk proteins 1, 2, and 3 in Drosophila melanogaster. Baeuerle PA, et al. **J Biol Chem** 1985 May 25;260(10):6434-9

pH-induced hysteretic transitions of ovoperoxidase. Deits T, et al. **J Biol Chem** 1985 Jul 5;260(13):7882-8

The interaction of slow-release immunoadjuvants with selected antigens measured in vitro. Penney C, et al. **J Biol Stand** 1985 Jan; 13(1):43-52

Clues from Xanthomonas campestris about the evolution of aromatic biosynthesis and its regulation. Whitaker RJ, et al. **J Mol Evol** 1984-85; 21(2):139-49

The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3-4):175-81

Inhibition of sodium transport in frog skin and iodination of tyrosine in vitro by a peptide of renal origin. Fregly MJ, et al. **Klin Wochenschr** 1985;63 Suppl 3:102-6

N-acetyl-L-tyrosine as a tyrosine source during total parenteral nutrition in adult rats. Im HA, et al. **Pediatr Res** 1985 Jun;19(6):514-8

TYROSINE AMINOTRANSFERASE

Deletions near the albino locus on chromosome 7 of the mouse affect the level of tyrosine aminotransferase mRNA. Schmid W, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):2866-9

TYROSINE HYDROXYLASE

Catecholamine microfluorometry of nigral perikarya and tyrosine hydroxylase assay in some telencephalic structures of rats exposed to different behavioral situations. Divac I, et al. **Acta Neurobiol Exp (Warsz)** 1984;44(6):262-72

Decrease in tyrosine hydroxylase synthesis in cultured adrenal medulla by N6-methyladenosine. Burke WJ, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2621-7

Effects of alpha-difluoromethylornithine on polyamine biosynthesis and tyrosine hydroxylase induction in the adrenal gland of the rat subjected to stress or apomorphine. Ekker M, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1315-20

Evidence for the involvement of Ca2+-calmodulin and cyclic AMP in the regulation of the tyrosine hydroxylase system in rat striatal tissue slices. Hirata Y, et al. **Biochem Pharmacol** 1985 Aug 1; 34(15):2637-43

Immunohistochemical evidence for phenylethanolamine-N-methyltransferase-positive/tyrosine hydroxylase-negative neurones in the retina and the posterior hypothalamus of the rat. Foster GA, et al. **Brain Res** 1985 Mar 18; 330(1):183-8

Synaptic interaction between catecholaminergic neurons and substance P-immunoreactive axons in the caudal part of the nucleus of the solitary tract of the rat: demonstration by the electron microscopic mirror technique. Kubota Y, et al. **Brain Res** 1985 Apr 29;333(1):188-92

Intrinsic tyrosine hydroxylase (TH) immunoreactive axons synapse with TH immunopositive neurons in the rat arcuate nucleus. Léránth C, et al. **Brain Res** 1985 Apr 8;331(2):371-5

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

A comparative study of tyrosine 3-monooxygenase from rat adrenal and brainstem. Okuno S, et al. **J Biochem (Tokyo)** 1985 Jan;97(1):265-73

Purification and characterization of rat striatal tyrosine hydroxylase. Comparison of the activation by cyclic AMP-dependent phosphorylation and by other effectors. Richtand NM, et al.

J Biol Chem 1985 Jul 15;260(14):8465-73

Characteristics of tyrosine hydroxylase activation by K+-induced depolarization and/or forskolin in rat striatal slices. el Mestikawy S, et al. **J Neurochem** 1985 Jul;45(1):173-84

Appearance of the noradrenergic markers tyrosine hydroxylase and neuropeptide Y in cholinergic nerves of the iris following sympathectomy. Björklund H, et al. **J Neurosci** 1985 Jun; 5(6):1633-40

A combined autoradiographic and immunocytochemical study of 3H-corticosterone target neurons and catecholamine neurons in rat and mouse lower brain stem. Duncan GE, et al. **Neuroendocrinology** 1985 Mar;40(3):262-71

Influence of perinatal androgen on the sexually dimorphic distribution of tyrosine hydroxylase-immunoreactive cells and fibers in the anteroventral periventricular nucleus of the rat. Simerly RB, et al **Neuroendocrinology** 1985 Jun;40(6):501-10

Differential effects of transection of the spinal cord and splanchnic nerve on adrenal tyrosine hydroxylase and catecholamines. Gagner JP, et al. **Neuroscience** 1985 Mar;14(3):907-20

Morphological evidence for a dopaminergic terminal field in the hippocampal formation of young and adult rat. Verney C, et al. **Neuroscience** 1985 Apr;14(4):1039-52

Distribution of CRF- and tyrosine hydroxylase-immunoreactive neurons in the brainstem of the domestic fowl (Gallus domesticus). Knigge KM, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):97-101

Sympathetic neuron density differentially regulates transmitter phenotypic expression in culture. Adler JE, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4296-300

[Comparative effect of the psychostimulants sidnocarb and fenamin on the tyrosine hydroxylase activity of the brain synaptosomes in rats] Ganiev MM, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):27-32 (Eng. Abstr.) **(Rus)**

VANILMANDELIC ACID

Liquid-chromatographic determination of vanillylmandelic acid in urine. Anderson GM, et al. **Clin Chem** 1985 Jun;31(6):819-21

VASOPRESSINS

Leukotriene D4 reduces pressor responses to sympathetic stimulation, angiotensin, and vasopressin. Bayorh MA, et al. **Adv Prostaglandin Thromboxane Leukotriene Res** 1985;13:51-4

Alpha 2-adrenoceptor antagonism of vasopressin-induced changes in sodium excretion. Smyth DD, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 2):F767-72

Stimulation of prostacyclin production in isolated rat adipocytes by angiotensin II, vasopressin, and bradykinin: evidence for two separate mechanisms of prostaglandin synthesis. Axelrod L, et al. **Endocrinology** 1985 Jun;116(6):2548-53

Foot shock stress-induced release of vasopressin in adenohypophysectomized and hypophysectomized rats. Knepel W, et al. **Endocrinology** 1985 Jul;117(1):292-9

Evidence for the formation of inositol 4-monophosphate in stimulated human platelets. Siess W. **FEBS Lett** 1985 Jun 3;185(1):151-6

The contribution of vasopressin and angiotensin to the maintenance of blood pressure after autonomic blockade. Hiwatari M, et al. **Hypertension** 1985 Jul-Aug;7(4):547-53

GABAergic inhibition of hypertonic saline-induced vasopressin-dependent hypertension. Brennan TJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):663-71

Hormonal control of renal potassium excretion. Field MJ, et al. **Kidney Int** 1985 Feb;27(2):379-87 (86 ref.)

Co-localization of corticotropin releasing factor and vasopressin mRNA in neurones after adrenalectomy. Wolfson B, et al. **Nature** 1985 May 2-8;315(6014):59-61

Senescent change in tissue weight and immunoreactive beta-endorphin, enkephalin, and vasopressin in eight regions of C57BL/6J mouse brain and pituitary. Rogers J, et al. **Neurobiol Aging** 1985 Spring;6(1):1-9

The compartmentalized hypothalamo-neurohypophysial system: evidence for a neurohypophysial action of acetylcholine on vasopressin release. Gregg CM. **Neuroendocrinology** 1985 May;40(5):423-9

Substance P, enkephalins, somatostatin, cholecystokinin, oxytocin, and vasopressin in human spinal cord. Schoenen J, et al. **Neurology** 1985 Jun;35(6):881-90

The microvasculature of the small-intestinal mucosa of the rat: quantification of hemodynamic effects of topically applied cimetidine, ranitidine, somatostatin, and vasopressin. Neff M, et al. **Scand J Gastroenterol [Suppl]** 1985;112:6-11

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

VIOLENCE

The limit of violence: psychotropic drugs, law and ethics. Tamm JM. **Med Law** 1985;4(2):155-66

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

WAKEFULNESS

Effects of acute and chronic treatment with amitryptyline on the sleep-wake activity of rats. Obál F Jr, et al. **Neuropharmacology** 1985 Mar;24(3):223-9

ZIMELIDINE

High incidence of multisystemic reactions to zimeldine. Langlois R, et al. **Eur J Clin Pharmacol** 1985;28(1):67-71

The *Psychopharmacology Bulletin* is available on subscription from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Subscription price $19.00 per year for the United States. All other countries add $4.75 for postage. This price was in effect at time of printing. Prices are subject to change. Please make check or money order payable to the Superintendent of Documents. An annual subscription for four quarterly issues begins with the next issue following receipt of the order. Single copies and back issues may also be ordered from the Superintendent of Documents. The expiration date is printed on the top line of the address label. Change of address and complaints about non-receipt of issues should be sent to the Superintendent of Documents and should include the old address, preferably a mailing label, as well as the new address.

ORDER FORM Mail To: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

Enclosed is $________ ☐ check,
(U.S. Currency Only)
☐ money order, or charge to my
Deposit Account No.
☐☐☐☐☐☐☐–☐

Order No. ______________

VISA®

master charge

Credit Card Orders Only

Total charges $________ Fill in the boxes below

Credit Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiration Date Month/Year ☐☐☐☐

Please enter my subscription to **PSYCHOPHARMACOLOGY BULLETIN** [PSBU]

☐ $19.00 domestic ☐ $23.75 foreign

Name—First, Last

Street address

Company name or additional address line

City State ZIP Code

(or Country)

PLEASE PRINT OR TYPE

For Office Use Only

	Quantity	Charges
Enclosed		
To be mailed		
Subscriptions		
Postage		
Foreign handling		
MMOB		
OPNR		
UPNS		
Discount		
Refund		

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
Alcohol, Drug Abuse, and
Mental Health Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

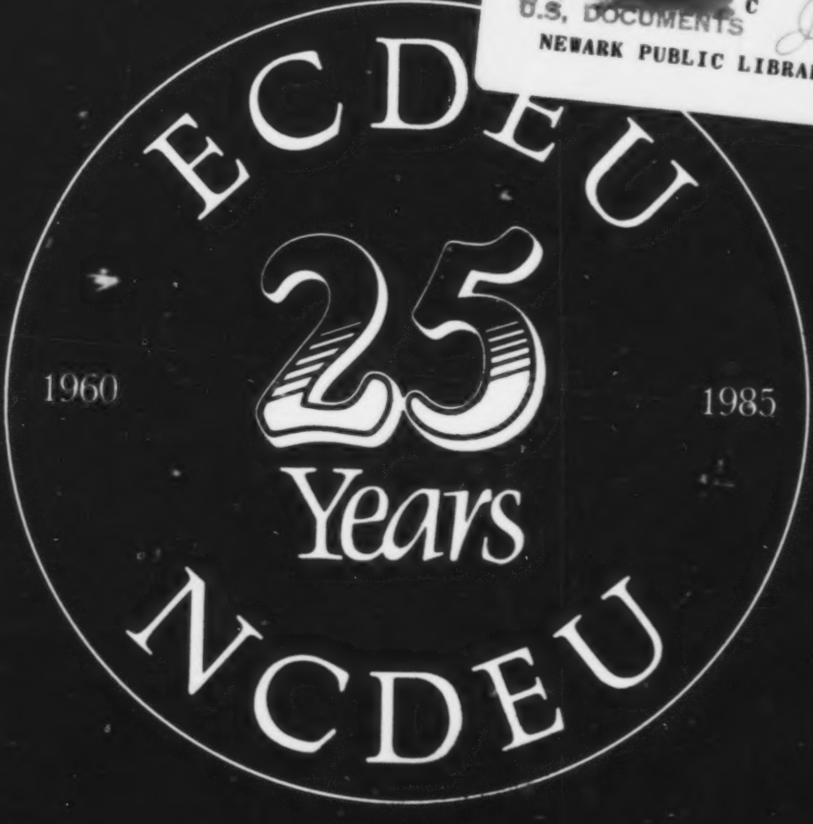
SPECIAL FOURTH CLASS MAIL
POSTAGE AND FEES PAID
PHS/ADAMHA
PERMIT NO. G-283

DHHS Publication No. (ADM) 86-173
Printed 1986

PSYCHOPHARMACOLOGY BULLETIN

NATIONAL INSTITUTE OF MENTAL HEALTH

LD [redacted] C
U.S. DOCUMENTS
NEWARK PUBLIC LIBRARY


ECDEU
1960
25
Years
1985
NCDEU

1986
Vol. 22, No. 1

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

Editor-in-Chief:

Nina R. Schooler, Ph.D.
NIMH, Rockville, Md.

Special Features Editor:

Allen Raskin, Ph.D.
Lafayette Clinic, Wayne State University
Detroit, Mich.

Managing Editor:

Lillian Altman
NIMH, Rockville, Md.

Associate Editors:

Jonathan O. Cole, M.D.
McLean Hospital, Belmont, Mass.

Seymour Fisher, Ph.D.
University of Texas Medical Center
Galveston, Texas

Arnold J. Friedhoff, M.D.
New York University School of Medicine

Gerald L. Klerman, M.D.
Cornell University Medical Center, New York

David J. Kupfer, M.D.
Western Psychiatric Institute & Clinic
University of Pittsburgh School of Medicine

Judith L. Rapoport, M.D.
NIMH, Bethesda, Md.

Donald S. Robinson, M.D.
Bristol-Myers Pharmaceuticals
Wallingford, Conn.

The *Psychopharmacology Bulletin* is prepared by the Division of Clinical Research of the National Institute of Mental Health. Its purpose is to facilitate the dissemination and exchange of information among the national and international scientific community. This emphasis is on rapid, informal reporting of work which has not appeared in the more formal literature. In accordance with new policy set forth by our Associate Editors, we are no longer accepting unsolicited papers for publication in the *Bulletin*.

All material published in the *Psychopharmacology Bulletin* is in the public domain unless otherwise noted. Publication in the *Bulletin* therefore does not preclude publication elsewhere.

VOL. 22, NO. 1

1986

PSYCHOPHARMACOLOGY BULLETIN

Table of Contents

Annual NCDEU Meeting (1985)—Abridged Proceedings—

3 **The ECDEU- NCDEU Program**—*Jonathan O. Cole*

Re-Updates: New Perspectives on Long-Standing Issues—

7 Problems With and Promises of Monoamine Oxidase Inhibitors—*Donald F. Klein and Frederic M. Quitkin*

12 New Perspectives on Long-Standing Issues: The Monoamine Oxidase Inhibitors—*Donald S. Robinson*

16 Discussion on the Monoamine Oxidase Inhibitors—*Burtrum C. Schiele*

19 Use of Placebo in Clinical Trials—*Karl Rickels*

25 Scientific and Ethical Considerations in the Use of Placebo Controls in Clinical Trials in Psychopharmacology—*Gerald L. Klerman*

30 The Placebo Control in Clinical Trials (A View From the FDA)—*Paul Leber*

33 Pharmacological Treatments of Schizophrenia—*George M. Simpson*

36 Research Methodology and the Pharmacotherapy of the Chronic Schizophrenias—*Thomas A. Ban, William Guy, and W.H. Wilson*

42 Discussion of Dr. George Simpson's Paper on Pharmacological Treatments of Schizophrenia—*Solomon C. Goldberg*

Multicenter International Clinical Trials—

45 Introduction—*Thomas A. Ban and Jerome Levine*

47 The AMDP System in International Clinical Trials—*B. Woggon, M. Linden, H. Beckmann, E. Krebs, B. Küfferle, B. Müller-Oerlinghausen, B. Pflug, and H.W. Schied*

52 Use of a Standardized Documentation System (BLIPS/BDP) in the Conduct of a Multicenter International Trial Comparing Fluvoxamine, Imipramine, and Placebo—*Giovanni B. Cassano, Luciano Conti, Gabriele Massimetti, Francesco Mengali, Jenifer S. Waekelin, and Jerome Levine*

59 The Design and Conduct of the Upjohn Cross-National Collaborative Panic Study—*Gerald L. Klerman, James H. Coleman, and Robert P. Purpura*

Microcomputers in Clinical Psychopharmacology

65 Why a Statistical Package on a Micro?—*MaryAnn Hill*

73 Microcomputerized Testing of Drug Effects on Divided Attention—*Joe E. Thornton, Joy L. Taylor, Elizabeth L. Gibson, Terry P. Miller, and Jared R. Tinklenberg*

Benzodiazepines—New Indications—

77 The Use of Benzodiazepines for Psychotic Disorders: A Literature Review and Preliminary Clinical Findings—*George W. Arana, Marjorie L. Ornsteen, Fred Kanter, H. L. Friedman, David J. Greenblatt, and Richard I. Shader*

88 New Strategies for the Treatment of Alcohol Withdrawal—*E.M. Sellers and C.A. Naranjo*

93 Benzodiazepines for Treatment of Panic Attacks: A New Look—*Karl Rickels and Edward E. Schweizer*

Cholinergic Mechanisms in the Treatment of Geriatric Disorders—

101 Physostigmine in Patients with Alzheimer's Disease—*Michael Davidson, Richard C. Mohs, Eric Hollander, Bonnie M. Davis, Theresa Ryan, Thomas B. Horvath, and Kenneth L. Davis*

106 Intercranial Drug Administration in Alzheimer's Disease—*Robert E. Harbaugh*

110 The Cholinergic Hypothesis of Memory Dysfunction in Alzheimer's Disease—Revisited—*Nunzio Pomara and Michael Stanley*

Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia—

119 Ceruletide for Schizophrenia: A Review—*Jeffrey A. Mattes, William Hom, and Joseph M. Rochford*

123 Clinical Evaluation of Ceruletide in Schizophrenia: A Multi-Institutional Cooperative Double-Blind Controlled Study—*Hitoshi Itoh, Yasuo Shimazono, Yukio Kawakita, Yoshio Kudo, Yorio Satoh, and Ryo Takahashi*

129 Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia—*Carol A. Tamminga, Robert L. Littman, and Larry D. Alphs*

Fenfluramine Therapy for Autism: Promise and Precaution—

133 Fenfluramine Treatment of Autism: UCLA Collaborative Study of 81 Patients at Nine Medical Centers—*Edward R. Ritvo, B.J. Freeman, Arthur Yuwiler, Edward Geller, Phillip Schroth, Alice Yokota, Anne Mason-Brothers, Gerald J. August, William Klykylo, Bennett Leventhal, Kay Lewis, Leonard Piggott, George Realmuto, E. Gene Stubbs, and Richard Umansky*

141 Short-Term Efficacy and Safety of Fenfluramine in Hospitalized Preschool-Age Autistic Children: An Open Study—*Magda Campbell, Stephen I. Deutsch, Richard Perry, Barbara B. Wolsky, and Michael Palij*

148 Fenfluramine: Neurotoxicity—*Charles R. Schuster, Marilyn Lewis, and Lewis S. Seiden*

152 Fenfluramine Treatment of Childhood Attention Deficit Disorder With Hyperactivity: A Preliminary Report—*Maureen Donnelly, Judith L. Rapoport, and Deborah R. Ismond*

155 The Effects of Fenfluramine on Suicidal Behavior—*Elaine Meyendorff, Anil Jain, Lil Traskman-Bendz, Barbara Stanley, and Michael Stanley*

Free Communications—Session A—

161 The Relationship of Antiobsessional and Antidepressant Effects of Tricyclic Antidepressants—*Matig Mavissakalian, Samuel M. Turner, Larry Michelson, and Rolf Jacob*

167 A Comparison of Alprazolam and Imipramine in the Treatment of Agoraphobia and Panic Disorder—*Ross Rizley, Richard J. Kahn, Douglas M. McNair, and Laura M. Frankenthaler*

173 Taper Withdrawal Studies With Alprazolam in Patients With Panic Disorder and Agoraphobia—*John C. Pecknold and Richard P. Swinson*

177 Amitriptyline and Haloperidol in Unstable and Schizotypal Borderline Disorders—*Paul H. Soloff, Anselm George, Swami Nathan, Patricia M. Schulz, Richard F. Ulrich, and James M. Perel*

183 Open Trial of Buspirone in the Treatment of Major Depressive Disorder—*Edward E. Schweizer, Jay Amsterdam, Karl Rickels, Myron Kaplan, and Marian Droba*

186 A Review of Controlled Studies of Adinazolam Mesylate in Patients With Major Depressive Disorder—*John P. Feighner*

192 Chronic Depression: Demographic and Clinical Characteristics—*James H. Kocsis, Carlyle Voss, J. John Mann, and Allen Frances*

196 Self-Rating of Personality Characteristics and Their Relationship to Treatment Response in Recurrent Unipolar Depressives: A Pilot Study—*Ellen Frank, David J. Kupfer, David B. Jarrett, and Miriam Jacob*

200 The Suicide Assessment Scale: A Scale Evaluating Change in Suicidal Behavior—*Barbara Stanley, Lil Träskman-Bendz, and Michael Stanley*

206 A Retrospective Clinical Analysis of the Overall-Rhoades Classification of Hamilton Depression Scale Profiles—*Robert H. Lenox, Lelon A. Weaver, James E. Shipley, and Stephen Cohen*

214 Understanding the Response Lag to Tricyclics: I. Application of Pulse-Loading Regimens With Intravenous Clomipramine—*Bruce G. Pollock, James M. Perel, Michael Shostak, Seymour Antelman, Barbara Brandom, and David J. Kupfer*

220 Pharmacology of Combined Antidepressant/H_2-Blocking Drug Therapy—*Stephen H. Curry, C. Lindsay DeVane, and M. Michael Wolfe*

Free Communications—Session B—

223 Methylphenidate: Rate-Dependent Effects on Hyperactivity—*Mark D. Rapport and George J. DuPaul*

229 The Therapeutic Effect of Clonidine in Attention Deficit Disorder with Hyperactivity: A Comparison With Placebo and Methylphenidate—*Robert D. Hunt, Ruud B. Minderaa, and Donald J. Cohen*

237 The Use of MK-801, a Novel Sympathomimetic, in Adults with Attention Deficit Disorder, Residual Type—*Fred W. Reimherr, David R. Wood, and Paul H. Wender*

243 The Prevalence of Tardive Dyskinesia in a Mentally Retarded Population—*Mary Ann Richardson, Gary Haugland, Raymond Pass, and Thomas J. Craig*

250 Neuroleptic-Induced Tardive Dyskinesia and Parkinsonism: Changes During Several Years of Continuing Treatment—*Daniel E. Casey, Uffe J. Povlsen, Birgit Meidahl, and Jes Gerlach*

254 Integrating Incidence and Prevalence of Tardive Dyskinesia—*John M. Kane, Margaret Woerner, Michael Borenstein, James Wegner, and Jeffrey Lieberman*

259 A Five-Year Follow-Up Study of Tardive Dyskinesia—*Guy Chouinard, Lawrence Annable, Pierre Mercier, and Andree Ross-Chouinard*

264 Plasma Fluphenazine Levels in Patients Receiving Two Doses of Fluphenazine Decanoate—*Stephen R. Marder, John W. Hubbard, Theodore Van Putten, Edward M. Hawes, Gordon McKay, Jim Mintz, Philip R.A. May, and Kamal K. Midha*

267 An Early Phase II Clinical Trial of Remoxipride in Schizophrenia With Measurement of Plasma Neuroleptic Activity—*Guy Chouinard and L. Turnier*

272 Measuring Adverse Drug Reactions in a Postmarketing Surveillance System—*Seymour Fisher, Stephen G. Bryant, and Ronica M. Kluge*

278 Estazolam in the Treatment of Insomnia—*Roberto A. Dominguez, Burton J. Goldstein, Alan F. Jacobson, and Richard M. Steinbook*

NCDEU Workshop/Microcomputer Interest Group—

281 Microcomputer Database Management Systems Concepts—*David Robert Gastfriend*

287 SAFTEE: Data System for Side Effect Assessment Scale—*Dean J. Clyde*

288 Microprocessor-Based Assessment of Attention Deficit Disorders (ADD)—*Michael Gordon*

291 A Microcomputer-Based Psychophysiology Data Acquisition and Analysis System—*C. Keith Conners, Roy Clymer, and Robert S. Sherrick*

297 A Brain Function Diagnostic and Study Unit for Psychotropic Drug Development and Psychopharmacology Research—*Turan M. Itil, Donald M. Shapiro, Emin Eralp, Ahmet Akman, and Kurt Z. Itil*

301 BMDPC: BMDP Statistical Software for Microcomputers—*MaryAnn Hill*

307 Communications: Microcomputer/Mainframe Interfacing—*Pierre Mercier*

311 Expert Systems in Psychiatry—*Michael Feinberg and Robert K. Lindsay*

317 **Cumulative Index—Psychopharmacology Bulletin—1985—**

Contents Index

Authors Index

B-1 **Psychopharmacology—A Recurring Bibliography—**

Announcements

Allen Raskin, Ph.D., Editor-in-Chief of the *Psychopharmacology Bulletin* since October 1980, has left the National Institute of Mental Health (NIMH) to become Director of the Psychology Division of Lafayette Clinic and Professor of Psychiatry at Wayne State University in Detroit, Michigan. As indicated in the masthead, he will continue his association with the *Bulletin* as "Special Features Editor."

* * *

The new Editor-in-Chief of the *Bulletin* is Nina R. Schooler, Ph.D., who has been a member of the NIMH staff active in both research and administration in psychopharmacology since 1965. In addition to her position of Editor-in-Chief of the *Bulletin*, Dr. Schooler is also Coordinator for Pharmacologic and Somatic Treatments Research and Assistant Chief of the Schizophrenia Research Branch of NIMH.

* * *

We are pleased to announce that the *Psychopharmacology Bulletin* is now being indexed and abstracted by Excerpta Medica.

* * *

ERRATUM

On page 611 of Vol. 21, No. 3, 1985, the second paragraph under *Methods* reads; "For atenolol, patients first received placebo for a week . . ." There was no placebo week, therefore it should read as follows: "Patients were simply started on atenolol, 50 mg/day. If not improved in 1 week, dosage was raised to 100 mg/day." We regret the error.

Annual NCDEU Meeting (1985)—Abridged Proceedings

The annual meeting of the New Clinical Drug Evaluation Unit (NCDEU) program of the Pharmacologic and Somatic Treatments Research Branch of the National Institute of Mental Health (NIMH) took place on May 1–4, 1985, in Key Biscayne, Florida. The program was developed by the staff of the Branch, Nina R. Schooler, Acting Chief, Jack Blaine, Robert Prien, Allen Raskin, Natalie Reatig, Joanne Severe, and Jerome Levine, former Chief of the Branch.

This was the 25th anniversary meeting of the NCDEU program. The program was established in 1959 by the NIMH as the Early Clinical Drug Evaluation Unit (ECDEU) program with 15 grantees. As described below by Jonathan Cole, the early "invitation-only" meetings for these grant-supported investigators developed into the current format of planned symposia and free communications. Sessions focus on recent research findings in psychopharmacology, methodologic problems and advances in clinical trials in this area, and updates or reviews of significant issues in the field.

The 1985 meeting had 340 attendees including 20 from countries other than the United States.

As in previous years, the Winter issue of the *Bulletin* is devoted to summaries of papers presented at the NCDEU meeting. These summaries are designed to provide early availability of the substance of the meeting to *Bulletin* readers. Publication in the *Bulletin* does not prejudice formal publication of the full papers elsewhere at a later time.

The ECDEU-NCDEU Program

Jonathan O. Cole, M.D.[1]

The New Clinical Drug Evaluation Unit (NCDEU) program had its beginning in the early days of modern clinical psychopharmacology when chlorpromazine was still controversial and psychoanalysis was still more popular and accepted than drug therapy. The National Institute of Mental Health (NIMH) had, perhaps slightly reluctantly, recognized that chlorpromazine and reserpine might be effective unique therapies and used its intramural group, led by Dr. Seymour Kety, to develop a special grant to support an evaluation of the new drugs. A major conference was developed by Dr. Ralph Gerard, then of the University of Illinois Medical School via the National Academy of Sciences (NAS), and I was the NAS staff member who did most of the leg work. The conference was held at the Statler Hotel in Washington, D.C., in September 1956 and eventually published in book form as *Psychopharmacology: Problems in Evaluation*.

About the same time, Dr. Nathan S. Kline and Mike Gorman testified to congressional appropriations committees demanding that the NIMH be given two million dollars a year in grant money to finance a multi-hospital collaborative study of drug efficacy in psychiatry. The NIMH reluctantly accepted the extra money and I was hired to run the new program, I believe because no more senior or distinguished individual was available or interested. The Psychopharmacology Service Center was created and staffed, in its early years, by Sherman Ross, Dean Clyde, Lorraine Bouthillet, Seymour Fisher, and Sol Goldberg. Gerald Klerman came on board for 2 years to help mount the original nine-hospital collaborative study of phenothiazines in acute schizophrenia.

---

[1] McLean Hospital, Belmont, MA 02178.

In those days the Program had the unique problem of having more money than it could spend. For a number of years the team of Kline and Gorman would urge Congress to appropriate still more money earmarked for research in psychopharmacology, and the NIMH administration would very reluctantly acquiesce and accept the new money. All the NIMH grant programs were rich and, believe it or not, the Mental Health Council would specially review the grants with the *lowest* 10% of the assigned priority scores to decide whether they, too, should be paid!

In this fiscal climate it was possible to propose and actually do large-scale collaborative studies, fund a major data analysis and computer facility to handle the data, and consider open-ended program support for early clinical drug evaluation units (ECDEUs).

The initial ECDEU program was designed to provide stable funding for investigators studying new drugs. Many investigators had programs functioning on fitful drug company grants and some state or Veterans Administration money. The Program was intended to provide core support for key staff and allow some kinds of research not possible on drug company money alone.

The Program was approved and advertised; eventually up to 18 such grants were funded. I believe Leo Hollister and Karl Rickels are the only Principal Investigators whose support has continued uninterrupted since the beginning of the Program. As time went by and research became more sophisticated and money got tighter, it became harder and harder for investigators to get continued support for straight-forward clinical trials of various and often unspecifiable new drugs. As review committees became more restrictive the ECDEU grant program, as originally conceived, gradually died a natural death.

However, the ECDEU meetings developed a life of their own. The meetings originally were designed to bring ECDEU grantees together with NIMH staff once or twice a year to discuss drugs they had been studying, to present data, and to compare impressions. Drug company representatives were originally excluded from the meetings entirely or invited in only when their drug was being discussed. Then there developed a second, open phase of the meeting at which drug company staff were allowed in. Gradually the meetings became totally open. Investigators who had lost grant support continued to attend, and gradually any interested investigator was welcome. The Food and Drug Administration (FDA) sent representatives, and foreign investigators often attended: two original ECDEU grantees were David Wheatley of the United Kingdom and Pierre Deniker of France. I believe the availability of this site in Key Biscayne and Burton Goldstein's willingness to continue as a semi-permanent arrangements committee, and the NIMH staff's availability as a secretariat, and the *Psychopharmacology Bulletin's* availability as a publication outlet, have all kept the meetings interesting, friendly, and productive. Jerry Levine, Nina Schooler, Allen Raskin, and Robert Prien, among others, have done a lot to keep the NCDEU meetings alive and well. They are a unique forum, more open and flexible than the American College of Neuropsychopharmacology, where investigators can exchange communications formally and informally with each other, drug company staff, and FDA staff.

The only comparable series of meetings I know of in medical research are those sponsored now by the Committee on Problems of Drug Dependence (CPDD). They go back well into the 1930's and also are attended by a mix of clinical investigators, basic scientists, drug company investigators and monitors, FDA staff, and foreign workers. Whether my early involvement with this drug abuse and analgesic testing group, then at the NAS, was influential in shaping the present NCDEU program, I cannot tell. If it was, we owe a debt to Dr. Nathan Eddy who essentially ran the CPDD program single handed for many years. He even raised money from drug companies to support free grants made by the NAS, now the CPDD, to investigators to carry out drug screening and clinical trials not committed to any particular company's drug. If federal funds continue to decrease and the drug companies to prosper, the NCDEU program could even end up trying this approach to the funding of some kinds of clinical drug studies.

In any event, I have always enjoyed and learned from NCDEU meetings. If I am partly responsible for the development of this unique and excellent program, I'm very glad. The real credit, obviously, belongs to all the participants over the years. I hope the programs are still as interesting and productive 20 years from now.

Re-Updates: New Perspectives on Long-Standing Issues

CHAIR: Robert F. Prien, Ph.D.
Pharmacologic and Somatic Treatments
Research Branch, NIMH
Rockville, Maryland

Problems With and Promises of Monoamine Oxidase Inhibitors[1]

Donald F. Klein, M.D.,[2] and Frederic M. Quitkin, M.D.[2]

We have been asked to discuss the past history of the use of monoamine oxidase inhibitors (MAOIs), the reason for the recent resurgence in interest, and the range of their demonstrated and possible clinical utility.

What are the characteristics that make for a desirable class of drugs that will incite both clinical investigation and application? A partial list would include the following:

They should be safe, especially from irreversible major side effects, such as stroke or hepatic necrosis.

Their lack of safety should not be made dramatically manifest by their being recalled from the market by the Food and Drug Administration (FDA) for deadly side effects, as occurred with tranylcypromine and iproniazid.

They should lack a wide variety of upsetting, even though reversible, side effects, such as orthostatic hypotension, insomnia, anorgasmia, erectile impairment, weight gain, and hypomania.

They should be easily explained to patients without incurring anxiety over potential catastrophies.

They should require no great modification in the patient's normal life processes. Therefore, they should not require that the patient be on a markedly modified diet.

There should be no threat of dangerous drug interactions.

There should be very clear guidelines as to just what foods or concurrent drugs incur what degree of risk.

There should be no class of drugs, such as the tricyclic antidepressants (TCAs), that are believed to be both safer and more effective for the same class of indications.

Finally, the pharmaceutical industry should believe that an investment in these agents may result in a substantial market penetration with a degree of profit which will make their efforts, in supporting clinical investigation and clinical use, profitable.

From the 1960's through the early 1970's the MAOIs failed by every one of these criteria and were generally considered both ineffective and dangerous. Therefore, they were shunned by both investigators and physicians.

We now know that the early research was flawed, primarily by low dose and inappropriate patient samples. We refer to this as a Phase II deficiency. Unfortunately, many pharmaceutical companies do not realize that controlled trials should be preceded by care-

---

[1] This study was supported in part by USPHS Grants MH-30906 and MH-39143-01 from the National Institute of Mental Health.

[2] New York State Psychiatric Institute, New York, NY 10032.

ful study of dose ranging, latency of onset of therapeutic effect, management of toxicity, and identification of patient types responsive to the drug being studied. Neglect of these essential steps has resulted in the history of psychopharmacology being marred by the frequent release of agents at doses far too low to be generally effective and prescribed for trials of inadequate length (Quitkin et al., 1984). Unfortunately, there are no systematic guidelines to determine the necessary information before proceeding to the design of double-blind, controlled randomized trials. Shortening the time to New Drug Application approval and, therefore, lengthening the time of profitable return is often the motivation for rushing to Phase III. Unfortunately, such a rush often proves shortsighted and poor economy since inadequate Phase III studies are the outcome.

With regard to inappropriate patient samples, the widely quoted Greenblatt et al. study (1964) was generally understood to indicate that isocarboxazid (Marplan) was actually worse than placebo and that phenelzine was equal to placebo. However, this state hospital-based study did not even show imipramine to be effective. Further, in the subgroup of neurotic depressives, phenelzine was 100% effective but, since placebo was 86% effective, the drug could not demonstrate specific benefits in this inappropriate population.

A few English psychiatrists held the fort by claiming specific superiority for the MAOIs over the TCAs for a subgroup of patients they referred to as atypical depressives (Sargant, 1960, 1961; West & Dally, 1959). These patients were primarily described as having non-autonomous mood disorder associated with high levels of anxiety, hyperphagia, and hypersomnia.

In 1969, Klein described a group of patients referred to as hysteroid dysphorics. These patients are characterized by flamboyance, seductiveness, and marked vulnerability to interpersonal rejection, with dramatic crashes in mood associated with leaden paralysis, retreating to bed, and often hypersomnia and hyperphagia (Klein & Davis, 1969). This depression was, however, responsive to positive social input, such as a new boyfriend. The description of this syndrome was important because it focused attention on pathologic rejection sensitivity as a predictor of beneficial effect from MAOI. This work also suggests that some aspects of psychopathology, historically attributed to personality or character disorders, may be a manifestation of an affective disorder, and responsive to antidepressants. Unfortunately, neither the English psychiatrists nor Klein (until recently) conducted any systematic comparative trials contrasting MAOIs and TCAs in the management of such patients.

The entire field was essentially turned around by the work of Robinson, Ravaris, Nies, and co-workers (1973, 1974, 1976, 1978a,b; Ravaris et al., 1976). This team focused clearly and definitively upon the question of dosage adequacy, and identified inhibition of platelet MAO as an objective indicator of dose effectiveness.

In 1973, they published an outpatient trial using 60 mg of phenelzine versus placebo, indicating the drug was effective, safe, and well accepted (Robinson et al., 1973). In 1976 they drove the point home in a comparative study of placebo, 30 mg and 60 mg of phenelzine indicating that 30 mg was no more effective than placebo, whereas 60 mg was substantially superior to both 30 mg and placebo (Ravaris et al., 1976).

These findings made more understandable the negative report of a large study published in 1974 that had used a maximum dose of 45 mg of phenelzine (Raskin et al., 1974). In 1977 there was another positive report by Mountjoy in the English literature of the benefits of 75 mg per day of phenelzine (Mountjoy et al., 1977).

In 1979, Quitkin et al. wrote a detailed critical review of the MAOI literature that summed up the persuasive evidence for their effectiveness in what were usually referred to as neurotic depressives and even the possible benefit of these agents for endogenous depression.

The identification of subtypes of depressives who selectively benefited from MAOIs or TCAs was approached by several investigators, the most prominent being Paykel and Robinson (Robinson et al., 1981; Rowan et al., 1982). Both investigators, in a heterogenous group of outpatients, compared MAOIs, TCAs, and placebo. They found similar overall efficacy for both drugs without very much in the way of predictors of specific efficacy. This was somewhat disheartening but was consistent with the failure of statistical methodology to identify specific drug responsive subgroups from heterogeneous groups of patients.

On moving to Columbia University in 1976, Fred Quitkin, of our group, developed a Depression Evaluation Service and promptly noted that a substantial proportion of our patients fit the criteria for atypical depression. We formalized these criteria emphasizing the essential role of non-autonomous mood disturbance associated with two of four frequently associated symptoms: hyperphagia, hypersomnia, leaden paralysis, and rejection sensitivity. This prospective study comparing phenelzine, imipramine, and placebo has been underway for some years now. It includes the efforts of a large team, in particular Fred Quitkin, Mike Liebowitz, Pat McGrath, Jonathan Stewart, Judy Rabkin, and Wilma Harrison (Liebowitz et al., 1984).

In 1981, Raft and Davidson studied a small sample of depressed patients derived from a pain clinic, and showed the superiority of phenelzine to amitryptyline and the superiority of amitryptyline to placebo (Raft et al., 1981). One conceivable drawback to this study was that it was not clear whether some of the patients might have already proven refractory to tricyclic treatment.

The first report of our effort was published in 1984 on a sample of 60 patients showing, as we had hoped, that phenelzine was indeed superior to imipramine which was superior to placebo (Liebowitz et al., 1984). Sub-analysis of these groups indicated the marked superiority of phenelzine for those considered hysteroid dysphorics and also for those who had a history of panic attacks. The relevance of a history of panic attacks to phenelzine superiority was promptly affirmed by Robinson et al. (1985). We are currently analyzing the data on 120 such patients, and our previous findings hold up well.

One major question is: just what are the boundaries of the atypical depressive syndrome? Our decision to require two out of four associated symptoms was quite arbitrary. As our study progressed, we found patients who only had one or even no associated vegetative atypical symptoms and simply manifested a non-autonomous mood disturbance. We entered these patients, also, along separate tracks, into our randomized trials.

Current analyses of the data revealed similar patterns of medication response. Patients with non-autonomous mood disturbance and any of the four atypical features appear to do better on MAOI, but patients with non-autonomous mood and no atypical features did equally well on a TCA or MAOI (Quitkin et al., 1984). These analyses should be considered preliminary.

Other syndromes also share some resemblance to atypical depression. Tim Walsh, who had been studying bulimics in collaboration with Jonathan Stewart of our Depression Evaluation Service, had developed a double-blind, placebo-controlled trial on phenelzine in bulimics that seemed to indicate that phenelzine is an excellent, at least short-term, treatment for bulimia (Stewart et al., 1984; Walsh et al., 1984).

The marked rejection sensitivity of atypical depressives calls to mind the tremendous fears of humiliation and social scorn present in social phobics and, after promising preliminary studies, Mike Liebowitz is now embarked on a placebo-controlled, double-blind trial contrasting phenelzine, atenolol, and placebo in social phobics.

An important heuristic question is whether the MAOI benefit is limited to patients with non-autonomous mood disorder. Pat McGrath of our Depression Evaluation Service has conducted two small open trials on phenelzine and tranylcypromine in outpatient melancholics. These patients had approximately a 75% response rate (McGrath et al., 1984). In other trials, this patient group had placebo response rates of less than 20%. Clearly, a controlled trial is indicated in this group, also.

There are many questions that remain to be answered. Even such simple issues such as whether tranylcypromine has different effects from phenelzine has not received investigative attention. More complex are the heuristic implications raised by the development of specific inhibitors for MAO A and MAO B (Knoll, 1984). A close reading of the literature indicates that the effect of clorgyline is not clearly established (McGrath & Klein, in press). This is somewhat surprising, considering that this drug has its major effects on just those neurotransmitters that are usually considered central to depressive illness. On the other hand, in a pilot study, deprenyl appears effective in atypical depressives (Quitkin et al., 1984). This drug is now being studied in a controlled trial.

On the horizon is a new class of reversible MAOIs. How they will help our patients and our science is quite unclear to date.

Many of our patients are chronic, dating their illness from adolescence. Can their chronic, dysthymic state be reversed by prolonged MAOI treatment? Do they require chronic maintenance treatment with MAOIs or can their improved state be maintained following drug cessation? Quitkin is pursuing this issue, which has substantial public health importance, in a double-blind discontinuation trial.

To sum up, we seem to be entering a burgeoning period of MAOI research and application. That these useful agents should have been ignored for so long is an unfortunate testimonial to the peculiarities of our profit-oriented drug development system and, in particular, the problems created by Phase II failures of adequate assessment.

References

Greenblatt, M., Grosser, G.H., and Wechsler, H. Differential response of hospitalized depressed patients to somatic therapy. *Am. J. Psychiatry*, 120:935–943, 1964.

Klein, D.F., and Davis, J.M. *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore: Williams & Wilkins Co., 1969.

Knoll, J. Deprenyl (selegiline): The history of its development and pharmacologic action. *Acta Neurol. Scand.* (Suppl.), 95:57–80, 1983.

Liebowitz, M.R., Quitkin, F.M., Stewart, J.W., et al. Phenelzine versus imipramine in atypical depression: A preliminary report. *Arch. Gen. Psychiatry*, 41:669–677, 1984.

McGrath, P.J., and Klein, D.F. Heuristically important mood altering drugs. Position paper. Dahlen Conference, Berlin, October 1982. (In press)

McGrath, P.J., Quitkin, F.M., Harrison, W., and Stewart, J.W. Treatment of melancholia with tranylcypromine. *Am. J. Psychiatry*, 141:288–289, 1984.

Mountjoy, M., Roth, R.F., Garside, G., et al. A clinical trial of phenelzine in anxiety depressive and phobic neuroses. *Br. J. Psychiatry*, 131:486–492, 1977.

Quitkin, F.M., Harrison, W., Liebowitz, M., et al. Defining the boundaries of atypical depression. *J. Clin. Psychiatry*, 45:19–21, 1984.

Quitkin, F.M., Liebowitz, M.R., Stewart, J.W., et al. L-Deprenyl in atypical depressives. *Arch. Gen. Psychiatry*, 41:777–781, 1984.

Quitkin, F.M., Rabkin, J.G., Ross, D., and McGrath, P.J. Duration of antidepressant drug treatment: What is an adequate trial? *Arch. Gen. Psychiatry*, 41:238–245, 1984.

Quitkin, F.M., Rifkin, A.E., and Klein, D.F. Monoamine oxidase inhibitors: A review of antidepressant effectiveness. *Arch. Gen. Psychiatry*, 36:749–760, 1979.

Raft, D., Davidson, J., Wasik, J., and Mattox, A. Relationship between response to phenelzine and MAO inhibition in a clinical trial of phenelzine, amitriptyline, and placebo. *Neuropsychobiology*, 7:122–126, 1981.

Raskin, A., Schulterbrandt, J.G., Reatig, N., et al. Depression subtypes and response to phenelzine, diazepam, and a placebo. *Arch. Gen. Psychiatry*, 3:66–75, 1974.

Ravaris, C.L., Nies, A., Robinson, D.S., et al. A multiple-dose controlled study of phenelzine in depression-anxiety states. *Arch. Gen. Psychiatry*, 33:347–350, 1976.

Robinson, D.S., Kayser, A., Corcella, J., et al. Panic attacks in outpatients with depression: Response to antidepressant treatment. *Psychopharmacol. Bull.*, 21(3):562–567, 1985.

Robinson, D.S., Nies, A., Corcella, J., and Cooper, T.B. MAO inhibitors, new biochemical and clinical findings. *Psychopharmacol. Bull.*, 17(3):154–157, 1981.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. The monoamine oxidase inhibitor, phenelzine, in the treatment of depressive-anxiety states. *Arch. Gen. Psychiatry*, 29:407–413, 1973.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Treatment response to MAO inhibitors: Relation to depressive typology and blood platelet MAO inhibition. In: *Classification and Prediction of Outcome of Depression*, Vol. 8. Symposia Medica Hoechst, Stuttgart, West Germany: F.K. Schattauer Verlag, 1974, pp. 259–267.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Clinical pharmacology of phenelzine: MAO activity and clinical response. In: Lipton, M., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978a.

Robinson, D., Nies, A., Ravaris, C., et al. Clinical pharmacology of phenelzine. *Arch. Gen. Psychiatry*, 35:629–635, 1978b.

Rowan, P., Paykel, E.S., and Parker, R.R. Phenelzine and amitriptyline: Effects on symptoms of neurotic depression. *Br. J. Psychiatry*, 140:475–483, 1982.

Sargant, W. Some newer drugs in the treatment of depression and their relation to other somatic treatments. *Psychosomatics*, 1:14–17, 1960.

Sargant, W. Drugs in the treatment of depression. *Br. Med. J.*, 1:225–227, 1961.

Stewart, J., Walsh, B.T., Wright, R.M., et al. An open trial of MAO inhibitors in bulimia. *J. Clin. Psychiatry*, 45:217–219, 1984.

Walsh, B.T., Stewart, J.W., Roose, S.P., et al. Treatment of bulimia with phenelzine. *Arch. Gen. Psychiatry*, 41:1105–1109, 1984.

West, E.D., and Dally, P.J. Effects of iproniazid in depressive syndromes. *Br. Med. J.*, 1:1491–1494, 1959.

New Perspectives on Long-Standing Issues: The Monoamine Oxidase Inhibitors[1]

Donald S. Robinson, M.D.[2]

Monoamine oxidase inhibitors (MAOIs) fell into disuse soon after their introduction into clinical practice 25 years ago. As Dr. Donald Klein points out in the preceding paper, this class of antidepressant drug was supplanted rapidly by the tricyclic antidepressants (TCAs). The MAOIs survived in limited use with a claimed specificity of therapeutic effect for what was termed "atypical depressions" based on experience from uncontrolled studies (Klein, 1969; Sargant & Dally, 1962; West & Dally, 1959). In later controlled trials other investigators (Johnstone & Marsh, 1973; Robinson et al., 1973) confirmed the therapeutic efficacy of phenelzine in the treatment of depression. Recent studies have shown the MAOI phenelzine to be as effective as the TCA amitriptyline in the treatment of depression (Paykel et al., 1980; Ravaris et al., 1980). MAOIs are also at least as effective as existing therapies for phobic and panic disorders (Sheehan et al., 1980). There is little doubt that over the past decade this class of drugs has undergone an impressive resurgence of interest.

Application of modern clinical pharmacologic methods to the study of MAOIs played a role in this recrudescence. Studies based on strict double-blind design, careful baseline evaluation and symptom ratings, with control of critical variables, is essential to clinical psychopharmacology. The importance of these principles was appreciated relatively late in this field and has contributed to conflicting claims about various psychopharmacologic treatments, including the MAOIs.

Burgeoning interest in MAOI research over the past 10 years has resulted in documentation of their effectiveness as general antidepressants. Somewhat unexpectedly, their therapeutic spectrum seems to be broader than the TCAs. Conclusive evidence now exists also for their efficacy in anxiety disorders, including panic disorder and phobic states, and atypical affective disorders such as patients with depression with hysteroid features (Kayser et al., 1985; Liebowitz et al., 1984; Quitkin et al., 1984).

The author's involvement with MAOIs began with development of an assay of *in vivo* MAO inhibition in man which permitted monitoring of the target pharmacologic effect of these drugs in platelets of treated patients (Robinson et al., 1968). This capability proved useful in the clinical pharmacologic study of these drugs, of which relatively little was known, since FDA approval preceded the 1962 amendments to the drug laws. As a consequence, most pre-1962 drugs were lacking in basic knowledge of their pharmacokinetics, therapeutic dose range, or appropriate doses in special populations such as the elderly, and hepatic or renal-impaired patients.

At the time of their approval in 1960, studies in the rat (Gey & Pletcher, 1961) and in man (Ganrot et al., 1962) demonstrated that significant degrees of brain MAO inhibition (75% or greater) were necessary to cause an increase in tissue levels of norepinephrine, serotonin, and dopamine. However, there had been little effort in clinical trials to define adequately the therapeutic dose range, and the prior studies were overlooked. In the early 1970's this led the Vermont group to examine the relationship between platelet MAO inhibition, phenelzine dose, and clinical response of depressed patients (Ravaris et al., 1976). These clinical pharmacologic studies of phenelzine provided a replication of the earlier placebo-controlled efficacy studies (Robinson et al., 1973) and established that the dose of phenelzine is critical in

---

[1] This study was supported in part by USPHS Grants MH-15533, MH-27836, MH-37617, and MH-36179 from the National Institute of Mental Health.

[2] Bristol-Myers Company, Pharmaceutical Research & Development Division, Wallingford, CT 06492.

achieving a therapeutic response. Existing labeling for phenelzine at the time called for inappropriately low doses. The lower end of the therapeutic dose range was found to be 45 mg/day. The data suggested also that the dose-response curve might not be linear. It appeared that a threshold inhibition level of at least 80% (using benzylamine as substrate) was associated with onset of therapeutic effect in depression (Ravaris et al., 1976; Robinson et al., 1978). Subsequently, dosage recommendations have been modified to be 60 to 90 mg/day for most patients.

An important question remaining to be answered is the optimal duration of treatment with an MAOI to maintain a patient in remission following treatment of an index episode. Studies are now in progress at two centers to address this critical issue. Interim results of these ongoing studies are not yet available, but there is early evidence that phenelzine treatment should be continued beyond 6 months for most patients. Selected patients with chronic or recurrent depression may require MAOI treatment for several years.

Studies have shown the optimum daily therapeutic dose of phenelzine to be approximately 1 mg/kg/body weight (Robinson et al., 1978a,b). Recent experience (Lerfald and Robinson, unpublished data) indicates that patients can be started initially at full therapeutic dosage. One would predict it should be possible to use a "loading dose" during the first week of treatment without increased risk of side effects which might accelerate the therapeutic response.

The strategy of employing a multiple fixed-dose design in Phase II studies of antidepressants is an important concept. The advantages of such designs are generation of vital dose-ranging data required for Phase III trials and clinical practice. Such dose-ranging studies, if properly designed, can also provide important efficacy data. Because of the time-consuming and expensive nature of Phase III studies, it is important to define an effective, safe dose as early as possible in the development of antidepressant drugs. Definitive, well-designed studies are key since outcome measures lack precision in psychopharmacology in comparison to many other fields of investigation, and perhaps even more critical is the temporal dissociation between initiating drug treatment, or making a dose adjustment, and the resulting therapeutic effect.

Finally, there is emerging evidence that MAOIs have specific anxiolytic effects in addition to intrinsic antidepressant activity. This possibility is supported by studies in phobic disorders (Solyom et al., 1973; Tyrer et al., 1973), depression with prominent somatic anxiety (Nies et al., 1982), depression with panic symptoms (Liebowitz et al., 1984; Robinson et al., 1985), and panic disorder (Sheehan et al., 1980). Studies by our group have shown phenelzine to have equivalent antidepressant efficacy to amitriptyline in major depression with enhanced antianxiety properties in these patients compared to the TCAs (Robinson et al., 1985). Phenelzine relieves both psychic and somatic symptoms of anxiety associated with depression.

The recent interest in serotonin as a primary neurotransmitter mediating mood and anxiety states (Peroutka & Snyder, 1980; Taylor et al., 1981) has important implications for the MAOIs. This class of drug is known to profoundly affect brain serotonin levels and to inhibit serotonergic neurotransmission (Blier & deMontigny, in press). There is increasing evidence that serotonergic systems may play a central role in modulating anxiety and tension states in conjunction with the noradrenergic systems which mediate outflow from the locus ceruleus. Anxiolytic agents, including the benzodiazepines and buspirone, share a common property of profoundly inhibiting serotonergic neurotransmission in the dorsal raphae nucleus. It is postulated that anxiety agents achieve their clinical effects by inhibiting raphae input to the septo-hippocampal system. However, buspirone, unlike the benzodiazepines, does not inhibit spontaneous firing of cells in the locus coeruleus (Sanghera et al., 1983) and actually mildly enhances noradrenergic firing. This would suggest that a decrease in serotonergic activity mediates a therapeutic anxiolytic drug effect.

An analogous situation may apply to the MAOIs which can markedly increase brain serotonin (Robinson et al., 1979) and inhibit dorsal raphae firing, in addition to their better known effects on noradrenergic systems. Current electrophysiologic and neurochemical studies may provide a basis for understanding the mechanism of action of MAOIs which probably involves a profound effect on serotonergic systems.

Summary

MAOIs are attracting intense interest, both scientifically and clinically, because of a broad spectrum of therapeutic actions. Studies support significant efficacy in the treatment of depression and anxiety disorders. Evidence from recent controlled trials, as well as clinical experience, shows MAOIs to be effective in both endogenous and nonendogenous types of major depressive disorder, atypical depression, depression with hysteroid features, and depression associated with panic attacks. In addition, MAOIs are considered to be one of the most effective treatments for panic disorder. Preliminary evidence suggests some benefit for eating disorders, social phobias, and obsessive compulsive disorder.

Relatively little is known about the need for long-term therapy with antidepressant drugs, including the MAOIs. Until the findings of ongoing studies become available, maintenance MAOI treatment should continue for a minimum of 6 months and probably longer in selected patients with chronic or recurrent depression.

At optimal dosage of phenelzine (1 mg/kg per day) an overall treatment response rate of 85 to 90% can be anticipated in major depression irrespective of subtype. Clinical pharmacology studies of antidepressant drugs can contribute to their rational use in a wide spectrum of mood and anxiety disorders.

References

Blier, P., and deMontigny, C. Serotonergic but not adrenergic neurones in rat CNS adapt to long-term treatment with monoamine oxidase inhibitors. *Neuroscience*. (In press)

Ganrot, P.O., Rosengren, E., and Gottfries, C.G. Effect of iproniazid on monoamines and monoamine oxidase in human brain. *Experientia*, 18:260–261, 1962.

Gey, K.F., and Pletcher, A. Activity of monoamine oxidase in relation to the 5-hydroxytryptamine and norepinephrine content of rat brain. *J. Neurochem.*, 6:239–243, 1961.

Johnstone, E.C., and Marsh, W. Acetylator status and response to phenelzine in depressed patients. *Lancet*, 1:567–570, 1973.

Kayser, A., Robinson, D.S., Nies, A., and Howard, D. Response to phenelzine among depressed patients with features of hysteroid dsyphoria. *Am. J. Psychiatry*, 142:486–488, 1985.

Klein, D.F., and Davis, J.M. *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore: Williams & Wilkins Co., 1969.

Liebowitz, M.R., Quitkin, F.M., Stewart, J.W., et al. Phenelzine versus imipramine in atypical depression: A preliminary report. *Arch. Gen. Psychiatry*, 41:669–677, 1984.

Nies, A., Howard, D., and Robinson, D.S. Antianxiety effects of MAO inhibitors. In: Mathew, R. (ed.), *Biology of Anxiety*, New York: Brunner/Mazel, Inc., 1982, pp. 123–133.

Paykel, E.S., Rowan, P.R., Parker, R.R., and Bhat, A.V. Response to phenelzine and amitriptyline in subtypes of outpatient depression. *Arch. Gen. Psychiatry*, 39:1041–1049, 1982.

Peroutka, S.J., and Snyder, S.H. Chronic antidepressant treatment lowers spiroperidol-labeled serotonin receptor binding. *Science*, 210:88–90, 1980.

Quitkin, F.M., Liebowitz, M.R., Stewart, J.W., et al. L-Deprenyl in atypical depressives. *Arch. Gen. Psychiatry*, 41:777–781, 1984.

Ravaris, C.L., Nies, A., Robinson, D.S., et al. A multiple-dose, controlled study of phenelzine in depression-anxiety states. *Arch. Gen. Psychiatry*, 33:347–350, 1976.

Ravaris, C.L., Robinson, D.S., Ives, J.O., et al. Phenelzine and amitriptyline in the treatment of depression. *Arch. Gen. Psychiatry*, 37:1075–1080, 1980.

Robinson, D.S., Lovenberg, W., Keiser, H., and Sjoerdsma, A. Effects of drugs on human blood platelet and plasma amine oxidase activity *in vitro* and *in vivo*. *Biochem. Pharmacol.*, 17:109–119, 1968.

Robinson, D.S., Nies, A., Ravaris, C.L., and Lamborn, K.R. The monoamine oxidase inhibitor, phenelzine, in the treatment of depressive-anxiety states. *Arch. Gen. Psychiatry*, 29:407–413, 1973.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Clinical pharmacology of phenelzine. *Arch. Gen. Psychiatry*, 35:629–635, 1978a.

Robinson, D.S., Nies, A., Ravaris, C.L., et al. Clinical psychopharmacology of phenelzine: MAO activity and clinical response. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Genera-*

tion of Progress, Vol. 2, New York: Raven Press, 1978b, pp. 961–973.

Robinson, D.S., Campbell, I.C., Walker, M., et al. Effects of chronic monoamine oxidase inhibitor treatment on biogenic amine metabolism in rat brain. *Neuropharmacology*, 18:771–776, 1979.

Robinson, D.S., Kayser, A., Corcella, J., et al. Panic attacks in outpatients with depression: Response to antidepressant treatment. *Psychopharmacol. Bull.*, 21(3):562–567, 1985.

Sanghera, M.K., McMillan, B.A., and German, D.C. Buspirone, a non-benzodiazepine anxiolytic, increases locus ceruleus noradrenergic neuronal activity. *Eur. J. Pharmacol.*, 86:107–110, 1983.

Sargant, W., and Dally, P. Treatment of anxiety states by antidepressant drugs. *Br. Med. J.*, 1:5–9, 1962.

Sheehan, D.V., Ballenger, J., and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch. Gen. Psychiatry*, 37:51–59, 1980.

Solyom, L., Heseltine, G., McClure, D., et al. Behavior therapy versus drug therapy in the treatment of phobic neuroses. *Can. Psychiatr. Assoc. J.*, 18:25–32, 1973.

Taylor, D.P., Allen, L.E., Ashworth, E.M., et al. Treatment with trazodone plus phenoxybenzamine accelerates development of decreased type–2 serotonin binding in rat cortex. *Neuropharmacology*, 20:513–516, 1981.

Tyrer, P., Candy, J., and Kelly, D. A study of the clinical effects of phenelzine and placebo in the treatment of phobic anxiety. *Psychopharmacologia*, 32:237–254, 1973.

West, E.D., and Dally, P.J. Effects of iproniazid in depressive syndromes. *Br. J. Psychiatry*, 1:1491–1494, 1959.

Discussion on the Monoamine Oxidase Inhibitors

Burtrum C. Schiele, M.D.[1]

Jonathan Cole gave the keynote address in which he described how Congress was impressed in the 1950's with the great potential of chlorpromazine and other antipsychotic drugs for reducing the morbidity of mental illness. As a result, Congress gave Dr. Cole's Psychopharmacology Service Center 2 million dollars in 1956 to stimulate research. There was a paucity of good research at that time and Jon Cole and his colleagues had to "beat the bushes" for suitable grantees. This probably explains why he told me in 1959 to apply for research money, stating that "you fellows in Minnesota are doing some pretty good work." We received 1.4 million dollars in direct costs over a 12-year period and the University received as overhead about 400,000 dollars. This support resulted in over 150 clinical trials on investigational compounds. The results from most of these trials were published.

More importantly, our Early Clinical Drug Evaluation Unit (ECDEU) operation stimulated similar efforts at other centers such as the St. Paul-Ramsey Medical Center, the Missouri Institute of Psychiatry, and the Veterans Administration Medical Center in St. Cloud, Minnesota. Approximately 50 colleagues participated in these clinical trials. For many, this was a first research effort resulting in publication. Over the years, these colleagues published several hundred additional articles in psychopharmacology. Even those who did not pursue research received lasting benefits through a greater appreciation of what psychotropic drugs can and cannot do, and through familiarity with the scientific measurement of behavioral change developed by psychopharmacologists.

"New Perspectives on Long-Standing Issues" was the title of the first scientific session. Dr. Donald Kline gave a scholarly dissertation on the ups and downs of the monoamine oxidase inhibitors (MAOIs). This class of drugs historically provided the first effective modern antidepressants. The original drug, iproniazid (Marsalid), initially generated great excitement, as it appeared to have potent antidepressant action. Unfortunately, it also produced jaundice and liver damage and was removed from the American market, though it is still commercially available in Canada and the United Kingdom. A number of MAOIs were marketed but only three remain on the American scene: isocarboxazid (Marplan) and phenelzine (Nardil) are hydrazine MAOIs and tranylcypromine (Parnate) is a nonhydrazine MAOI.

The early studies evaluating the effectiveness of the MAOIs were slip-shod and poorly designed by today's standards. Nevertheless, the drugs were widely used until tricyclic antidepressants (TCAs) became available. At this time, the so-called "cheese" reaction, or hypertensive headache crisis, began to appear in patients who were taking the MAOIs. In a short time, these drugs were in disrepute and were rarely used. However, in the late 1970's there was a considerable resurgence of interest in them. This is due to the fact that better designed studies were being conducted. One of the best was a study by Dr. Donald Robinson on Nardil. He demonstrated that the effective dose level was considerably greater than what had originally been recommended, and that patients must be carefully selected. In carefully controlled trials, Nardil proved to be equal in efficacy to the TCAs. Also, a biologic measure of MAO action was available by measuring the platelet MAO content.

A second factor that created further interest in these agents was the advent of several new types of MAOIs based upon the discovery of agents that were highly selective for the two major classes of MAO, Types A and B. A selective MAOI, chlorgyline, acted on

---

[1] Emeritus Professor of Psychiatry, University of Minnesota, Minneapolis, MN 55455.

MAO-A but showed no safety advantage over the already existing MAOIs and is no longer manufactured. One of the more promising drugs is L-deprenyl, which is selective for MAO-B. MAO-A denatures norepinephrine, 5–HT, and dopamine, while MAO-B denatures dopamine and phenethylamine. L-Deprenyl apparently does not alter tyramine and, thus, is considerably less dangerous than the traditional MAOIs. It is marketed in England and other European countries as an antiparkinson drug where it is causing few difficulties and is associated with little orthostatic hypotension.

My main role in this presentation is to discuss Parnate (tranylcypromine). This agent is unlike the other MAOIs in that it has a bimodal stimulating action that occurs very quickly, whereas the hydrazine MAOIs may require several days or weeks before the antidepressant effect is apparent. Parnate has not been associated with liver troubles, tremor, or sweating as have the hydrazine drugs. In the early days, it appeared to be a drug of choice, partly because of its rapid onset of action and high potency. Before long, however, the drug began to show a higher incidence of hypertensive crisis than did the other drugs and so fell into disrepute. This was particularly true in England, where many people eat a whole meal of cheese: patients who were on Parnate often had hypertensive crises after eating ripe cheese or other tyramine-laden foods. A number suffered strokes, and there were some deaths. As a result, in 1964 the FDA threatened to seize the drug and the manufacturer removed it voluntarily from the market. Because of the large number of letters of protest, mostly from physicians who claimed to have patients who were benefiting greatly from Parnate and who had benefited from nothing else, the FDA reversed its decision and the drug was returned to the marketplace within a few months. However, severe restrictions were placed upon its use. The dose was lowered, it was not to be given to people over 60 years of age, and there was a long list of prohibited foods and drugs which should not be used while the patient was taking Parnate.

When the Drug Evaluation Scientific Inventory (DESI) studies were completed, Parnate was given a rating of less than efficacious. The rating has not been changed in spite of the fact that the manufacturer claims to have completed two well-designed studies in the last year that show its efficacy. I understand that new labeling is being developed and that the dose will be raised and restrictions lessened.

Most patients do not respond to Parnate, but it is easy to determine in a few days whether or not they will respond. Of those who do, many demonstrate dramatic improvement. To illustrate, a 43-year-old university graduate had been incapacitated by anxiety and depression for over 20 years. He had failed to respond to psychotherapy, ECT, and many new drugs and had spent the last 10 years in Anoka State Hospital. He had the good fortune to be placed on Parnate while a subject in one of our first double-blind trials under the ECDEU program. Within 3 days he was vastly improved. That Parnate was largely responsible for this improvement is supported by the fact that his fears and anxiety began to return when Parnate was taken off the market. He improved when Parnate supplies were made available to him, and went on to a complete and lasting recovery.

The aforementioned patient is a classical MAOI responder. Some responders, however, may be schizophrenic. One such patient had had florid schizophrenia for many years and had failed to obtain lasting benefit from extensive ECT, many drugs, and years of hospitalization. Surprisingly, she obtained lasting benefits from Parnate. A trial of Parnate (or other MAOI) in treatment-resistant schizophrenics who are tense and anxious or fearful may be worthwhile. A problem is that some schizophrenics may develop more florid symptomatology on Parnate, in which event the MAOI should be discontinued.

The official label says Parnate should be used only in "severe depressions." This wording needs to be improved because most of those who benefit have atypical depression, if they are depressed at all. They often have chronic fears and anxiety, and a few have frank schizophrenia or schizophrenic tendencies.

Parnate is sufficiently different from the hydrazine MAOIs and should not be lumped with these. Studies are needed to compare Parnate against the hydrazine MAOIs. If

Parnate responders would do as well on the hydrazine MAOIs, the latter may be preferred because of a somewhat better safety record.

One of my last ECDEU projects (about the time of my retirement) was an interesting study of Parnate's isomers. Commercial Parnate is a racemic mixture of plus and minus isomers. Dr. Solomon Snyder told us that animal studies suggested that the minus isomer might have greater therapeutic value and less toxicity. Our short-term trial on 11 depressed subjects indicated that he was correct. Unfortunately, as far as I know, no further studies on this intriguing matter have been carried out.

Use of Placebo in Clinical Trials[1]

Karl Rickels, M.D.[2]

It is now almost 40 years since the "Cornell Conference on Therapy" was held (Cornell Conference on Therapy, 1946). It was a "first" in medicine with its primary focus on placebo effects and double-blind methodology. In the late 1940's and early to late 1950's, Beecher and his associates conducted leading research on the patients' subjective response to active drug treatment, primarily analgesics, and to placebo (Beecher, 1955, 1959).

But it was the discovery of chlorpromazine and reserpine, two antipsychotic drugs, in the early 1950's that began to revolutionize clinical research methodology. The discipline of "psychopharmacology" was born.

Psychiatry, a medical specialty that in the early 1950's had almost rejected its medical roots and had embraced a concept of psychological and behavioral causation for most psychiatric illnesses, suddenly found itself with pharmacological tools to modify behavior significantly and to produce frequently lasting improvement. Soon, other neuroleptic agents, as well as drugs to treat anxiety and insomnia, such as meprobamate and the benzodiazepines, drugs to treat depression such as monoamine oxidase inhibitors (MAOIs) and tricyclics, and lithium to treat mania, were also introduced into medicine. The young leaders of this new field of psychopharmacology took the opportunity which was offered to them and forged ahead to develop the discipline of psychopharmacology and make it a leader in clinical research and clinical pharmacology.

The Psychopharmacology Service Center (NIMH-PSC) was created in 1956, changing its name in the early 1960's to the Psychopharmacology Research Branch (NIMH-PRB). NIMH research support multiplied and the judicious support of well-controlled, frequently placebo-controlled clinical trials, conducted both at individual research centers and as collaborative enterprises, carried out with schizophrenic, depressed, manic-depressed, and anxious patients, led to important clinical findings and to advances in research methodology not found, at least at that time, in other medical specialties. Another important driving force behind the excellent clinical collaborative research conducted in the early years of psychopharmacology was the central office of the Veterans Administration.

In these early years of psychopharmacology, industry lagged in its support of clinical research. In fact, most well-controlled studies in the 1960's were government supported. Industry had no real incentive as drugs could get approved rather easily, having to demonstrate only safety but not efficacy.

It is for this reason, but also for the fact that most schizophrenic patients lived in state hospitals and were not treated by private or academic psychiatrists, that much of the early clinical research with neuroleptics and antidepressants was conducted in relatively few State hospitals by such early leaders of psychopharmacology as Fritz Freyhan, Nathan Kline, Milton Greenblatt, Heinz Lehmann, and others.

In 1960, the first NIMH-sponsored collaborative study involving the treatment of anxious outpatients was conducted jointly by NIMH, Johns Hopkins, and the University of Pennsylvania (Fisher et al., 1964; Uhlenhuth et al., 1966), soon to be followed by in- and outpatient studies in depression.

All of these early NIMH and VA-sponsored studies employed already sophisticated research methodology, including the use of placebo and standard controls, randomization, placebo washout, and double-blind design.

---

[1] This study was supported in part by USPHS Research Grant MH-08957 from the National Institute of Mental Health.

[2] Stuart and Emily B.H. Mudd Professor of Human Behavior and Professor of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104.

Since in psychiatry probably more than in any other field of medicine, nondrug or nonspecific factors, including the treatment milieu (Rickels, 1968), exert an important impact on treatment outcome, the use of controls, frequently placebo, became a methodological necessity. The more patients were studied, the more the phenomenon to be studied changed, the well-known Heisenberg phenomenon.

Thus interest in the placebo response in psychiatry intensified during the late 1950's and 1960's and led to a burst of publications including many by the author and his colleagues (Downing & Rickels, 1970; Downing et al., 1981; Honigfeld, 1964). Placebo controls were and are still being used primarily for two reasons: to control for effects due to suggestibility, including milieu or psychotherapy, bias, and enthusiasm of both patient and physician; and also to control for spontaneous symptom change or remission occurring while in treatment but being unrelated to the specific treatment offered.

While the use of placebo is probably more important in evaluating new treatments for anxiety, panic disorder, depression, Alzheimer's disorder, and insomnia, it also plays an important role in drug trials conducted with chronic and acute schizophrenic patients.

The appropriate use of placebo controls in psychopharmacology has been clearly defined in the Food and Drug Administration (FDA) guidelines for clinical trials of psychotropic drugs. These guidelines were drafted by a committee consisting of members of the American College of Neuropsychopharmacology (ACNP) and Early Clinical Drug Evaluation Unit (ECDEU), coming from government, academia, and industry (FDA Guidelines for Psychotropic Drugs, 1974; International Guidelines for Clinical Trials of Psychotropic Drugs, 1978; FDA Guidelines for the Clinical Evaluation of Psychotropic Drugs—Antidepressants and Antianxiety Drugs, 1978; Wittenborn, 1977). In fact, the discipline of psychopharmacology was instrumental in the development of FDA guidelines, not only for psychiatry, but also for other fields in medicine. One of the most important publications relevant to the topic at hand which resulted from close collaboration between members from NIMH and ACNP, many of them also members of ECDEU, should be mentioned here. It is edited by Jerome Levine and was entitled "Principles and Problems in Establishing the Efficacy of Psychotropic Agents" (Levine et al., 1971).

Today it is difficult sometimes to separate activities sponsored by PRB, ECDEU, or ACNP. Yet the PRB and the ECDEU are probably most closely intertwined. It is now 25 years since the ECDEU, later changed to NCDEU, was launched to bring together clinical researchers, scientists, and administrators from academia, government, and industry with the explicit goal to improve communications between those involved in psychiatric clinical research.

Another important factor contributing to improved drug evaluation methodology has been the Kefauver-Harris Amendment to the Food, Drugs, and Cosmetic Act of 1962 (Kefauver-Harris Amendments of October 10, 1962, to the Food, Drugs, and Cosmetic Act, 1962). It mandated that the FDA evaluate not only safety but also efficacy claims for any new experimental agent before approving it for general use.

As a member of the drug efficacy study (National Academy of Sciences/National Research Council, 1969) evaluating psychiatric drugs, a study which was conducted between 1966 and 1968, sponsored by the National Academy of Sciences, and which reviewed for the FDA all drugs introduced between 1938 and 1962, I became clearly aware of industry's frequent lack of interest in controlled research methodology, at times not without reason, as drugs were possibly only of marginal effectiveness. The absence of well-controlled clinical trials could again not be missed (Department of Health, Education, and Welfare, 1978) when I was chairman of the FDA Psychiatric OTC Review Panel in the 1970's.

Since clinical drug trials and the use of experimental drugs and placebo are intimately interwoven with ethical questions involving the protection of human subjects, the USPHS and the FDA independently moved ahead over the years with a number of regulations to assure subject rights and good research methodology. For example, in 1966 the USPHS published its first proposal to establish Institutional Review Boards (U.S. Public Health Service, 1966) and in 1970 the FDA published its first final rules for "Adequate and Well-Controlled Clinical Evaluations" (*Federal Register*, 1970).

Improvement of research methodology and the use of placebo parallels the increasing ethical and methodological concerns regarding the use of placebo in double-blind studies (Helmchen & Müller-Oerlinghausen, 1978).

The conduct of clinical research and the protection of human subjects has been guided since World War II by the Nuremberg Code (Office of the Adjutant General of the United States, 1947), the Declarations of Helsinki (World Medical Assembly, 1964) and Tokyo (World Health Assembly, 1975), and the Declaration of Hawaii (World Psychiatric Association, 1977). This is not to say that ethical concerns regarding clinical research and the use of placebo have not been around for some time. Sir Thomas Percival, for example, discussed placebo use in his 1803 published treatise on "Medical Ethics," and Hooper's "Medical Dictionary," published in 1811, described placebo as "an epithet given any medicine adopted more to please than to benefit the patient." Placebo controls were advocated by Dr. James Lind as early as 1753 when he evaluated the effects of lime juice on scurvy.

More recently, Beecher has given a striking example of placebo effects in surgery (1968). In the 1940's it was an in-vogue procedure to perform a ligation of the internal mammary arteries for the treatment of angina pectoris. Starting in Italy, this surgical procedure entered the United States with great enthusiasm, but when finally a controlled study was evaluated in which half the patients received ligation and the other half simply a skin incision, both groups of patients showed similar levels of improvement.

Over the years, many criticisms of the use of placebo have been voiced (Burkhardt & Kienle, 1978; Freiman et al., 1978; Editorial, 1979). Let us first discuss those voiced on methodological grounds, as placebo is frequently attacked by the statement that "everyone can break the design." To such criticism, Lasagna answered most succinctly many years ago (1971):

1. It is rare for a drug to produce side effects in all patients.
2. It is rare for a placebo not to produce side effects in some patients.
3. The production of side effects is not clearly correlated with desired therapeutic effects.
4. Analyses can always be performed to investigate the possible correlation of side effects and therapeutic success.
5. Coding can and should be done individually so that one code break does not bias all of the subsequent observations.
6. Even an obvious detectable placebo may still serve as a control for spontaneous improvement, unrelated to suggestibility which is at times the main or sole component of the placebo response.
7. Even a partial control on subject and observer bias is infinitely better than no control at all.

There do exist, however, a couple of problems when including placebo control groups. First, patients assigned to placebo studies may tend to be less ill than patients assigned to studies not including a placebo group and thus are not representative of all patients and, secondly, study enrollment will be more difficult.

What are some of the major ethical concerns?

1. Placebo use is a deception.
2. Placebo use withholds otherwise available effective therapy.
3. Placebo use actually endangers the life and welfare of the patient.

Some suggest that one can deal with some of these issues by using a small "ineffective" dose of an active drug as a control. I am against such an approach since I consider it indeed a deception of the patient.

Opponents of placebo use seem to suffer from the delusion that placebos are always ineffective and experimental drugs are always safe and effective. I personally subscribe to the statement made by Lasagna some time ago that "too often the placebo-treated patients turn out to be the lucky ones in a drug trial, deprived only of a toxic and ineffective chemical" (Lasagna, 1970). In fact, it is indeed surprising to me how frequently any, at least potentially, poisonous experimental compound will be readily prescribed to patients without great ethical concerns while a safe placebo will be considered unethical.

This lack of placebo control renders the results of many clinical drug trials meaningless, useful only for drug promotion. I subscribe to Robert Temple's view (Temple, 1984) that an "escape clause" or "easy escape" can be developed for almost any placebo application in situations where it appears to be difficult to use placebo controls for ethical and/or clinical reasons. Many examples could be quoted for such consideration. Suffice it to say that placebo has been meaningfully used in all psychiatric conditions, including schizophrenia and mania.

In some conditions, for example, instead of starting with a parallel group design, one might treat patients only with an experimental or standard agent, and then shift those responding to treatment to either placebo or continued medication. An escape clause should allow a subject to resume active drug therapy only after minimal signs of relapse occur. Such designs have certainly been successfully used in mania, schizophrenia, and depression, to mention only some psychiatric indications.

What are other control options if a placebo is not used? One is the use of "historical controls," an option which in my opinion is not very helpful in most instances. Another option is the use of dose response curves but, in my opinion, even here a placebo group is needed. Finally, the use of standard agents without a placebo control group is recommended. However, unless studies comparing an experimental with a standard agent are of large sample size, involving 100 to 200 patients per treatment cell, only positive but not negative findings are interpretable (Gillings et al., 1984). A failure to include a placebo in such trials may lead to difficulty in interpreting the results. For example, the test drug may turn out to be inferior to the standard drug. Without a placebo, however, it will be impossible to say whether the test drug has any activity at all, a question probably of interest, particularly if the experimental agent has many fewer side effects than the standard agent. In another experiment, the test drug and standard drug may perform equally well. Without a placebo control, however, one does not know whether both drugs are equally effective or ineffective, or whether one was merely dealing with an experimental sample or design unable to discriminate between treatments. Therefore, it is my considered opinion that three treatment groups, namely experimental agent, placebo, and standard agent, are necessary for most appropriate study results interpretation. Here we can compare the experimental drug against the yardstick of standard drug versus placebo response.

Once clinical efficacy has been clearly established, however, I am the last person to demand a placebo group in all additional studies. Yet I know even here of many instances in which the sponsors wished they had included a placebo group. Nevertheless, research questions such as those related to differential drug effects or safety, to the relationship of drug response and drug plasma levels, and many others can be answered without using a placebo control group.

Before concluding, allow me to cite two recent experiences pointing out the importance of placebo controls. In an ongoing trial involving alprazolam, imipramine, and placebo in agoraphobic panic patients, a patient entered the trial who, after gradual increase of dosage during the first 4 weeks, responded with full remission of symptoms, symptoms she had had for many years and which had not responded to psychotherapy and other therapeutic modalities. In fact, the patient was so much improved that she appeared together with me on a radio show and before a class of 165 medical students where she completely upstaged me. Her symptoms clearly responded to treatment and the drug in question appeared to be (to everyone concerned) alprazolam, as the patient described temporary memory problems and sedation with increased dosages but no autonomic nervous system side effects. After 8 weeks, her daily dosage was slowly decreased and when she reached half the daily dosage her symptoms returned. Once a full daily dosage was again established, the patient was symptom-free for about 4 months, at which time she began slowly to relapse, needing increasing amounts of "medication," until finally she demanded to be taken off the study and to know what she was receiving. To our great surprise, when the code was broken, the patient was found to have been on placebo. Thus for more than 4 months the patient responded significantly and better than she had ever before to the supportive milieu of a special panic disorder clinic, an effect not at all drug related.

The second example is a patient suffering from major depressive disorder of the melancholic subtype who participated in a study comparing the use of imipramine, alprazolam, and placebo in depression. The patient showed positive drug response and after the double-blind phase was over and the patient was shifted to a 1 week no-drug schedule, she called her physician 3 days later describing typical withdrawal reactions which included gastrointestinal symptoms, increased sensitivity to sound and light, increased anxiety, distress, and marked lethargy. The patient was seen at once and the psychiatrist evaluating the patient was so sure about the drug the patient was receiving that he did not even request a break of the code. He placed the patient on alprazolam for 2 weeks followed by a slow medication taper without any problems. When the study was completed and the code broken, everyone can imagine our surprise when we learned that the patient had been on placebo the whole time.

In summary, let me state unequivocably my firm belief that no psychiatric treatment method, be it a pharmacological or nonpharmacological one, be recommended for general use unless controlled studies have been conducted which clearly confirm the treatment's claimed efficacy. And in the evaluation of psychopharmacological agents this should always include at least several placebo-controlled studies, some of these also including a standard drug as a third treatment group. This statement holds true not only for the assessment of new agents in the treatment of anxiety, depression, insomnia, pain, and Alzheimer's disease, but also schizophrenia. In all psychiatric conditions, such nondrug factors as milieu change, amount of support, social and familial manipulations and many others, including the mere passage of time, do exert important treatment effects, effects which have to be controlled for in psychiatric drug trials.

References

Beecher, H.K. The powerful placebo. *JAMA*, 159:1602–1606, 1955.

Beecher, H.K. *Measurement of Subjective Responses*. New York: Oxford University Press, 1959.

Beecher, H.K. Placebo effects of situations, attitudes, and drugs: A quantitative study of suggestibility. In: Rickels, K. (ed.), *Non-Specific Factors in Drug Therapy*. Springfield, Ill.: Charles C Thomas, 1968, pp. 27–39.

Burkhardt, R., and Kienle, G. Controlled clinical trials and medical ethics. *Lancet*, 1978/II:1356–1359, 1978.

Cornell Conference on Therapy. The Use of Placebo in Therapy. *NY State J. Med.*, 46, 1946.

Department of Health, Education, and Welfare, Food and Drug Administration. Over-the-counter nighttime sleep-aid and stimulant products. Tentative final orders. *Fed. Register*, 42:25544, 1978.

Downing, R.W., and Rickels, K. The prediction of placebo response in anxious and depressed outpatients. In: Wittenborn, J.R., Goldberg, S.C., and May, P.R.A. (eds.), *Psychopharmacology and the Individual Patient*. New York: Raven Press, 1970, pp. 160–168.

Downing, R.W., Rickels, K., and Ota, K.Y. Evaluation of psychotropic agents with emphasis on the role of the clinical trial . In: van Praag, H.M., Lader, M.H., Rafaelsen, O.J., and Sachar, E.J. (eds.), *Handbook of Biological Psychiatry/Part VI-Practical Applications of Psychotropic Drugs and Other Biological Treatments*. New York: Marcel Dekker, Inc., 1981, pp. 327–358.

Editorial. Controlled trials: Planned deceptions? *Lancet*, I:534–535, 1979.

FDA Guidelines for the Clinical Evaluation of Psychotropic Drugs—Antidepressants and Antianxiety Drugs. *Psychopharmacol. Bull.*, 14(2):45–63, 1978.

FDA Guidelines for Psychotropic Drugs. *Psychopharmacol. Bull.*, 10:184, 1974.

Federal Register, 35:7250, 1970.

Fisher, S., Cole, J.O., Rickels, K., and Uhlenhuth, E.H. In: Bradley, P.B., Fluegel, F., and Hoch, P. (eds.), *Neuropsychopharmacology*. Vol. 3. Amsterdam: Elsevier Publishing Company, 1964, pp. 149–156.

Freiman, J.A., Chalmers, T.C., Smith, H. Jr., and Kuebler, R.R. The importance of beta, the Type II error and sample size in the design and interpretation of the randomized control trial. *N. Engl. J. Med.*, 299:690–694, 1978.

Gillings, D., Grizzle, J., Koch, G., et al. Pooling 12 nomifensine studies for efficacy and generalizability. *J. Clin. Psychiatry*, 45 (No. 4, Sec. 2):78–84, 1984.

Helmchen, H., and Müller-Oerlinghausen, B. *Psychiatriche Therapie-Forschung*. New York: Springer-Verlag, 1978.

Honigfeld, G. Non-specific factors in treatment. *Dis. Nerv. Syst.*, 25:145–156, 225–239, 1964.

International Guidelines for Clinical Trials of Psychotropic Drugs. *Psychopharmacol. Bull.*, 14(1):47–65, 1978.

Kefauver-Harris Amendments of October 10, 1962 to the Food, Drugs and Cosmetic Act, *Code of Federal Regulations*. Washington: U.S. Government Printing Office, 1962.

Lasagna, L. Drug evaluation problems in academic and other contexts. *Ann. NY Acad. Sci.*, 169:503–508, 1970.

Lasagna, L. Decision processes in establishing the efficacy and safety of psychotropic agents. In: Levine, J., Schiele, B.C., and Bouthilet, L. (eds.), *Principles and Problems in Establishing the Efficacy of Psychotropic Agents*. Washington, D.C.: U.S. Government Printing Office, 1971, pp. 29–50.

Levine, J., Schiele, B., and Bouthilet, L. (eds.), *Principles and Problems in Establishing the Efficacy of Psychotropic Agents*. USPHS Publication No. 2138. Washington, D.C.: U.S. Government Printing Office, 1971.

Lind, J. *A Treatise of the Scurvy*. Edinburgh, 1753.

National Academy of Sciences/National Research Council. *Final Report, Drug Efficacy Study*. Washington, D.C.: U.S. Government Printing Office/Food and Drug Administration Publication, July 9, 1969.

Office of the Adjutant General of the United States. *Trials of War Criminals. Volume 2*. Washington, D.C.: U.S. Government Printing Office, 1947, pp. 181–183.

Percival, Sir Thomas. *Medical Ethics*. Manchester: J. Johnson, 1803.

Rickels, K. (ed.) *Non-Specific Factors in Drug Therapy*. Springfield, Ill.: Charles C Thomas, Inc., 1968.

Temple, R. Current issues in the design, conduct, and interpretation of clinical trials. Workshop Proceedings, Washington, D.C., September 10, 1984.

Uhlenhuth, E.H., Rickels, K., Fisher, S., et al. Drug, doctor's verbal attitude, and clinic setting in the symptomatic response to pharmacotherapy. *Psychopharmacologia*, 9:392–418, 1966.

U.S. Public Health Service, *Policy and Procedure Order No. 129, July 1, 1966*. Washington, D.C.: U.S. Government Printing Office, 1966.

Wittenborn, J.R. (ed.). Guidelines for clinical trials of psychotropic drugs. *Pharmakopsychiatrie-Neuropsychopharmakologie*, 10:205–231, 1977.

World Medical Assembly. *Declaration of Helsinki*. Helsinki, 1964.

World Health Assembly. *Declaration of Tokyo*. Tokyo, 1975.

World Psychiatric Association. *Declaration of Hawaii*. Hawaii, 1977.

Scientific and Ethical Considerations in the Use of Placebo Controls in Clinical Trials in Psychopharmacology

Gerald L. Klerman, M.D.[1]

On the occasion of the 25th anniversary of NCDEU, it is appropriate to reconsider the issues involved in the use of placebo controls in clinical trials in psychopharmacology. In the current scene, these issues involve scientific considerations and ethical problems.*

Historical Background

The theoretical and statistical basis for clinical trials had been established for many years, particularly with the work of Fisher and other British statisticians. However, it was not until after World War II that the pace of clinical research accelerated, and clinical trial designs became increasingly utilized in medicine, notably in the evaluation of treatment for cardiac problems, specifically angina pectoris, and in the evaluation of treatments for tuberculosis. Government agencies played a major role in this expansion of the use of clinical trial designs, particularly the Veterans Administration in the United States and the Medical Research Council (MRC) in the United Kingdom.

Although a few clinical trials were attempted in psychiatry in the 1930's and 1940's to assess the claims for the efficacy of convulsive therapy, insulin coma therapy, and even prefrontal lobotomy, it was not until the advent of the newer psychopharmacologic agents in the mid–1950's that clinical trials became involved in psychiatry. The rapid arrival of chlorpromazine and other phenothiazine derivatives, rauwolfia and its derivatives, and meprobamate led to intense controversy and, in partial response to that controversy, a number of controlled clinical trials were begun.

Government agencies in both the United States and the United Kingdom played a major role in organizing these trials of psychiatric drugs. In the United States, credit should be given to the Veterans Administration and also to the National Institute of Mental Health (NIMH). In the United Kingdom, the Medical Research Council initiated a number of trials.

At NIMH, the creation of the Psychopharmacology Service Center in 1956, under the imaginative leadership of Jonathan O. Cole, M.D., stimulated the development of trials, notably the Collaborative Study on the Assessment of Phenothiazines (Cole et al., 1964).

In the 1950's and early 1960's, the scientific issues of design and methodology were in the forefront. There was considerable debate as to the necessity for controlled trials. Experienced clinicians argued that controls were not necessary since they could distinguish placebo effect from drug effect and, by knowing the individual patient well, could identify the specific pharmacologic actions. Doubts were also raised about the feasibility of conducting clinical trials with psychiatric patients because of the variability of their responses, the important role of psychosocial influences on symptom fluctuation, and the absence of objective measures of psychopathology.

These issues dominated discussions in the 1950's and early 1960's, but rapidly receded through the late 1960's with the growing evidence for the efficacy of drugs and the value of clinical trials (Levine et al., 1971).

A powerful governmental impetus to the application of controlled clinical trial designs came in 1962 with the passage of the

---

[1] George Harrington Professor of Psychiatry, Harvard Medical School and Director, Stanley Cobb Research Laboratories, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114. (Now at Cornell University Medical Center, New York, NY 10021).

*Dr. Rickels (this issue) has addressed the major historical background.

Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act. It took 10 years for the Food and Drug Administration (FDA) to implement fully the provisions of that act. During that period, the National Academy of Sciences established the Drug Evaluation Scientific Inventory project (DESI) to review all classes of drugs approved prior to the 1962 Act, including psychopharmacologic agents. That panel was chaired by Daniel X. Freedman, then at the University of Chicago. In addition, the FDA commissioned the American College of Neuropsychopharmacology (ACNP) to participate in the guideline projects, and members of the psychopharmacologic community, through ACNP, participated in developing guidelines for the evaluation of antipsychotic, antidepressant, and antianxiety agents. These guidelines reaffirmed the necessity for controlled studies and, in particular, mandated the use of placebo controls.

By the mid–1970's, the scientific issues around the use of placebo controls subsided and ethical issues began to emerge. In the current scene, the ethical issues are predominant. There are often confounding scientific and ethical issues. Ethical concerns sometimes serve as a rationalization for avoiding the use of placebos. This is particularly so in individuals who advocate evaluating a new drug against some available drug in a two-group comparison design without necessarily using placebo.

The Scientific Consensus

It is useful at this point to restate the consensus arrived at in the 1960's. Why use placebos? Why use control groups? The placebo control group represents a control for a "package" of effects which potentially could obscure and confound the demonstration of drug efficacy.

Do placebo controls control for package of effects? These include:

1. The passage of time, particularly for patients with disorders with an inherent tendency to remit, such as acute depressive reactions, transient stress responses, adjustment disorder with mood, etc.

2. The increased attention given to the patient by the warmth, sympathy, and encouragement of the medical and nursing staff.

3. The patient's expectations and hope for improvement.

4. The psychosocial consequences of being legitimized in the sick role being given the role of patient, often has profound effects on family relations by recasting the patient's problems and behavior into an illness explanation rather than his actions being judged as badness.

In addition, there may be extensive cognitive reframing of the meaning given by the patient to his or her experience through the research interviews, rating scales, and checklists. Being asked to reconstruct the sequence of symptoms and events often gives patients a sense of meaning to the experience and serves to demystify the sequence of symptoms, distress, etc.

The multiple rating scales and checklists may serve as a form of self-monitoring, a behavioral technique shown effective in many forms of behavioral psychotherapy.

There are at least two other important reasons why a placebo control is desirable from a scientific point of view.

1. The placebo control serves as a means of calibrating the skills of the research group. In psychopharmacology, the research group and the research setting are the "instruments" for the detection of change, similar to the use of chemical instruments, such as gas chromatograph in blood assays for drugs. Just as the chemical laboratory would need to calibrate its instruments against blanks and standards on a periodic basis to maintain quality control, so the research group needs to calibrate itself to establish its sensitivity. Can this research group detect the difference between an active drug and a placebo or no-pill? Are they treating a patient population that is sensitive to drug effect? Are they adequately trained? Are they using assessment devices, including rating scales and checklists, which are capable of detecting change? There, the placebo control serves as a test of the sensitivity of the research group.

2. A placebo-washout period between the time the patients enter the study and the initiation of active drug treatment is particularly important in the current scene. In our socie-

ty, a high percentage of individuals are taking psychoactive drugs, including benzodiazepines, sedative-hypnotics, and recreational drugs. Very often patient experiences are symptomatic effects due to the pre-existing drugs, and the placebo-washout period establishes a new baseline for the amount of drug effect. This may particularly be the case in chronically ill patients who are treatment resistant, for example, the improvement noted in chronic schizophrenics when they were discontinued from maintenance treatment with neuroleptics by Paul and Lentz (1977).

Distinguishing Nonspecific Effects From Placebo Effects

Sometimes these effects are called "nonspecific" effects; sometimes nonspecific effects are equated with placebo effect.

It is desirable to distinguish within the package of nonspecific effects, that effect which may be related to pill-taking (i.e., the placebo effect). The optimum way to assess this would be a drug trial in which there was a placebo-pill group, as well as a no-pill control group and an active drug group. Where drugs and psychotherapy are being compared, there may be important reasons to employ both a placebo and a no-pill group, as has been argued by Hollon and DeRubreis (1981). Only a very few such efforts have been undertaken, most notably the trial of drugs and psychotherapy in depression by the Boston-New Haven Collaborative Group (Klerman, 1974). In that study, no effect of placebo pill-taking was noted above the no-pill situation, suggesting that there is no specific effect due to the expectation of pill-taking and prescription over and above the other nonspecific effects listed above.

Ethical Considerations

In recent years, ethical considerations have gained importance in designing trials of illnesses for which standard treatments exist, as in psychoses, or where the control group may have potential adverse effects, as, for example, "sham" electroconvulsive therapy (ECT) with induced unconsciousness, ethical considerations may preclude the use of placebos.

Space does not permit a full discussion of the constraints upon demonstration of efficacy that follow from the ethical restraints on the use of placebo groups. However, it is pertinent to identify a number of solutions that have been proposed and utilized.

On a nonscientific basis, the situation would be improved by increased interaction and communication between investigators and the Institutional Review Boards (IRBs) at their institutions. This communication should be extended to the national scene. A future conference should be planned to provide systematic interchange between scientific groups and representatives of review committees, such as the Editorial Board of IRB, or an organization such as Physician's Responsibility in Medical Research (PRIMR). This might make a useful topic for a future NCDEU meeting.

At the scientific level, a number of design options have been proposed. One is the use of a "treatment on demand" as a control. In this situation, patients are told that treatment is available to them as they feel their symptomatic state may require. Patients who exceeded a certain number of calls or visits per week are then considered treatment failures and removed from the protocol, but treatment is provided to them on a clinical basis. This option has been employed in a study on drugs and psychotherapy in acute depression (Richman et al., 1980).

Second, some investigators have allowed very liberal clinical judgment for removal from the study. Here the decision lies with the clinician. The clinician can remove the patient from the study because of concern for failure to improve, worsening in clinical condition, or adverse effects. In this design, the rate of removal from the study becomes an indirect measure of efficacy of the treatment. At the same time, the patient's clinical needs are adequately met. In order for this design to be adequately executed, it is desirable that the criteria for removal be operationally specified in advance, preferably in quantitative terms. The three categories mentioned above (failure to improve, worsening in clinical condition, adverse effects) are subject to marked variation in clinical judgment and prior agreement as to criteria in terms of rating scale change, or symptomatic or social functioning to enhance reliability and reduce variability among clinicians when the study is conducted across sites or with multiple clinicians at a single site.

Third, is the use of constructive designs. Where an established standard treatment exists, such as neuroleptic treatment for schizophrenics, constructive designs can be used. In these designs, all the patients receive the established treatment and subgroups receive the new treatments. The assumption is that the combination of the standard treatment plus the new treatment will have an additive, synergistic (cocktail) effect (Klerman, in press).

Three recently designed studies employ constructive designs in an interesting way. One, the NIMH study of strategies for the treatment of schizophrenia (Schooler and Keith, unpublished), employs a design in which all patients receive neuroleptic medication; however, the drug sample is divided into a high-dose group and a low-dose group and the design also allows for comparison of two forms of psychosocial intervention, including family psychoeducational efforts. Thus, there is simultaneous exploration of variation in drug dose as it may interact with psychosocial intervention. However, all patients are receiving neuroleptic medication based on the prior demonstration of the efficacy of neuroleptic medication.

Second, the Philadelphia study of drug dependence in the treatment of opiate dependent individuals (Woody et al., 1983) has reported the efficacy of professional psychotherapy. In this study at the Philadelphia VA Hospital, opiate dependent patients in the trial all received a "standard package" consisting of methadone maintenance plus psychotherapeutic counseling by ex-addict peer counselors. One-third of the sample received only the standard treatment, one-third received professional psychotherapy of the cognitive-behavioral type developed by Beck et al. (1979), and the other third received psychoanalytically derived supportive-expressive therapy (Luborsky, 1984). In this study, the two forms of professional therapy showed significant advantage over the standard treatment of methadone maintenance plus peer counseling.

Third, Mavissakalian (1984) has recently reported on treatment of agoraphobia in which the standard treatment involved all patients receiving instruction for in-vivo exposure. Exposure via instruction had previously been shown to have moderate efficacy, helping about 50 percent of patients with agoraphobia. Imipramine or professional exposure therapy was then compared. These constructive designs assume prior demonstration of the efficacy of the standard treatment. The standard treatment may be a drug treatment; as in the case of the schizophrenia study, the standard treatment was a neuroleptic. The standard treatment may be psychotherapy, as in the case of Mavissakalian's study of phobia, or the standard treatment may be a combination as in the Woody study, where the combination of methadone maintenance plus ex-addict peer counseling was the standard.

Conclusions

A scientific consensus has emerged as to the necessity of placebo controls in psychopharmacology. A similar consensus does not exist for psychotherapy research. It is of interest that the placebo group in psychopharmacology includes a package of social psychological factors such as the sick role, and the interaction between patient and therapist expectations. For the psychotherapy research, it is this very package of effects which is among the specific component of psychotherapy and which merits dismantling strategies (Kazdin, in press; Wilkins, 1984).

However, in the current context, the predominant issues regarding the use of the placebo controls in psychopharmacology are not scientific but ethical. The interactions between scientific and ethical considerations continue to be an important area in clinical psychopharmacology. The need exists to explore more fully the principles upon which ethical considerations constrain the use of placebo and in those instances where the ethical issues are predominant, alternative designs need to be developed. A number of promising constructed designs are being employed in conditions where standard treatments exist. The other major design innovation is the use of patient or clinician judgment for removal from the study and using the rate of removal as an indirect measure of efficacy. NIMH should consider the desirability of a conference to promote communication between bioethicists and leaders of IRBs on one hand, and clinical psychopharmacologists, statisticians, and methodologists on the other. Such a conference could provide the arena for intense discussion of unresolved problems and, hopefully, modes of their resolution.

References

Beck, A.T., Rush, J., Shaw, B., and Emergy, G. *Cognitive Therapy of Depression: A Treatment Manual.* New York: Guilford Press, 1979.

Cole, J.O., Goldberg, S., and Klerman, G.L. Phenothiazine treatment in acute schizophrenia. *Arch. Gen. Psychiatry,* 10:246–261, 1964.

Hollon, S.D., and DeRubeis, R.J. Placebo-psychotherapy combinations: Inappropriate representations of psychotherapy in drug-psychotherapy comparative trials. *Psychol. Bull.,* 90:467–477, 1981.

Katz, M.M., and Klerman, G.L. Introduction: Overview of the clinical studies program. *Am. J. Psychiatry,* 136:49–51, 1979.

Kazdin, A.E. Research design and methodology. In: Garfield, S.L., and Bergin, A.E. (eds.), *Handbook of Psychotherapy and Behavior Change.* 3rd ed. New York: John Wiley & Sons. (In press)

Klerman, G.L. Drugs and psychotherapy. In: Garfield, S.L., Bergin, A.E. (eds.), *Handbook of Psychotherapy and Behavior Change.* 3rd ed. New York: John Wiley & Sons. (In press)

Klerman, G.L., DiMascio, A., Weissman, M.M., et al. Treatment of depression by drugs and psychotherapy. *Am. J. Psychiatry,* 131:186–191, 1974.

Levine, J., Schiele, B., and Bouthilet, L. *Principles and Problems in Establishing the Efficacy of Psychotropic Agents.* Washington, D.C.: U.S. Government Printing Office, PHS Publication No. 2183, 1971.

Luborsky, L. *Principles of Psychoanalytic Psychotherapy: A Manual for Supportive-Expressive Treatment.* New York: Basic Books, 1984.

Mavissakalian, M.R. Agoraphobia: Behavioral therapy and pharmacotherapy. In: Beitman, B.D., Klerman, G.L. (eds.), *Combining Pharmacotherapy and Psychotherapy in Clinical Practice.* New York: Spectrum Publishers, 1984, pp. 187–212.

Paul, G.L., and Lentz, R.J. *Psychosocial Treatment of Chronic Mental Patients: Milieu vs Social-Learning Programs.* Cambridge: Harvard University Press, 1977.

Richman, J., Weissman, M.M., Klerman, G.L., et al. Ethical issues in clinical trials: Psychotherapy research in acute depression. *IRB,* 2:1–4, 1980.

Rickels, K. Use of placebo in clinical trials. *Psychopharmacol. Bull.* 22(1):19–24, 1986.

Schooler, N.R., and Keith, S.J. NIMH Protocol for treatment strategies in schizophrenia study. (unpublished manuscript)

Wilkins, W. Psychotherapy: The powerful placebo. *J. Consult. Clin. Psychol.,* 52:570–573, 1984.

Woody, G.E., Luborsky, L., McLellan, T., et al. Psychotherapy for opiate addicts: Does it help? *Arch. Gen. Psychiatry,* 40:639–645.

The Placebo Control in Clinical Trials (A View From the FDA)

Paul Leber, M.D.[1]

In many quarters, placebo controls are maligned; yet, their use is virtually indispensable to the intelligent assessment of efficacy of most psychopharmacologic drug products. It is, therefore, especially gratifying to find the use of placebo resoundingly endorsed by two distinguished investigators, Drs. Rickels (1986) and Klerman (1986). Indeed, their arguments for the use of placebo are so compelling and complete that this discussion must retrace ground they have already traversed.

Federal regulations governing drug product development recognize five types of control conditions that may be employed in clinical investigations intended to meet the regulatory standard of "adequate and well-controlled" investigations (21 CFR 314.126), the standard that must be met if a trial is to be accepted as a source of "substantial" evidence of drug product efficacy. The five control conditions (i.e., placebo, dose-comparison, no treatment, active, and historical), however, vary considerably in the number and nature of assumptions required for their interpretation and, therefore, in their degree of reliability.

The historical control is highly unreliable (Sachs et al., 1982) and, therefore, considered a control of last resort in almost every area of drug development. Because the no-treatment concurrent control does not allow blinding, its usefulness in psychopharmacologic drug development is minimal. Thus, only placebo, dose-comparison, and active control designs which employ prospective and concurrent randomization of experimental and control treatments are of much use in psychopharmacology. In theory, these three designs are capable of generating equivalently persuasive evidence of efficacy; a demonstration of a difference (in the appropriate direction) between experimental and control treatments, provided it cannot be attributed to fraud, bias, or chance, must be attributed to a pharmacologic effect of the experimental drug.

However, as commonly used in psychopharmacologic drug development programs, only placebo-controlled trials have regularly provided this sort of unambiguous evidence of efficacy. Active control investigations rarely document the superiority of an experimental treatment to standard drug and, to date, experience with fixed-dose response designs is so limited that it is impossible to make any informed judgment about their potential usefulness. From a regulatory vantage point, therefore, the placebo control trial has been an indispensable tool for the assessment of psychopharmacologic drug product efficacy.

What accounts for the value of the placebo control? The placebo control allows one to distinguish between true drug effects and improvements due to 1) spontaneous remission; 2) inconstancy of illness course (i.e., if subjects are recruited at a time of symptomatic exacerbation, their subsequent improvement may reflect only a regression to the mean); 3) biased (intentional or unintentional) assessment of outcome; and 4) nonpharmacologic effects of the treatment arrangement or contract (i.e., the placebo effect, per se).

Do placebo control trials have any faults? Of course. One concern is that the very possibility of assignment to a pharmacologically inert treatment may alter the behavior of subjects and investigators in ways that may seriously compromise the external validity of the study. In particular, the chance that placebo may be assigned can affect 1) sample selection (e.g., the very ill may be systematically excluded), and 2) trial conduct (e.g., investigators may be more willing to drop patients who do not immediately respond to their assigned treatment than they would in a trial employing only "active" drugs).

Another shortcoming of studies that employ only a placebo control is that they fail to provide any data about comparative efficacy and safety. While such data are not germane to a regulatory judgment concerning efficacy, knowledge of the relative utility and risk of treatments is important for drug labeling. Moreover, the interpretation of a trial that fails to discriminate between an experimental drug and placebo can be markedly affected by knowledge of the performance of a standard treatment in that same trial. In particular, if a study fails to discriminate between the investigational agent, standard drug, and placebo, the study can be more readily discounted (i.e., it can be given lesser weight) in the agency's overall assessment of evidence bearing on the experimental drug's efficacy.

---

[1] Food and Drug Administration, Rockville, MD 20857.

Consequently, the clinical trial design that employs placebo, standard drug, and investigational drug is an ideal marriage of the placebo and active control designs. Placebo provides an estimate of what would have been had no pharmacologic treatment been given. Standard drug provides an estimate of both the intrinsic responsiveness of the patient sample to pharmacologic treatment and the sensitivity of the assay system (i.e., the investigator and his assessment methodology). The design offers the same sort of reference points as do the blank and standard solutions in a spectrophotometric analysis.

Overall, it seems fairly obvious that the placebo alone or, still better, combined with a standard drug control, is an essential tool in psychopharmacologic drug development.

This favorable view of placebo, however, is not universally held. Objections to its use have been raised on both practical and ethical grounds.

One practical objection to placebo is that it retards subject recruitment. Physicians and patients are often reluctant to forego or delay treatment with an effective drug, or even a putatively effective one, to use placebo. The objection, however, cannot be fully assessed without reference to the implied comparison; namely, what experimental design is it easier to recruit for? Unless the alternative design has a utility equivalent to the placebo design, the advantage is illusory.

Indeed, many of those who raise objections to placebo appear to assume, albeit incorrectly, that the active and placebo controls provide equivalent protection against error. If this were true, of course, there would be no justification to employ placebo. In fact, however, active controls, as commonly used in psychopharmacology, rarely provide any useful information about efficacy.

When an active control trial fails to distinguish between the effects of an experimental agent and a standard "active" control, it does *not* prove that the two drugs are equally effective. The same result might occur if both treatments were inert, if the study had inadequate statistical power, or if the study were carelessly conducted. Thus, those who argue that a finding of no difference is evidence of efficacy rely upon a series of sanguine assumptions about the conditions under which the active control study was conducted. Many of these assumptions may be unwarranted (Leber, 1985). In particular, the assumption that a standard psychopharmacologic control treatment is "active" in a particular experiment is especially tenuous. Anyone familiar with the nature of psychiatric symptoms, their intrinsic variability, and the variable nature of treatment response among psychiatric patients will recognize why.

Furthermore, the ability to detect a difference between treatments is influenced by both the size of a study and the quality of its conduct. In trials where the goal is to demonstrate a difference, it is in the interest of those who conduct them to increase power and maintain high standards of trial execution. In contrast, in trials where the aim is to fail to show a difference, the incentives, as Temple has noted (1982), are reversed.

Thus, any potential advantage in recruitment rate offered by the active control design would seem to be completely offset by its epistemological flaws. There is no advantage in carrying out a worthless study rapidly!

As noted earlier, objections to placebo are also made on ethical grounds. It seems likely that the failure to recognize the intrinsic flaws of active controls may contribute to the debate about the "ethics" of placebo use. That is, many who object to the use of placebo controls on so-called ethical grounds may do so based on the false belief that the active control is a reasonable alternative to the placebo.

In any case, there are those who believe that the use of placebo is unethical in settings where established treatments exist for the condition for which an experimental drug is being developed (Way, 1984).

This discussant finds this view inconsistent. If one believes that it is unethical to deny a patient immediate access to a known effective treatment in order to assign him to placebo, it should be equally unacceptable to delay his access to definitive treatment in order to assign him to an investigational agent which may not only be ineffective, but dangerous.

In summary, the placebo control is an indispensable tool. If it (or some reasonable substitute for it such as the fixed dose, dose-response control) were not available, we would have to approach each new drug with the skepticism expressed by the 19th century physician who advised his colleagues ". . . to treat as many patients as possible with the new drugs while they still have the power to heal." (Trousseau, quoted by Benson and McCallie, 1979).

Placebo controls are our surest protection against fads and fashions that come and go in pharmacology, against the reckless claims of therapeutic enthusiasts, and, most important, against our own mistaken beliefs and prejudices.

References

Klerman, G. Scientific and ethical considerations in the use of placebo controls in clinical trials in psychopharmacology. *Psychopharmacol. Bull.*, 22(1):25–29, 1986.

Leber, P. The implicit assumptions of active control trials (a critical examination). Presented at the 1983 annual meeting of the Society for Clinical Trials. *Controlled Clin. Trials*. (Submitted, 1985)

Rickels, K. Use of placebo in clinical trials. *Psychopharmacol. Bull.*, 22(1):19–24, 1986.

Sachs, H., Chalmer, T.C., and Smith, H. Randomized versus historical controls for clinical trials. *Am. J. Med.*, 72:233–240, 1982.

Temple, R. Government viewpoint of clinical trials. *Drug Informa. J.*, 10–17, 1982.

Trousseau, A., quoted by Benson, H., and McCallie, D.P. Angina pectoris and the placebo effect. *N. Engl. J. Med.*, 300:1424–1429, 1979.

Way, W. Control placebos. (Letter) *N. Engl. J. Med.*, 311(6):413–414, 1984.

Pharmacological Treatments of Schizophrenia

George M. Simpson, M.D.[1]

As this is an anniversary meeting, it seems appropriate to give some information about the early clinical drug evaluation units (ECDEU), later the NCDEU. This group of investigators was created by the Psychopharmacology Research Branch (PRB) and was exceptionally important for the development of psychopharmacology in this country. In the early days of drug studies, it was reported (perhaps somewhat tongue-in-cheek) that one might receive large bottles of pills, give out handfuls of them, and report that "this is great stuff," and that was the study. Indeed, I once saw an investigator who had a pocket notebook and less than half a page of medium-size handwriting was the sum total information for each patient on his clinical trial. I might also add that his records were much superior to the other studies that I had occasion to see at that time. My own work at that time involved the notion that resting endocrinological measures would predict outcome in major mental illness, specifically schizophrenia. This was funded in the late 1950's by the PRB under the title "Research in Endocrinology and Drugs," later "The Red Project." Spin-offs from this study were trials of triiodothyronine as a treatment in schizophrenic patients with low thyroid tests who were also receiving neuroleptics, trials of Enovid in female patients who showed regular exacerbations of their psychotic symptoms thought to be associated with their menses, papers on the effects of antipsychotic drugs on reproductive function, effects of antidepressants on genito-urinary function, and a publication that showed an increase in spermatogenesis associated with the administration of a monoamine oxidase inhibitor (MAOI). On further consideration, this latter was most likely related to the fact that the two colleagues who happened to get depressed and who had been measuring their own semen count, motility, and morphology weekly for several years also drank quite a bit. The MAOIs may have been less the agent for change than the withdrawal of alcohol which was ordered during the course of this treatment.

At all events, these and other clinical trials outside the endocrinological research ward interested me and led to my applying for a grant and becoming an ECDEU member. There were many drugs available at that time and several new drugs were evaluated in the course of any 1 year. Multiple rating scales were used, many of which are seldom used today. It is not that they were poor scales but that, as ECDEU grew, the Psychopharmacology Research Branch (PRB) developed a data analysis capability, and some standardization of rating scales was essential. Thus, the Brief Psychiatric Rating Scale (BPRS) and Nurses' Observation Scale for Inpatient Evaluation (NOSIE) became standard scales. Many individual and cooperative studies were carried out by these investigators, and the science of clinical trials received a hefty shot in the arm. Diagnosis was, if not frowned on, certainly at a very primitive level in the early 1960's. One saw some very raucous and intrusive people labeled schizophrenics who were textbook manics. Perhaps because of this lack of interest in diagnosis, there were some peculiar ideas about drug actions. The idea of target symptoms was clearly a good one and was incorporated into rating scales, but there was also a notion that target symptoms were individual items and did not belong in groups to syndromes or were unrelated to diagnosis. Thus, the notion that there might be drugs specifically for hallucinations, for example, resulted in a drug marketed for that purpose—Frenquel.

Many clinical trials at this time at ECDEU units studied new drugs in chronic schizophrenic patients. The dramatic effect of chlorpromazine in an open study, coupled with the large number of hospitalized patients, made this a reasonable strategy. Hospitals had many patients who could not be discharged and who had many positive symptoms when off drugs and made mild to moderate improvement on neuroleptics. Studies invariably took 6, 8, or 12 weeks of active treatment with several weeks of no drug or placebo before and after treatment. Weekly NOSIE, BPRS, Global, and other scales were employed. It was not difficult to demonstrate in such a study that a drug was an active antipsychotic agent. All of the current antipsychotics were first tested in this fashion with the initial findings confirmed in placebo-controlled studies. It is not too surprising, if we consider that all of these drugs were developed from a similar animal model developed after the discovery of chlorpromazine, which worked so well that a variety of chlorpromazine-like drugs was developed. After the production of many, many drugs that differed in their side effects rather than in their therapeutic effects, this procedure reached a dead end. The number of new drugs diminished. There has not been a new antipsychotic drug on the U.S. market since loxapine (1975)—one of the last drugs studied collectively by ECDEU investigators. ECDEU researchers in effect received funds as an investment in them rather than in specific projects. The drop in the number of new drugs left more and more investigators with time to devote to their own pet projects which soon resembled R01 studies, e.g., our staff was involved in studying plasma levels of neuroleptics and in studying tardive dyskinesia at the time the NCDEU change took place.

---

[1] The Medical College of Pennsylvania, Philadelphia, PA 19129.

During this time, psychopharmacology progressed enormously—the sophistication of the methodology, the concern with selection of patients, diagnosis, new rating scales, inter-rater reliability, validity, etc. To an extent, the science of clinical trials which was practically nonexistent in psychiatry was now better developed in psychiatry than in any other medical specialty. Individual investigators also asked many questions about conventional drugs and produced much of the knowledge that supports present-day practices. For instance, during this period we showed that in a double-blind, controlled study one- versus three-times-a-day neuroleptic medication was equally efficacious and resulted in no increase and perhaps even a decrease in side effects if the single dose was all given at bedtime. Later, we studied the same phenomenon but also measured plasma levels. We studied fluphenazine decanoate and showed that it was active at 12.5 mg every 2 weeks. We showed that patients in general responded similarly to repeated administrations of medication, that patients who gained weight did so on each occasion, and patients who did not gain weight did so on both occasions. We showed that the immediate symptoms of withdrawal of antipsychotics were mainly related to the concomitant withdrawal of anti-parkinson agents. Therefore, a patient receiving a neuroleptic plus an anti-parkinson agent should not have both withdrawn simultaneously; the anti-parkinson agent should be continued for at least 1 week in order not to have an upsurge of extrapyramidal reactions. In 1968, we studied "the behavioral and anti-epileptic effects of an iminostilbene derivative," one of the earliest studies of Tegretol in a psychiatric population; and in 1967, a preliminary evaluation of the sedative effects of Catapres, a new antihypertensive agent in chronic schizophrenic patients. A series of papers on extrapyramidal side effects (EPS) resulted in the development of a rating scale for EPS. From this and other studies came our interest in trying to cut down the very high dose of drugs that psychiatrists used and continue to use. In these studies, it appeared that doctors used 300 percent more neuroleptics than were required. In the 1960's began the studies of lithium, studies of naltrexone in chronic schizophrenia, studies of antipsychotics in the elderly, studies with clozapine, and so on. Each ECDEU would have a similar range of different studies that they carried out, all of which added to our knowledge of psychopharmacology.

Nearly all of the investigators were active in teaching and training and so, to a large extent, these units reached a stage where they were perhaps no longer necessary, i.e., there were groups of young psychiatrists who were now being trained in psychopharmacology, the journals were replete with good studies to be read in journal clubs, etc. The introduction of clozapine raised new hopes for the type of different drug that everyone had been looking for, and this remains a not-impossible dream but certainly an unrealized one. In the meantime, use of neuroleptics has advanced the treatment of schizophrenia. It is safe to say that without neuroleptics, social psychiatry and the community mental health movement would have had great difficulties in coming about. The surge of interest in psychosocial treatment of schizophrenia highlights this, since clearly psychosocial interventions are helpful but are not very helpful in the absence of neuroleptic agents. Thus, this anniversary of the ECDEU truly represents the end of a cycle in the search for new treatments in schizophrenia. A substantial advance has been made in the treatment of schizophrenia and, while we have far to go, I feel secure that NCDEU investigators will be in the forefront of the advances to come.

Research Methodology and the Pharmacotherapy of the Chronic Schizophrenias[1]

Thomas A. Ban, M.D., William Guy, Ph.D., and W.H. Wilson, Ph.D.[2]

Introduction

Schizophrenic disorders occur in 0.86% of the general population. This implies that 86 out of 10,000 people randomly chosen from the general population will develop a schizophrenic disorder during their lifetime (Tsuang & Vandermey, 1980). Almost half of all patients diagnosed as schizophrenic will need long-term treatment, and it has been estimated that 30 to 60% of all new long-term patients suffer from one or another form of schizophrenia (Mann & Cree, 1976). There is evidence that 15% of patients who are diagnosed today as suffering from a schizophrenic disorder will become chronically hospitalized at some time in the future. Consequently, it is estimated that one-third to one-half of all psychiatric beds, i.e., one-sixth to one-fourth of all hospital beds—since nearly 50% of all beds are psychiatric—are occupied by schizophrenic patients (Todd et al., 1977).

The prevailing treatment modality for patients with chronic schizophrenia is pharmacotherapy with neuroleptics. This is to the extent that, in a multi-national survey carried out in 768 chronic hospitalized schizophrenic patients, 739 or 96.2% were treated with one or more of 33 different neuroleptics. The total population of this study was contributed by nine centers geographically located in eight countries (Tables 1 and 2) (Ban et al., 1984b).

In spite of their extensive use, it is difficult to demonstrate the therapeutic effectiveness of neuroleptics in chronic schizophrenic patients. This may be due to the lack of sensitive instruments for the assessment of change in this population. An alternative possibility is that chronic schizophrenia consists of a biologically heterogeneous population. In favor of this latter contention is the fact that not every schizophrenic patient shows a similar response to neuroleptics.

TABLE 1

Number and Percentage of Patients Receiving One or More Neuroleptics

Country	*N*	Neuroleptic *N*	Neuroleptic %
Brazil	95	71	74.7
Hungary	59	58	98.3
Italy	93	90	96.8
Japan	200	200	100.0
Nigeria	10	10	100.0
Panama	86	86	100.0
USA	150	149	99.3
Yugoslavia	75	75	100.0
Total	768	739	96.2

TABLE 2

Thirty-Three Neuroleptics Employed in Eight Countries (rank order)

1–11	12–22	23–33
Haloperidol	Promazine	Methylperidol
Chlorpromazine	Clothiapine	Oxypertine
Levomepromazine	Loxapine	Mesoridazine
Thioridazine	Pimozide	Alimenazine
Fluphenazine	Carpipramine	Trifluoperidol
Perphenazine	Perazine	Clopenthixol
Thiothixene	Reserpine	Molindone
Trifluoperazine	Floropipamide	Spiperone
Sulpiride	Fluspirilene	Moperone
Clozapine	Butaperazine	Fluphenazine Decanoate*
Propericiazine	Flupenthixol	Fluphenazine Enanthate*

*The long-acting preparations are not included in the ranking.

Demonstration of Therapeutic Efficacy

Demonstration of therapeutic efficacy is one of the prerequisites for the introduction of a new treatment modality into clinical

---

[1] This study was supported in part by USPHS Grant MH-35720 from the National Institute of Mental Health.

[2] Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN 37217.

practice. For drugs which are not causal treatments for a particular disease, e.g., neuroleptics for schizophrenia, this represents a methodological problem which includes the development of an appropriate experimental design and the employment of a discriminative instrument for the measurement of change. It is important that the assessment instrument employed in the measurement of change have the necessary sensitivity to demonstrate differences between the new treatment and the untreated course of the disease (placebo) at the accepted level of probability.

The most frequently employed instrument in the assessment of neuroleptic-induced changes in chronic schizophrenic patients is the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) which consists of 18 items scored on a 7-point scale of intensity.

Since an essential prerequisite for the usefulness of the BPRS in chronic schizophrenic patients is the necessity that the majority of the 18 items (symptoms) be present in a considerable percent of the target population, we have reviewed our data to determine the presence of 18 psychopathological symptoms corresponding to the BPRS items in the same population of 768 patients (Ban et al., 1985).

Data were collected with a specially devised instrument, the Psychopathological Symptom Profile (PSP), developed from the Psychopathological Assessment form of the second edition of the AMP-System by adding items from the Present State Examination (Wing et al., 1974), the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer & Endicott, 1978), and on the recommendation of special consultants. The PSP consists of 176 psychopathological symptoms and includes most items of the Psychopathological Symptoms section of the English edition of the AMDP–III System (Guy & Ban, 1982). Each item is followed by a brief definition and is scored from 0 to 3, indicating whether the symptom is definitely absent (0), probably absent (1), probably present (2), or definitely present (3). Accepting scores 2 or 3 as "present," it was revealed that, of the 176 symptoms of the PSP, 33 were present in at least 40% of the 768 patients (Table 3). We chose the 40% as cutoff point on the basis that any symptom present in a lower percent would not be a useful item in the assessment of change. As shown on Table 4, 8 of the 18 BPRS items are included among the 33 most frequently encountered symptoms of the PSP. While these represent some of the most frequently encountered symptoms of schizophrenia, it is clear that there are a number of significant symptoms which are simply not encompassed by the BPRS. A differently structured instrument would be more suitable in the assessment in order to avoid the possibility of covering up therapeutic changes (Type II or β error) resulting from the administration of neuroleptic drugs.

TABLE 3

Psychopathological Symptom Profile (The 33 Items Present in 40% or More of the 768 Patients)

Rank	Item	N	%
1	Lack of insight	717	93.4
2	Blunted affect	632	82.3
3	Asocial behavior	606	78.9
4	Delusions	561	73.0
5	Autistic	553	72.0
6	Unkempt	515	67.1
7	Hallucinations	508	66.1
8	Lack of interest	500	65.1
9	Auditory hallucinations	494	64.3
10	Lack of energy	473	61.6
11	Apathy	458	59.6
12	Derailment (thought)	440	58.5
13	Restricted thinking	426	55.5
14	Inhibition (drive)	426	55.5
15	Concentration difficulties	419	54.6
16	Concreteness (ideas)	411	53.5
17	Thrusts (episodes)	394	51.3
18	Suspiciousness	391	50.9
19	Delusion of reference	390	50.8
20	Impaired attention	387	50.4
21	Emotional rigidity	380	49.5
22	Delusional ideas	377	49.1
23	Persecutory delusions	367	47.8
24	Blocking	341	44.5
25	Mannerisms	334	43.5
26	Incoherent/confused	328	42.7
27	Delusional mood	328	42.7
28	Delusional perception	327	42.6
29	Irritability	315	41.0
30	Thought withdrawal	315	41.0
31	Delusional dynamics	314	40.9
32	Ambivalence	312	40.6
33	Impaired retention	309	40.2

TABLE 4

Corresponding BPRS and PSP Items Present in 40% or More of the 768 Patients

Item No.	BPRS	Item No.	PSP	%	Rank
1.	Somatic concern	33.	Hypochondriasis	–*	50
2.	Anxiety	95.	Anxiety	–	40
3.	Emotional withdrawal	82.	Apathy	59.6	11
4.	Conceptual disorganization	57.	Incoherent/confused	42.7	26
5.	Guilt feelings	111.	Feelings of guilt	–	112
6.	Tension	105.	Tension	–	38
7.	Mannerisms and posturing	127.	Mannerisms	43.4	25
		128.	Posturing	–	97
8.	Grandiosity	70.	Delusions of grandeur	–	72
9.	Depressive mood	98.	Depression	–	70
10.	Hostility	107.	Hostility	–	47
11.	Suspiciousness	106.	Suspiciousness	50.9	18
12.	Hallucinatory behavior	24.	Hallucinations	66.1	7
13.	Motor retardation	115.	Lack of energy	61.5	10
14.	Uncooperativeness	154.	Uncooperativeness	–	34
15.	Unusual thought content	60.	Delusions	73.5	4
16.	Blunted affect	81.	Blunted affect	82.2	2
17.	Excitement	113.	Restlessness	–	35
		118.	Agitation	–	88
18.	Disorientation		Disturbance of Orientation:		
		14.	Self	–	90
		15.	Time	–	73
		16.	Place	–	102
		17.	Situation	–	59

* = < 40%

Shortcomings of Classification

Introduction of neuroleptics, the most effective single treatment modality employed in chronic schizophrenic patients, has brought attention to the differences in therapeutic responsiveness among patients. In spite of this recognition, which suggests that chronic schizophrenia consists of a biologically heterogeneous population, examination of the nature of this heterogeneity, by studying the natural course of the disease with special emphasis to the end-state syndromatology of patients, has been given little attention This is especially surprising since there is little, if any, evidence that patients with different types of schizophrenia as classified by the Diagnostic and Statistical Manual—3rd ed., 1980 (DSM–III) or ICD–9 respond differentially to neuroleptic drugs, while there are indications for differential responsiveness in the different subtypes (end-states) described in Leonhard's (1979) classification of chronic schizophrenias. This complex classification which distinguishes 19 distinct syndromes belonging to two groups of disorders within the schizophrenias has shifted emphasis from the acute to the chronic forms of the illness. Leonhard maintains that schizophrenic disorders can best be studied after the acute manifestations common to all schizophrenias have subsided and the illness has progressed into its disease-specific final form (Ban, 1982) (Table 5).

By employing Leonhard's classification, Fish, as early as 1964, found that 117 out of 123 nonsystematic schizophrenics (95%) showed a favorable therapeutic response, while only 289 out of 351 systematic schizophrenics (69%) showed a favorable response. From both a practical and a theoretical point of view, however, the important findings were that among the nonsystematic patients, the favorable therapeutic response was rated marked to moderate in 79% of the treatment responsive patients, while among the systematic patients only 23% were so rated. Fish also noted that, among the nonsystematic patients, those suffering from periodic catatonia responded less favorably than patients with affect-laden paraphrenia and especially

TABLE 5

Leonhard's Classification of Chronic Schizophrenias

Nonsystematic			Systematic		
Cataphasia	Affect-laden Paraphrenia	Periodic Catatonia	Paraphrenias	Hebephrenias	Catatonias
			Phonemic	Autistic	Parakinetic
			Hypochondriacal	Eccentric	Proskinetic
			Confabulatory	Shallow	Speech-prompt
			Expansive	Silly	Speech-inactive
			Fantastic		Manneristic
			Incoherent		Negativistic

cataphasia; among the systematic patients, therapeutic responsiveness was not evenly distributed among the three major classes of illness. Thus, while as many as 40% of the paraphrenics showed a moderate or marked therapeutic response to neuroleptics, only 23% of the hebephrenics and 0.9% of the systematic catatonics showed a similar response.

Corresponding with these findings are our observations and results. We have reported on a patient with the diagnosis of periodic catatonia (febrile catatonia), a nonsystematic subtype, in whom an increase in neuroleptic dosage was associated with exacerbation, a decrease in dosage with amelioration, and discontinuation of medication with remission of psychopathological symptoms (Kelwala & Ban, 1981a). In another case report of two patients with diagnoses of shallow hebephrenia, a systematic subtype, discontinuation of neuroleptic medication had no detectable effect for an extended period (Kelwala & Ban, 1981b). Thus, in our two shallow hebephrenic patients, the usefulness of maintaining neuroleptic treatment was questionable; in our periodic catatonic patient, neuroleptic treatment seemed to have a negative therapeutic effect.

The notion that neuroleptic treatment in certain patients may not just be ineffective but may actually be harmful received further substantiation in our survey of 24 patients treated with lithium/neuroleptic combinations. A common characteristic of these patients was that they had previously shown insufficient therapeutic response to neuroleptic drugs alone. Analyses of data revealed that 9 of 10 patients of the nonsystematic population exhibited a favorable therapeutic response to the combination, while 9 of 14 systematic patients showed no response or an unfavorable therapeutic response. In addition, 5 of the 24 patients developed neurotoxicity during the course of treatment; 2 of the 5 patients were silly hebephrenics and 1 each belonged to the expansive, fantastic, and confabulatory subtypes of paraphrenia. While 5 out of the 14 patients with systematic schizophrenia manifested neurotoxicity, none of the 10 patients with nonsystematic schizophrenia, predominantly affect-laden paraphrenia, developed a similar undesirable response to the lithium/neuroleptic combination (Prakash et al., 1982).

Most important in this context are the findings regarding tardive dyskinesia in our multi-national survey (Ban et al., 1984a). While the overall prevalence rate for the population was 11% when determined by clinical judgment and 13% when determined by the Research Diagnostic Criteria for Tardive Dyskinesia (Schooler & Kane, 1982), within the Leonhard system, rates were found to be significantly lower in the therapeutically more responsive nonsystematic group (4.3%). Furthermore, while within the systematic catatonias, the manneristic subtype (53 patients, 32.7%) attained a prevalence rate of 28% and, within the systematic hebephrenias, the silly subtype (56 patients, 19.1%) had a prevalence rate of 53%, within the paraphrenic category, in the expansive (14 patients, 5.4%) and confabulatory (6 patients, 2.3%) subtypes, tardive dyskinesia was not encountered at all. On the basis of these findings, one may hypothesize that there is an inverse relationship between positive symptoms and adverse effects of the neuroleptic drugs at least insofar as tardive dyskinesia is concerned. Since there is no indication that the action mechanism of neuroleptics would be different in patients belonging to different diagnostic groups, one may speculate that, in the development of tardive dyskinesia, not just the administered drug but the biology of the host also plays an important role.

Concluding Remarks

One of the most important contributions for psychiatry which has resulted from psychopharmacologic progress is the recognition that schizophrenia consists of a biologically heterogeneous population. In view of this, it is rather paradoxical that identification of the role of dopaminergic structure in the action mechanism of neuroleptics and demonstration that neuroleptics produce dopamine receptor blockade led to speculations about the nature of schizophrenia in terms of dopamine excess which, in turn, provided sufficient incentive to develop a large number of "me-too" neuroleptics with similar therapeutic but somewhat different adverse effect profiles.

Ignoring the biological heterogeneity of chronic schizophrenia has created considerable difficulties for research in this population, while its recognition has provided new endpoints for preclinical research especially useful for drug development. One tangible result of this research is the introduction of a new category of psychotropic drugs, referred to as "les produits de transition" (transition compounds) in France.

Included among these substances are amoxapine, a dibenzoxazepine which combines the pharmacologic profile of a tricyclic antidepressant with a neuroleptic: carpipramine and chlorcarpipramine: tricyclic dibenzazepines with butyrophenone side chains: and carbamazepine, an anticonvulsant structurally related to the cyclic antidepressants. While the old methodology should suffice for the demonstration of therapeutic effectiveness of these drugs, the identification of the therapeutically responsive populations may require the employment of new diagnostic assessment instruments.

It is a common contention that psychopharmacology has opened unforeseen possibilities for psychiatric progress leading to a reintegration of psychiatry with other medical disciplines. Reevaluation of psychiatric concepts with consideration to psychopharmacologic contributions could open unforeseen possibilities for psychopharmacologic progress with a shift of emphasis from simple therapeutic efficacy based on statistical probabilities to the identification of therapeutically responsive chronic schizophrenic patients to specific treatment modalities.

References

Ban, T.A. Chronic schizophrenias: A guide to Leonhard's classification. *Compr. Psychiatry*, 23:155–169, 1982.

Ban, T.A., Guy, W., and Wilson, W.H. Description and distribution of the subtypes of chronic schizophrenia based on Leonhard's classification. *Psychiatr. Devel.*, 3:179–199, 1984a.

Ban, T.A., Guy, W., and Wilson, W.H. Pharmacotherapy of chronic hospitalized schizophrenics: Diagnosis and treatment. *Psychiatr. J. Univ. Ottawa*, 9:191–195, 1984b.

Ban, T.A., Guy, W., and Wilson, W.H. The AMDP-System in chronic hospitalized schizophrenics. *Compr. Psychiatry*, 26:370–374, 1985.

Fish, F. The influence of tranquilizers on the Leonhard schizophrenic syndromes. *Encephale*, 1:245–249, 1964.

Guy, W., and Ban, T.A. The AMDP-System: A Manual for the Assessment and Documentation of Psychopathology. Berlin: Springer-Verlag, 1982.

Kelwala, S., and Ban, T.A. Febrile catatonia sustained by neuroleptics. *Psychiatr. J. Univ. Ottawa*, 6:135, 1981a.

Kelwala, S., and Ban, T.A. Is maintenance neuroleptic therapy necessary in shallow hebephrenia? *J. Clin. Psychiatry*, 42:482, 1981b.

Leonhard, K. *The Classification of Endogenous Psychoses.* New York: Irvington Publishers, 1979.

Mann, S.A., and Cree, W. New long-stay psychiatric patients: A national sample survey of fifteen mental hospitals in England and Wales, 1972/3. *Psychol. Med.*, 6:603–616, 1976.

Overall, J.E., and Gorham, D.R. The brief psychiatric rating scale. *Psychol. Rep.*, 10:799–812, 1962.

Prakash, R., Kelwala, S., and Ban, T.A. Neurotoxicity with combined administration of lithium and a neuroleptic. *Compr. Psychiatry*, 23:567–571, 1982.

Schooler, N., and Kane, J.M. Research diagnoses for tardive dyskinesia (RD-TD). *Arch. Gen. Psychiatry*, 39:486–487, 1982.

Spitzer, R.I., and Endicott, J. *Schedule for Affective Disorders and Schizophrenia.* 3rd ed. New York: State Psychiatric Institute, 1978.

Todd, N.A., Bennie, E.H., and Carlisle, J.M. Some features of new long-stay male schizophrenics. *Br. J. Psychiatry*, 129:424–[illegible]7, 1977.

Tsuang, M.T., and Vandermey, R. *Genes and the Mind.* New York: Oxford University Press, 1980.

Wing, J.K., Cooper, J.E., and Sartorius, N. *The Measurement and Classification of Psychiatric Symptoms.* London: Cambridge University Press, 1974.

Discussion of Dr. George Simpson's Paper on Pharmacological Treatments of Schizophrenia

Solomon C. Goldberg, Ph.D.[1]

In the earlier days of neuroleptics, there was substantial success in treating chronically hospitalized or chronic ambulatory schizophrenic patients. Unfortunately, most of the chronic patients who remain now are treatment resistant. They are a poor sample of patients on which to test new antipsychotic drugs whose mechanism is dopamine blockade. Indeed, they can lead to misunderstandings concerning the effectiveness of neuroleptics in schizophrenia if these patients are employed in a test of neuroleptic effectiveness. Paul's work (1972), in which he failed to find a drug effect in chronic schizophrenic patients, was interpreted by him to mean that antipsychotic drugs in general were not effective in chronically psychotic patients. His error was in generalizing from his results to other situations in which standard antipsychotic drugs are effective in the treatment of many schizophrenic patients. These nonresponders to dopamine blockers become prime candidates for the testing of other antipsychotic agents. We are morally obligated to try to find some treatment that will help these patients. This thought has occurred to a number of investigators, and nonresponsive patients have been tried on such agents as propranolol, alprazolam, carbamazepine, lithium, and *d*-amphetamine.

Before starting a patient on one of these agents, it may be well to confirm that the patient is indeed a nonresponder to standard neuroleptics. State hospitals are notoriously conservative in their dosing strategies because of self-protective policies which prohibit the administration of doses higher than those recommended by the *Physician's Desk Reference*. Prien and Cole (1971), for example, found a substantial number of patients who profited from very high doses of phenothiazines after not responding to standard doses.

In a nearby state hospital we are exploring lithium and carbamazepine for the treatment of neuroleptic nonresponders. There has been no difficulty in getting such patients transferred to our unit. When the patients arrive, they are almost invariably on a variety of medications, and our first step is to taper them from these while building them up on a dose of fluphenazine HCl. The fluphenazine dose is increased for 2 weeks until there is no further improvement or until side effects intervene. So far we have found a few patients who are responders to higher doses of fluphenazine, and they are no longer regarded as nonresponders. Those who do not respond become candidates for our trial drugs, but not on a double-blind clinical trial basis. We feel that this is premature until we generate some hypotheses regarding the characteristics of those who will profit from them. The formal clinical trial of any of the new drugs is postponed until a later time.

If a patient is a complete nonresponder to neuroleptics, he is first put on a trial of lithium alone. If he is a partial responder, he would be put on a combination of lithium and his neuroleptic, which in this case would be fluphenazine. If he does not respond to the first medication, he automatically is then given a trial of carbamazepine. On a case study basis, the characteristics of responders and nonresponders to the different drugs are observed.

Beyond the empirical search for new treatments for nonresponders, there is the more theoretical question of why some schizophrenic patients do not respond to neuroleptics. Here there is another line of research which proposes that the schizophrenic nonresponder shows evidence of organicity. There are now at least two studies, Weinberger et al. (1980) and Schulz et al. (1983), showing an association between enlarged ventricles on the CT scan and nonresponse to neuroleptics. These studies were partly an outgrowth of the Johnstone (1976) and Crow

---

[1] Director of Psychiatric Research, Medical College of Virginia, Richmond, VA 23298.

(1980) hypothesis to the effect that schizophrenic patients with negative symptoms have enlarged ventricles and do not respond to neuroleptics. Murray and his associates (in press–b) go a step further to indicate that the schizophrenic with organic signs has a low genetic loading by virtue of family history for schizophrenia, has a history of birth complications involving signs of asphyxia, and was born in a winter month, implying a greater likelihood of viral infection. Murray, in a recent editorial in *The Lancet* (in press–a), proposes that the time has come to recognize two major etiological types of schizophrenia, a genetically transmitted disorder, and a nongenetic disorder whose etiology is more likely environmentally induced brain damage.

What was begun as an empirical search for new treatments for nonresponders has developed a theoretical facet to try to explain the differences in the characteristics of responders and nonresponders. The heuristic value of the theoretical orientation is that it may be capable of suggesting why some of the new treatments may be effective. For example, Slater's (1963) cases of epilepsy who showed schizophrenic symptomatology might be most treatable with the anticonvulsant carbamazepine. To borrow a phrase from social science, "There is nothing so practical as a good theory."

References

Crow, T.J. Molecular pathology of schizophrenia. More than one disease process. *Br. Med. J.*, 1:66–68, 1980.

Johnstone, E.C., Crow, T.J., Frith, C.D., et al. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*, 924–926, 1976.

Murray, R.M., Lewis, S.W., and Reveley, A.M. Towards an etiological classification of schizophrenia. *Lancet*. (In press–a)

Murray, R.M., Reveley, A.M., Reveley, M.A., et al. Genetic and environmental influences in schizophrenia. In: Sakai, T., and Tsuboi, T. (eds.), *Genetic Aspects of Human Behavior*. Tokyo: Igaku-Shoin. (In press–b).

Paul, G.L., Tobias, L.L., and Holly, B.L. Maintenance psychotropic drugs in the presence of active treatment programs: A triple-blind withdrawal study with long-term mental patients. *Arch. Gen. Psychiatry*, 27:106–115, 1972.

Prien, R.F., Levine, J., and Switalski, R.W. Discontinuation of chemotherapy for chronic schizophrenics. *Hosp. Community Psychiatry*, 22:4–8, 1971.

Schulz, S.C., Sinecrop, P., Kishore, P., and Friedel, R.O. Treatment response and ventricular brain enlargement in young schizophrenic patients. *Psychopharmacol. Bull.*, 19(3):510–512, 1983.

Slater, E., Beard, A.N., and Glithero, E. The schizophrenia-like psychoses of epilepsy. *Br. J. Psychiatry*, 109:95–150, 1963.

Weinberger, D.R., Bigelow, L.B., Kleinman, J.E., et al. Cerebral ventricular enlargement in chronic schizophrenia: An association with poor response to treatment. *Arch. Gen. Psychiatry*, 37:11–13, 1980.

Multicenter International Clinical Trials

CHAIRS: Thomas Ban, M.D.
Department of Psychiatry
Vanderbilt University
Nashville, Tennessee

and

Jerome Levine, M.D.
Maryland Psychiatric Research Center
Baltimore, Maryland

Introduction

Thomas A. Ban, M.D.,[1] and Jerome Levine, M.D.[2]

The multi-center approach has been used in clinical psychopharmacology since the late 1950's. Collaborative studies coordinated by the United States National Institute of Mental Health (NIMH), United States Veterans Administration, and the United Kingdom Medical Research Council contributed to the establishment of proper usage of antidepressant and neuroleptic drugs. Without employing a multi-center approach this would have taken considerably longer, and generalization of the findings would have encountered considerably greater difficulties.

Multi-center clinical trials are particularly advantageous for studying the effect of psychotropic drugs in rare disorders. But even in common disorders such as Alzheimer's type of dementia, if one aims to study a homogeneous sample with progressive deterioration at a particular stage, only in a multi-center clinical trial can one expect to find an adequate number of suitable patients within a reasonable period of time.

International participation adds another dimension to multi-center clinical research. Such studies have at least three essential prerequisites: 1) multidimensional description of patient's condition, because of the possible differences in diagnostic practices among participating centers in different countries; 2) assessment instruments in the measurement of change which are reliable and valid across cultures; and 3) feasibility of coordination for making operational the collaboration.

In this session, findings in three multicenter international clinical trials will be presented, one carried out with an antipsychotic (fluperlapine), another with an antidepressant (fluvoxamine), and the third with an anxiolytic drug (alprazolam).

The topic of the first paper is the AMDP System in International Clinical Trials: A Report on Fluperlapine. The AMDP System stands for Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie or, in English, Association for Methodology and Documentation in Psychiatry. It was founded in 1965 by a group of psychiatrists from Germany, Switzerland, and Austria to develop a uniform system for the documentation of information which would be useful in both clinical practice and psychopharmacologic research. Since the Psychopathological Symptom Form, the instrument employed in the assessment of change in the AMDP was developed with emphasis on form, i.e., the mode by which the patient encounters contents, and as such is not contaminated by social-cultural contingents, and should be particularly suited for international collaborative psychopharmacologic research.

The first paper dealt with an international multi-center clinical trial with an antipsychotic, the second dealt with an international multi-center clinical trial with an antidepressant. Professor Cassano and his colleagues presented findings from a multi-center international trial comparing fluvoxamine, a specific serotonin reuptake inhibitor with imipramine and placebo. It should be noted that in all the different phases of this study a modification of the Biometric Laboratory Information Processing System usually referred to as BLIPS has played an important role. This system was developed at the Biometric Laboratories of George Washington University in collaboration with the Psychopharmcology Research Branch of NIMH under the leadership of one of us (J.L.). This system, which has played an important role in the development of clinical trial methodology in the United States, has been implemented in Europe, where Dr. Cassano and his colleagues have created an even more versatile system, BLIPS/BDP.

---

[1] Department of Psychiatry, Vanderbilt University, Nashville, TN 37217.

[2] Maryland Psychiatric Research Center, Baltimore, MD 21228.

The third paper by Dr. Klerman and colleagues presents, for the first time, the results of Phase I of the Upjohn worldwide panic disorder study.

In addition to the results of these studies, this session demonstrates the different ways in which multinational trials can be organized depending on the roles played by the sponsors, investigators, and the availability of computer-based data documentation and analysis systems.

The AMDP System in International Clinical Trials: A Double-Blind Comparison of Fluperlapine and Haloperidol

B. Woggon,[1] M. Linden,[2] H. Beckmann,[3] E. Krebs,[4] B. Küfferle,[5] B. Müller-Oerlinghausen,[2] B. Pflug,[6] and H.W. Schied[7]

Introduction

One important methodological problem in international collaborative studies is the selection of suitable rating scales. The translation of a psychopathological rating scale is complicated by different concepts of psychopathological symptoms and syndromes in different languages and countries. The Association for Methodology and Documentation in Psychiatry, a collaborative group of German, Swiss, and Austrian psychiatrists, was founded in 1965 and the first AMP manual was established in 1971 (Angst et al., 1969; Scharfetter, 1971). Based on broad clinical experience, many drug trials, and a number of methodological studies, a revision of the AMP system was completed in 1979, called the AMDP System (Association for Methodology and Documentation in Psychiatry) (AMDP, 1979, 1983). The AMDP System is currently available in many languages including German, Croatian, English, French, Russian, Spanish, Japanese, Portuguese, Greek, Italian, Danish, and Dutch.

This paper is composed of two parts: a) a description of the AMDP System; and b) an example of an international collaborative trial: a double-blind comparison of fluperlapine* and haloperidol in schizophrenic patients that utilizes the AMDP System.

Description of the AMDP System

AMDP consists of five integrated parts, each printed on a single sheet of paper: 1) demographic data; 2) life events; 3) psychiatric history; 4) psychopathological symptoms; and 5) somatic signs. The 100 psychopathological symptoms and 40 somatic signs are clearly arranged into groups, an aid for the rater (Tables 1 and 2). It is also possible to add write-in items of specific interest to a clinical trial.

Each symptom can be rated as "absent," "present," or "not ascertained." A symptom is rated as "not ascertained" if reliable information is not available. If a symptom is present, three degrees of severity can be rated: mild, moderate, or severe. This judgment is based on frequency, intensity, and duration of a symptom.

Each rating of psychopathological and somatic symptoms is based on a specified time period, for example 24 hours, and combines

TABLE 1

Psychopathological Symptoms (Sheet 4 of the AMDP System)

	Group	No. of Symptoms
1.	Disorders of consciousness	4
2.	Disturbances of orientation	4
3.	Disturbances of attention and memory	6
4.	Formal disorders of thought	12
5.	Phobias and compulsions	6
6.	Delusions	14
7.	Disorders of perception	6
8.	Disorders of the ego	6
9.	Disorders of affect	21
10.	Disorders of drive and psychomotility	9
11.	Circadian rhythms	3
12.	Other disturbances	9

---

[1] Department of Psychiatry of the University of Zurich, Switzerland.

[2] Department of Psychiatry of the Free University of Berlin, Federal Republic of Germany.

[3] Psychiatry Clinic of the Central Institute of Mental Health, Mannheim, Federal Republic of Germany.

[4] Psychiatric Hospital of Wil, Switzerland.

[5] Department of Psychiatry of the University of Vienna, Austria.

[6] Department of Psychiatry of the University of Frankfurt, Federal Republic of Germany.

[7] Department of Psychiatry of the University of Tübingen, Federal Republic of Germany.

*Based on recent toxicological data, the manufacturer (Sandoz AG) has suspended all clinical trials with fluperlapine.

TABLE 2

Somatic Signs
(Sheet 5 of the AMDP System)

	Group	No. of Signs
1.	Sleep	5
2.	Appetite	4
3.	Gastrointestinal	7
4.	Cardiac-respiratory	4
5.	Other autonomic	5
6.	General	6
7.	Neurological	9

both subjective (reported) and objective (observed) information.

Factor analyses of data from various patient samples have led to the development of subscales representing psychopathological syndromes. For statistical analyses of data from clinical trials, different sets of subscales can be used. A comprehensive monograph in English that describes the system includes studies of subscales, interrater reliability, validity, and sensitivity in drug trials (Bobon et al., 1983).

Double-Blind Comparison of Fluperlapine and Haloperidol

As an example of the use of the AMDP System in an international collaborative trial, we report preliminary results of a double-blind study comparing fluperlapine and haloperidol. Fluperlapine (a dibenzazepine) is very similar in structure to clozapine (Figure 1). In open trials, it showed a strong antipsychotic effect (Angst, 1984).

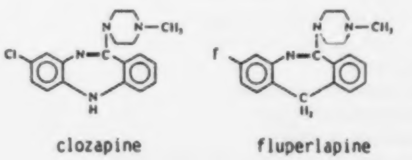

clozapine fluperlapine

FIGURE 1. Chemical structures of clozapine and fluperlapine.

Seven psychiatric hospitals participated in the study, four in the Federal Republic of Germany, two in Switzerland, and one in Austria. These hospitals are linked to the AMDP and, therefore, the investigators and staff are familiar with and trained in the use of the AMDP System.

The following results are based on data from 120 inpatients who were randomly assigned to treatment with either fluperlapine ($N = 60$) or haloperidol ($N = 60$). Some patient characteristics are given in Table 3; diagnoses according to the ICD-9 (International Classification of Disease) are given in Table 4. The planned duration of treatment was 28 days. Early dropouts (before day 7) were excluded from the final analysis.

Using a flexible dose regimen, the recommended initial daily dose was 2.5 mg haloperidol or 50 mg fluperlapine, three times a day. Maximum daily dose was 60 mg haloperidol and 800 mg fluperlapine. At the end of the trial, the average daily dose was 23 mg haloperidol (s.d. = 12 mg) and 441 mg fluperlapine (s.d. = 210 mg).

Data analysis was performed at the Department of Psychiatry of the University of Zurich, Switzerland, using a set of 13 subscales (Table 5). Raw scores of the subscales are calculated by adding the included items according to the following values: absent and

TABLE 3

Description of the Patients

	Fluperlapine ($N = 60$)	Haloperidol ($N = 60$)
Male	30	30
Female	30	30
First manifestations	19	19
Duration of symptoms prior to hospitalization:		
Unknown	8	6
Less than 1 week	10	7
Less than 1 month	22	23
Less than 6 months	13	17
Less than 1 year	2	–
More than 1 year	5	7
Age in years:		
$\bar{x}$ (s.d.)	33.0 (9.7)	35.6 (12.3)
Range	19-59	20.63
Duration of illness (years):		
$\bar{x}$ (s.d.)	5.6 (5.9)	5.9 (8.5)
Maximum	21	39

TABLE 4

Diagnosis

ICD No.	Diagnosis	Fluperlapine ($N = 60$)	Haloperidol ($N = 60$)
295.0	Schizophrenia simplex	3	–
295.1	Hebephrenic schizophrenia	5	3
295.2	Catatonic schizophrenia	1	3
295.3	Paranoid schizophrenia	41	45
295.4	Acute schizophrenic episode	1	1
295.5	Latent schizophrenia	1	1
295.6	Residual schizophrenia	1	1
295.7	Schizoaffective psychosis	7	5
195.8	Other schizophrenia	–	1
297.8	Other paranoid syndrome	–	1

*Degkwitz et al., 1980.

not ascertained = 0; mild = 1; moderate = 2; and severe = 3. In order to normalize the distributions, logarithmic transformations were performed for the scores of subscales 1 to 12. The scores of subscales 13 and 14 are nearly normally distributed and do not require transformation. Because the number of items in each syndrome is different (range 7 to 27), all scores are further transformed ($\bar{x} = 50$, s.d. = 10, range 20-80).

TABLE 5

AMDP Syndromes (Zurich version)

Primary

1. Apathetic
2. Hallucinatory-Disintegrative
3. Hostility
4. Manic
5. Somatic-Depressive
6. Paranoid
7. Catatonic
8. Retarded-Depressive
9. Hypochondriac
10. Psycho-organic
11. Autonomic
12. Neurological

Second Order

13. Manic-Depressive
14. Schizophrenic

Construction of subscales:
1-9: Baumann, 1974.
10: Monbour et al., 1975.
11 and 12: Without factor analysis.
13 and 14: Woggon & Dittrich, 1979.

TABLE 6

Items of the Hallucinatory-Disintegrative AMDP-Syndrome

(57)*	Thought insertion
(58)	Other feelings of alien influence
(38)	Delusional dynamics
(48)	Verbal hallucinations
(50)	Visual hallucinations
(55)	Thought broadcasting
(37)	Systematized delusions
(49)	Other auditory hallucinations
(51)	Bodily hallucinations
(54)	Depersonalization

*Item No. on AMDP sheet 4.

The analysis of the Hallucinatory-Disintegrative syndrome clarifies the antipsychotic efficacy of fluperlapine and haloperidol. The symptoms are listed in Table 6. Table 7 shows mean values and s.d. for the syndrome on each rating day. Significant reduction during treatment occurred in both treatment groups [Friedman's analysis of variance (ANOVA)]. The comparisons between day 0 and subsequent rating days in each group separately indicated a significant improvement beginning on day 3. Because of multiplicity of significance, *t* tests were done; and alpha was adjusted from 5% to 1% (Figure 2).

T tests between the two treatment groups on each rating day revealed no significant differences. An analysis of covariance (ANCOVA) following the model for factorial experiments with repeated measurements, and constant covariates (unequal cell frequencies) was calculated using the scores at day 0 as a covariate (Winer, 1962). No significant differences between the two groups were found.

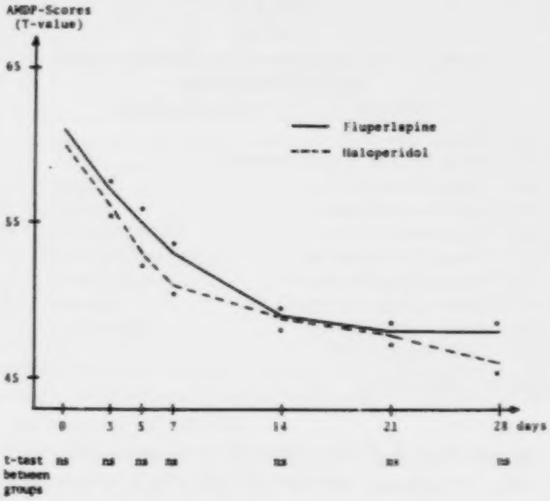
We predicted a difference in extrapyramidal side effects between the two treatments. The subscale that includes extrapyramidal symptoms is the Neurological Syn-

TABLE 7

Hallucinatory-Disintegrative Syndrome

Day	Fluperlapine ($N = 60$)		Haloperidol ($N = 60$)	
	$\bar{x}$	s.d.	$\bar{x}$	s.d.
0	61.4	7.4	60.4	7.7
3	57.2	8.7	56.4	8.9
5	55.1	9.4	52.7	8.5
7	52.6	8.6	50.7	8.6
14	49.4	8.0	49.4	8.6
21	48.4	8.3	48.1	7.8
28	47.8	8.2	46.4	6.9

Mean Values ($\bar{x}$) and Standard Deviations (s.d.)



* $p \leq 0.01$ for comparisons in each group with day 0 t-test, 2-tailed, a adjusted from 5 to 1% because of multiple t-tests)

FIGURE 2. Course of the Hallucinatory-Desintegrative AMDP-Syndrome (mean values).

drome (Table 8). Mean values and s.d. of this syndrome in both treatment groups are listed in Table 9. A significant change over time in the group treated with haloperidol was found (Friedman's ANOVA). Comparison between day 0 and the following rating days demonstrated a significant increase in the haloperidol-treated patients from day 3 onward (Figure 3). *T*-test comparisons at each rating day showed no difference between the groups at pretreatment. From day 3 on, the haloperidol-treated patients had significantly higher values than the fluperlapine-treated group in this syndrome. The ANCOVA showed a significant difference between the two groups.

TABLE 8

Items of the Neurological Syndrome

(132)*	Rigor
(133)	Hypotonia
(R5)**	Tremor
(134)	Moderate to gross tremor
(139)	Nystagmus
(135)	Dyskinesia (acute)
(R6)	Persistent hyperkinesia
(136)	Hypokinesis
(R7)	Pareses
(R8)	Signs of the pyramidal tract
(138)	Ataxia
(R9)	Other neurological symptoms
(137)	Akathisia
(R10)	Primitive reflexes

*Item No. on AMDP sheet 5.
**Write-in items are marked with R.

TABLE 9

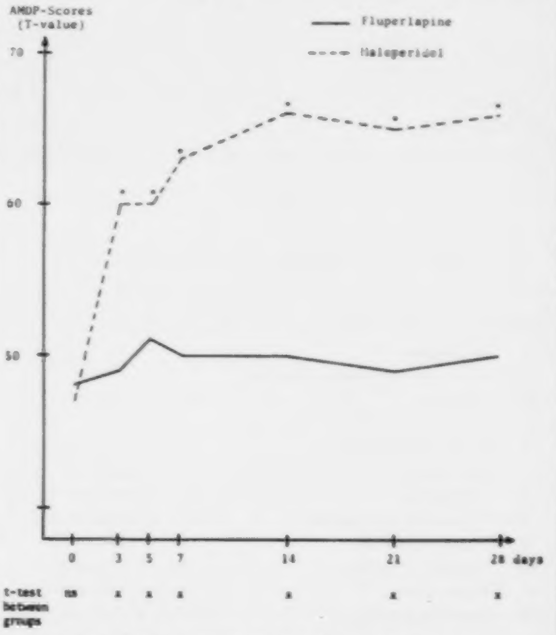
Neurological Syndrome

Day	Fluperlapine ($N = 60$)		Haloperidol ($N = 60$)	
	$\bar{x}$	s.d.	$\bar{x}$	s.d.
0	48.2	8.4	47.4	8.1
3	48.7	8.8	60.1	15.2
5	50.8	10.7	59.6	16.7
7	49.7	10.5	63.0	15.7
14	50.4	10.3	65.7	16.6
21	49.4	9.0	65.4	14.8
28	49.5	9.6	66.1	14.2

Mean Values ($\bar{x}$) and Standard Deviations (s.d.)

Summary

Analysis of the Hallucinatory-Disintegrative AMDP Syndrome demonstrates an



* $p \leq 0.01$ for comparisons in each group with day 0 (t-test, 2-tailed, a adjusted from 5 to 1% because of multiple t-tests)

x $p \leq 0.01$ for comparisons (t-test) between groups on each day

FIGURE 3. Course of the Neurological AMDP Syndrome (mean values).

equally strong antipsychotic effect of fluperlapine and haloperidol with an early onset (day 3). Analysis of the Neurological AMDP Syndrome indicates that haloperidol, in contrast to fluperlapine, causes frequent and strong extrapyramidal side effects.

References

AMDP, Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (Hrsg.). Das AMDP-System. Manual zur Dokumentation psychiatrischer Befunde. Berlin: Springer-Verlag, 1979.

AMDP, Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (Hrsg.). Testmanual zum AMDP-System. Empirische Studien zur Psychopathologie. Berlin: Springer-Verlag, 1983.

Angst, J. (ed.) Fluperlapine (NB 106-689): A new nonclassical neuroleptic. *Drug Res.*, (special issue) 34(1): 109-137, 1984.

Angst, J., Battegay, R., Bente, D., et al. Das Dokumentationssystem der Arbeitsgemeinschaft fur Methodik und Dokumentation in der Psychiatrie. *Arzneimittel-Forschung*, 19: 339-405, 1969.

Baumann, U. Diagnostische Differenzierungsfähigkeit von Psychopathologie-Skalen. *Arch. Psychiatr. Nervenkr.*, 219: 89-103, 1974.

Bobon, D., Baumann, U., Angst, J., et al. *AMDP-System in Pharmacopsychiatry*. Basel: S. Karger, 1983.

Degkwitz, R., Helmchen, H., Kockott, G., and Mombour, W. ICD-Diagnoseschlüssel und Glossar psychiatrischer Krankheiten. Deutsche Ausgabe der internat. Klassifikation der WHO: ICD, 9. Rev., 5. Auflage. Berlin: Springer-Verlag, 1980.

Mombour, W., Gammel, G., Von Zerssen, D., and Heyse, M. Die Objektivierung psychiatrischer Syndrome durch multifaktorielle Analyse des psychopathologischen Befundes. *Nervenarzt*, 44: 352-358, 1973.

Scharfetter, Ch. Das AMP-System. Manual zur Dokumentation psychiatrischer Befunde. Berlin: Springer-Verlag, 1971.

Winter, D.J. *Statistical Principles in Experimental Design*. London: McGraw Hill, 1962.

Woggon, B., and Dittrich, A. Konstruktion übergeordneter AMP-Skalen: "Manisch-depressives" und "schizophrenes" Syndrom. *Int. Pharmacopsychiatry*, 14: 325-337, 1979.

Use of a Standardized Documentation System (BLIPS/BDP) in the Conduct of a Multicenter International Trial Comparing Fluvoxamine, Imipramine, and Placebo

Giovanni B. Cassano, M.D.,[1] Luciano Conti, M.D.,[1] Gabriele Massimetti, M.D.,[1] Francesco Mengali, M.D.,[1] Jenifer S. Waekelin, M.D.,[2] and Jerome Levine, M.D.[3]

Introduction

When in 1978 Duphar BV, Holland, decided to organize a multicenter international clinical trial with the aim of assessing efficacy and safety of a new selective serotoninergic antidepressant compound, fluvoxamine maleate (FUVOX), the BLIPS/BDP system (Biometric Laboratory Information Processing System/Data Bank for Psychopharmacology), used at the Center for Clinical Psychopharmacology Data Documentation (CCPDD) of the Institute of Clinical Psychiatry of the University of Pisa, appeared to provide the necessary underlying structure for the study by offering an efficient standard data documentation system.

The organizational model that was used for the study provided that the company would maintain their usual role in the selection of sites, monitoring and collecting data, and supplying drugs to the sites. The role of the Pisa center included consultation on the design of the study, choice of the rating scales, and provision of a standardized documentation and analysis system, namely the BLIPS/BDP.

The company provided the raw original data collected from the investigators to the CCPDD. They organized several meetings with principal investigators in which the Pisa center participated, but the Pisa center had no additional contacts with the participating investigators.

The advantages of this organizational model include: a) open choice of sites and investigators (investigators do not need to belong to a previously organized group); b) the company plays its usual role with regard to site selection and monitoring; and c) the BLIPS/BDP documentation and analysis system does not require the use of special purpose (trial specific) rating scales but only the use of a standardized identification block. Therefore, widely used rating scales can be utilized by investigators without the necessity of special training, only checks of interrater reliability. This results in a very cost-effective flexible model which, as we will show, is sufficiently sensitive to establish efficacy and safety.

Material and Methods

The planned "Duphar" trial was an international multicenter, double-blind, prospectively randomized clinical trial aimed at comparing the antidepressant activity and safety of FLUVOX with that of imipramine (IMI) and placebo (PBO) in in- or outpatients aged over 18 years and suffering from a major depressive illness (according to the DSM-III definition).

Initially, there were 12 participating centers, 7 in North America and 5 in Europe (Table 1). FLUVOX and IMI, in unit doses of 50 mg, and PBO, in indistinguishable capsules, were administered according to a fixed-flexible dosage schedule: one capsule the first day, two capsules the second day, and three capsules from the third to the seventh day. After the first week the dosage could be adjusted, according to clinical judgment, from a minimum of one to a maximum of six capsules per day and administered, where possi-

---

[1] Institute of Clinical Psychiatry, University of Pisa, Pisa, Italy.
[2] Department of Clinical Research, Duphar BV, Weesp, The Netherlands.
[3] Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD 21228.

TABLE 1

Participating Centers and Data Available for Analyses

Locations	Principal Investigators	Patients Enrolled No.	Patients for the Intent to Treat Analysis[a] No.	Patients for the Intent to Treat Analysis[a] %	Patients for the Efficacy Analysis[b] (No.)	Patients for the Efficacy Analysis[b] %
Miami, USA	Goldstein[c]	101	87	86.1	59	58.4
New York, USA	Farkas[c]	52	44	84.6	28	53.9
Ottawa, Canada	Lapierre[d]	63	60	95.2	45	71.4
Montreal, Canada	Ananth[d]	31	29	93.6	24	77.4
London, England	Paykel/Sirelig[c]	46				
London, England	Paykel/Norton[c]	45	91	100.0	83	91.2
Montreal, Canada	Amin[c]	91	89	97.8	75	82.4
Nice, France	Darcourt[d]	52	48	92.3	43	82.7
	Totals	481	448	93.1	357	74.2
Jackson, USA	Caranza[e]	3				
Houston, USA	Caranza[e]	16				
Turin, Italy	Ravizza[e]	3				
Pisa, Italy	Cassano/Conti[f]	45				

[a] Patients with at least two evaluations on drug.

[b] Patients with at least 14 days medication and not dropped out after the 14th day because of possible study drug-related concurrent signs and symptoms or for reasons unrelated to study group.

[c] Outpatients.

[d] Inpatients.

[e] Study stopped after only a few patients enrolled: data not included in the analysis.

[f] Placebo-controlled study conducted under the same protocol: data not included in the analysis.

ble, three times a day. No other psychotropic medications were allowed with the exception of chloral hydrate or flurazepam, as hypnotics, only when this was unavoidable.

Patients with an established diagnosis of major depressive illness and with a score of at least 15 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D) at the end of the pretreatment period, and not precluded by the exclusion criteria (childbearing potential or pregnant women; antidepressant therapy in the past 2 weeks; electroconvulsive therapy within the last month; depressive symptoms secondary to other psychiatric illness; dependence upon licit or illicit drugs; serious organic diseases; need for concurrent medications which could interact with the study drugs or obscure their effects; and patients unwilling or unable to cooperate in the study) were included in the trial.

After a pretreatment period of 3 to 7 days, during which one capsule of PBO indistinguishable from the treatment capsules was given, patients received drugs for up to 28 days. For the North American centers, the treatment period was extended to 42 days. Analyses presented here are focused on 28-day data in order to utilize both European and North American data.

Assessment instruments were mostly the standard rating instruments of the BLIPS/BDP and the assessments were done on entry, at the last pretreatment day, and weekly thereafter (Table 2).

The main aim of this paper is to demonstrate the utility of the organizational model for this kind of study. Because of that, we will consider only the Adult Personal Data Inventory (APDI) for the demographic data, the Patient Termination Record (PTR) for the trial data, the HAM-D and the Clinical Global Impression Scale (CGI) for efficacy data, and the Dosage and Treatment Emergent Symptoms Scale (DOTES) and Treatment Write-in Scale (TWIS) for safety data.

Results

Of the 12 participating centers, only 8 furnished sufficient data for analyses (Table 2). Three centers (Nos. 3, 4, and 7) studied inpatients; all the others studied outpatients. Two North American centers (Nos. 8a and 8b) and one European center (No. 9) have been excluded from the analyses because of the small number of patients enrolled. Due to a delay in obtaining permission to conduct the trial

TABLE 2

Assessment Instruments and Schedule

	On Entry	Past Pretreatment Day	Day 7	Day 14	Day 21	Day 28[a]
Adult Personal Data Inventory (APDI)[b]	X					
Prior Medication Record (PMR)	X					
Clinical Examination	X					
Clinical Global Impression (CGI)[b]	X	X	X	X	X	X
Brief Psychiatric Rating Scale (BPRS)	X	X	X	X	X	X
Hamilton Rating Scale for Depression (HAM-D)[b]	X	X	X	X	X	X
Self-Report Symptom Inventory (SCL-90)		X	X	X	X	X
Self-Rating Depression Scale (SDS)		X	X	X	X	X
Dosage Record and Treatment Emergent Symptom Scale (DOTES)[b c]	X	X	X	X	X	X
TESS Write-in (TWIS)[b c]	X	X	X	X	X	X
Concurrent Medication		X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Hematology/Biochemistry		X		X		X
Drug Level		X		X		X
Electrocardiograph	X			X		X
Patient Termination Record (PTR)[b]						X
Investigator Summary						X

[a] Or if the patient leaves the study before day 28.

[b] Assessment instruments utilized in the present analysis.

[c] And at each change of dosage or if new important symptoms should emerge.

from the Italian authorities, the Pisa center (No. 10) conducted a separate PBO-controlled trial under the same protocol; the Pisa data are not included in these analyses.

Of the 481 enrolled patients, 448 had at least two evaluations during the drug intake period (Table 1) and have been included in the APDI, PTR, and DOTES analyses.

The distribution of the patients according to their major demographic characteristics (APDI)—age, sex, marital status, prior treatments, significant medical conditions, and previous hospitalizations—is approximately the same in the three treatment groups. The less-than-1-year duration of the actual episode is less (but not significantly so) in the PBO group (Table 3).

Data from the PTR (Table 4) provide significant differences among the three groups. The duration of treatment is approximately the same, but the reasons for premature termination differ significantly between active drugs and PBO. As can be expected, in the PBO group premature interruptions for ineffectiveness are relatively more frequent than in the two active drug groups, whereas the opposite is true for the adverse reactions. There were no differences among the groups in the number of patients requiring hypnotics, but a trend in suggesting mainly that patients on active drugs required more gastro-

TABLE 3

Demographic Summary (APDI)

Variables	FLUVOX	IMI	PBO
Total Number of Patients:	161	153	149
Age: Mean (± SD)	42.7 (± 13.7)	41.3 (± 13.8)	42.1 (± 11.8)
Min. - Max.	19 – 70	10 – 70	21 – 68
Sex: Female	99 (61.5%)	92 (60.1%)	95 (63.8%)
Marital Status: Ever Married	131 (81.4%)	104 (68.0%)	119 (79.9%)
Prior Treatments: Any Prior Treatment	102 (63.4%)	107 (70.0%)	99 (66.4%)
Duration of Present Episode: Less than 1 year	108 (67.1%)	103 (67.3%)	111 (74.5%)
Significant Medical Conditions: Any Condition	20 (12.4%)	11 (7.7%)	21 (14.1%)
Previous Hospitalization: None	117 (72.7%)	108 (70.6%)	104 (69.8%)

TABLE 4

Patient Termination Summary (PTR) — 4 Weeks' Treatment

Variables	FLUVOX	IMI	PBO
Total Days in Study: Mean (± SD)	23.3 (± 7.6)	23.9 (± 7.3)	24.5 (± 6.4)
Premature Termination*			
Ineffectiveness	12	10	26
Improvement	2	3	1
Adverse Reactions	19	17	5
Unrelated to Treatment	21	17	17
Completed 28 Days of Treatment:	102 (63.4%)	104 (63.0%)	100 (67.1%)
Ancillary Medications:			
Gastrointestinal Preparations	24 (14.9%)	21 (13.7%)	9 (6.0%)
Hypnotics	77 (47.8%)	72 (47.1%)	63 (42.3%)
Given the choice, would you continue on this study medication (1)			
Mean (± SD)**	2.24 (± 1.4)	2.11 (± 1.5)	1.74 (± 1.5)

* Chi-square = 19.08, $p < 0.05$

** Analysis of variance regular: $p < 0.05$

(1) Scale Points:

0 = Definitely No
1 = Inclined to Say No
2 = Undecided
3 = Inclined to Say Yes
4 = Definitely Yes

intestinal preparation. To the question: "Given the choice, would you continue on this study medication?" the investigators' answer is significantly in favor of the two active drugs.

The mean daily dosage of the three treatments is similar in both the week-by-week analysis and in the overall treatment period. Maximum dosage is reached in the third week (Table 5). The most frequent side effect (rated at least moderate) observed in the FLUVOX group is "nausea." "Dry mouth," "sweating," and "dizziness" are more frequent in the IMI group (Table 6).

These preliminary findings allow us to discriminate between the two active compounds and PBO and, on the basis of side effects, to differentiate FLUVOX from IMI.

TABLE 5

Mean Daily Dosage

	Fluvoxamine		Imipramine		Placebo	
	Mg	(No. of Capsules)	Mg	(No. of Capsules)	Mg	(No. of Capsules)
Week 1	115.03	2.3	118.09	2.4	124.83	2.5
Week 2	157.16	3.1	161.48	3.2	184.17	3.7
Week 3	177.47	3.5	176.56	3.5	203.70	4.1
Week 4	134.55	2.7	144.20	2.9	153.52	3.1
All Periods	144.95	2.9	149.06	3.0	166.02	3.3

At this point, rather than describe further the standard output of the BLIPS/BDP system, we would rather emphasize the flexibility and potential for rapidly and easily looking at the data in different ways. We will demonstrate the possibilities offered by the BLIPS/BDP system in handling and analyzing the pooled data of a large multicenter trial.

The major statistical procedure employed in the following analyses was a two-way analy-

TABLE 6

Emergent Signs and Symptoms (Moderate and Severe)

	FLUVOXAMINE	IMI	PBO
No. of Patients	161	153	149
Dry mouth	8	31	10
Nausea	29	9	6
Somnolence	17	15	2
Insomnia	15	10	6
Constipation	13	11	5
Headache	14	6	10
Sweating	7	13	4
Dizziness	2	15	4
Agitation	8	8	3
Anorexia	6	4	4
Tremor	4	7	2
Hyperkinesia	4	4	4
Hypokinesia	8	2	1
Hypotension	1	6	3
Manic reaction	1	4	2

TABLE 7

CGI — Severity of Illness: Results of Two-Way Covariance Analysis

	Intent-to-Treat Analysis			Efficacy Analysis		
	Score* Initial	Score* Final	Percent of Improvement	Score* Initial	Score* Final	Percent of Improvement
Fluvoxamine	4.41	3.26	26.1	4.46	2.99	33.0
Imipramine	4.47	3.29	26.4	4.47	3.08	31.1
Placebo	4.51	3.62	19.7	4.54	3.53	22.3**

*Standardized scores.

**Analysis of covariance: FLUVOX PBO $> p < 0.05$
IMI PBO $> p < 0.05$

TABLE 8

CGI — Global Improvement and Efficacy Index*: Final Scores

	Intent-to-Treat Analysis		Efficacy Analysis	
	Global Improvement Score	Efficacy Index Score	Global Improvement Score	Efficacy Index Score
Fluvoxamine	2.67	1.95[a]	2.30[b]	2.23[c]
Imipramine	2.74	1.72	2.49	1.73
Placebo	3.01	1.80	2.85	1.90

[a] Analysis of variance: FLUVOX>IMI $p < 0.05$

[b] Analysis of variance: FLUVOX>IMI $p < 0.05$

[c] Analysis of variance: FLUVOX>IMI $p < 0.05$
FLUVOX>PBO $p < 0.05$

*The Efficacy Index from the CGI combines a global rating of improvement and side effects.

sis of covariance ANCOVA where drug conditions and centers were the two factors in the design. For the efficacy data we performed two types of analyses "in parallel": the first includes all patients with at least two evaluations on drug (the so-called "intent-to-treat analysis"); the second method, which we call "efficacy analysis," is limited only to cases with at least 14 days' medication and not withdrawn after the 14th day because of possible study drug-related concurrent signs and symptoms, or for reasons unrelated to study drug (Table 1). With the BLIPS/BDP system, it is possible to perform the two types of analysis, one immediately after the other, by simply giving the computer the different selection criteria.

The score on the CGI item "severity of illness" is approximately the same in the three treatment groups (intermediate between "moderately" and "markedly ill") at the beginning of the treatment; the final score is close to "mildly ill" for FLUVOX and IMI and close to "moderately ill" for PBO in the intent-to-treat analysis. In the efficacy analysis, these differences are more marked and they reach the statistical significance in favor of the two active compounds (Table 7). Although significant differences were found between centers (Centers 2 and 3 in both analyses, Centers 3 and 6 in the efficacy analysis), no interactions between centers and drugs emerged.

For the CGI item "global improvement" the improvement is greater with FLUVOX and IMI than with PBO, but the statistical significance is reached only in the "efficacy analysis" where the FLUVOX- and IMI-treated patients are rated approximately "much improved" and the PBO-treated patients rated "minimally improved" (Table 8). The results of Center 2 are significantly different from all other centers except for Center 7, but no significant interactions between centers and drugs exist.

At the end of treatment, the number and percentage of patients judged as "much" or "very much improved" are greater in the FLUVOX and IMI groups than in the PBO group. These differences are greater (chi-square analysis) in the efficacy analysis (Table 9). The analysis of the CGI item "efficacy index" seems to favor FLUVOX over PBO and especially over IMI (Table 8).

TABLE 9

CGI — Global Improvement: Number and Percentage of Improved Patients

		Intent-to-Treat Analysis				Efficacy Analysis			
		FLUVOX	IMI	PBO	Total	FLUVOX	IMI	PBO	Total
Much or Very Much Improved	No.	84	72	53	209	79	65	51	195
	%	52.2	48.3	37.1	46.1	65.8	54.6	41.5	53.9
Minimally Improved	No.	31	32	38	101	20	22	34	76
	%	19.3	21.5	26.6	22.3	16.7	18.5	27.6	21.0
No Change or Worse	No.	46	45	52	143	21	32	38	91
	%	28.6	30.2	36.4	31.6	17.5	26.9	30.9	25.1
Total		161	149	143	453	120	119	123	362

The above examples give an idea of the utility of the BLIPS/BDP system in analyzing data derived from clinical trials of psychotherapeutic agents. However, the flexibility of this system enables us to perform many other analyses with very few additional simple external commands.

If, for instance, we want to study how the initial severity influences the results of treatment, we can stratify patients according to the initial severity on a selected assessment instrument and analyze the resulting groups as new cohorts. In this example, we used the initial HAM-D total score as an index of severity. In this study, 25.75 is the mean initial total score of the HAM-D and 5.72 the standard deviation (SD). We therefore consider "mildly" severe patients to be those with a score less than or equal to 20 (mean minus SD), "severe" patients with scores equal to or more than 31, and "moderately" severe patients with scores between 21 and 30. The ANCOVA (in this case drug conditions and level of severity are the two factors in the design) demonstrates that the pattern of improvement is almost the same for all analyzed items and factors (CGI and HAM-D). The improvement, however, is greater for the FLUVOX- and IMI-treated patients than for the PBO-treated patients. As is clearly seen in Table 10, the greater the initial severity, the greater is the improvement.

TABLE 10

Stratification by Initial Severity of HAM-D Total

		Total HAM-D Score*		Percent of Improvement
		Initial	Final	
Total Sample	F	25.61	13.41	47.6
	I	25.92	13.74	47.0
	P	25.60	17.34	32.3**
Mild	F	17.86	13.42	24.9
20	I	18.43	15.63	15.2
	P	17.18	17.62	-
Moderate	F	25.62	14.18	44.6
$21 \leq 30$	I	25.08	13.52	46.1
	P	24.66	16.87	31.6
Severe	F	34.53	10.24	70.3
31	I	34.96	12.74	63.6
	P	34.05	19.20	43.6

F = Fluvoxamine: I = Imipramine: P = Placebo
*Adjusted scores.
**Analysis of covariance: $F > P$ - $p < 0.05$
$I > P$ - $p < 0.05$

TABLE 11

Stratification by Treatment Setting: HAM-D Retardation Factor

		Score*		
		Initial	Final	Improvement
Total Sample	F	2.38	1.23	48.3
	I	2.20	1.26	42.7
	P	2.29	1.62	29.3**
Inpatients	F	2.77	1.18	57.4
	I	2.54	.98	61.4
	P	2.63	1.44	45.2
Outpatients	F	2.18	1.26	42.2
	I	2.05	1.38	32.7
	P	2.14	1.69	21.0
Total Sample:				
Inpatients		2.65	1.20	54.7
Outpatients		2.12	1.45	31.7***

F = Fluvoxamine: I = Imipramine: P = Placebo
*Adjusted scores.
**Covariance analysis: $F > P$ - $p < 0.05$
$I > P$ - $p < 0.05$
***Covariance analysis: Inpatients > Outpatients - $p < 0.05$

As both inpatients and outpatients are included in this trial, one of the obvious analyses would be the comparison of results between the inpatients and the outpatients. With very few instructions, we stratified patients according to the treatment setting and again ran the two-way ANCOVA. The results demonstrate that the initial severity of the analyzed items and factors on CGI and HAM-D is higher in the inpatients than in the outpatients. This is shown in Table 11. For the HAM-D "retardation" factor, these differences are statistically significant.

Conclusions

In this paper, data from a multicenter international clinical study on FLUVOX have been presented to exemplify both the problems raised and the potential information that can be obtained using a comprehensive and standardized system of analyses.

The BLIPS/BDP standardized output provides a clear profile of FLUVOX from its efficacy to its safety through the comparison with IMI and PBO. Drug and center interactions, when present, are immediately in evidence, as well as possible limitations and inadequacies of the design or of the conduct of the study.

Once the cleaned data are stored in the computer data bank and processed, the first standard analyses can be presented to the principal investigators. This will stimulate suggestions for specific analyses. Multicenter trials, because of the number of subjects and centers, offer the possibility of a more complete study of a drug's profile as well as of the population in the study, and of the instruments employed in the ratings. In this way, there can be a complete exploration of the data which provides not only psychopharmacological information but also information on clinical, psychopathological, epidemiological, and transcultural aspects of the population under study. The BLIPS/BDP accomplishes this by a completely automated procedure, capable of answering a wide array of questions. Moreover, the standard outputs can be interpreted with great facility because they are in a uniform format.

Frequently, investigators collect data which are grossly underused in terms of the clinical information being analyzed. For this reason, we strongly recommend that multicenter clinical studies should be planned with a view to using an established proven data handling, processing, and documenting system.

In conclusion, we have shown that a multicenter international study can be successfully accomplished using customary pharmaceutical industry procedures and monitoring linked to an established standardized documentation system.

The Design and Conduct of the Upjohn Cross-National Collaborative Panic Study

Gerald L. Klerman, M.D.,[1] James H. Coleman,[2] and Robert P. Purpura, M.D.[3]

The decision by the Upjohn Company in the early 1980's to initiate a large and complex study came from two scientific developments: 1) new developments in understanding the psychopathology, diagnosis, and classification of anxiety disorders, and 2) the early experience with alprazolam, a new triazolobenzodiazepine.

New Developments in Psychopathology, Diagnosis, and Classification of Anxiety Disorders

The continuum model of anxiety (as shown in Figure 1) had been the dominant view of anxiety states for many decades. This model proposed a continuum from normal fears and tension through intermediate stages of stress reactions, to full-blown anxiety neurosis (whose most severe form was agoraphobia). From World War I through the 1970's, most clinicians, whether of biological, behavioral, or psychoanalytic persuasion, accepted this continuum model of anxiety. This model emphasized the gradients of severity and was built upon the experience of anxiety and fear in everyday situations and in adaptation, and evolution.

This model drew upon the psychological research of Cannon (1936) on "fight or flight" and his demonstration of the role played by the autonomic sympathetic nervous system. Later, biological research was extended by Selye to include the hypothalamic-pituitary-adrenal-cortical system as a mediator of "stress."

In the 1960's, a number of observers challenged this continuum view. Roth and associates (1960) in England described the "phobic-depersonalization syndrome," sometimes called the "calamity syndrome." West and Dally (1959) and Sargant (1960) described a group of atypical depressives with predominant anxiety symptoms who appeared responsive to monoamine oxidase inhibitors (MAOIs). In the United States, Klein and his associates (1964) described the failure of chlorpromazine to influence severe phobic anxiety and reported that imipramine, tricyclics, and antidepressants improved panic episodes and agoraphobia.

Further research demonstrated the value of two classes of antidepressant drugs: MAOIs and tricyclic antidepressants, in contrast to the limited efficacy of conventional benzodiazepines (Sheehan, et al., 1980).

As a result of these observations, the proposal was made (*see* Figure 2) to separate agoraphobia and panic disorder from other forms of anxiety disorders and to group these conditions together. These proposals were partially embodied in the Diagnostic and Statistical Manual—3rd ed., 1980 (DSM-III) classification of Anxiety Disorders, which represented a significant departure from previous U.S. classifications as in the DSM-I, DSM-II, ICD-8, and ICD-9.

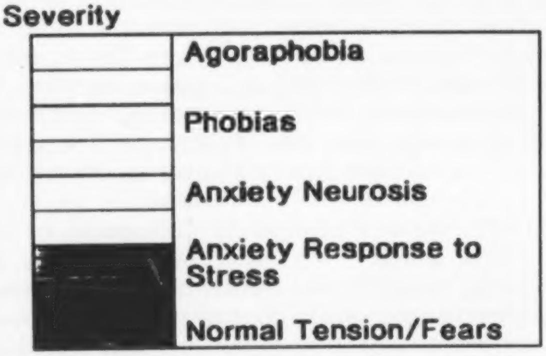


FIGURE 1. Continuum of anxiety.

---

[1] George Harrington Professor of Psychiatry, Harvard Medical School and Director, Stanley Cobb Research Laboratories, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114. (Now at Department of Psychiatry, Cornell University Medical Center, New York, NY 10021.)

[2] Coordinator, Worldwide Panic Disorder Program, The Upjohn Company, Kalamazoo, MI 49001.

[3] Medical Manager, Psychopharmacology Research Unit, The Upjohn Company, Kalamazoo, MI 49001.

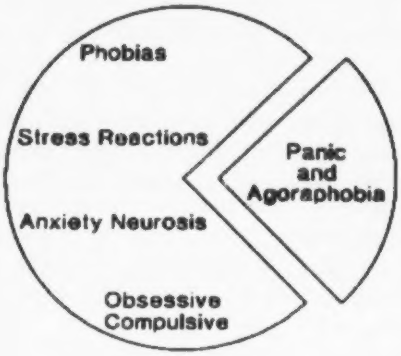


FIGURE 2. Panic and agoraphobia—separated.

In this new view, the central feature of the clinical psychopathology is the panic attack. The panic attack involves not just greater intensity of anticipatory anxiety, fears, and tension, but is a discrete time-limited episode with sudden onset of intense dread, accompanied by bodily symptoms suggestive of automonic arousal such as sweating, palpitations, tremor, and fear of losing control, going crazy, fainting, or dying.

There has been considerable controversy around the nosologic status of panic attacks, but also a continuing disagreement over the relative roles of drug treatment, MAOIs, tricyclics, beta-blocking agents, benzodiazepines, and also the efficacy and role of behavior therapy, particularly desensitization and exposure in vivo and flooding.

Alprazolam: A New Triazolobenzodiazepine

The chemical structure of alprazolam represents a modification of the conventional benzodiazepine ring structure by the addition of a triazolo group to the ring. The Upjohn Company developed a number of triazolo compounds, notably triazolam (Halcion) and alprazolam (Xanax). Trazadone (Desyrel), which has demonstrated antidepressant action, is also a triazolo compound.

Preliminary reports by Chouinard et al. (1982) suggest the value of alprazolam in panic disorder and agoraphobia, and these observations were confirmed in two controlled trials reported by Carr and Sheehan (1984).

The evidence presented by Ballenger at this meeting indicates the efficacy of alprazolam over placebo in the acute treatment of panic attacks and agoraphobia. Still unresolved is the question of the relative efficacy of alprazolam against other benzodiazepines, particularly diazepam. Experienced clinicians who have worked with patients with panic and agoraphobia are of the opinion that the efficacy of alprazolam is far superior to that of other benzodiazepines. Most patients entering recent trials with MAOIs, alprazolam, and tricyclics have had extensive prior treatment with benzodiazepines with limited success.

Should further studies demonstrate the superiority of alprazolam to other benzodiazepines, in what way can we account for this action of alprazolam? The efficacy of alprazolam in panic disorder could be due to pharmacokinetic or pharmacodynamic mechanisms.

There are suggestions that alprazolam has pharmacodynamic effects on the down-regulation of beta-blocking receptors. If substantiated, this pharmacologic profile of alprazolam would share certain similarities with antidepressant drugs such as tricyclics. Alprazolam has been effective in mild to moderate forms of depression, but not in severe endogenous, melancholic, or psychotic forms (Laakmann, in press).

The differences between alprazolam and other benzodiazepines may be pharmacokinetic. Assuming a ten-to-one equivalence between diazepam and alprazolam, 6 to 8 mg of alprazolam, the dose used in studies of panic disorder, would be the equivalent of 60 to 80 mg per day of diazepam, a dose which is seldom tolerated by most ambulatory patients.

TABLE 1

Upjohn Cross-National Project Centers

United States	New York City, New York
	Iowa City, Iowa
	Torrance, California
	Rockville, Maryland
	Charleston, South Carolina
Canada	Montreal
	Toronto
Australia	Melbourne

Studies comparing alprazolam with diazepam at equivalent doses are underway and should help resolve this question.

Goals of the Upjohn Cross-National Panic Project

In 1982, the Upjohn Company initiated a worldwide panic program (Purpura, in press) which includes a number of interrelated pharmacologic, biologic, and clinical studies. Within the large program, the Cross-National Collaborative Panic Study focuses on clinical efficacy and safety.

The major goal of the Cross-National Panic Study is to assess the efficacy and safety of alprazolam in the treatment of panic disorder and agoraphobia. Subsidiary goals include: 1) better understanding of the psychopathology and diagnosis, and 2) improved means of diagnostic assessment and of evaluation of change in clinical trials of anxiety disorders.

Another subsidiary goal is to develop improved collaboration between industry, academic medical centers and universities, and governmental agencies in the U.S. and other countries.

To achieve these goals, the Cross-National Project is being conducted in two phases.

The *First Phase*, eight centers collaborating on the common design, which involves a comparison of alprazolam versus placebo, has been completed and results are being reported today. The eight centers are shown in Table 1 and include five in the U.S. (New York City, N.Y.: Iowa City, Iowa; Torrance, California: Rockville, Md.: and Charleston, S. Carolina), two in Canada (Montreal and Toronto), and one in Melbourne, Australia. Over 500 patients have been studied for an 8-week period in these eight centers. The dose schedule was a fixed, flexible dose with the attempt that all patients receive 6 mg per day of alprazolam, a dose considerably higher than previously used in studies of anxiety and depression. Diagnostic consistency is accomplished by the use of the Structured Clinical Interview for DSM-III Diagnosis (SCID), developed by Spitzer and Williams (unpublished).

In the *Second Phase*, alprazolam is being compared against placebo and against a standard drug, imipramine. The choice of imipramine as a standard drug was a difficult one, inasmuch as no drug treatment has been approved by the FDA for this condition. In the case of depressions, the tricyclic drug is the standard drug. In the case of beta-blocking agents for cardiovascular illness, propranolol is the standard drug. However, in the case of panic disorder and agoraphobia, no drug had been approved by the FDA, and there was no consensus in the field as to what should be the standard drug; conventional benzodiazepines, such as diazepam (Valium), a tricyclic, or an MAOI. Imipramine was chosen because of the extensive evidence for its efficacy (Liebowitz, in press).

This Second Phase of the study is now underway in 12 countries, and by the spring of 1986, approximately 1,000 patients will have been entered into treatment.

The First Phase and Second Phase studies utilize the same diagnostic criteria (modified from DSM-III), the same structured interview (SCID-up), and the same battery of scales and ratings for the assessment of clinical improvement and adverse effects. All data are encoded on upscan forms and sent to a central data processing facility in Kalamazoo, Michigan.

Assurance of Diagnostic Standardization and Quality Control

In any clinical trial, attention must be given to standardization of procedures for the selection of patients, randomization, assessment of change, control of concurrent medication, etc. In multicentered trials, particularly those which involve more than one nation, these considerations become all the more paramount. In addition, in this trial, since there was some degree of controversy over the validity of the diagnostic concept of panic disorder and its relationship to agoraphobia, considerable attention had to be given to the techniques to assure standardization of diagnostic assessment.

Among the techniques utilized, the following are noteworthy:

1) A very detailed protocol and procedures manual was prepared. The attempt was made to anticipate as many contingencies as possible, so as to provide explicit instructions to

the investigators, and to increase the likelihood that the study would be conducted in a similar way at all eight sites.

2) To ensure diagnostic consistency, a modification of the DSM-III criteria for panic attack, panic disorder, and agoraphobia were developed as part of an ongoing consensus project among the investigators at the eight sites, and involve a large group of consultants who have been active in the field.

3) A structured interview, the SCID-up, was commissioned for the explicit purpose of standardizing the interview procedure, so as to reduce information variance and criterion variance. Drs. Spitzer and Williams at the New York State Psychiatric Institute and Columbia University, College of Physicians and Surgeons, developed the SCID-up to operationalize the criteria for the study, including inclusion and exclusion criteria. The SCID-up has been translated into a number of languages for the participating countries in phase two, and extensive training and reliability exercises have been conducted.

4) A 1-week training workshop was held in Boston in 1983 for the first-phase investigators, and in Pisa, Italy, in November of 1983 for the second-phase investigators. During this training exercise, the protocol was reviewed in great detail, the concept and criteria for panic attack and agoraphobia were discussed extensively, video tapes were viewed, the SCID-up was explained, and experience was gained in the use of the SCID-up in interviews with patients from local clinical settings.

5) Special attention was given to provide operational definition and systematic assessment of panic attacks. Since the reduction of panic attacks was the major outcome of the study, it was necessary to devise a new instrument. Based upon Dr. Sheehan's previous experience, with assistance from consultants (particularly Drs. Spitzer and Williams), a detailed assessment of panic attack was devised which incorporated distinctions between spontaneous and unexpected panic attacks and situationally provoked panic attacks and limited symptom attacks, and these were further distinguished from anticipatory anxiety. In addition to the physician-guided ratings, each patient completed a weekly log in which daily records were kept of the number, intensity, and duration of attacks, medication taken, and activities outside of the home.

6) As a further assurance of systematic standardization in quality, a quality assurance program was instituted in which teams of two consultants not directly involved in any of the clinical sites were recruited and trained and then made on-site visits to each of the sites at least twice during the conduct of the trial. During these visits, the records were reviewed for diagnostic consistency, and interviews with patients were observed and assessed.

Organization of the Study

The overall project, including the two phases, is coordinated by Mr. Coleman and Dr. Purpura of the Upjohn Company. I serve as a consultant.

In addition, there is a *Study Review Committee* chaired by Dr. Daniel X. Freedman which operates similarly to operations committees in VA cooperative studies, namely, it is unblinded and periodically reviews the progress of the study and evidence as to indices of safety and efficacy, in order to terminate a study for ethical reasons either because of the adverse effects which pose risks to the patient or the evidence of overwhelming efficacy which would lead to compromising the needs of patients exposed to placebo. This group also advises informally on matters of research design, statistics, and interpretation of findings.

For each two phases of the study, a *steering committee* composed of the senior investigators and co-chaired by Mr. Coleman and Dr. Klerman meets periodically to review decisions and protocol, to plan data analyses, and to monitor progress. In addition to the meetings two or three times a year, monthly teleconference calls provide for ongoing discussion of issues in the conduct of the trial, management of possible complications, and to ensure data processing and data analysis.

Training sessions have been held for each phase. The phase-one investigators met in Boston, Massachusetts in February 1983, for 1 week to review the protocol and to obtain training and experience in the use of a structured interview, the SCID.

Similar training sessions for the second phase of investigators were held in Pisa, Italy, in November 1983.

Data Processing and Data Analysis

This study has generated considerable amounts of data. Data processing is facilitated by the use of upscan forms for primary entry of data. Manual editing is conducted by the Upjohn Company and the data is entered into a computer in Kalamazoo, Michigan. Once the data processing has been completed and an edited tape is prepared, analyses are conducted at two sites — Kalamazoo, Michigan, and Massachusetts General Hospital, Boston, Massachusetts. The primary responsibility of the group at the Upjohn Company in Kalamazoo is the conduct of analyses to ensure proper information for the NDA submission to the FDA for the expected indication of treatment of panic attacks. Analyses primarily for scientific value for research undertaken by the investigators is conducted at the Massachusetts General Hospital under the leadership of Philip Lavori, Ph.D., and myself. Decisions as to scientific publications are made by the principal investigators at their respective steering committees. The Upjohn Company does not assume responsibility for scientific presentation or publication, although it has underwritten a considerable amount of the cost required for statistical analyses, preparation of graphic material, and secretarial assistance.

Conclusions

The findings to be reported here indicate the success of the overall design and the procedures utilized to ensure standardization of diagnosis and maintenance of the protocol across multiple sites in three different countries. It is expected that these procedures and techniques will prove useful in the second-phase study. Inasmuch as the second-phase study involves at least 12 different countries with multiple languages, cultural, and professional traditions, the attention given to diagnostic specification and careful assessment should prove helpful.

Preliminary experience indicates that over the cou[illegible] of the 2 1/2 years since this project was initiated, there have been greater acceptance and diffusion of the concept of panic attacks and panic disorder in relation to agoraphobia, and that participants in this study have increasingly accepted these diagnostic concepts as well as the importance of structured interviews and diagnostic algorithms for the selection of subjects, particularly in an area where there is controversy as to the validity of the diagnostic concept.

A clinical trial such as this one can serve as a partial validation of diagnostic concepts, in this case, panic disorder. The capacity to generate large numbers of cases in multiple sites and to demonstrate consistency of diagnosis and similarity of symptom pattern and of treatment response serves as an indirect validation of the concept of separating panic attacks from other forms of anxiety and linking panic attacks with agoraphobia as a diagnostic complex.

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder (DSM-III)*, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

Cannon, W.B. *The Wisdom of the Body*. New York: W.W. Norton, 1936.

Carr, D.B., and Sheehan, D.V. Panic anxiety: A new biological model. *J. Clin. Psychiatry*, 45:323–330, 1984.

Chouinard, G., Annable, L., Fontaine, R., and Solyom, L. Alprazolam in the treatment of generalized anxiety and panic disorders: A double-blind placebo controlled study. *Psychopharmacology*, 77:229–233, 1982.

Klein, D.F. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia*, 5:397, 1964.

Laakmann, G. Alprazolam vs. amitriptyline in the treatment of depressed outpatients: A randomized double blind trial. In: *Current Concepts in the Drug Treatment of Neurotic Disorders: Focus on Alprazolam*. New York: Churchill Livingstone, Inc. (In press)

Liebowitz, M.R. Alprazolam in the treatment of panic disorders. In: *Current Concepts in the Drug Treatment of Neurotic Disorders: Focus on Alprazolam*. New York: Churchill Livingstone, Inc. (In press)

Purpura, R.P. Controlled clinical trials. Paper presented at the Collegium Internatiónale Neuropsychopharmacologicum. (In press)

Roth, M. The phobic anxiety-depersonalization syndrome and some general aetiological problems in psychiatry. *J. Neuropsychiatry*, 1:293–306, 1960.

Sargant, W. Some newer drugs in the treatment of depression and their relation to other somatic treatments. *Psychosomatics*, 1:14–17, 1960.

Sheehan, D.V., Ballenger, J., and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch. Gen. Psychiatry*, 37:51–59, 1980.

Spitzer, R.L., and Williams, J.B. *Structured Clinical Interview for DSM-III (SCID-10/1/84).* (Unpublished)

West, E.D., and Dally, P.J. Effect of iproniazid in depressive syndromes. *Br. Med. J.*, 1:1491–1494, 1959.

Microcomputers in Clinical Psychopharmacology

CHAIRS: John E. Overall, Ph.D.
Department of Psychiatry
University of Texas Medical School
Houston, Texas

and

Joanne B. Severe, M.S.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Why a Statistical Package on a Micro?

MaryAnn Hill, Ph.D.[1]

The explosion in microcomputer sales promises to alter our society in fundamental way, changing the way we work, plan, and organize our lives. But without effective software, the microcomputer remains an engaging toy. Many researchers are currently evaluating the role of the micro in their research environment and are asking, "What kind of statistical software do we need?", "Will we have to give up familiar mainframe options?", etc.

There are several advantages in using a microcomputer to do the statistical analysis in research. Locating a micro close to the research team and its original data sheets facilitates data screening and also communication between the technical support staff and the research team. The technical support staff find it easier to focus on the data analysis, because on a micro the interface with the system is more "user-friendly"—allocation and naming of files is greatly simplified and there is no mainframe job control language (JCL). Even if the project is part of a large multicenter trial, much of the data monitoring and screening can be done on the micro and the clean data shipped or networked to the mainframe for final analyses with data from all centers. Finally, most project managers are happy to reduce mainframe computer bills.

Regardless of machine size, it pays to use a statistical package. Advantages include:

- — *Correct computations*. The well-known packages have been "debugged" over a broad range of applications, and they use appropriate algorithms—they do *not* simply code textbook formulas.
- — *More time for research*, because less time is spent programming.
- — It is easier to do *"good" data analysis* because many data screening features appear automatically—e.g., histograms for each group in a two-sample t test.
- — *One-time specification of data description instructions*. Variable names, formats, acceptable range limits, flags for missing data, transformations, etc. do not need to be tailored for each individual analysis.
- — *Documentation and help facilities*. The major package distributors provide extensive manuals, short courses in data analysis, and help via telephone. You are not stuck because your programmer disappears to Tahiti.

---

[1] Department of Psychiatry, UCLA School of Medicine, West Los Angeles VA Medical Center (Brentwood Division), and BMDP Statistical Software, Inc., Los Angeles, CA 90025.

— The use of packaged software *facilitates communication of results* when submitting grant proposals and papers to refereed journals, since the methods are well known and documented.

Unfortunately, much of the statistical software for the micro is woefully inadequate. A data analyst needs a wide spectrum of techniques that can be applied easily to a collection of data. If I were called in to consult with your research team, I would need access to a number of features, all of which are currently available on an IBM PC XT or AT (and compatibles). I do not intend to present a detailed explanation of the statistics, but hope to impart a flavor of the breadth of supports required for proper data analysis. From these examples, I hope that you will understand my concern when a research group shows me preliminary results consisting of nothing but means, standard deviations, *F* statistics, and *p* values.

In addition to statistical supports for data analysis, packages often have data manipulation features that merge files and functions that extract information from nonrectangular files. Without such features on a micro, a longitudinal study would be seriously hampered.

Software Features for Data Analysis

Many of the features I would hope to find on your micro are needed for data screening. The term "screening" indicates not only finding errors and inconsistencies in the data, but also ensuring that the data conform to assumptions necessary for subsequent analyses.

```
    TREATMENT                        CONTROL
     x                                x
    xx                                xx
   xxxx                               xxx x
   xxxxx x                            xxxx x       x
MIN--------------MAX            MIN--------------MAX
                                        case no
                                                   -
                                           max       24

Ho:  μT - μC            t tests
                        p         = .0048
                        p(trim)   = .0007
```

H_0: $\mu_T - \mu_C$

FIGURE 1. Does the presence of an extreme value change our conclusions about differences in group means?

```
                 **************
HISTOGRAMS FOR * HAMILTON *
                 **************

     DOCTOR A          DOCTOR B          DOCTOR C
48
45
42
39   *
36
33   *                                   **
30   ***               *                 ***
27   M*                                  **
24   *                 ***               M*
21   **                **                **
18   *                 M*                ***
15                     ***
12                     **
 9                     *
 6
 3
```

FIGURE 2. After weeks of training, why did one doctor's ratings differ? The midpoints of histogram intervals for Hamilton depression scores are printed along the left. Each asterisk represents an observation.

Screening is not one set of procedures carried out prior to the analysis—each stage of the data analysis uncovers information that affects later steps. In sizable studies, the primary analysis of interest may consume 5% of the staff time and computer costs, while data screening takes 95%. The data analyst will want to check for recording errors and compliance to protocol, as well as assess the influ-

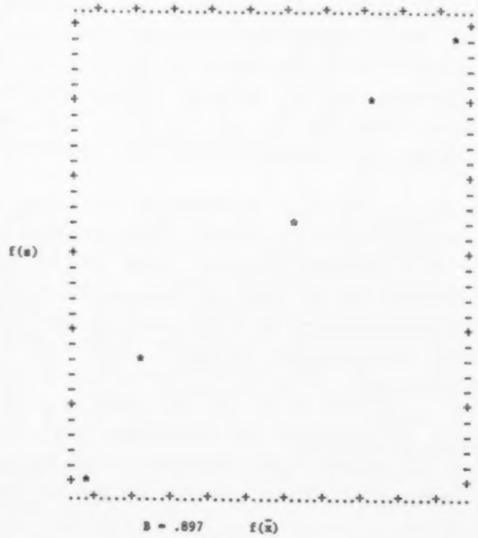


FIGURE 3. Box-Cox diagnostic plot for selecting power transformations to stabilize cell variances in an analysis of variance.

ence of outliers, distributional shape, subpopulations, patterns of missing observations, etc. Having a good statistical package at the research site makes it possible to check the data soon after they are captured—while it may still be possible to make corrections.

Testing group differences

The data analyst needs graphical displays, diagnostics, and alternative tests to help estimate the impact of problems encountered. In comparing responses for a treatment group and a control group, recording errors and other anomalies pop out when you scan small histograms for each group (high resolution graphics are not needed). In Figure 1, case 24, a control subject has a very high response. Does this real, but unusual response change our conclusions about group differences? Compare the results for the usual two-sample *t* test with those for the trimmed *t* test (note the trimmed test does not simply delete the smallest and largest values from each group—an adjustment is made to the standard deviations used in the denominator of the test statistic). Here both tests are significant.

The data analyst wants to study the distribution of values within each cell: scanning a printout of means and standard deviations may be far from adequate. In a recent project, one criterion for study entry was a Hamilton depression score of 18 or above. In a screening run of baseline scores, by doctor, (*see* Figure 2), 6 subjects appear unacceptable for study entry. This was distressing since the admitting psychiatrists had just spent weeks being trained on the anchor points for each individual scale item. So why did one doctor's rating differ? From a quick telephone call we learned that he made his evaluation using the previous 12 hours instead of the patient's history for the past week. Seeing a printout of means would not have had the same impact (the mean for doctor B was over 19).

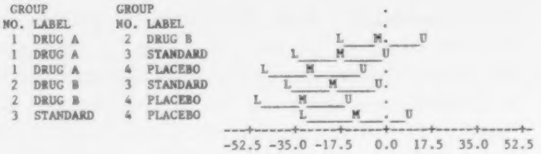


FIGURE 4. 95% confidence intervals for differences in group means with Bonferroni adjustment (means differ significantly when 0.0 is not in the interval).

As structure is added to the design—e.g., we study differences between treated and untreated subjects who are males and females, smokers and nonsmokers, etc.—the data analyst still wants to scan distributions within each cell for outliers and other anomalies. He also needs tests to assess the equality of cell variances, diagnostics to identify the appropriate power transformation, and extensions for the two-sample trimmed *t* test to analysis of variance (ANOVA). In an ANOVA, there should be no relation between the size of the cell standard deviation and the size of the cell mean—i.e., the cell variances should be equal. From information printed with the BOX-COX diagnostic plot (Figure 3), the data analyst would determine that the equal variance assumption is best satisfied if the data are analyzed in log units.

If an effect in an ANOVA is significant, the analysis is still not complete—the researcher wants to report which group means differ from one another. Probabilities from the usual two-sample *t* test cannot be used to find significant differences (since this test assumes that only one pair of means is compared). When many comparisons are made

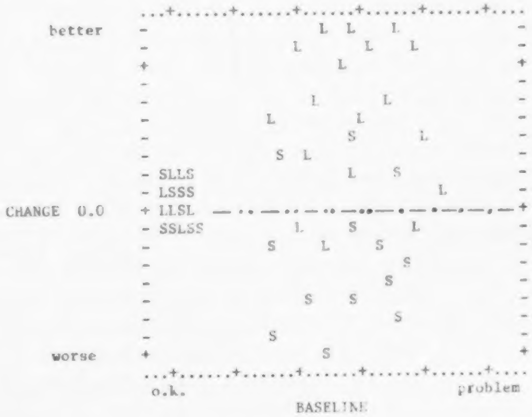


FIGURE 5. A bivariate scatterplot with symbols S and L denoting subjects on DRUG S and DRUG L, respectively, highlights the fact that the CHANGE in cardiovascular status after drug therapy becomes worse for a small subset of DRUG S patients; while several DRUG L patients improved.

simultaneously, the Bonferroni procedure can be used to protect against interpreting too many differences as significant. In Figure 4, confidence intervals (with Bonferroni adjustments) are displayed for differences among four means (DRUG A, DRUG B, STANDARD drug, and PLACEBO)—there is one line in the display for each pair. If zero is not in the interval (draw a vertical line down through the dots to 0.0), the pair has a significant difference in means. The difference between DRUG A and the STANDARD drug is questionable—the upper end of the confidence interval (U) touches the zero line, while the differences between both DRUG A and DRUG B versus PLACEBO are highly significant.

Relating two or more variables

When studying the relation among two or more variables, linear models (e.g., regression models and analyses based on correlations) may not be enough. By scanning a printout of correlations and regression coefficients, the researcher may not be able to see that a small subset of the subjects responds differently from the others. Bivariate scatterplots are useful in such situations, especially when symbols are used to identify subpopulations. In Figure 5, CHANGE in cardiovascular status after drug treatment is plotted against baseline values. Holter monitors were used to obtain the measurements. The majority of the subjects (more than 85% of the sample) exhibited no problems at baseline and no change after being on a drug. However, among those subjects with problems on baseline, several DRUG L subjects improved, while the status of several DRUG S subjects became worse.

Labeling subpopulations in scatterplots is also useful for identifying situations where the presence of subpopulations may mask or falsely enhance the relation between two measures. Two pairs of measures from the Fisher Iris data (Fisher) illustrate this point well. Pooling data for three types of iris flowers into one sample in Figure 6a, masks the relationship between sepal length and width—there is no relationship or at most a slight *negative* correlation. The points labeled "S" in the lower right are Setosa flowers—note how the relation for them appears to be *positive* (for the Setosa flowers alone, the correlation is +.74). In Figure 6b, when data are pooled for a plot of petal length versus width the correlation is .96; for Setosa alone, the correlation drops to .33.

When studying the intercorrelations of many variables—e.g., in the development of a questionnaire or a rating instrument—it is helpful to use a factor analysis to sort the rows and columns of a correlation matrix into blocks of similar values, and then to use a single character space to represent each correlation (*see* Figure 7, for a shaded correlation matrix for a 43-item questionnaire about smoking habits and emotional stress). The 13 smoking items appear highly intercorrelated, with the possible exception of the last item in the list, SMOKING 3. The question about

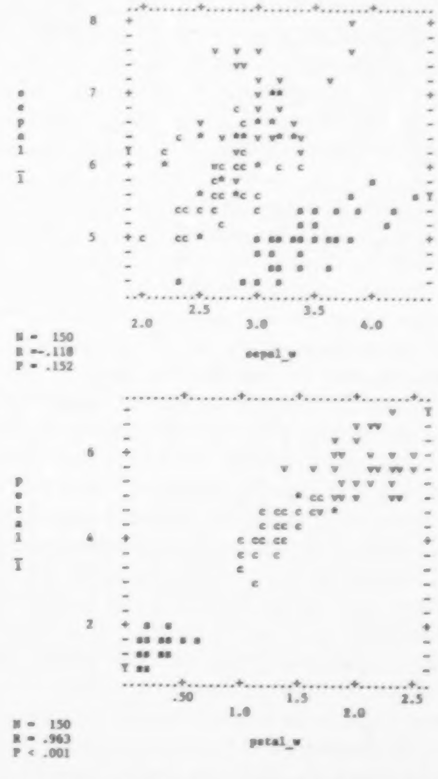
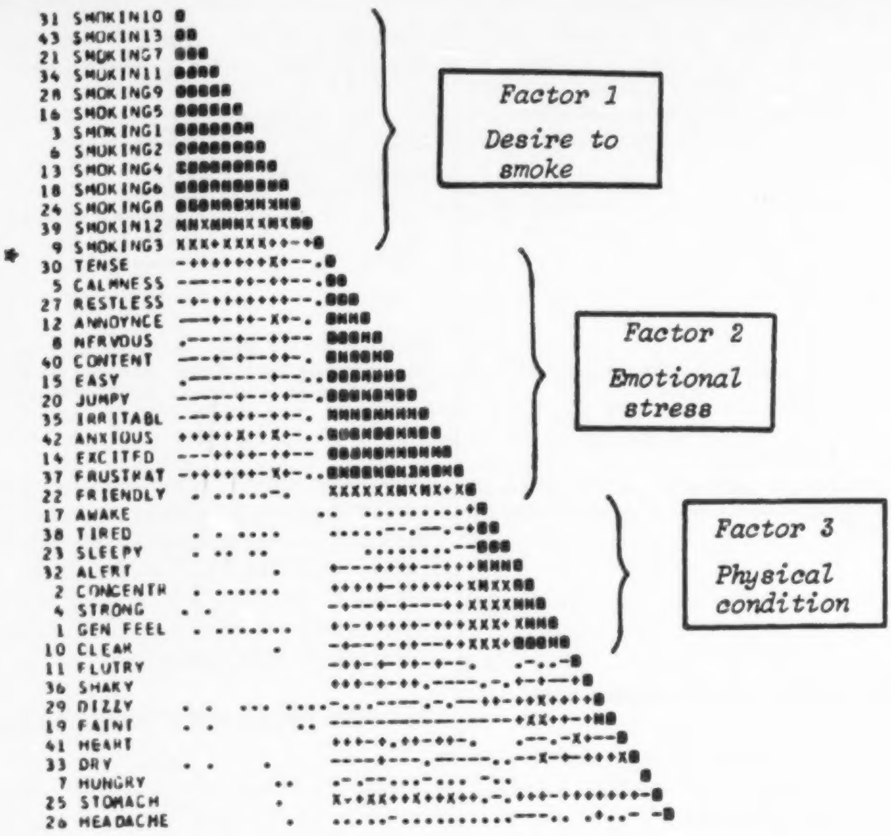


FIGURE 6. **a) The presence of subpopulations can mask a relationship: sepal length versus sepal width. b) For petal length and width, the presence of subpopulations gives a false impression of the strength of the relationship.**



```
THE ABSOLUTE VALUES OF
THE MATRIX ENTRIES HAVE BEEN PRINTED ABOVE IN SHADED FORM
ACCORDING TO THE FOLLOWING SCHEME
             LESS THAN OR EQUAL TO          0.109
 .     0.109   TO AND INCLUDING             0.217
 -     0.217   TO AND INCLUDING             0.326
 +     0.326   TO AND INCLUDING             0.434
 X     0.434   TO AND INCLUDING             0.543
 M     0.543   TO AND INCLUDING             0.651
 ■     0.651   TO AND INCLUDING             0.760
 ●                  GREATER THAN            0.760
```

FIGURE 7. A shaded correlation matrix is used to display the interrelations among items on a questionnaire. A factor analysis was used to cluster the rows and columns of the matrix.

hunger (HUNGRY—the third up from the bottom of the display) appears to have little relation to any of the other items.

When there are only two variables of interest, much can be gleaned from studying a scatterplot. However, as the number of variables in a multivariate analysis increases, additional diagnostics are needed to identify outliers and cases that exert unusual influence on the analysis. In the plot of Andrews-Pregibon statistics in Figure 8, unusual values of the statistic plotted on the AP1 axis indicate outliers in the dependent variable. One value at the top right stands apart from the others and should be checked. Unusual values on the AP2 axis are "leverage" points—cases that exert the greatest influence on the regression coefficients. Here two cases are separated from the others and identified as

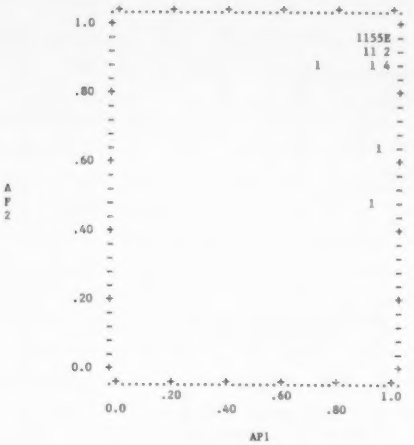


FIGURE 8. Andrews-Pregibon diagnostics AP1 and AP2 for identifying outliers and leverage points in multiple regression.

unusual. The case numbers for the three cases identified are printed in the output.

Studying the pattern of incomplete data

Missing data are often a nightmare for the data analyst. Procedures for dealing with incomplete data usually assume that values are missing randomly. The pattern of how values are missing should be investigated, since non-randomly incomplete data can bias results. One of the first things the data analyst does when searching for patterns is to print a display of the data with one character per variable: a blank if an observation is present: a letter "M" if missing. In Figure 9, the LAB chemistry measures tend to be missing as a set. In Figure 10, a multiway table is used for deciding if this pattern is related to the outcome, SURVIVAL. Over two-thirds of the survivors (68.5%) are missing all three lab values, while fewer than 10% of the non-survivors have data missing.

```
                      AS  D             LLL       S
                      GE..R....Y....AAA......M.....
                      EX  U             BBB       O
                          G             ...       K
                                        123       E
Subject          ______________________________________
   1                                    MMM
   3                                    MMM
   6                                              M
  12                                    MMM
  13                                    MMM
  15                                    MMM
  18                                    MMM
  20                   M
  23                                    MMM
  24                                    MMM
  25                                    MMM
  28                  M
  31                                    MMM
   .                                     .
   .                                     .
   .                                     .
```

FIGURE 9. A graphical display of the data matrix (using one character per variable) highlights the pattern of incomplete data.

```
                                            SURVIVAL
LAB_1      LAB_2      LAB_3               no     yes
_____________________________________________________
miss       miss       miss               9.7    68.5
                      present             .0      .0
                      ______________________________
           present    miss                .0      .0
                      present             .0      .0
           _________________________________________
present    miss       miss                .0      .0
                      present             .0      .0
                      ______________________________
           present    miss                .0      .0
                      present           90.3    31.5
_____________________________________________________
                                       100.0   100.0
```

FIGURE 10. Column percents in a multiway table for assessing the relation between SURVIVAL and the pattern of incomplete data for three lab chemistries.

Software Features for Managing the Data

Data in longitudinal studies often fail to conform to the nice tidy rectangle required for analyses based on classical statistics. Patients may have varying numbers of visits and different patterns of return across time. For example, it may be necessary to extract from a series of records the number of visits, total time on study, percent improvement for the clinical rating score, worst side effect score, drug dose for week prior to worst score, etc., for each patient. For analysis, the summary of the patient's clinical experience will need to be merged with laboratory results and patient history data.

The entry of patients into the study may be staggered over time, making it hard to visualize the pattern of return visits and the total time on study for members within each treatment group. In order to plan analyses, the data analyst needs this information. In Figure 11, a record map is displayed for a study where patients are asked to return weekly for evaluation (one computer record is generated for each return visit). Week-on-study is recorded on the horizontal axis, and each row represents the pattern of returns for a single patient over time. The drug code is used as a

```
ID                     WEEK
         5        15        25        35        45
    0        10        20        30        40        50
    +----+----+----+----+----+----+----+----+----+----+----+
 1  3333 333333444 44 44 4 42222222222222 22222222 22   2
 2   22222222222  2    2 2 2  2   2   24
 7   222222222222  222222222222 22 2 2 2222 2 2  2  2 2
 8   *2222 2   2   2     2  2 4 44
10  11111 1 1   1   1   1
12  11111111111111   1         1     1  1
14  33422222
16  111111111111
18  33333333 333  3333   3  33
19  111111111111111111442222222 22 22222 2 222 22 2222 22
20  11111111111111 1   1    1   1   1   1
21  333222222222 2 2   2 2   2 2   2     22 2 2  2
22  333333411111111111  4  4 444 44 444222222222 222 222
23   2222222    2   2    2   2    2
26  222222222222  41111111111 11 11 111   1   1 1 1   1
27   1111111.
28  22222222 2 22   2   2   2   2 2     .
29  3333 33333 3411 11 11111111111 1 1 .111 111111 1 11 1
30  1 111111
31  111 11111 11
33  3333 33333 3   3   3    .
36  33332222222222  2 2 222222  222 2 2 22  2 2 .
37  33 3
38  344411111111 1 1111111 1111.
46  1.
49  222444111 111 1111 1111
54  2222222 2 2222  22  2   2    2  2   2  2
56  11142222222222 22  2 2    22   2   2   2   2   2 2 22
57  1111111111111111 1111 1   1   1 1 1 1    1
59  222222 2222222 2   .
61  111111  1    1  1   1     .
63  22
68  222   2 2 2 2 2 2 2 2 2 2    2  2  2    2   2   2   2
69  11111111111 111111 11 1 1 1 1   1    1  1  1 1 1  1
71  22  22222 2 222 2 2 2 2 2 2 2 2 2 2 2  2  2 2   2 2
72  111111 111 1111 1 1 1 1 1 1 1 1  1  1   1 1  1 1
    +----+----+----+----+----+----+----+----+----+----+----+
    0        10        20        30        40        50
         5        15        25        35        45
```

FIGURE 11. Record map for clinical trial with weekly outpatient visits.

plot symbol; blanks mark missed visits. Subject 19 (*see* underlined row) was randomly assigned to drug 1 (the plot character is 1) and continued on it for 17 weeks; had 2 weeks of wash-out (code 4); and then was randomized to drug 2. It is immediately apparent that, as time on study increases, many patients drop out and the frequency of returns decreases.

With such a distribution of values across time it is hard to use a classic repeated measures design to test for differences among the drug groups. Instead, our strategy might be to extract information from each patient's set of records (the number of records varies by patient). This summary information would then form a rectangular file and be available for plots, histograms, analysis of variance, logistic regression, etc. The data for each patient might include clinical ratings (at baseline, 4 weeks, 8 weeks, and so on.), proportion of visits with side effects present, maximum dose, drug dose for week prior to worst side effects score, and within-subject correlation between dose and side effects.

Conclusion

A microcomputer can be an effective tool for data analysis, but only if adequate software is available. A statistical package for a micro must go far beyond the simple computations of commonly used statistics. Indeed, it must encompass most of the power of the standard mainframe packages.

Reference

Fisher, R.A. The use of multiple measurements in taxonomic problems. *Ann. Eugen.*, 7:179–188, 1936.

Microcomputerized Testing of Drug Effects on Divided Attention[1]

Joe E. Thornton, M.D.,[2] Joy L. Taylor, Ph.D.,[2] Elizabeth L. Gibson, M.A.,[2] Terry P. Miller, M.D.,[2] and Jared R. Tinklenberg, M.D.[2]

In this paper we describe the use of a microcomputerized, dual-task methodology to test drug effects on divided attention. This dual-task methodology is designed to be sensitive to psychoactive drugs and to be useful in research that entails repeated assessments of the same individual. The theoretical rationale for this approach is that drug effects may be especially discernible on pervasive, non-specific processes such as attention and may be most amenable to quantification on performance tasks that are attention demanding. Certain additional psychometric and technical features of these microcomputerized tasks which make them suitable for psychopharmacologic studies will also be discussed.

Methods

The essential feature of the dual-task method is that the subject must perform two activities simultaneously. In one version of this method, which is described below, the subject also performs each task individually to provide comparisons for the dual-task condition. The decrement in performance observed when the two tasks are done simultaneously, relative to the performance observed when they are done separately, provides a measure of the extent to which the available attentional capacity is exceeded.

In our basic dual-task procedure, the first task involves manipulating an x-y joystick to pursuit track a randomly moving target, which is displayed on a video screen. The subject manipulates this control stick up/right and left/right with the preferred hand. The target is a 1.5 cm horizontal line and the joystick position is displayed as a 1.5 cm vertical cursor line. The task is to maintain a "crosshair" configuration by keeping the middle of the vertical cursor line as close as possible to the middle of the randomly moving horizontal target line. The target moves at a maximal rate of about 6.6 cm/sec throughout an unmarked 12 × 18 cm rectangle, positioned at the center of a standard 42 cm diagonal video screen. The screen is approximately 50 cm from the subject's eyes.

The second task involves the continuous monitoring of visual probe stimuli embedded in the horizontal tracking target line. The stimuli are a pair of boxes, about 4 mm long × 5 mm high, at each end of the target line. They both blink in synchrony at a baseline rate of about 1 blink/sec. The subject presses the reaction button, which is held in the non-preferred hand, as soon as he or she notices an increase in blink frequency of the boxes (to 1.8 blinks/sec). This change occurs at quasi-random intervals, approximately 4 times per minute. The button press restores the blink frequency to baseline. The temporal perceptions required in this task and the relatively high rate at which the visual stimuli must be processed combine to enhance drug sensitivity. Both tasks are designed to be intrinsically uninteresting and subtle in their measurement of performance changes. Most subjects perceive these tasks as undemanding commercial videogames, which are meant to arouse and stimulate.

The basic procedure involves three test conditions: a) a single-task only is performed, the other is ignored; b) the other single-task only is performed, the first is ignored; and c) then both tasks are performed concurrently. In the dual-task condition the subjects are

---

[1] This study was supported in part by the Medical Research Service of the Veterans Administration.

[2] Gero-Psychiatric Rehabilitation Unit, Veterans Administration Medical Center, Palo Alto, CA 94304 and Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305.

instructed to do the tracking task as well as possible and do the visual probe monitoring with whatever abilities remain. In experiments where we focus on attentional capacity, each task condition lasts 5 minutes. The order of tasks is first tracking only, then reaction task only, and then both tasks simultaneously (dual-task). Any decrement in the dual-task condition relative to the single task conditions indicates the extent to which the available attentional capacity is exceeded. In experiments where we are most interested in drug effects on general performance, we use only the dual-task condition and measure time-on-task changes during 15 or 20 minutes of continuous performance. Continuous performance obviates the confounding effects of any task interruption. The subjects receive no feedback about their performance in either paradigm.

We use Apple II and Apple IIe hardware with programming done in UCSD-Pascal. The tasks are run on an Apple II (or IIe) microcomputer using the UCSD Pascal Operating System. It requires a) an x-y joystick; b) a California Computer Systems programmable timer module (PTM) card, appropriately modified, in slot seven of the Apple II; c) a press button switch connected to the PTM; and d) dual floppy disk drives for data storage. The software for the pursuit tracking and visual monitoring procedure (PTRAK), described above, is written in UCSD Pascal and 6502 machine code. The Pascal portion of PTRAK controls the presentation of the secondary visual probe and records performance; the 6502 routine draws the positions of the target and cursor. Every 75 msec tracking accuracy is measured as the radial distance in pixels between target and control stick cursor. A pixel in this system is about a 1.0 mm horizontal and 0.6 mm vertical dot. Reaction time to the probe (to 1 msec accuracy) or a "miss" (i.e., no response within 1500 msec) are recorded. Additional technical and theoretical considerations are described elsewhere (Tinklenberg & Taylor, 1984; Tinklenberg et al., 1984, 1985).

Results

In repeated measures research designs such as those usually used in clinical psychopharmacology, an essential requirement for any performance assessment procedure is adequate test-retest reliability. We determined the test-retest reliability of PTRAK on five normal volunteers in the basic divided attention paradigm. When testing was done 1 day apart the Pearson correlation coefficients were greater than 0.80 on both tracking and reaction time performance. Testing after 1 week, the Pearson coefficients were greater than 0.69 for both tasks. One subject was tested 20 times over a 6-month period. Examination of his performance indicates an immediate improvement or practice effect in the 5-minute paradigms if testing is done on the same day or on consecutive days. This practice effect is not evident if testing sessions are more than a week apart. When the subject was tested for 10 consecutive days, performance stabilized by the fifth testing day. In the 20-minute time-on-task paradigm, practice effects are less evident.

Another obvious requirement for any psychopharmacological assessment procedure is appropriate drug sensitivity. Initial studies with dual-task procedures are promising. In a single-blind study with normal subjects, single doses of diphenhydramine 50 mg orally significantly impaired performance; 100 mg of caffeine 3 hours after diphenhydramine ingestion restored most of the performance deficit. When diphenhydramine followed caffeine, performance did not improve. We have also shown PTRAK to be sensitive to drug effects in abstinent alcoholics (Miller et al., in press). There was consistent impairment of dual-task performance with diphenhydramine: 50 mg, diazepam: 10 mg and 20 mg, and secobarbital: 100 mg.

Discussion

These preliminary results suggest to us that microcomputerized dual-tasks have adequate reliability and drug sensitivity for use in research. They also have many practical advantages in psychopharmacological studies relative to traditional tasks. Patient acceptance is generally good, and they often enjoy the game-like quality of the task. Since specific feedback is not given and level of performance is not apparent, performance anxiety is minimized. Also, the equipment is portable, relatively inexpensive, and can be adapted to obtain concurrent physiological measures of arousal such as heart rate. Personnel requirements are minimal. A tester requires little training and once the task instructions are given to the subject, the tester does not have to be present. The testing conditions are standardized and exactly replicable, even among different research groups. This is especially important with the repeated measures designs often required in testing for effects of drugs on cognitive performance.

There are also psychometric characteristics of these dual-task procedures that make them attractive for pharmacological studies. A common problem in psychopharmacology is the wide range in the performance abilities of patients. Tests that are too easy for some subjects are too difficult for others. With dual tasks these "ceiling" and "floor" restrictions are circumvented to some degree. The tracking task can be performed at widely varying levels of proficiency—ranging from continuous close contact with the target to distances on the order of 4 to 5 cm—and still be statistically and psychometrically meaningful. This feature of the tracking task is in contrast to our experience with, for example, verbal learning tasks. A second psychometric advantage is the tests' suitability for repeated assessments. Unlike some standard intelligence and memory tests, which have only a single form of the test, each session of this computerized performance test consists of randomized presentation of stimuli.

There are more potential advantages with microcomputerized dual tasks. Adaptive logic can be used so that task difficulty varies during a single test session, e.g., the performance of subjects with different abilities can be kept within specified error limits. The priority assigned to each task can be systematically manipulated so additional inferences can be made about attentional capacitites and control. Dual-task results can be interpreted on the basis of extensive theoretical and experimental work in human factors research.

There are some problems with the microcomputerized testing. Our experience indicates the need for experimental designs which can control for practice effects and performance variability due to factors such as time of day, smoking, diet, exercise, emotional state, etc. Also, some subjects change performance strategies, so that testers occasionally have to monitor the subjects performance throughout a session. With the procedure described above there is a lack of face validity, i.e., a more meaningful task might require the same perceptual and motor skills but use a graphics and hardware system that resembles an automobile. But even at this simple level the technical demands of initial development and modification are formidable and require professional engineers and computer programmers.

In summary, we believe the special psychometric characteristics and sensitivity to experimental interventions make microcomputerized dual tasks a potentially important tool in clinical psychopharmacology.

References

Miller, T.P., Taylor, J.L., and Tinklenberg, J.R. A comparison of assessment techniques measuring the effects of methylphenidate, secobarbital, diazepam, and diphenhydramine in abstinent alcoholics. (In review)

Tinklenberg, J.R., and Taylor, J.L. Assessments of drug effects on human memory functions. In: Squire, L.R., and Butters, N. (eds.), *The Neuropsychology of Memory.* New York: Guilford Press, 1984, pp. 213–223.

Tinklenberg, J.R., Taylor, J.L., Peabody, C.A., et al. Dual task peformance measures in geriatric studies. *Psychopharmacol. Bull.*, 20:441–444, 1984.

Tinklenberg, J.R., Taylor, J.L., Miller, T.P., and Redington, D. Dual-task assessment of attentional capacities in aging and dementia. In: Gaitz, C.M., Niederehe, G., and Rabinowitz, H. (eds.), *Aging 2000: Our Health Care Destiny, Volume II.* New York: Springer-Verlag, 1985, pp. 135–144.

Benzodiazepines—New Indications

CHAIRS: David J. Greenblatt, M.D.
Division of Clinical Pharmacology
Tufts University
Boston, Massachusetts

and

Allen Raskin, Ph.D.
Lafayette Clinic
Detroit, Michigan

The Use of Benzodiazepines for Psychotic Disorders: A Literature Review and Preliminary Clinical Findings[1]

George W. Arana, M.D.,[2] Marjorie L. Ornsteen,[2] Fred Kanter, M.D.,[2] H. L. Friedman, M.D.,[2] David J. Greenblatt, M.D.,[2] and Richard I. Shader, M.D.[2]

Introduction

Although antipsychotic agents (neuroleptics) have been shown to be effective for the treatment of various psychotic disorders including schizophrenia and the affective psychoses, limiting factors such as latency for onset of action (10 to 14 days) and short- (acute dystonias, neuroleptic malignant syndrome), medium- (parkinsonism, akathisia), and long-term side effects (tardive dyskinesia [TD]) have necessitated the search for other compounds that may be effective for psychotic symptoms (Baldessarini, 1980). Recent findings suggest that certain subgroups of psychotic patients may be at increased risk for TD depending on age, diagnosis, and duration of treatment (Mukherjee et al., 1982; Toenniessen et al., 1985), although much controversy still exists about these associations (Kane & Smith, 1982). Benzodiazepines, because of their low toxicity, have been studied both as potential non-neuroleptic antipsychotic agents and as adjunctive treatments for psychotic disorders, to increase sedation and possibly to allow for a significant reduction of neuroleptic dose.

We will review briefly the available literature on the use of benzodiazepines for psychotic disorders, present data from a retrospective chart review on the utility of combined use of neuroleptics and lorazepam, and review preliminary findings of an ongoing study assessing the use of lorazepam alone and lorazepam combined with haloperidol in two groups of psychotic inpatients.

In the literature review we included only those publications containing the actual number of patients responding to a specific regimen. This allowed us to construct efficacy and toxicity data about those who either responded or developed toxicity as a function of the total number treated across studies. Because the efficacy criteria were not uniform among the individual publications, it was not possible to clearly specify whether improvement was in core psychotic symptoms or in such associated symptoms as anxiety and agitation.

---

[1] This study was supported in part by USPHS Grant MH-34223 by the National Institute of Mental Health.

[2] Departments of Psychiatry at the Boston Veterans Administration Medical Center and Tufts University School of Medicine, Boston, MA 02130.

Efficacy of Benzodiazepines for Psychotic Illnesses

Diazepam

Although a variety of benzodiazepines have been employed in the treatment of psychotic disorders, diazepam is the most frequently studied compound. Table 1 presents the selected literature on the use of diazepam for schizophrenic disorders (Beckman & Haas, 1980; Hollister et al., 1963; Jimerson et al., 1982; Jos et al., 1985; Maculans, 1964; Nestoros et al., 1982, 1983; Ruskin et al., 1979; Weizman et al., 1984).

Early uncontrolled studies using relatively lower doses of diazepam were conflicting, some reporting dramatic reductions in hallucinations mand delusions in schizophrenics (Irvine & Schaechter, 1969; Kramer, 1967; Sussex et al., 1961) and others reporting that diazepam had little effect. As is evident from Table 1, few patients were studied in well-controlled clinical trials with fixed-dose regimens.

When double-blind trials are assessed separately, only 14 of 47 subjects (29%) were found to have responded, an efficacy rate equal to what is generally regarded as placebo response rate. Factors which could contribute to response rate such as clinical presentation, response to other medications, or the utility of combined therapies are inconsistent when reviewing this literature. One double-blind study described the use of diazepam for schizophrenic patients who previously were poor neuroleptic responders (Maculans, 1964); another reported a response rate to diazepam comparable to the neuroleptic response rate (Jimerson et al., 1982). Two groups, in double-blind crossover studies using diazepam, found no antipsychotic effect as compared with placebo in doses from 40 to 80 mg/day in one (Ruskin et al., 1979) and 300 mg/day in the other (Jimerson et al., 1982). In contrast to these negative findings, another group reported a dramatic reduction in both positive and negative psychotic symptoms, a broad range of diazepam doses were employed (70 to 400 mg/day) (Nestoros et al., 1982). Finally, in a double-blind randomized trial of haloperidol and diazepam (not shown in Table 2), both compounds were equally effective for the treatment of psychotic symptoms in the first 24 hours, with a trend in favor of diazepam in the first 4 hours (Lerner et al., 1979). The authors speculate that some components of psychosis may be secondary to arousal or anxiety, thus leading to the apparent efficacy of a benzodiazepine compound for psychotic symptoms (Lerner et al., 1979).

TABLE 1

The Use of Diazepam for Psychotic Disorders: A Literature Review

Author	Year	N	Dose*	Design†	Antipsychotic# Effect
Hollister et al.	1963	25	40	Open	9/25
Maculans	1964	35	20–60	DB	8/35
Ruskin et al.	1979	8	40–80	DB-CO**	0/8
Beckman & Haas	1980	15	200–400	Open	10/15
Jimerson et al.	1982	6	300	DB-CO	1/6
Nestoros et al.	1982	6	70–400	DB-PC	5/6
Nestoros et al.	1983	10	35–200	Open	7/10
Weizman et al.	1984	13	100–400	Open	0/13
Jos et al.	1985	2	15,40	Open	2/2
Totals		120			42/120 (34%)
Double-Blind Trials		47			14/47 (29%)

*Dose range of diazepam/24 hrs.

†Open = open trial; DB-CO = double-blind, crossover; DB-PC = double-blind, placebo-controlled.

#(Patients with antipsychotic response)/(Total patients studied).

**Patients concomitantly treated with haloperidol, 15 mg/day.

When all cases (double-blind and others; Table 1) are totalled, response rate is 34% (42/120). The studies reporting the use of diazepam at doses below 40 mg ($N = 60$; 51%) yielded a response rate of 28% (17/60); the three reports using over 100 mg of diazepam had an overall response rate of 33% (11/34). There does not appear to be a dose-related response pattern for diazepam in psychotic illnesses. An overall response rate of approximately 30% emerges regardless of dose used or the design of the studies.

In addition to diazepam, other benzodiazepines have been used for the treatment of psychosis (*see* Table 2). Although these reports are brief and preliminary, they offer some data on the efficacy of this class of drugs for psychotic and bipolar disorders (Astrup & Vatten, 1984; Chouinard et al., 1983; Csernansky et al., 1984; Deberdt et al., 1973; Freinhar & Alvarez, 1985; Guz et al., 1972; Hekimian & Friedhoff, 1967; Holden et al., 1968; Karson et al., 1982; Kellner et al., 1975; Lingjaerde, 1982; Modell et al., 1985; Monroe & Wise, 1965; Victor et al., 1984).

Clonazepam

Recently, interest has developed in the use of clonazepam, a benzodiazepine usually employed for its anticonvulsant properties (Browne, 1976). A number of papers have appeared exploring its value for the treatment of psychotic illnesses, particularly mania (*see* Table 2). Unlike neuroleptics, there is little risk of extrapyramidal or anticholinergic side effects, although drowsiness and ataxia, apparently dose-related symptoms occurring early in treatment, appear to be problematic (Browne, 1976).

Few controlled clinical trials of clonazepam have been conducted to assess its efficacy in the treatment of mania and psychosis. In a double-blind crossover study of 12 acutely manic patients, one group has reported that clonazepam was as effective as lithium for manic symptoms and superior to lithium for motor activity and logarrhea (excessive speech) (Chouinard et al., 1983). Two reports describing 5 patients found that clonazepam ameliorated anxiety and agitation and a limited number of manic symptoms, but psychotic symptoms (delusions, hallucinations) were refractory (Freinhar & Alvarez, 1985; Victor et al., 1984). Two reports suggest that clonazepam may precipitate aggressiveness and irritability (Browne, 1976; Karson et al., 1982). One group, in a double-blind study of 9 schizophrenic patients concomitantly treated with neuroleptics, found clonazepam to be ineffective for target symptoms of psychosis. In addition, 4 patients developed aggressive, violent outbursts, 3 of whom had no prior history of violence. The assaultive episodes occurred when the dose was being adjusted (Karson et al., 1982). These investigators concluded that clonazepam was not effective in the treatment of exacerbations of psychosis in chronic schizophrenics receiving neuro-

TABLE 2

The Use of Selected Benzodiazepines for Psychotic Disorders: A Literature Review

Author	Year	N	Dose[*]	Design[†]	Diagnosis	Response Rate#
			Clonazepam			
Karson et al.	1982	13	1–5	DB	C Schizophrenia	0/13
Chouinard et al.	1983	12	4–10	DB-CO	Mania	Decreased activity
Victor et al.	1984	3	0.5–4	Open	Affect Psych[a]	3/3
Freinhar and Alvarez	1985	2	16	Open	Mania	2/2
			Lorazepam			
Guz et al.	1972	–	6	—	—	—
Deberdt	1973	2	15,40	Open	Schizophrenia	0/2
Modell et al.	1985	4	5–30	Open	Mania[b]	4/4
			Estazolam			
Lingjaerde	1982	58	6	DB	C Schizophrenia[a]	Decreased hallucin.
Astrup and Vatten	1984	53	4–6	Open	Schizophrenia[a]	15/53
			Alprazolam			
Csernansky et al.	1984	8	5–7	Open	Schizophrenia[a]	4/8
			Chlordiazepoxide			
Monroe and Weiss	1965	37	40–200	Open	Schizophrenia[a]	17/37
Hekimian and Friedhoff	1967	10	200 +	Open	Schizophrenia	4/10
Holden et al.	1968	22	60–100	DB-CO	Schizophrenia	6/22
Kellner et al.	1975	6	200–225	DB	Schizophrenia[a]	3/6
Totals						(36.2%) 58/160

[*] Dose range of benzodiazepine/24 hrs.

[†] Open = open trial; DB-CO = double-blind, crossover; DB-PC = double blind, placebo-controlled.

#(Patients with antipsychotic response) / (Total patients studied).

[a] Patients treated concomitantly with neuroleptics.

[b] Patients treated concomitantly with lithium.

leptics, and that it had the potential for inducing aggressive behavior. Finally, another report has indicated that psychotic symptoms, including irritability and aggression, may worsen in adolescents treated with clonazepam (Browne, 1976).

Lorazepam

Lorazepam is well established in psychiatry as an anxiolytic. Its efficacy in psychotic disorders is less well studied and confounded by secondary anxiety and arousal that may coexist in many psychotic patients. One investigator suggests that lorazepam is an effective adjuvant for the anxiety which accompanies psychosis but has no effect on the target symptoms of psychosis (Deberdt, 1973). A recent open clinical trial found lorazepam effective in the control of manic agitation and in promoting compliance and cooperation during the institution of lithium therapy, concluding that manic as well as other psychotic symptoms resolved within 10 days when both lithium and lorazepam were used (Modell et al., 1985). However, the course of recovery from the manic episode left it unclear as to which drug was more effective (Modell et al., 1985).

Estazolam

The effects of estazolam, a benzodiazepine not currently marketed in the United States, have been tested in psychotic illnesses. In a double-blind study of estazolam in 58 chronic schizophrenics, it was found that estazolam in combination with a neuroleptic was better than neuroleptic alone for the treatment of hallucinations and compulsive thoughts as evident in global clinical improvement (Lingjaerde, 1982). Another group reported the use of 4 to 6 mg of estazolam in an open trial for 53 chronic schizophrenics, concluding that this drug decreased delusional and paranoid symptoms in 15/53 patients (Astrup & Vatten, 1984). In both studies, patients were characterized as poor neuroleptic responders and were maintained on neuroleptics during the treatment with estazolam. Although encouraging, further placebo-controlled studies are needed to assess the specific efficacy of estazolam in these patients.

Alprazolam

In an open trial of alprazolam evaluating its therapeutic effect on the negative symptoms in 8 chronic schizophrenics, partial reversal of negative symptoms was observed in 6 patients, and an anxiolytic effect in all 8. (Csernansky et al., 1984). Conclusions that can be drawn from this particular study are limited, as all patients were concomitantly treated with neuroleptics. Fifty percent of the patients had a moderate overall clinical response to alprazolam. Because alprazolam is known to be effective for anxiety, panic, and depressive disorders, this improvement may have been secondary to other possible effects of this drug.

Chlordiazepoxide

Seven reports on the use of chlordiazepoxide reveal generally inconsistent findings on its efficacy in psychosis. In particular, the question of increased efficacy for psychosis if both chlordiazepoxide and neuroleptics are employed is unanswered. Three studies between 1966 and 1970 compared the combination of an antipsychotic and chlordiazepoxide with an antipsychotic alone in newly hospitalized acutely psychotic patients at Spring Grove State Hospital in Maryland and found that the combination drug treatment was less effective than the antipsychotic alone (Hanlon et al., 1969, 1970: Michaux et al., 1966). In an open trial comparing chlorpromazine, chlordiazepoxide, and placebo in 30 schizophrenic patients, 4/10 treated with chlordiazepoxide alone improved with regard to psychotic symptoms: also, chlordiazepoxide in combination with an antipsychotic was more effective than the antipsychotic alone in regard to thought disorder and motor behavior (Hekimian & Friedhoff, 1967). Consistent with these observations is a report showing that the addition of chlordiazepoxide to an antipsychotic regimen was effective in controlling acutely psychotic, episodically dyscontrolled patients (Monroe & Wise, 1965). Another group of investigators reported that chlordiazepoxide was not effective in the treatment of psychosis and that most changes in global ratings were due to the sedative and calming effects of chlordiazepoxide (Holden et al., 1968). Finally, a report on 6 schizophrenic patients concomitantly treated with neuroleptics found that 3/6 patients demonstrated an adequate response. Overall, the response rate with chlordiazepoxide in psychotic illnesses among 75 patients is just over 50%, but over half of these patients also were treated with neuroleptics. Therefore, conclusions regarding efficacy of chlordiazepoxide alone must be tentative.

Benzodiazepine Toxicity in Psychotic Illnesses

A review of seven publications (Beckman & Haas, 1980; Haas et al., 1982; Hollister et al., 1963; Jimerson et al., 1982; Karson et al., 1982; Lerner et al., 1979; Maculans, 1964) revealed a variety of side effects reported with both diazepam and clonazepam in a total of 114 patients (Table 3). Except for the final study cited which reported on manic patients (Chouinard et al., 1983), all patients were reportedly schizophrenic. However, the diagnostic criteria employed varied and many of these may have fallen in the affective spectrum if DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) were being used. In this group of patients, it was evident that the two general types of side effects seen in these reports included sedation/quieting and arousal/stimulation. This preliminary literature review would suggest that certain benzodiazepines may have a significant likelihood of producing sedation or stimulation in certain psychotic patients. The particular pattern of behavioral toxicity in an individual may be idiosyncratic, or may be mediated via other poorly understood factors not readily apparent in the limited sample reviewed.

It is of note that the arousal/stimulation pattern of toxicity seen in a number of schizophrenic patients is reminiscent of manic symptoms, i.e., hypersexuality, hyperkinesis, excitation, euphoria, and impulsive behavior. This would suggest that caution must be exercised in interpreting these symptoms in diagnostically complicated cases who are treated with benzodiazepines during the clinical evaluation period. This arousal pattern seen with the use of certain benzodiazepines in chronically psychotic individuals may confound the diagnostic process, as is mentioned in the Discussion section.

Preliminary Clinical Results With the Use of Lorazepam in Psychotic Illnesses

Retrospective Chart Review of Patients Treated With Neuroleptics and Lorazepam Over a 6-Month Period

Between January 1984 and July 1984 a total of 380 patients were admitted to one of three 22-bed acute inpatient units in the Department of Psychiatry at the Boston Veterans Administration Medical Center. When clinically indicated, patients were treated

TABLE 3

Toxicity Reported With Benzodiazepines in Psychotic Disorders

Author	Year	Benzodiazepine	Toxicity Rate	Description
Hollister et al.	1963	Diazepam	9/25	"Worsening of psychosis
Maculans	1964	Diazepam	7/35	Sedation
Beckman and Haas	1980	Diazepam	5/15	Hypersexuality; hyperkinesis; excitation.
Haas et al.	1982	Diazepam	4/8	Euphoria; hyperkinesis.
Jimerson et al.	1982	Diazepam	3/6	Ataxia; sedation
Karson et al.	1982	Clonazepam	3/13	Violent behavior
Chouinard et al.	1983	Clonazepam	7/12	Sedation
Totals	Sedation		17/53 (32%)	
	Arousal/Stimulation		21/61 (34%)	

NOTE: All patients were diagnosed as schizophrenic except in the Chouinard study in which patients were diagnosed as bipolar disorder, manic type.

TABLE 4

Neuroleptic Dose Requirements in Psychotic Disorders: Neuroleptics With and Without Lorazepam (LZP)

Treatments	*N* (Total = 30)	CPZ-EQ (mg)* (mean ± SEM)
A Neuroleptics	22	560 ± 85
B Neuroleptics + LPZ [a]	8	265 ± 50

*Chlorpromazine-equivalents/24 hrs./patient: doses were at discharge and were determined to be lowest dose for effective control of psychotic target symptoms.
[a] Mean lorazepam dose = 2.75 mg/24 hrs.
Statistical Data:
B vs. A: $t = 2.99$; $df = 28$; $p < .01$

with doctor's choice of neuroleptic, doses being tapered continuously during hospitalization to achieve the lowest effective dose. Of the 380 admissions, it was found that 30 patients were discharged with either neuroleptic or neuroleptic with lorazepam at the lowest doses clinically possible without an exacerbation of symptoms. Mean discharge dose of neuroleptic was comparable for the three units as was average length-of-stay. Patients with a significant degree of agitation initially were treated with lorazepam and were discharged with the lowest effective dose of this compound.

Table 4 presents the neuroleptic dosages employed, converted to chlorpromazine-equivalents (CPZ-EQ) (Baldessarini, 1980), on these 30 patients separated into treatment groups: 1) neuroleptics, and 2) neuroleptics with lorazepam. In 22 patients discharged on neuroleptics alone, mean CPZ-EQ/day was 560 mg whereas in 8 patients treated with both neuroleptics and lorazepam (mean lorazepam dose = 2.75 mg/day), the mean CPZ-EQ/day on discharge was 265 mg, a difference found to be statistically significant ($t = 2.99$; $df = 28$; $p < .01$). Data on 32 patients not shown were separated into two other treatment subgroups: 1) neuroleptics and benztropines, and 2) neuroleptics, lorazepam, and benztropine. The group of patients treated with both neuroleptics and benztropines ($N = 18$; mean dose benztropine = 2.2 mg) had a mean CPZ-EQ dose of 771 mg/day (SEM ± 164). The group of 14 patients treated with neuroleptics, lorazepam, and benztropine had a mean CPZ-EQ dose of 933 mg (SEM ± 227) (*see* Table 4).

Although patients were tapered to lowest effective dose for treatment of psychotic symptoms, the heterogeneity of the population made it difficult to separate dose requirement of neuroleptic from severity of illness. Because lorazepam was initiated for agitation and irritability, it is unlikely that this cohort represented less severe forms of psychosis although, without controlling for severity, this assumption remains untested. The dose of neuroleptics in the group receiving concomitant lorazepam therapy was clearly lower than the other group shown. This lower dose of neuroleptics also may have led to a lower incidence of extrapyramidal side effects and/or akathisia, therefore not requiring the use of benztropine. This reduced requirement for neuroleptics may have reduced the incidence of neuroleptic-induced toxicity which may have reflected itself as an overall improved clinical picture at relatively lower doses of antipsychotics. Further research with carefully controlled groups of psychotic patients with uniform symptom profiles on fixed doses of neuroleptics is needed to assess whether there is a significant interaction between these two medications which allows for use of lower doses of neuroleptics. Also, it remains to be assessed whether the reduced neuroleptic dose lowered the incidence of neuroleptic-induced side effects, i.e., akathisia, hence leading to apparent efficacy which, in fact, was reduced toxicity.

Preliminary Results of the Efficacy and Toxicity of Lorazepam in 14 Psychotic Patients

Preliminary results from an ongoing study on the efficacy of lorazepam vs. lorazepam with haloperidol for psychotic disorders were reviewed. Acutely psychotic patients between the ages of 18 and 65 were admitted to a research inpatient service at the Boston Veterans Administration Medical Center, underwent a complete battery of clinical and laboratory tests to exclude active medical conditions, and were stabilized with regard to diet and fluid intake. Subjects able and willing to sign informed consent were observed clinically for 48 hours following admission and rated daily with the Brief Psychiatric Rating Scale (BPRS) to determine the nature and intensity of psychotic symptoms. Those patients who demonstrated a clear improvement in psychotic symptomatology in this time period were excluded from study and the remaining patients were treated either with lorazepam or lorazepam with haloperidol. Blood samples for analysis of lorazepam and haloperidol were drawn into heparin-containing tubes, centrifuged, separated, and kept frozen at −20° C until assay. Lorazepam was measured by gas liquid chromatography with electron-capture detection (Greenblatt et al., 1978); haloperidol was measured by gas liquid chromatography with a nitrogen-phosphorus detector (Abernethy et al., 1984).

Table 5 presents data on the 14 patients studied including basic demographics, diagnostic data, doses of lorazepam and haloperidol employed, and specific items on the BPRS showing significant improvement over the 48-hour period of treatment. Diagnostic evaluations were performed by a research psychiatrist and a research assistant employing DSM-III criteria with the aid of the Structured Clinical Interview for DSM-III (SCID). Eight patients with diagnoses of mania ($N = 4$), schizophrenia ($N = 3$), and atypical psychosis ($N = 1$) were treated with a mean dose of 20.9 mg/day of lorazepam alone and demonstrated a mean drop in BPRS scores of 20; BPRS items showing significant improvement ($p < .05$) were tension, hostility, suspiciousness, hallucinations, unusual thoughts, conceptual disorganization, excitement, and emotional withdrawal. Six patients divided equally between mania, schizophrenia, and atypical psychosis were treated with both lorazepam and haloperidol. The mean lorazepam dose was 16.5 mg/day and mean haloperidol dose was 14.2 mg/day. The items on the BPRS which showed significant improvement were grandiosity, unusual thoughts, conceptual disorganization, blunted affect, and emotional withdrawal ($p < .05$).

In order to assess the differences between high-dose (>30 mg/day; $N = 3$) vs. low-dose (<10 mg/day; $N = 5$) lorazepam among the lorazepam-treated group ($N = 8$), and to assess the differences between low-dose lorazepam ($N = 5$) vs. low-dose lorazepam with low-dose haloperidol ($N = 4$), clinical response data were analyzed in this same cohort of patients (*see* Table 6; N.B. Two patients treated with lorazepam and haloperidol who were included in Table 5 were treated with >20 mg/

TABLE 5

Lorazepam for Acutely Psychotic Patients With and Without Haloperidol: Clinical Characteristics and 48-Hour Response Data

Characteristics	Treatment Groups: Lorazepam	Treatment Groups: Lorazepam + Haloperidol
	$N = 8$	$N = 6$
Sex (M/F)	8/0	6/0
Median Age (Range)	31 (22–63)	29 (22–47)
Race (Black/White)	4/4	3/3
Diagnosis (DSM-III)		
Manic (N)	4	2
Schizophrenic (N)	3	2
Atypical Psychotic (N)	1	2
Lorazepam Dose (mg/Day)*	20.9	16.5
Haloperidol Dose (mg/Day)*	—	14.2
Baseline BPRS Score*	60.3	47.5
48 Hr BPRS Score*	40.3	32.3
BPRS Items Improved ($p < .05$)	Tension Hostility Suspiciousness Hallucinations Unusual Thoughts Conceptual Disorganization Excitement Emotional Withdrawal	Grandiosity Unusual Thoughts Conceptual Disorganization Blunted Affect Emotional Withdrawal

*Means

TABLE 6

48-Hour Clinical Change in Psychotic Patients in Three Treatment Groups: High- and Low-Dose Lorazepam and Low-Dose Lorazepam With Haloperidol

	Lorazepam		
	High-Dose ($N=3$)	Low-Dose ($N=5$)	Lorazepam - Haloperidol ($N=4$)
Lorazepam Dose[*] (mg/24 hrs)	45	6.2	5
Haloperidol Dose[*] (mg/24 hrs)	—	—	15
Plasma Lorazepam[*] (ng/ml)	688	29.5	—
Clinical Improvement[a]			
BPRS Items[b]:			
Anxiety	—	—	—
Tension	$p<.05$	—	—
Hostility	$p<.01$	—	—
Suspiciousness	$p<.05$	—	—
Excitement	$p<.05$	$p<.05$	—
Conceptual Disorganization	$p<.05$	—	$p<.01$
Unusual Thoughts	—	$p<.01$	$p<.01$
Emotional Withdrawal	—	$p<.01$	$p<.05$
Clinical Worsening[a]			
BPRS Items:			
Motor Retardation	$p<.05$	—	—
Blunted Affect	$p<.05$	—	—

[*] Means

[a] Paired Student's t-test; baseline vs. 48 hours of treatment.

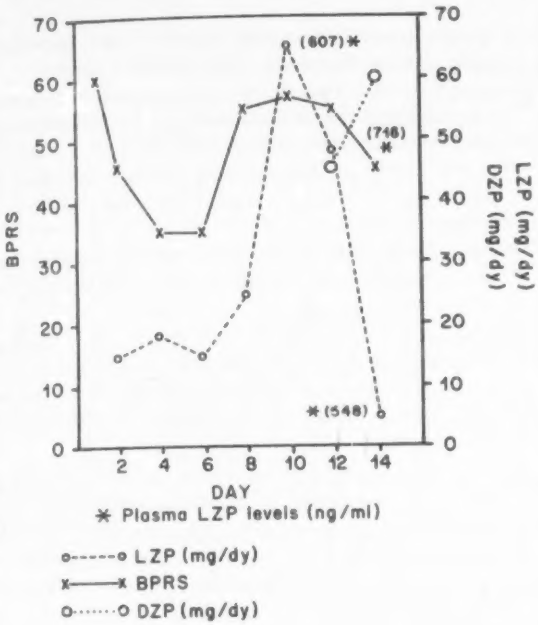
[b] BPRS items 3.5 at baseline in all three treatment groups.

day of lorazepam and were not included in the data analysis in Table 6). Mean daily lorazepam dose in the high-dose lorazepam group was 45 mg with a mean plasma level of 688 ng/ml. Nonpsychotic symptoms that were significantly improved included tension, hostility, and excitement; psychotic symptoms showing improvement were suspiciousness and conceptual disorganization. In the group receiving high-dose lorazepam, significant worsening in motor retardation and blunted affect was noted. The low-dose lorazepam group ($N=5$) received a mean daily dose of 6.2 mg/day with mean plasma levels of 29.5 ng/ml. Clinical improvement was noted with excitement, unusual thoughts, and emotional withdrawal. The 4 patients treated with both lorazepam and haloperidol were treated with mean doses of 5 mg/day and 15 mg/day, respectively. Improvement was noted in conceptual disorganization, unusual thoughts, and emotional withdrawal.

Time Course of Treatment Response of a Manic Patient

The Figure (p. 85) outlines the 2-week course of a 42-year-old white male, bipolar manic patient treated only with lorazepam and diazepam over a 14-day period. Presenting symptoms on admission included paranoia, grandiosity, insomnia, loss of appetite, restlessness, agitation, labile affect, pressured speech, racing thoughts, and poor judgment. The total BPRS score on admission was 60. By history, this episode began 4 months prior to admission.

The patient was begun on 8 mg oral lorazepam daily with 2 mg doses administered as needed for agitation. A BPRS to assess severity of psychosis and response to treatment was completed daily by a research psychiatrist. Within the first 24 hours of treatment, he received 15 mg of lorazepam and showed moderate improvement in symptoms such as



uncooperativeness, excitement, and suspiciousness as defined by a 2-point decrease on BPRS subscales. After 48 hours of treatment, total BPRS score had dropped to 33. There continued to be marked improvement in grandiosity, tension, unusual thought content, and conceptual disorganization through day 6. Unexpectedly, between day 6 and day 8, with little change in daily lorazepam dose (between 16 to 24 mg) he demonstrated a clear worsening in his clinical state as reflected in increasing BPRS scores with manic symptoms similar to those evident on admission (*see* Figure). The lorazepam dose was increased to 65 mg daily with a plasma lorazepam level of 607 ng/ml with no improvement in psychotic symptoms. Because of his failure to respond, lorazepam was rapidly tapered and on day 12, diazepam was started in order to avoid possible withdrawal symptoms from the high-dose lorazepam regimen. On day 15, haloperidol treatment was initiated with marked improvement in 3 days and remission in 2 weeks.

This case characterizes the time course observed with other psychotic patients treated with lorazepam in whom rapid improvement is not sustained beyond 4 to 6 days, with little benefit attained by increasing lorazepam dosage. This was evaluated with lorazepam levels which confirmed that drug levels increased with increasing dosage. Because antipsychotic effect was not attained with increased levels of lorazepam, this would not suggest that tolerance was developing to the antipsychotic effect of lorazepam. Further clinical and preclinical work is needed to better understand this pattern of clinical effect in psychotic illnesses.

Discussion

It is evident from this literature review that benzodiazepines are not as effective in the treatment of psychotic disorders as neuroleptics or lithium salts. The efficacy rate of benzodiazepines for the treatment of psychosis, usually reported as schizophrenia (not necessarily DSM-III), is approximately what would generally be expected from placebo rates of response (Tables 1 and 2; 98/278 = 35.2%). Because many of these reports were retrospective and/or included patients concomitantly treated with neuroleptics or lithium, the actual response rate may be lower than the apparent 35.2%.

Toxicity seen when psychotic disorders were treated with benzodiazepines included the expected sedation and drowsiness characteristic of this class of medication (32%), but also included arousal and excitation (34%) manifesting as manic symptoms in some cases and, more seriously, as assaultive behavior in others. Clinicians employing benzodiazepines for behavioral management of psychotic patients need to be alerted to this potentially confounding effect of these drugs. The literature would suggest that schizophrenia mistakenly may be seen as an affective psychosis if the clinician is not aware of these patterns of toxicity. An alternate view would hold that benzodiazepines, like tricyclic antidepressants or monoamine oxidase inhibitors, may produce a "switch" phenomenon (Goodwin, 1983) and what may have appeared initially as schizophrenia may be affective illness "unmasked" by the benzodiazepine. Because there is little evidence presently to support this hypothesis, more research is needed to delineate the meaning of the arousal evident in psychotic disorders treated with benzodiazepines.

The preliminary findings in 14 psychotic patients treated with lorazepam alone would suggest that this compound may be helpful initially (48 hours) for the treatment of acutely psychotic individuals. This effect was seen both with high- and low-dose lorazepam, the high-dose regimen apparently quite effective for a range of behavioral, affective, and cognitive symptoms of psychosis, but also more likely to cause motor retardation and blunted affect. The pattern seen in the Figure is representative of many patients we have observed in which the rapid initial improvement in psychotic symptoms is short-lived and does not respond to increasing the dose of lorazepam.

Our retrospective chart review revealed that combined neuroleptic and lorazepam treatment required significantly lower doses of neuroleptic (CPZ-EQ = 265 mg) as compared to neuroleptics alone (CPZ-EQ = 560 mg). This finding would suggest that further work is needed to assess whether combined neuroleptic and lorazepam regimens would allow for the use of lower doses of neuroleptics to achieve comparable clinical effects, i.e., a shift to the left of the dose-response curve for neuroleptics in psychosis.

References

Abernethy, D.R., Greenblatt, D.J., Ochs, H.R., et al. Haloperidol determination in serum and cerebrospinal fluid using gas-liquid chromatography with nitrogen-phosphorus detection: Application to pharmacokinetic studies. *J. Chromatogr.*, 307:194–199, 1984.

Astrup, C., and Vatten, L. Effect of the benzodiazepine derivative estazolam in schizophrenia. *Biol. Psychiatry*, 19(1):85–88, 1984.

Baldessarini, R.J. Drugs and the treatment of psychiatric disorders. In: Gilman, A.G., Goodman, L.S., and Gilman, A. (eds.), *The Pharmacological Basis of Therapeutics*. New York: Macmillan Publishing Co., Inc., 1980, pp. 391–447.

Beckman, H., and Haas, S. High dose diazepam in schizophrenia. *Psychopharmacology*, 71:79–82, 1980.

Browne, T.R. Clonazepam: A review of a new anticonvulsant drug. *Arch. Neurol.*, 133:326–332, 1976.

Chouinard, G., Young, S.N., and Annable, L. Antimanic effect of clonazepam. *Biol. Psychiatry*, 18(4):451–467, 1983.

Csernansky, J.G., Lombrozo, L., Gulevich, G.D., and Hollister, L.E. Treatment of negative schizophrenic symptoms with alprazolam: A preliminary open-label study. *J. Clin. Pharmacol.*, 4(6):349–352, 1984.

Deberdt, R. Lorazepam in the treatment of severe anxiety and anxiety associated with psychotic conditions. *Curr. Med. Res. Opin.*, 1:296–300, 1973.

Freinhar, J.P., and Alvarez, W.H. Use of clonazepam in two cases of acute mania. *J. Clin. Psychiatry*, 46:29–30, 1985.

Goodwin, F.K. The impact of tricyclic antidepressants and lithium on the course of recurrent affective disorders. *McLean Hosp. J.*, 8:1–16, 1983.

Greenblatt, D.J., Franke, K., and Shader, R.I. Analysis of lorazepam and its glucuronide metabolite by electroncapture gas-liquid chromatography: Use in pharmacokinetic studies of lorazepam. *J. Chromatogr.*, 146:311–320, 1978.

Guz, I., Morales, R., and Sartoretto, J. The therapeutic effects of lorazepam in psychotic patients treated with haloperidol. *Curr. Ther. Res.*, 14:767–774, 1972.

Haas, S., Emrich, H.M., and Beckman, H. Analgesic and euphoric effects of high dose diazepam in schizophrenia. *Neuropsychobiology*, 8:123–129, 1982.

Hanlon, T., Ota, K., Agallianos, D., et al. Combined drug treatment of newly hospitalized acutely ill psychiatric patients. *Dis. Nerv. Syst.*, 30:104–116, 1969.

Hanlon, T., Ota, K., and Kurland, A. Comparative effects of fluphenazine, fluphenazine-chlordiazepoxide, and fluphenazine-imipramine. *Dis. Nerv. Syst.*, 31:171–177, 1970.

Hekimian, L., and Friedhoff, A. A controlled study of placebo, chlordiazepoxide, and chlorpromazine in 30 male schizophrenic patients. *Dis. Nerv. Syst.*, 28:675–678, 1967.

Holden, J., Itil, T., Keskiner, A., and Fink, M. Thioridazine and chlordiazepoxide, alone and combined in the treatment of acute schizophrenia. *Compr. Psychiatry*, 9:633–693, 1968.

Hollister, L.E., Bennett, J.L., Kimbell, I., et al. Diazepam in newly admitted schizophrenics. *Dis. Nerv. Syst.*, 24:746–750, 1963.

Irvine, B.M., and Schaechter, F. "Valium" in the treatment of schizophrenia. *Med. J. Aust.*, 1:1387, 1969.

Jimerson, D.C., Van Kammen, D.P., Post, R.M., et al. Diazepam in schizophrenia: A preliminary double-blind trial. *Am. J. Psychiatry*, 139(4):489–491, 1982.

Jos, C.J., Schneider, R., and Gannon, P. Diazepam in the treatment of hallucinations. *Am. J. Psychiatry*, 142:1130–1131, 1985.

Kane, J.M., and Smith, J.M. Tardive dyskinesia: Prevalence and risk factors, 1959-1979. *Arch. Gen. Psychiatry*, 39:473–481, 1982.

Karson, C.N., Weinberger, D.R., Bigelow, L., and Wyatt, R.J. Clonazepam treatment of chronic schizophrenia: Negative results in a double-blind, placebo-controlled trial. *Am. J. Psychiatry*, 139(12):1627–1628, 1982.

Kellner, R., Wilson, R.M., Muldawer, M.D., and Pathok, D. Anxiety in schizophrenia: The responses to chlordiazepoxide in an intensive design study. *Arch. Gen. Psychiatry*, 32:1246–1254, 1975.

Kramer, J.C. Treatment of chronic hallucinations with diazepam and phenothiazines. *Dis. Nerv. Syst.*, 28:593–594, 1967.

Lerner, Y., Lwow, E., Levitan, A., and Belmaker, R.H. Acute high-dose parenteral haloperidol treatment of psychosis. *Am. J. Psychiatry*, 136(8): 1061 – 1064, 1979.

Lingjaerde, O. Effect of the benzodiazepine derivative estazolam in patients with auditory hallucinations. *Acta Psychiatr. Scand.*, 65:339–354, 1982.

Maculans, G.A. Comparison of diazepam, chlorprothixene, and chlorpromazine in chronic schizophrenic patients. *Dis. Nerv. Syst.*, 25:164–168, 1964.

Michaux, M., Kurland, A., and Agallianos, D. Chlorpromazine-chlordiazepoxide, and chlorpromazine-imipramine treatment of newly hospitalized, acutely ill patients. *Curr. Ther. Res.*, 8:117–152, 1966.

Modell, J.G., Lennox, R.H., and Weiner, S. Inpatient clinical trial of lorazepam for the management of manic agitation. *J. Clin. Psychopharmacol.*, 5(2):109–113, 1985.

Monroe, R., and Wise, S. Combined phenothiazine, chlordiazepoxide, and primidone therapy for uncontrolled psychotic patients. *Am. J. Psychiatry*, 122:694–698, 1965.

Mukherjee, S., Rosen, R.M., Cardenas, C., et al. Tardive dyskinesia in psychiatric outpatients: A study of prevalence and association with demographic, clinical, and drug history variables. *Arch. Gen. Psychiatry*, 39:466–469, 1982.

Nestoros, J.N., Suranyi-Cadotte, B.E., Spees, R.C., et al. Diazepam in high doses is effective in schizophrenia. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:513–516, 1982.

Nestoros, J.N., Nair, N.P.V., Pulman, J.R., et al. High doses of diazepam improve neuroleptic-resistant chronic schizophrenic patients. *Psychopharmacology*, 81:42–47, 1983.

Ruskin, P., Averbuch, I., Belmaker, R.H., and Dasberg, H. Benzodiazepines in chronic schizophrenia. *Biol. Psychiatry*, 14(3):557–558, 1979.

Sussex, J.N., Linton, P.A., and Herlihy, C.E. Anxiety and depression in "borderline" schizophrenic states—Treatment with Valium, a librium analog. *Psychosomatics*, 2:256–265, 1961.

Toenniessen, L.M., Casey, D.E., and McFarland, B.H. Tardive dyskinesia in the aged: Duration of treatment relationships. *Arch. Gen. Psychiatry*, 42:278–284, 1985.

Victor, B.S., Link, N.A., Binder, R.L., and Bell, I.R. Use of clonazepam in mania and schizoaffective disorders. *Am. J. Psychiatry*, 141(9):1111–1112, 1984.

Weizman, A., Tyano, S., Wijsenbeck, H., and Ben David, M. High dose diazepam treatment and its effect on prolactin secretion in adolescent schizophrenic patients. *Psychopharmacology*, 82:382–385, 1984.

New Strategies for the Treatment of Alcohol Withdrawal

E.M. Sellers, Ph.D.,[1] and C.A. Naranjo, Ph.D.[1]

Introduction

The goals in the treatment of alcohol withdrawal are the relief of subjective symptoms, the prevention or treatment of the serious complications (e.g., seizures, hallucinations, arrhythmias, and delirium), and preparation for long-term rehabilitation. Such treatment should be standardized, humane, as simple and economic as possible, and it should have a pharmacokinetic and pharmacodynamic rationale.

Over the past 10 years we have conducted studies directed toward the development of trial methodology and diagnostic and tracking criteria of the withdrawal syndrome, the determination of the natural history of the withdrawal syndrome, the assessment of the importance of nonpharmacologic treatment measures, the simplification of drug therapy, and the determination of the role of adjunctive drugs, such as phenytoin. Recently, we have been testing the hypothesis that the pharmacotherapy of alcohol withdrawal can be improved by the use of selective, nonsedating drugs.

Diagnostic Criteria and Scales to Track the Clinical Syndrome

In an effort to develop an instrument for assessing the alcohol withdrawal syndrome, Gross et al. (1973, 1974) identified disturbances in 30 clinical variables during experimental alcohol withdrawal studies. Two instruments were developed: a research battery (total severity assessment, TSA) and a clinical instrument (selected severity scale, SSA). The TSA contained all of the original 30 clinical variables, while the SSA consisted of a short list of 11 items. The SSA correlated highly with the TSA (Gross et al., 1973, 1974); however, full prospective validation of the SSA was not done. We modified this scoring system for rapid repeated use (Shaw et al., 1981). Our 15-item scale, Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) includes tremor; nausea and vomiting; paroxysmal sweating; tactile, auditory, and visual disturbances; hallucinations; quality of contact; anxiety; agitation; thought disturbances; seizures; headache; and flushing of face (Shaw et al., 1981). Heart rate, temperature, and blood pressure are also recorded, but not included in the scoring.

Several prospective studies show that the CIWA-A scale is valid, reliable, and sensitive (Naranjo et al., 1983; Sellers et al., 1983; Shaw et al., 1981). CIWA-A scores correlate with physician global ratings of withdrawal severity. Nine items in particular contribute most weight to the total score (nausea; tremor; sweating; tactile, auditory, and visual disturbances; hallucinations; anxiety; and agitation) and correlate highly with the total score ($r = 0.95$). Inter-rater and intra-rater reliability has been determined ($r = 0.8$–0.92). The scale has been successfully used in assessing the therapeutic response in clinical trials in ambulatory and hospitalized patients in withdrawal (Naranjo et al., 1983; Sellers et al., 1983; Shaw et al., 1981). Several other advantages of this standardized procedure are that medical and other health workers become aware of the symptoms that make up the alcohol withdrawal syndrome, and staff training is facilitated. Because of its brevity, this procedure can be incorporated into "routine" patient care. We are currently testing whether validity and reliability can be retained with a further simplification of the scale (i.e., reduction of number of items) and change in the scoring ranges (Sullivan et al., 1985).

---

[1] Departments of Pharmacology and Medicine, University of Toronto and Clinical Pharmacology Program, Addiction Research Foundation, Toronto, Ontario, Canada.

Nonpharmacologic Interventions

Uncontrolled studies showed that reassurance, reality orientation, frequent monitoring of signs and symptoms, personal attention, and general nursing care can be effective in over two-thirds of patients in a mild alcohol withdrawal reaction (Toshney, 1978; Whitfield et al., 1978).

Recent controlled studies using a standardized form of "supportive care" have confirmed the potency of such nonpharmacologic interventions (Naranjo et al., 1983; Sellers et al., 1983; Shaw et al., 1981). Eighty-five percent of emergency room patients (Naranjo et al., 1983) and 75% of inpatients without, and 56% with, medical complications respond to supportive care in less than 6 to 8 hours (Sellers et al., 1983).

The effectiveness of nonpharmacologic interventions has important implications for design and interpretation of studies assessing drug therapies in alcohol withdrawal. In this context, it is notable that the frequency of placebo-controlled studies of alcohol withdrawal has declined markedly. Placebos were used in 11 of the 19 controlled studies published during the 1960's but in only 4 of the 19 in the 1970's (Gessner, 1979). Since our data indicate that, to a substantial extent, the apparent efficacy of a drug can be due to the influence of nonpharmacologic interventions, it is essential to use a placebo control group (Naranjo et al., 1983).

Even though supportive care decreases the general symptoms of withdrawal, it does not appear to completely prevent hallucinations, seizures, or arrhythmias: hence, drugs are still required by patients. Since patient characteristics do not predict the occurrence of such complications, patients in moderate to severe withdrawal should receive drugs such as diazepam in addition to supportive care (Sellers et al., 1983).

Dosage Strategies and Pharmacotherapy

Benzodiazepines are currently the drugs of choice (Linnoila, 1983: Sellers & Kalant, 1976, 1982; Sellers et al., 1983). They combine at least equal efficacy as other agents with superior anticonvulsant activity and less toxicity than phenothiazines, barbiturates, and paraldehyde (Sellers & Kalant, 1982). Numerous benzodiazepines including alprazolam, bromazepam, chlordiazepoxide, chlorazepate, clobazam, diazepam, flurazepam, lorazepam, and oxazepam, have been studied and all can be effective (Linnoila, 1983; Moskowitz et al., 1983; Sellers & Kalant, 1976, 1982). Approximate equivalent doses relative to chlordiazepoxide 100 mg are diazepam 20 mg, oxazepam 120 mg, and lorazepam 5 mg.

Both chlordiazepoxide and diazepam are long-acting drugs with pharmacologically active metabolites (Greenblatt et al., 1983). Repeated daily administration at a constant dosage would result in cumulation of the parent compound and/or metabolites in the body (Sellers & Kalant, 1976; Sellers et al., 1983). Such a dosing regimen could delay the onset of maximum therapeutic and unwanted toxic effects for several days. Similar cumulation would occur with prazepam or chlorazepate which are biotransformed to desmethyldiazepam, the pharmacologically active long half-life metabolite formed after diazepam administration (Sellers & Kalant, 1976; Victor, 1966). If dosages are not adjusted carefully, excessive drowsiness, lethargy, ataxia, diplopia, and confusion may occur.

The usual strategy to avoid such side effects is to give larger doses on the first day and progressively lower the dose on subsequent days (Sellers & Kalant, 1976). Typically, multiple doses of diazepam (20 to 40 mg) or chlordiazepoxide (100 to 400 mg) are given on the first day (Sellers & Kalant, 1976, 1982). Lower doses were given daily thereafter and dose-tapering decreased by about 25% to 50% of the initial daily dose (Sellers & Kalant, 1976; Sellers et al., 1983). However, because of variability in the severity of withdrawal symptoms and in the metabolic disposition of the drugs, strict adherence to such dosage schedules may cause toxicity or ineffective treatment in some patients (Sellers et al., 1983). Recently, the dose-tapering approach to treating alcohol withdrawal has been further simplified (Sellers et al., 1983).

The procedure consists of a rapid oral loading-dose strategy using diazepam. Patients are assessed clinically or with the CIWA-A scale and unit doses of 20 mg of

TABLE

Diazepam Loading Trial*
Complications-Placebo Group Only

Subject Trial #	Complication	Time (Hour)
245	Seizure	3
213	Supraventricular tachycardia	2
222	Seizure	7.5
211	Hallucinations	7.5
201	Severe vomiting/anxiety	6
240	Seizure × 3	6

*Sellers et al., 1983.

diazepam, orally, are administered every 1 to 2 hours until the patient shows clinical improvement (CIWA-A<10) or becomes mildly sedated. The rationale of this approach is to take advantage of rapid and complete absorption of diazepam and the pharmacokinetic tapering afforded by diazepam's and N-desmethyldiazepam's long half-lives, i.e., 30 and 40 hours, respectively (Sellers et al., 1983). This pharmacokinetic "umbrella" of active drug is eliminated at about the same rate as the resolution of the withdrawal syndrome.

In a recent double-blind controlled study, patients treated with diazepam using the loading-dose approach had a faster and greater improvement than those receiving placebo (Sellers et al., 1983). Fifty percent of the patients responded to 60 mg of diazepam orally within 7.6 hours, and only an occasional patient required treatment for more than 24 hours. More importantly, complications (seizures, hallucinations, arrhythmias) occurred exclusively in those treated with placebo, indicating that delay in therapy may be responsible for the appearance of complications in withdrawal (Sellers et al., 1983) (*see* Table). We recommend that all hospitalized patients in moderate to severe withdrawal should be loaded with at least 60 mg of diazepam.

Treatment of Alcohol Withdrawal Seizures

The optimal treatment of alcohol withdrawal seizures remains controversial (Gessner, 1974; Naranjo, 1983; Sellers & Kalant, 1982; Thompson, 1978). In particular, the therapeutic and prophylactic value of phenytoin in alcohol withdrawal seizures is uncertain. The contradictory findings in the reported clinical studies possibly arise from the indiscriminate inclusion of patients with pre-existing seizure disorder and those with a previous history of withdrawal seizures only, as well as the failure to standardize and give sufficient benzodiazepine or other drugs as "baseline therapy" (Rothstein, 1973; Sampliner & Iber, 1974; Sandor et al., 1981).

To further investigate this, we have conducted studies in laboratory animals (Solorzano et al., 1985). To determine if phenytoin exhibits pharmacologic selectivity or augments the activity of diazepam in alcohol withdrawal syndrome, male Long-Evans rats were made physically dependent by the administration of intragastric ethanol (3 to 5 g/kg) twice daily for 6 days (Rothstein, 1973). In animal models of alcohol withdrawal, diazepam and phenytoin can be protective against audiogenic seizures; however, the two drugs differ in potency and intrinsic activity. For example, diazepam (3.0 mg/kg) will decrease seizures by up to 50% whereas phenytoin (100 mg/kg) can completely abolish seizures. For phenytoin, a 50% reduction in seizures occurs at 35 mg/kg.

With respect to combinations of diazepam and phenytoin, lower doses of phenytoin (25 mg/kg) plus diazepam (1.0 mg/kg) are more effective than diazepam alone and approximately equal to phenytoin (100 mg/kg) (Rothstein, 1973).

From these studies, one can suspect that diazepam's anticonvulsant action will be sufficient when seizure risk is low, but that phenytoin could increase diazepam's anticonvulsant action in a clinically important way. This will be true, however, only as long as full therapeutic doses of phenytoin are given. However, about 30% of dosing in chronic alcoholics is not straightforward, because chronic alcoholics have clearances of phenytoin that are two- to three-fold greater than normal (Sandor et al., 1981). Hence, daily maintenance doses must be increased to 600 to 900 mg/day to maintain adequate steady-state concentrations. Since some chronic alcoholics may have impaired clearance, daily measurement of phenytoin concentrations is imperative to use this drug properly (Sandor et al., 1981).

In our clinical studies, we have been impressed that patients who have received an adequate diazepam load (i.e., 60 mg or more) do not have seizures even though they may have a relatively strong history of withdrawal seizures (Sellers et al., 1983). In most patients without a previous history of seizures, benzodiazepines alone probably have sufficient anticonvulsant activity to prevent withdrawal seizures (Sellers et al., 1983). Phenytoin is reserved for patients with epilepsy or a history of recurrent or severe withdrawal seizures. A recent uncontrolled open study in 20 "high-risk" seizure patients is consistent with this approach and reiterates our previous advice (Devenyi & Harrison, 1985).

Future Treatment Strategies

Past studies that have attempted to use drugs with greater selectivity in the treatment of alcohol withdrawal have not been terribly encouraging. Lithium decreased only a few subjective symptoms (Sellers et al., 1976). Propranolol decreased tremor, heart rate, and anxiety; however, it caused an increased frequency of hallucinations (Jacob et al., 1983; Sellers et al., 1977). Clonidine appeared to be minimally effective or to actually increase the frequency of clinical seizures (Bjorkqvist, 1975; Blum et al., 1983). If drugs could be developed that were anxiolytic and anticonvulsant and at the same time had a decreased risk of sedation, interaction with ethanol or other central nervous system depressants, and dependence liability, some advances in therapy could occur. A number of newer anxiolytics of the benzodiazepine type and non-benzodiazepine type appear to demonstrate some selective anxiolytic properties (Lippa et al., 1982; Solorzano et al., 1985).

Irrespective of whether more selective drugs will prove to have therapeutic advantages, the methodologic standards for clinical trials in this area have been established. Clinical scales such as the CIWA-A should be used to quantitate drug effects (Shaw et al., 1981). There must be a clear specification of the supportive care given. The importance of such care can be estimated by the inclusion of a placebo-control group. Such a group is necessary because of the potential magnitude of the supportive care effect. In light of the simplification achieved through the diazepam loading-dose technique, it seems likely that other optimal drug therapy strategies for alcohol withdrawal should employ a similar type of titration technique. For this to be clinically feasible, a new drug should be rapidly absorbed and have an intermediate to long half-life in order to avoid withdrawal rebound.

Acknowledgments: We thank our students and other collaborators for their contribution to our studies: Drs. L. Solorzano, H. Kaplan, J. Schneiderman, P. Devenyi, D. Donat, and Ms. J. Shaw, Ms. M. Harrison, and Ms. C. Hamilton. In addition, we thank Ms. D. Campbell and Ms. Karen Cauch-Bontje for their typing and editorial assistance.

References

Bjorkqvist, S.E. Clonidine in alcohol withdrawal. *Acta Psychiatr. Scand.*, 52:256–263, 1975.

Blum, K., Briggs, A.H., and DeLallo, L. Clonidine enhancement of ethanol withdrawal in mice. *Subst. Alcohol Act/Misuse*, 4:59–63, 1983.

Devenyi, P., and Harrison, M.L. Prevention of alcohol withdrawal seizures with oral diazepam loading. *Can. Med. Assoc. J.*, 132:798–800, 1985.

Gessner, P.K. Failure of diphenylhydantoin to prevent alcohol withdrawal convulsions in mice. *Eur. J. Pharmacol.*, 27:120–129, 1974.

Gessner, P.K. Drug therapy of the alcohol withdrawal syndrome. In: Majchrowicz, E., and Noble, E. (eds.), *Biochemistry and Pharmacology of Ethanol*, Vol. 2. New York: Plenum Press, 1979, pp. 374–435.

Greenblatt, D.J., Shader, R.I., and Abernethy, D.R. Drug therapy: Current status of benzodiazepines. *N. Engl. J. Med.*, 309:354–358, 1983.

Gross, M.M., Lewis E., and Hastey, J. Acute alcohol withdrawal syndrome. In: Kissin, B., and Begleiter, H. (eds.), *The Biology of Alcoholism, Clinical Pathology*, Vol. 3. New York: Plenum Press, 1974, pp. 191–263.

Gross, M.M., Lewis, E., and Nagarajan, M. An improved quantitative system for assessing the acute alcohol psychoses and related states (TSA and SSA). In: Gross, M.M. (ed.), *Alcohol Intoxication and Withdrawal: Experimental Studies, Advances in Experimental Medicine and Biology*, Vol. 35. New York: Plenum Press, 1973, pp. 365–376.

Jacob, M.S., Zilm, D.H., MacLeod, S.M., and Sellers, E.M. Propranolol-associated confused states during

best copy available

alcohol withdrawal. *J. Clin. Psychopharmacol.*, 3:185–187, 1983.

Linnoila, M. Benzodiazepines and alcoholism. In: Trimble, R. (ed.). *Benzodiazepines Divided*. New York: John Wiley & Sons, Ltd., 1983, pp. 291–308.

Lippa, A.S., Meyerson, L.R., and Beer, B. Molecular substrates of anxiety: Clues from the heterogeneity and benzodiazepine receptors. *Life Sci.*, 31: 1409–1417, 1982.

Moskowitz, G., Chalmers, T.C., Sacks, H.S., et al. Deficiencies of clinical trials of alcohol withdrawal. *Alcoholism: Clin. Exp. Res.*, 7:42–46, 1983.

Naranjo, C.A. Recent advances in the pharmacotherapy of alcoholism. In: Velasco, M. (ed.), *Clinical Pharmacology and Therapeutics*. Amsterdam: Excerpta Medica, 1983, pp. 132–139

Naranjo, C.A., Sellers, E.M., Chater, K., et al. Nonpharmacologic interventions in the treatment of acute alcohol withdrawal. *Clin. Pharmacol. Ther.*, 34:214–219, 1983.

Rothstein, E. Prevention of alcohol withdrawal seizures: The role of diphenylhydantoin and chlordiazepoxide. *Am. J. Psychiatry*, 130:1381–1382, 1973.

Sampliner, R., and Iber, F.L. Diphenylhydantoin control of alcohol withdrawal seizures: Results of a controlled study. *JAMA*, 230:1430–1432, 1974.

Sandor, P., Sellers, E.M., Dumbrell, M., and Khouw, V. Effect of short- and long-term alcohol use on phenytoin kinetics in chronic alcoholics. *Clin. Pharmacol. Ther.*, 30:390–397, 1981.

Sellers, E.M., and Kalant, H. Drug therapy: Alcohol intoxication and withdrawal. *N. Engl. J. Med.*, 294:757–762, 1976.

Sellers, E.M., and Kalant, H. Alcohol withdrawal and delirium tremens. In: Pattison, E.M., and Kaufman, E. (eds.), *The Encyclopedic Handbook of Alcoholism*. New York: Gardner Press, 1982, pp. 147–166.

Sellers, E.M., Cooper, S.D., Zilm, D.H., and Shanks, C. Lithium treatment during alcohol withdrawal. *Clin. Pharmacol. Ther.*, 20:199–206, 1976.

Sellers, E.M., Zilm, D.H., and Degani, N. Comparative efficacy of propranolol and chlordiazepoxide in alcohol withdrawal. *J. Stud. Alcohol.*, 38:2096–2108, 1977.

Sellers, E.M., Naranjo, C.A., Harrison, M., et al. Oral diazepam loading: Simplified treatment of alcohol withdrawal. *Clin. Pharmacol. Ther.*, 34:822–826, 1983.

Shaw, J.M., Kolesar, G.S., Sellers, E.M., et al. Development of optimal treatment tactics for alcohol withdrawal: I. Assessment and effectiveness of supportive care. *J. Clin. Psychopharmacol.*, 1:382–383, 1981.

Solorzano, L., Keller, J., Kaplan, H.L., et al. Selectivity of drug action in ethanol withdrawal. Proceedings of the Canadian Federation of Biological Societies 28th Annual Meeting, Toronto, June 1985, p. 143.

Sullivan, J., Schneiderman, J., Sykora, K., et al. Alcohol withdrawal (AW): Diagnostic criteria and clinical course. Abstract presented at the Royal College of Physicians and Surgeons Annual Meeting, Vancouver, September 1985.

Thompson, W.L. Management of alcohol withdrawal syndrome. *Arch. Intern. Med.*, 138:278–283, 1978.

Toshney, J. An alcoholism and detoxification centre. *Nurs. Times*, 74:573–576, 1978.

Victor, M. Treatment of alcoholic intoxication and the withdrawal syndrome. *Psychosom. Med.*, 28:636–650, 1966.

Whitfield, E.L., Thompson, G., Lamb, A., et al. Detoxification of 1,024 alcoholic patients without psychoactive drugs. *JAMA*, 293:1409–1410, 1978.

Benzodiazepines for Treatment of Panic Attacks: A New Look[1]

Karl Rickels, M.D.,[2] and Edward E. Schweizer, M.D.[2]

Introduction and Recent Literature

Panic disorder (PD) has only recently emerged as a distinct psychiatric diagnosis with the advent of DSM-III (American Psychiatric Association, 1980). Its separate status is largely an American nosological refinement, not yet officially sanctioned in Europe (Editorial, 1983). Under DSM-II (American Psychiatric Association, 1952), patients with panic presentations had been categorized under a diagnosis of either Anxiety Neurosis or Phobic Neurosis, depending on the degree of concurrent phobic avoidance behavior or agoraphobia.

The impetus for this new subtyping of anxiety stemmed from Klein (1964) and his associates (Zitrin et al., 1978, 1983) who first observed a preferential treatment response to the tricyclic antidepressant imipramine over benzodiazepines in a subset of anxious patients with crescendo anxiety associated with agoraphobia. Other researchers confirmed the utility of antidepressants in panic patients with agoraphobia and extended it to include monoamine oxidase (MAO) inhibitors such as phenelzine (Liebowitz et al., in press; Sheehan et al., 1984b). Various behavior therapies (Marks, 1976; Mavissakalian & Michelson, 1982) also proved beneficial in the treatment of such patients.

We thus have a new anxiety diagnosis—PD, with or without complicating agoraphobia—that owes its existence, in no small measure, to research suggesting the relative *ineffectiveness* of traditional benzodiazepine anxiolytics and the relative superiority of certain antidepressants in its treatment.

With the exception of alprazolam, the lack of specific effectiveness of other benzodiazepines in panic states has, in recent years, become an almost unquestioned assumption in much of clinical practice. It is a rather sweeping generalization, though, based on slim scientific evidence indeed. We are aware of only two well-controlled studies assessing the efficacy of non-triazolobenzodiazepines in PD: one is a negative, and one a positive study.

McNair and Kahn (1981) reported that chlordiazepoxide (60 mg/day) was significantly less effective in alleviating symptoms of PD than was imipramine. In contrast, Noyes et al. (1984) compared, in a 2-week, double-blind crossover study, diazepam with propranolol in patients suffering from panic disorder accompanied by various degrees of phobic avoidance behavior. They reported a significant reduction in number and intensity of panic symptoms, phobic symptoms, and social impairment in patients being treated with diazepam in the usual therapeutic daily dosage, but not in patients treated with the beta blocker propranolol (Table 1).

The question that arises is: what is the role of the benzodiazepines in PD, if any? Is it merely as a minor adjunct to antidepressant

TABLE 1

Mean (± SE) Number and Severity of Panic Attacks and Severity of Phobic Symptoms and Social Impairment During Drug Therapy

	Baseline	Propranolol Week 2	Diazepam Week 2
Panic Attacks ($N = 17$)			
Number	8.5 ± 2.79	6.4 ± 1.26	2.9 ± 0.84
Severity	2.2 ± 0.20	2.0 ± 0.19	1.2 ± 0.26
Phobic Symptoms ($N = 19$)			
Severity	2.2 ± 0.21	1.6 ± 0.27	1.0 ± 0.19
Social Impairment ($N = 21$)			
Severity	2.2 ± 0.18	1.9 ± 0.18	1.0 ± 0.26

From Noyes et al., *Arch. Gen. Psychiatry* 41:287, 1984 treatment? Do triazolo compounds such as alprazolam have a unique treatment specificity? Do associated features such as degree of phobic avoidance behaviors or degree of generalized or anticipatory anxiety have a bearing on drug choice or treatment response? From most literature reporting on the treatment of panic attacks and agoraphobia, it is quite difficult to determine whether patients included in these studies suffered primarily from PD *without* agoraphobia or from PD *with* agoraphobia. Thus, no answer presently exists to the important clinical question of whether benzodiazepines, prescribed in therapeutic dosages, are effective agents in the treatment of patients suffering from PD without marked agoraphobia. In the succeeding sections the authors will comment on some of these issues.

---

[1] This study was supported in part by USPHS Research Grant MH-08957 from the National Institute of Mental Health.

[2] Department of Psychiatry, University of Pennsylvania, University Hospital, Philadelphia, PA 19104.

Alprazolam in Panic Disorder

Sheehan (1984a) conducted the first study of alprazolam in PD and agoraphobia. It was an uncontrolled, single-blind, crossover study comparing ibuprofen (Motrin) versus alprazolam which indicated that alprazolam was more effective in reducing PD symptoms than ibuprofen. In another larger and double-blind controlled study, Sheehan then compared alprazolam with imipramine, phenelzine, and placebo in patients suffering from PD and/or agoraphobia (Sheehan et al., 1984b) and observed that all three active agents produced significantly more improvement than placebo. Again, patients suffering only from PD were not differentiated from those suffering from both PD and agoraphobia. Chouinard et al. (1982) compared alprazolam with placebo under double-blind conditions in two groups of patients, those suffering from PD and those suffering from generalized anxiety disorder (GAD). Using the Hamilton Anxiety Scale (HAM-A) as outcome criterion, Chouinard et al. (1982) observed that alprazolam was equally effective in PD and in GAD but that placebo appeared slightly more effective in GAD than in PD patients. Medications were prescribed within Food and Drug Administration (FDA) recommended dosages.

Several years ago the Upjohn Company instituted a large controlled trial comparing the effects of alprazolam prescribed in dosages up to 10 mg/day versus placebo in PD patients with and without secondary phobic avoidance behavior or agoraphobia. The Upjohn study was conducted in a multinational, multicenter fashion and its preliminary results have recently been reported (Ballenger et al., 1985). Alprazolam, when prescribed in higher than recommended therapeutic dosages for the treatment of GAD, produced significantly more improvement than placebo in all aspects of behavior assessed, be it anxiety, number and intensity of panic attacks, phobic avoidance behavior, or work and family adjustment. However, no evidence as to whether or not alprazolam's effectiveness depended on the intensity of the agoraphobic condition present was presented.

The effective dosage range of alprazolam for panic appears, from these studies, to be 6 to 8 mg/day (though doses up to 10 mg or higher have not infrequently been required). On an equipotent basis, this translates into a diazepam dose of 60 to 100 mg/day or higher. Controlled studies of benzodiazepines in panic using equipotent dosages have, to our knowledge, not yet been conducted.

Non-Triazolobenzodiazepines and Panic Disorder: Some New Data

Recently, one of the present authors (Schweizer) treated 5 patients diagnosed by SCID-UP (Structured Clinical Interview for DSM-III Diagnosis—Upjohn) as suffering from PD with lorazepam in an open-label trial. Patients with moderate to severe degrees of agoraphobia were excluded, as were patients suffering from concomitant depression. Dosing was begun with lorazepam 0.5 mg three times a day (t.i.d.) and then gradually increased to a daily dose of 3 to 8 mg, i.e., the same dosage range as recommended for the treatment of GAD. Improvement was monitored by both the HAM-A and a Panic Attack Diary. Four of five patients obtained more than 80% control of panic attacks associated with a reduction in Hamilton scores to <8. Some well-controlled double-blind stud-

TABLE 2

Intake Criteria for Studies A and B

1) HAM-A ≥ 18
2) Covi-Anxiety ≥ 8
3) Raskin Depression < Covi-Anxiety
4) 17-item Anxiety Entry Checklist (FDA): ≥5 items
5) Duration of symptoms:
   Study A: >3 months
   Study B: >1 month
6) DSM-II anxiety diagnosis (patient later reclassified according to DSM-III)
7) Excluded:
   a) Phobic disorders including marked agoraphobia
   b) Depressive disorders
8) Considered by psychiatrist to be in need of anxiolytic treatment
9) Diazepam dosage (~25 mg/day)

ies presently under way at several clinical research centers should be able to confirm or refute the antipanic effects of such non-triazolobenzodiazepines as diazepam and lorazepam.

Since patients suffering from panic disorder without marked agoraphobia were diagnosed prior to the introduction of the DSM-III in 1980 as belonging to the large group of patients suffering from anxiety neurosis, the authors felt it important to review two studies conducted by their research group prior to 1980, and to divide all anxious patients into those with and those without panic symptoms. It should be stressed, however, that patients who received a DSM-II diagnosis of phobic neurosis, which would have included agoraphobia, were excluded from these studies.

Hopkins Symptom Checklist (HSCL) (Derogatis et al., 1974) data were available for both studies. Entry criteria employed in these studies are given in Table 2, and the items which make up the HSCL anxiety and panic factors are given in Table 3. The HSCL anxiety factor was further divided into a GAD subfactor and a PD subfactor, as only one of the two studies included the HSCL panic factor as a criterion measure.

Table 4 reports 6 weeks' improvement results obtained in the first of the two reviewed studies (Rickels et al., 1983). Diazepam was the treatment agent and the HSCL anxiety factor, its two subfactors, and the HSCL panic factor were used as outcome criteria. Patients improved highly significantly in all measures. When analyzing only the subgroup of patients scoring high on the HSCL panic factor (≥1.60) (Table 5), even more significant improvement was observed in both general anxiety and panic anxiety symptoms.

Table 6 presents results obtained in the second study (Rickels et al., 1982). Diazepam and placebo treatment outcome was compared as a function of initial level of panic symptoms as assessed with the HSCL panic subfactor. (A score of ≥1.60 was considered high panic level.) Table 6 clearly indicates no evidence for a drug X panic level interaction, only highly significant main drug effects, with anxious patients improving significantly more on diazepam than on placebo, irrespective of their initial level of panic symptomatology.

Some additional evidence of the usefulness of benzodiazepines in the treatment of PD

TABLE 3

Hopkins Symptom Checklist (HSCL) Anxiety and Panic Factors

HSCL-Anxiety Factor

GAD Subfactor:

1. Nervousness or shakiness inside
2. Trembling
3. Feeling fearful
4. Feeling tense or keyed up

Panic Subfactor:

1. Suddenly scared for no reason
2. Heart pounding or racing
3. Having to avoid certain things, places, activities because they frighten me

HSCL-Panic Factor

1. Feeling afraid in open spaces or on the streets
2. Feeling afraid to go out of the house alone
3. Feeling uneasy in crowds, such as shopping or at a movie
4. Feeling afraid of fainting in public
5. Feeling afraid to travel on buses, subways, or trains
6. Feeling nervous when left alone

TABLE 4

Six Weeks' Improvement on Diazepam of Anxious Outpatients (*N* = 236) (Study A)

	Treatment		
	Pre	Post	Δ*
HSCL-Anxiety Factor	2.21	1.70	.51
GAD Subfactor	2.43	1.87	.56
Panic Subfactor	1.92	1.48	.44
HSCL-Panic Factor	1.55	1.28	.27

*Student *t* test: $p < .001$

TABLE 5

Six Weeks' Improvement on Diazepam in a Subgroup of Anxious Outpatients Scoring High (>1.60) on HSCL Panic Factor (*N* = 78) (Study A)

	Treatment		
	Pre	Post	Δ*
HSCL-Anxiety Factor	2.83	2.06	.77
GAD Subfactor	2.96	2.19	.77
PD Subfactor	2.66	1.89	.77
HSCL-Panic Factor	2.41	1.67	.74

*Student's *t* test: $p < .001$

TABLE 6

Diazepam and Placebo Response of Anxious Neurotic Outpatients as a Function of Initial Level of Panic Symptoms (HSCL Panic Subfactor) (*N* = 138) (Study B)

	Adjusted Post-treatment Means (4-week endpoint)		F	F
HSCL Anxiety Factor	Diazepam (*N* = 67)	Placebo (*N* = 71)	Drug X Panic Effect	Mean Drug Effect
High Panic	1.79	2.11	.30	8.45
Low Panic	1.89	2.07		
HSCL GAD Subfactor:				
High Panic	1.93	2.30	.46	9.22*
Low Panic	1.94	2.14		
HSCL-Panic Subfactor:				
High Panic	1.59	1.77	.12	5.32**
Low Panic	1.85	1.95		

*$p < .005$
**$p < .025$

comes from a study of 117 long-term chronic benzodiazepine users (in preparation). Preliminary results obtained for the first 31 of these 117 patients were recently reported (Rickels et al., 1984). An intensive psychiatric history, including an administration of the SADS-L, indicated that 31% of 117 patients who initiated benzodiazepine therapy many years ago started their treatment because of symptoms closely resembling panic attacks (Table 7). When these 117 patients were asked prior to benzodiazepine withdrawal whether they were deriving any benefit from their benzodiazepine medication, about 80% of those originally diagnosed as suffering from GAD and 72% of those originally diagnosed as suffering from PD, but only 40% of those originally diagnosed as suffering from depressive states, claimed that they had derived significant benefit from treatment with various long as well as short half-life benzodiazepines.

TABLE 7

Psychiatric Diagnosis of Chronic Benzodiazepine Users When Initiating Anxiolytic Therapy

Diagnosis	Percent
Anxiety	40
Panic	31
Depression	20
Other	3
No Diagnosis	6

These data seem to indicate to the authors that the recent "discovery" of the beneficial effect of the benzodiazepine alprazolam in the treatment of PD does not seem to be unique for alprazolam, but may also be true for some of the older benzodiazepines.

Comments

Several points of clinical interest may be deduced from the data presented.

1. Klein's (1964) earlier observation that "anticipatory anxiety" of agoraphobic patients is beneficially influenced by benzodiazepine supports the benzodiazepines' efficacy in GAD, as Klein's anticipatory anxiety would probably be diagnosed within the framework of DSM-III as GAD.

2. Whether or not other benzodiazepines besides alprazolam, particularly if prescribed in higher than FDA-approved therapeutic dosages, will be helpful in patients suffering from PD with and without marked agoraphobia cannot be determined at this time. PD patients suffering from marked agoraphobia have so far not responded as well to older benzodiazepines prescribed in the usual ther-

apeutic dosages than to imipramine, phenelzine, or alprazolam. However, since studies frequently do not separate patients suffering from pure PD from those suffering from panic disorder with agoraphobia, the question is left unanswered whether the improvement registered in these studies was largely contributed by patients suffering from pure PD or patients suffering from more severe agoraphobia. It is hoped that the completed, as well as ongoing, multicenter Upjohn trials will provide important answers to this question.

3. If differences in antipanic/antiagoraphobic efficacy between alprazolam and other benzodiazepines should indeed exist, one may ask: Are these differences related to the fact that patients are better able to adjust to the sedative effects of alprazolam than to those of other benzodiazepines, or are they related to the triazolo-ring structure unique to alprazolam? Similar speculations may also be made to explain alprazolam's "antidepressive" properties (Feighner et al., 1983; Rickels et al., 1985). In fact, in a recently completed study by this research group (in preparation) alprazolam and imipramine produced equal degrees of improvement and significantly more improvement than placebo or diazepam in patients suffering from major depressive disorders.

4. If the original experience of the alprazolam research program, namely that alprazolam has to be given in relatively high daily dosages (6 to 10 mg in the Upjohn-supported studies and up to 15 mg in the authors' own experience in selected patients), should be confirmed, one certainly has cause for concern regarding treatment discontinuation, treatment which for PD with agoraphobia may last for at least 6 to 12 months. In fact, if abruptly stopped, seizures (Breier et al., 1984) or other severe withdrawal symptoms (Noyes et al., 1985) can be expected. Fortunately, at least in the authors' experience, most PD patients are not in need of such excessive daily dosages but respond well to only 2 to 4 mg/day of alprazolam. Higher daily dosages may be required, however, for patients suffering from marked agoraphobia. Research is presently under way by our research group to determine the safest and most convenient management of discontinuation from alprazolam treatment after prolonged use.

Among the many potential problems, just one should be mentioned here. Patients frequently experience panic attacks during alprazolam discontinuation which then is interpreted by patient and physician as a return of the original panic symptoms, while indeed they may represent for many patients a rebound phenomenon or withdrawal reaction. Needless to say, if other benzodiazepines are used in equipotent dosages for prolonged periods of time in the treatment of PD, similar problems to those possibly caused by alprazolam discontinuation can be expected.

5. The authors suggest that one may be dealing with several subgroups of PD patients. One group of patients either outlasts their initial panic attacks without treatment or will adjust to them in such a way that they cease to be a hindrance, such as, for example, sitting on the aisles in movie theaters or having to stand close to a door in a subway. A second group of patients suffering from panic attacks obtain relief with the usual dosages of various benzodiazepines and their panic attacks are aborted or prevented and thus little chance exists to develop secondary phobic avoidance behavior. For these two patient groups, GAD might be in many cases as appropriate a diagnosis as PD. Finally, there are those patients whose panic attacks do not go away on their own or do not respond to benzodiazepine treatment; these patients will with time either develop secondary avoidance behavior (agoraphobia) or hysterical and somatization behavior (Katon, 1984). It is probably this subgroup of PD patients, who also suffer from marked agoraphobia, who are in need of pharmacological intervention with such agents as imipramine, phenelzine, or alprazolam prescribed alone or in conjunction with various methods of behavior modification.

Conclusion

The authors suggest that the role of benzodiazepines for the treatment of panic disorder needs yet to be clarified. Good clinical evidence indicates that many patients who suffer from PD with or without agoraphobia respond to alprazolam therapy, particularly if alprazolam is prescribed in higher than FDA-approved therapeutic daily dosages. It has further been shown that patients suffering from agoraphobia and panic attacks do respond to imipramine and phenelzine. Evidence also exists, albeit based on less than the most rigorous research, that PD patients without marked agoraphobia respond well to nontriazolo benzodiazepines, such as diazepam, for example.

No answer has yet been provided to the question of whether or not benzodiazepines differ among each other in their potential to help patients suffering from PD with or without agoraphobia, when prescribed in equipotent dosages. And if differences should be found, are they related, for example, simply to the patients' ability to tolerate alprazolam's side effects, or are they related to its unique triazolo ring structure?

Much more research needs to be carried out to clarify the role of benzodiazepines for the treatment of panic disorder *with* and *without* agoraphobia. Various benzodiazepines have to be compared in equipotent dosages over similar periods of time in well-controlled studies. What is the minimum daily dosage necessary to produce desired results? Could it be that most PD patients respond to FDA-recommended therapeutic dosages and that only a limited group of severe agoraphobics may require excessive dosages not yet approved by the FDA?

Since some research has recently reported that imipramine also may possess antianxiety effects (Lipman et al., 1981), it may well be that the effect of phenelzine, a monoamine oxidase inhibitor (MAOI), and imipramine, a tricyclic, in PD may be similar to their effects in GAD when prescribed in appropriate dosages and for adequate periods of time (i.e., if patients could be persuaded not to drop out of treatment because of side effects). Thus we might learn in time that there are more similarities than dissimilarities between antidepressant, antianxiety, and antipanic agents.

In the meantime, it behooves the psychiatrist treating patients suffering from PD with or without agoraphobia to use the lowest daily medication dose which will produce desired clinical results and to treat the patients for the shortest time possible. A general guide might be that the more chronic and the more severe the panic disorder and the more intense the presence of secondary avoidance behavior and/or agoraphobia, the longer should be the duration of treatment and the higher the daily dosage. If patients have been on therapeutic or certainly if on higher than recommended therapeutic dosages of benzodiazepines for 6 to 12 months, drug discontinuation has to be conducted slowly and carefully, and physician and patient should be reminded that only a drug-free period of at least several weeks will allow for determining with some certainty whether the "reoccurrence of panic attacks" represents a return of original symptoms or a rebound phenomenon. Best results may well be obtained with a treatment regimen which combines the use of medication with some method of behavior modification.

References

American Psychiatric Association, Taskforce on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

American Psychiatric Association, Taskforce on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders (DSM-II)*, 2nd ed. Washington, D.C.: American Psychiatric Association, 1952.

Ballenger, J.C., Burrows, G.D., Noyes, R., et al. Alprazolam treatment of agoraphobia/panic disorder. Presented at the 138th Annual Meeting of the American Psychiatric Association, Dallas, May, 1985.

Breier, A., Charney, D.S., and Nelson, J.C. Seizures induced by abrupt discontinuation of alprazolam. *Am. J. Psychiatry*, 141(12):1606-1607, 1984.

Chouinard, G., Annable, L., Fontaine, R., and Solyom, L. Alprazolam in the treatment of generalized anxiety and panic disorders: A double-blind placebo-controlled study. *Psychopharmacology*, 77:229-233, 1982.

Derogatis, L.R., Lipman, R.S., Rickels, K., et al. The Hopkins symptom checklist (HSCL): A self-report inventory. *Behav. Sci.*, 19 (1):1-15, 1974.

Editorial. Panic-symptom or disorder? *Lancet*, I:1418-1419, June 25, 1983.

Feighner, J.P., Aden, G.C., Fabre, L.F., et al. Comparison of alprazolam, imipramine, and placebo in the treatment of depression. *JAMA*, 249 (22):3057-3064, 1983.

Katon, W. Panic disorder and somatization. *Am. J. Med.*, 77:101-112, 1984.

Klein, D.F. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia (Berlin)*, 5:397-408, 1964.

Liebowitz, M.R., Quitkin, F.M., Stewart, J.W., et al. Phenelzine versus imipramine in atypical depression: A preliminary report. *Arch. Gen. Psychiatry* (In press).

Lipman, R.S., Covi, L, Downing, R.W., et al. Pharmacotherapy of anxiety and depression. *Psychopharmacol. Bull.*, 17 (3):91-94, 1981.

Marks, I.M. The current status of behavioral psychotherapy: Theory and practice. *Am. J. Psychiatry*, 133:253-261, 1976.

Mavissakalian, M., and Michelson, L. Agoraphobia: Behavioral and pharmacological treatments, preliminary outcome, and process findings. *Psychopharmacol. Bull.*, 18 (4):91-103, 1982

McNair, D.M., and Kahn, R.J. Imipramine compared with a benzodiazepine for agoraphobia. In: Klein, D.F., and Rabkin, J. (eds.), *Anxiety: New Research and Changing Concepts*. New York: Raven Press, 1981, pp. 69-79.

Noyes, R., Clancy, J., Coryell, W.H., et al. A withdrawal syndrome after abrupt discontinuation of alprazolam. *Am. J. Psychiatry*, 142 (1):114–116, 1985.

Noyes, R., Anderson, D.J., Clancy, J., et al. Diazepam and propanolol in panic disorder and agoraphobia. *Arch. Gen. Psychiatry*, 41:287–292, 1984.

Rickels, K., Case, W.G., Downing, R.W., and Winokur, A. Long-term diazepam therapy and clinical outcome. *JAMA*, 250 (6):767–771, 1983.

Rickels, K., Case, W.G., Winokur, A., and Swenson, C. Long-term benzodiazepine therapy: Benefits and risks. *Psychopharmacol. Bull.*, 20 (4):608–615, 1984.

Rickels, K., Feighner, J.P., and Smith, W.T. Alprazolam, amitriptyline, doxepin, and placebo in the treatment of depression. *Arch. Gen. Psychiatry*, 42:134–141, 1985.

Rickels, K., Wiseman, K., Norstad, N., et al. Buspirone and diazepam in anxiety: A controlled study. *J. Clin. Psychiatry*, 43(12):81–86, 1982.

Sheehan, D.V., Coleman, J.H., Greenblatt, D.J., et al. Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J. Clin. Psychopharmacol.*, 4(2):66–75, 1984.

Sheehan, D.V., Claycomb, J.B., Surman, O.S., et al. The relative efficacy of alprazolam, phenelzine, and imipramine in treating panic attacks and phobias. Read before the 137th Annual Meeting, American Psychiatric Association, Los Angeles, May 6, 1984.

Zitrin, C.M., Klein, D.F., and Woerner, M.G. Behavior therapy, supportive psychotherapy, imipramine, and phobias. *Arch. Gen. Psychiatry*, 35:307–316, 1978.

Zitrin, C.M., Klein, D.F., Woerner, M.G., and Ross, D.C. Treatment of phobias: I. Comparison of imipramine hydrochloride and placebo. *Arch. Gen. Psychiatry*, 40:125–138, 1983.

Cholinergic Mechanisms in the Treatment of Geriatric Disorders

CHAIR: Allen Raskin, Ph.D.
Pharmacologic and Somatic
Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Physostigmine in Patients With Alzheimer's Disease

Michael Davidson, M.D.,[1] Richard C. Mohs, Ph.D.,[1] Eric Hollander, M.D.,[1] Bonnie M. Davis, M.D.,[1] Theresa Ryan, M.S.,[1] Thomas B. Horvath, M.D.,[1] and Kenneth L. Davis, M.D.[1]

Postmortem examination of brain specimens from patients with clinical diagnosis of Alzheimer's disease (AD) repeatedly demonstrated neurotransmitter deficiencies in the neocortex. The most consistent evidence point towards a reduction in markers reflecting cholinergic activity (Davies, 1979; Perry et al., 1977, 1978). While other neurotransmitters like norepinephrine and somatostatin were found deficient, this was in addition to, and not instead of, the cholinergic deficiency (Adolfsson et al., 1979; Rossor et al., 1980). Furthermore, reduction in choline acetyltransferase (CAT) activity was reported in brain areas related to memory and learning and the deficit quantitatively correlates with severity of dementia (Perry et al., 1978). Additional support for the role of acetylcholine (ACh) in learning and memory, and implicitly in AD, comes from pharmacological studies.

Administration of cholinomimetics to young normal subjects was found to enhance encoding of new information beyond immediate memory (Davis et al., 1978). Conversely, administration of scopolamine, a centrally active anticholinergic, resulted in transient cognitive improvements phenomenologically similar to age-related memory dysfunctions (Drachman & Levitt, 1974). For all those reasons, enhancement of cholinergic neurotransmission in patients with AD would be expected to ameliorate some cognitive dysfunction.

Pharmacologic strategies employed in this attempt included administration of direct cholinergic receptor agonists; increasing ACh synthesis by precursor loading; and limiting ACh breakdown by inhibiting acetylcholinesterase (AChE). Clinical trials of cholinergic agonists have produced very mild improvements in symptoms of AD; however, these studies were seriously hampered by adverse effects. In spite of encouraging results in laboratory animals, the precursor loading strategy using lecithin and choline produced minimal or no improvements in patients with AD (Etienne, 1983).

Physostigmine, a competitive AChE inhibitor, has been used in at least nine clinical studies of patients with a clinical diagnosis of AD (Ashford et al., 1981; Caine, 1980; Caltagiorne et al., 1982; Kaye et al., 1982; Muramato et al., 1984; Peters & Levin, 1979; Smith & Swash, 1979; Sullivan et al., 1982; Thal et al., 1983). In contrast to the tonic effect of muscarinic agonist, physostigmine administration may better mimic the more phasic effect of endogenous ACh. Furthermore, physostigmine can be administered relatively safely, an important consideration in a target population with an often compromised cardiovascular system. This paper discusses our results of clinical trials with physostigmine in AD patients together with methodological implications relevant to this pharmacologic strategy.

---

[1] Department of Psychiatry, Bronx VA Medical Center, Bronx, NY 10468.

Patients meeting National Institute for Neurological and Communicative Disorders and Stroke (NINCDS) criteria for "probable AD" were included in the study (McKhann et al., 1984). The diagnosis of AD was supported by a clinical history demonstrating at least 1 year of progressive deterioration in cognition and other higher cortical functions: Dementia Rating Scale scores higher than 4; and a Memory and Information Test score of less than 10. Other tests used in the diagnostic process were the CAT scan, biochemical screening tests, thyroid function tests, serum B_{12} and folate levels, and neurological and psychiatric examinations. Particular care was taken to rule out patients whose dementia might be due to alcoholism, depression, or other neurological or medical conditions. To rule out patients with multi-infarct dementia, all patients were assigned a Hachinski Ischemic Score (Hachinski et al., 1975) and any patient with a score over 4 was excluded. All patients were free of psychoactive medications except those administered as part of these investigations, during and for at least 2 weeks prior to any study.

In order to establish the effect of physostigmine on cognitive symptoms of AD patients, the drug was initially administered intravenously. Previous animal and human studies demonstrated that intravenous physostigmine has a narrow therapeutic window. Doses slightly below this window produced no cognitive improvement while doses slightly exceeding the therapeutic window may in fact worsen performance on cognitive testing (Bartus, 1979; Davis et al., 1976). Therefore, an adequate test of physostigmine's efficacy requires a dose-finding phase in which a best dose is assigned to individual patients. Such a study design involves several testing sessions on the drug condition and only one testing session on placebo, thus increasing the likelihood of a drug effect to occur by chance.

In order to avoid this methodological flaw at the end of the dose-finding phase, a trial of the best physostigmine dose and a trial of placebo were repeated. Physostigmine (0.125 mg, 0.25 mg, and 0.5 mg) or saline placebo was randomly infused over 30 minutes. Starting 15 minutes into the infusion and ending 5 minutes after the end of the infusion, patients were given three trials on a visual recognition memory task. On each trial the patient was first presented with 12 words or pictures which were subsequently mixed with 12 additional items not previously shown to the patient. The 24 items were then presented, one at a time, and the patient was asked for each item whether or not it was one of the previously presented. Thirteen of the 16 patients included in the study showed a moderate transient improvement while receiving a dose of physostigmine and 3 patients performed best on placebo. A significant effect was demonstrated for the 13 "responders" included in the replication phase (F 1,11) = 8.00, $p<.02$), indicating that patients gave more correct responses while receiving physostigmine.

In spite of the theoretical importance of this finding, confirmed by others (Christie et al., 1981), its clinical applicability is limited by the short action of intravenous physostigmine. A meaningful evaluation of the drug's therapeutic potential in AD required a better and safer delivery route which would enable a comprehensive evaluation of this drug over an extended period of time. Such a comprehensive evaluation needs to assess cognitive and non-cognitive symptoms and possess the flexibility to include AD patients in different stages of this progressive disease. Alzheimer's Disease Rating Scale (ADRS) (Rosen et al., 1984) is such an assessment instrument and its reliability and validity are established. It is specifically designed to evaluate severity of symptoms in pharmacological studies. Cognition and language are assessed by task such as object naming, following commands, orientation, and constructional and ideational praxis. Non-cognitive behaviors are assessed by item such as depression, cooperation, psychotic symptoms, motor activity, and vegetative signs. The scale includes a broad range of tasks so that both very severe and mildly symptomatic patients can be evaluated. A higher score on the scale represents a more severe form of illness. Using this scale in conjunction with repeated oral administration of physostigmine provides a framework to study the more chronic effects of this treatment.

When this oral physostigmine trial was conceived, it was predicted that not all patients would benefit from the drug. The ability of oral physostigmine to improve AD systems depends on the drug's absorption, central penetrance, and the number of functioning cholinergic neurons still intact. It should be anticipated that in patients with extensive cholinergic cell loss or major abnormalities in other neurotransmitter systems, physostigmine would be unlikely to either increase neurotransmission or improve symptoms. Consequently, it is necessary to obtain a measure of physostigmine's biological effect in the central nervous system along with measures of drug-induced behavioral change. Cortisol secretion may be a potential indicator of physostigmine effect on cholinergic activity, as suggested by human and animal studies, demonstrating that cholinergic drugs increase and anticholinergics suppress cortisol nocturnal secretion (Davis et al., 1982; Hillhouse et al., 1975; Krieger & Krieger, 1967). Therefore, the effect of physostigmine on plasma cortisol levels was measured in concomitance with the cognitive effect of the drug.

Twelve AD patients were given oral physostigmine in a dose-finding/replication study. Physostigmine (0.5 mg, 1 mg, 1.5 mg, and 2 mg) or placebo was given every 2 hours for 3 to 4 days between 7 a.m. and 11 p.m. The ADRS was administered on the last day of each drug condition between 1:30 p.m. and 3:30 p.m. On the last night of drug and placebo condition in the replication phase, blood was drawn each half hour between 11 p.m. and noon the next day and assayed for cortisol. To ensure the drug effect on the early morning cortisol secretion, physostigmine or placebo were continued until 11 a.m. on the next morning following the sleep study. Eleven of 12 patients studied had lower (better) ADRS scores on a dose of physostigmine which were maintained in 7 patients during the replication phase. Only about one-third of patients showed a consistent and clinically evident improvement on physostigmine. However, it is encouraging to note that patients who improved during the replication phase also tended to show the greatest improvement during the dose-finding phase, and this improvement was generally achieved on the highest dose of physostigmine. Examination of plasma cortisol values revealed a strong linear relationship between percent increase in cortisol and symptoms improvement (r (6) = .88, $p<.02$), suggesting that physostigmine improved AD symptoms only to the extent that the drug has a central cholinomimetic activity. Similarly, a study by Thal et al. (1983) suggests that AD patients are benefitted by physostigmine only to the extent that this drug had a significant inhibitory effect on cerebrospinal fluid AChE.

Physostigmine-induced improvement in some AD patients reported here is in agreement with most (Muramoto et al., 1984; Sullivan et al., 1982; Thal et al., 1983), but not all reported studies (Ashford et al., 1981), with consistently more robust effect being noted. These heterogeneous results have to be interpreted in light of the problems inherent in pharmacological studies of AD and, in particular, pharmacological studies with putative cholinomimetics. The diagnosis of AD is inherently problematic without tissue verification. Misdiagnosed patients have other neurologic disorders or lack the characteristic histopathologic findings required for postmortem validation of AD (Liston & Rue, 1983; Nott & Fleminger, 1975; Ron et al., 1979). Even rigorous diagnostic criteria as described in this study have a 10% error rate. Hence, typical pharmacological trials with relatively small sample sizes are less likely to find statistically significant group means if they include an inevitable misdiagnosed patient. Nevertheless, a recent study reported a mean effect of physostigmine for the entire group (Beller et al., 1985).

In addition to the uncertainty of the antemortem diagnosis of AD and suggesting a complex pathophysiology for this disorder are postmortem biochemical findings of other neurotransmitter deficiencies along with the well-established cholinergic differences. Noradrenergic, serotonergic, and occasionally dopaminergic deficiencies were reported in patients with a clinical diagnosis of AD and postmortem presence of plaques, tangles, and reduced cholinergic activity (Adolfsson et al., 1979; Bondareff et al., 1982; Bowen et al., 1983; Rossor et al., 1984). If these neurotransmitters have a functional role in symptoms of AD, a pharmacological strategy restricted to cholinergic enhancement may not benefit AD patients with multiple neurotransmitter deficiencies. Future studies should include combined neurotransmitter replacement.

Obviously any pharmacological intervention that will aid AD patients must ultimately address the cholinergic deficit. However, the ability of physostigmine to enhance cholinergic activity is dependent on the amount of ACh made available to the synaptic cleft by viable cholinergic neurons. The presumed retrograde neuronal distinction occurring in the course of this disease and the limited overlapping innervation of cholinergic receptors may decrease the efficacy of physostigmine as the disease progresses (Coyle et al., 1983). This may also explain the heterogeneous effects produced by physostigmine in AD patients in different stages of this disease.

However imperfect the theoretical background for the use of physostigmine in AD is, issues related to this drug delivery must be addressed. Little is known about physostigmine pharmacokinetics or central nervous system (CNS) penetrance; nevertheless it is presumed that a constant and stable drug presence in the CNS would be desirable. Also, experience derived from pharmacological trials of physostigmine suggest that most AD patients benefit from higher doses of this drug. This has to be reconciled with the peripheral adverse effects of physostigmine and the difficulties involved in chronic administration of multiple drug doses to a demented population. Slow oral capsules, and subcutaneous and intrathecal devices are some of the alternatives presently under consideration.

References

Adolfsson, R., Gottfries, C.G., Roos, B.F., and Winblad, B. Changes in the brain catecholamines in patients with dementia of Alzheimer type. *Br. J. Psychiatry*, 135:216–223, 1979.

Ashford, J.W., Soldinger, S., Schaeffer, J., et al. Physostigmine and its effect on six patients with dementia. *Am. J. Psychiatry*, 138:829–830, 1981.

Bartus, R.T. Physostigmine and recent memory effects in young and aged nonhuman primates. *Science*, 206:1087-1089, 1979.

Beller, S.A., Overall, J.E., and Swann, A.C. Efficacy of oral physostigmine in primary degenerative dementia. *Psychopharmacology*, 87:147-151, 1985.

Bondareff, W., Mountjoy, C.Q., and Roth, M. Loss of neurons of origin of the adrenergic projections to cerebral cortex (nucleus locus coeruleus) in senile dementia. *Neurology*, 32:164, 1982.

Bowen, D.M., Allen, S.J., and Benton, J.S. Behavioral assessment of serotonergic and cholinergic dysfunction and cerebral atrophy in Alzheimer's disease. *J. Neurochemistry*, 41:266-272, 1983.

Caine, E.D. Cholinomimetic treatment fails to improve memory disorders. *N. Engl. J. Med.*, 303:585–586, 1980.

Caltagirone, C., Gainotti, G., and Masullo, C. Oral administration of chronic physostigmine does not improve cognitive or amnesic performances in Alzheimer's presenile dementia. *Int. J. Neurosci.*, 16:247–249, 1982.

Christie, J.E., Shering, A., and Ferguson, J. Physostigmine and arecoline: Effects of intravenous infusions in Alzheimer's presenile dementia. *Br. J. Psychiatry*, 138:46–50, 1981.

Coyle, J.T., Price, D.L., and DeLong, M.R. Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science*, 219:1184–1190, 1983.

Davies, P. Neurotransmitter-related enzymes in senile dementia of the Alzheimer type. *Brain Res.*, 171:319-327, 1979.

Davis, B.M., Brown, G.M., Miller, M., et al. Effects of cholinergic stimulation of pituitary hormonal release. *Psychoneuroendocrinology*, 7:347–354, 1982.

Davis, K.L., Hollister, L.E., and Overall, J. Physostigmine: Effects on cognition and affect in normal subjects. *Psychopharmacology (Berlin)*, 51:22–27, 1976.

Davis, K.L., Mohs, R.C., Tinklenberg, J.R., et al. Physostigmine treatment of long term memory processes in normal humans. *Science*, 201:272–274, 1978.

Drachman, D.A., and Levitt, J. Human memory and the cholinergic system. *Arch. Neurol.*, 30:113–121, 1974.

Etienne, P. Treatment of Alzheimer's disease with lecithin. In: Reisberg, B. (ed.), *Alzheimer's Disease: The Standard Reference*. New York: Free Press, 1983, pp. 353–354.

Hachinski, V.E., Iliff, L.D., and Zicha, E. *Arch. Neurol.*, 32:632–637, 1975.

Hillhouse, E.W., Burden, J., and Jones, M.T. The effect of various putative neurotransmitters on the release of corticotrophin releasing hormones from the hypothalamus of the rat in vitro, I: The effect of acetylcholine and noradrenaline. *Neuroendocrinology*, 17:1–11, 1975.

Kaye, W.H., Sitaram, N., Weingartner, H., et al. Modest facilitation of memory in dementia with combined lecithin and anticholinesterase therapy. *Biol. Psychiatry*, 17:271–274, 1982.

Krieger, D.T., and Krieger, H.P. Circadian pattern of plasma 17-hydroxycorticosteroid: alteration by anticholinergic agents. *Science*, 155:1421–1422, 1967.

Liston, E.H., and Rue, A.L. Clinical differentiation of primary degenerative dementia: A critical review of the evidence. *Biol. Psychiatry*, 18:1451–1484, 1983.

McKhann, G., Drachman, D., Folstein, M., et al. Clinical diagnosis of Alzheimer's disease: Report of NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services. Task force of Alzheimer's disease, *Neurology*, 34:939–944, 1984.

Muramoto, O., Sugishita, M., Kazuya, A., et al. Cholinergic system and constructional praxis: a further study of physostigmine in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry*, 47:485–491, 1984.

Nott, P.N., and Fleminger, J.J. Presenile dementia: The difficulties of early diagnosis. *Acta Psychiatr. Scand.*, 51:210–217, 1975.

Perry, E.K., Perry, R.H., Blessed, G., and Tomlinson, B.E. Necropsy evidence of central cholinergic deficits in senile dementia. *Lancet*, i: 189, 1977.

Perry, E.K., Perry, R.H., Blessed, G., and Tomlinson, B.E. Changes in brain cholinesterases in senile dementia of Alzheimer disease. *Neuropathol. Appl. Neurobiol.*, 4:273–277, 1978.

Perry, E.K., Tomlinson, B.E., Blessed, G., et al. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Br. Med. J.*, 2:1457–1459, 1978.

Peters, B.H., and Levin, H.S. Effects of physostigmine and lecithin on memory in Alzheimer's disease. *Ann. Neurol.*, 6:219–221, 1979.

Ron, M.A., Toone, B.K., Garralda, M.E., and Lishman, W.A. Diagnostic accuracy in presenile dementia. *Br. J. Psychiatry*, 134:161–168, 1979.

Rosen, W.G., Mohs, R.C., and Davis, K.L. A new rating scale for Alzheimer's disease. *Am. J. Psychiatry*, 141:11, 1356–1361, 1984.

Rossor, M.N., Emerson, P.C., and Mountjoy, C.Q. Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of the Alzheimer type. *Neurosci. Lett.*, 20:373, 1980.

Rossor, M.N., Iversen, L.L., and Reynolds, G.P. Neurochemical characteristics of early and late onset types of Alzheimer's disease. *Br. Med. J.*, 288:961–964, 1984.

Smith, C.M., and Swash, M. Physostigmine in Alzheimer's disease (letter). *Lancet*, 1:42, 1979.

Sullivan, E.V., Shedlack, K.H., Corkin, S., et al Physostigmine and lecithin in Alzheimer's disease. In: Corkin, S., Davis, K.L., Growdin, J.H., et al. (eds.), *Alzheimer's Disease: A Report of Progress in Research*. New York: Raven Press, 1982.

Thal, L.J., Fuld, P.A., and Masur, D.M. Oral physostigmine and lecithin improve memory in Alzheimer's disease. *Ann. Neurol.*, 13:491–496, 1983.

Intracranial Drug Administration in Alzheimer's Disease

Robert E. Harbaugh, M.D.[1]

Introduction

During the last decade there has been an explosion of information regarding the neurochemical activity of the central nervous system (CNS). The identification of numerous neurotransmitter, neuromodulator, and neurohormone candidates, and the elucidation of their roles in normal and pathological brain function, have vastly expanded the possibilities for pharmacologic manipulation in the treatment of neurologic disease.

Clinical application of this neurochemical information has, however, been plagued by difficulties with drug delivery to the CNS. Long-standing problems in clinical neuropharmacology include adverse systemic effects of neuroactive drugs, peripheral metabolism or inactivation of drugs, difficulties with blood-brain barrier penetration, erratic drug absorption and binding by serum proteins, adverse effects at one level of the neuraxis to achieve therapeutic effects at another (e.g., sedation with narcotic analgesics), and problems with patient compliance. One can think of few neuroactive drugs where at least one of these problems is not clinically significant. In addition, a number of potentially therapeutic compounds may never reach clinical trials because of these problems.

With implantable drug infusion devices and stereotactic neurosurgical techniques, the technology is available today to circumvent all of the above difficulties. Direct infusion of drugs into the cerebrospinal fluid (CSF) bypasses the problems of systemic side effects, peripheral drug inactivation, poor drug absorption, serum protein binding, and blood-brain barrier penetration. Continuous or programmable drug infusion devices ensure patient compliance. Regional drug infusions can obviate adverse effects at other levels of the neuraxis and it may, in time, be possible to infuse minute quantities of drugs directly into circumscribed areas of the brain parenchyma, thereby achieving neuroanatomically precise pharmacologic manipulations of brain function.

The rationale behind drug delivery to the CNS by central infusion and selection criteria for drugs for infusion will be briefly discussed. Experience here with central drug infusion for patients with Alzheimer's disease (Harbaugh et al., 1984) will be used to illustrate the application of this technology in a clinical setting. Potential complications of this treatment approach will also be discussed.

Rationale Of Central Drug Infusion

By and large, intrathecal drug administration has not proven to be effective (Aird, 1984). Therefore, the first question to be addressed regarding central drug infusion is whether these drugs achieve adequate brain penetration. The answer to this question depends not only on the drug involved but also on the method of central drug administration.

Most clinical trials of central drug administration have employed single or intermittent bolus injections into the subarachnoid space or ventricular system. Of all the ways to deliver drugs to the CNS, this is probably the worst. Single bolus injections result in very high CSF drug concentrations and relatively limited parenchymal penetration (Blasberg et al., 1977; Lee et al., 1960). In addition, a single large bolus of drug is likely to be more toxic and less effective than more frequent, smaller doses (Bleyer et al., 1978). However, even with bolus administration, drugs will penetrate the parenchyma and, as CSF is cleared by bulk flow, diffuse back into the subarachnoid space (Blasberg et al., 1977). In situations where high drug concentrations in the CSF or immediately adjacent parenchyma are desired (carcinomatous meningitis, spinal anesthesia/analgesia, chemical rhizotomy), bolus injections are effective. However, if deeper diffusion into parenchyma is necessary, longer term infusion is preferable.

---

[1] Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756.

Intravascular administration of drugs which cross the blood-brain barrier shows a rapid onset of action due to the short circulation time and extensive vascular-CNS interface (Aird, 1984). However, drugs administered into the CSF require much longer for adequate diffusion into the parenchyma (Lee et al., 1960). As the duration of central drug administration increases, the depth of parenchymal penetration, even of large protein molecules, also increases (Brightman et al., 1969). Therefore, to adequately evaluate the effectiveness of central drug administration, infusions must be carried out over a prolonged time.

In addition to the duration of central drug infusion, the rate of infusion may be important. Rates of infusion rapid enough to elevate CSF pressure will result in increased CSF absorption and therefore increase drug elimination by bulk flow (Katzman et al., 1970).

The site of infusion within the central compartment may also be of significance. Drug penetration into the parenchyma appears to occur more readily through the ependymal than the pial surface (Rall, 1968), and drugs administered into the subarachnoid space may not enter the ventricular system (Yen et al., 1978). Therefore, intraventricular drug infusion is a more reasonable approach for achieving diffuse brain penetration than is lumbar intrathecal administration. Conversely, if one wishes to confine drug effects to the spinal cord with minimal effects at higher levels of the neuraxis, then intraspinal infusion may be beneficial (Coombs et al., 1983; Harbaugh et al., 1982). Thus, some relatively restricted neuropharmacologic effects can be achieved. Theoretically, with stereotactic cannula placement and very low flow-rate infusion devices, delivery of minute quantities of drugs to very circumscribed regions of brain parenchyma is possible.

When evaluating the effectiveness of central drug administration, the choice of drug is at least as important as the method of delivery. The ability of a drug to cross the blood-brain barrier is more likely to be detrimental than beneficial if the drug is given as a continuous central infusion. Drugs which readily cross brain capillaries can be rapidly cleared from the CNS when infused into the CSF (Blasberg et al., 1975). The use of such drugs may be valuable if high local concentrations in tissue adjacent to the subarachnoid space or ependyma are desired. However, if deeper parenchymal penetration is the goal, then lipid insoluble, polar molecules are better candidates for infusion (Blasberg et al., 1975).

When considering drugs for long-term central infusion, chemical and biological stability become important criteria. For continuous infusion via an implantable pump, the infused drug must be stable at body temperature for at least as long as the cycle time of the infusion pump. In addition, if widespread diffusion of active drug into parenchyma is desired, then the drug infused cannot be rapidly metabolized within the CNS or CSF. This last consideration may not apply to local intraparenchymal infusion where a steep concentration gradient of active drug could be beneficial.

Clinical Experience

Our clinical experience at Dartmouth (Coombs et al., 1983; Harbaugh et al., 1982, 1984) with implantable infusion devices for central drug administration may serve to illustrate some of the points raised above. The clinical studies referred to were approved by our institution's committee for the protection of human subjects and informed consent was obtained before instituting any experimental treatment trials.

The evidence for the cholinergic hypothesis of Alzheimer's disease has been extensively reviewed (Coyle et al., 1983) and need not be repeated here. If this cholinergic hypothesis is correct, then augmentation of brain cholinergic activity may ameliorate some of the symptoms in these patients. Previous attempts at increasing brain cholinergic activity by administration of acetylcholine precursors, cholinesterase inhibitors, or systemic cholinergic agonists had been attended by some of the difficulties with drug delivery to the brain which have previously been discussed. Intracranial cholinergic drug infusion in patients with Alzheimer's disease was started as a means of testing the validity of the cholinergic hypothesis and as an attempt at therapy for a devastating neurologic disease with no known treatment.

By delivering a muscarinic agonist into the ventricular system or cisterna magna, the problems of systemic drug inactivation, serum protein binding, and drug absorption are avoided. The use of an implantable continuous infusion pump permits long-term intracranial infusion of drug or placebo on an outpatient basis and avoids any problems of patient compliance. Pump flow rates range from 1 to 2 ml/day, an insignificant amount compared to normal daily CSF production. Because of small daily drug doses (0.05 to 0.7 mg), systemic side effects are not encountered.

Bethanechol chloride, a pure muscarinic agonist, was chosen for infusion. The drug is a polar, water-soluble molecule which is not degraded by cholinesterases and is stable in solution.

For patients with Alzheimer's disease, drug distribution to the hippocampi, locus ceruleus, reticular nucleus of the thalamus, and cerebral cortex was desired and, for the reasons described above, a drug which does not cross the blood-brain barrier when infused into the ventricular system was chosen.

Potential Complications of Central Drug Infusion

The potential advantages of central drug infusion have been discussed. There are, however, some potential disadvantages which require equal consideration. These include the operative risks of catheter placement and pump implantation, and the risk of increased neurotoxicity.

As for any neurosurgical procedure, the risks of catheter placement and pump implantation include anesthetic complications, hemorrhage, and infection. Although all these risks are low, there is probably an irreducible minimum, and some complications must be anticipated. Our personal experience here with pump implantation now includes about 40 patients who have had pumps implanted for various indications. We have encountered no significant anesthetic complications but have had one infectious and one hemorrhagic complication.

The risk of neurotoxicity with intracranial drug infusions must also be considered. Certainly, toxicity studies in animals are mandatory before considering intracranial or intraspinal infusion of drugs in patients. Although such toxicity studies decrease the risk of human neurotoxicity, some unexpected reactions to drug infusions in patients are likely to occur. We have now been infusing bethanechol chloride intracranially in patients with Alzheimer's disease for up to 20 months. One patient developed a reversible parkinsonian syndrome of rigidity and bradykinesia and another developed a reversible CSF inflammatory response which may or may not have been related to drug infusion (Harbaugh et al., 1984). Certainly, experience with more patients infused for longer periods of time will be necessary before any accurate figures on the risk of neurotoxicity are available. However, to date, drug infusions appear to be well tolerated.

The feasibility of intracranial and intraspinal administration of neurotransmitter analogues has been demonstrated (Coombs et al., 1983: Harbaugh et al., 1982, 1984). However, the value of these therapeutic endeavors over presently available therapy remains to be proven. We are conducting studies of the effect of intracranial bethanechol infusion on activities of daily living and neuropsychologic test scores in a double-blind, placebo-controlled crossover design. Preliminary studies showed family reports of decreased confusion, increased initiative, and improvements in activities of daily living during drug infusion but no subjective improvement in short-term memory was reported. A battery of short-term memory tests has also not shown a statistically significant difference between drug and placebo scores.

Almost certainly, the technique of central drug infusion for neurologic disease is more important than the outcome of any single therapeutic trial. Neurologic disorders in which abnormalities of neurotransmitter activity or availability are pathogenetically implicated and structural damage to the CNS is minimal, may prove to be the most fruitful areas for the application of this technique. Movement disorders, epilepsy, and functional and psychiatric disease are obvious possibilities. Only time and further investigation will tell if this new approach for drug delivery to the brain will come to naught or herald a new era in neuropharmacology and functional neurosurgery.

Acknowledgments: David W. Roberts, M.D., Charles M. Culver, M.D., Ph.D., Mark C. Johnson, Ph.D., and Teddi M. Reeder, B.S., R.N., have been instrumental in developing and carrying out the Alzheimer's disease studies.

References

Aird, R.B. A study of intrathecal, cerebrospinal fluid-to-brain exchange. *Exp. Neurol.*, 86:342–358, 1984.

Blasberg, R.G., Patlak, C.S., and Fenstermacher, J.D. Intrathecal chemotherapy: Brain tissue profiles after ventriculocisternal perfusion. *J. Pharm. Exp. Ther.*, 194:73–83, 1975.

Blasberg, R.G., Patlak, C.S., and Shapiro, W.R. Distribution of methotrexate in cerebrospinal fluid and brain after intraventricular administration. *Cancer Treat. Report*, 61:633–641, 1977.

Bleyer, W.A., Poplack, D.R., Simon, R.M., et al. Concentration X time methotrexate via a subcutaneous reservoir: A less toxic regimen for intraventricular chemotherapy of central nervous system neoplasms. *Blood*, 51:835–842, 1978.

Brightman, M.W., and Reese, T.S. Junctions between intimately apposed cell membranes in the vertebrate brain. *J. Cell Biol.*, 40:648–677, 1969.

Coombs, D.W., Saunders, R.L., Gaylor, H.S., et al. Relief of continuous chronic pain by intraspinal narcotics infusion via an implanted reservoir. *JAMA*, 250:2336–2339, 1983.

Coyle, J.T., Price, D.L., and DeLong, M.R. Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science*, 219:1184–1190, 1983.

Harbaugh, R.E., Coombs, D.W., Saunders, R.L., et al. Implanted continuous epidural morphine infusion system. Preliminary report. *J. Neurosurg.*, 56:803–806, 1982.

Harbaugh, R.E., Roberts, D.W., Coombs, D.W., et al. Preliminary report: Intracranial cholinergic drug infusion in patients with Alzheimer's disease. *Neurosurgery*, 15:514–518, 1984.

Katzman, R., and Hussey, F. A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. *Neurology*, 20:534–544, 1970.

Lee, J.C., and Olszewski, J. Penetration of radioactive bovine albumin from cerebrospinal fluid into brain tissue. *Neurology*, 10:814–822, 1960.

Rall, D.P. Transport through the ependymal linings. *Prog. Brain Res.*, 29:159–167, 1968.

Yen, J., Reis, F.L., Kimelberg, H.K., et al. Direct administration of methotrexate into the CNS of primates. Part 2. Distribution of H3 methotrexate after intrathecal lumbar injection. *J. Neurosurg.*, 48:895–902, 1978.

The Cholinergic Hypothesis of Memory Dysfunction in Alzheimer's Disease—Revisited

Nunzio Pomara, M.D.,[1] and Michael Stanley, Ph.D.[2]

Of all the neurotransmitter deficits which have been reported in Alzheimer's disease (AD), by far the most extensive and consistent changes have involved the cholinergic system (Bartus et al., 1982; Davies & Maloney, 1976; Price et al., 1982; Rossor, 1982). Correlations between the severity of dementia before death, the density of senile plaques, and the reduction in the activity of choline acetyltransferase (CAT), a marker of presynaptic cholinergic neurons, strongly support the role of these cholinergic deficits in the pathophysiology of memory dysfunction (Perry et al., 1978). To date, no such relationships have been established between severity of dementia and any of the other neurotransmitter abnormalities which have also been described in this illness (Greenwald & Davis, 1983).

Another finding which has lent further support to the possible involvement of the cholinergic dysfunction in the pathophysiology of memory deficits observed in patients with AD has been the observation that the administration of agents such as scopolamine, which interfere with cholinergic transmission, produces memory deficits in normals. These deficits are qualitatively similar to those found in early AD (Drachman, 1977).

All of the foregoing observations, together with the precedent of alleviating motoric dysfunction in Parkinson's disease (PD) by means of dopaminergic agents, have provided a rationale for several AD treatments, i.e., cholinergic precursors (choline, lecithin) and indirect and direct muscarinic agonists (physostigmine, bethanechol chloride, RS-86).

In contrast to the successful therapeutic interventions that have been developed for the treatment of PD, by and large none of these cholinergically based therapeutic strategies has led to clinically useful improvements in AD (Mohs et al., 1985; Wettstein & Spiegel, 1984).

Several explanations have been offered for the poor therapeutic outcome which has been observed in these clinical trials. It has been suggested that:

1. CAT needs two substrates for acetylcholine synthesis, i.e., choline and acetyl coenzyme A. Therefore, if both substrates are depleted in AD, simply increasing choline by means of cholinergic precursors would not be sufficient to increase acetylcholine synthesis.
2. High-affinity uptake system for choline, acetylcholine synthesis, and release are all dependent on neuronal activity and, therefore, simply increasing choline would not be sufficient to effect these parameters.
3. The therapeutic action of physostigmine and other cholinesterase inhibitors might be limited by the failure of enough acetylcholine to be released pre-synaptically, by their narrow therapeutic window, by poor penetration into the central nervous system, and possibly by their action to cause a "feedback" inhibition of acetylcholine synthesis and release.
4. The use of exogenous direct muscarinic agonists also might have a very narrow therapeutic window which may be difficult to overcome.
5. Misdiagnosis of patients has diluted treatment effects.
6. Deficits in other neurotransmitters, e.g., somatostatin, serotonin, dopamine, or noradrenaline, also might contribute to the pathophysiology of cognitive dysfunction in patients with AD.

Even when dose has been carefully titrated to optimize response, or when problems of entry into the brain have been circumvented by direct administration of a cholinergic agonist into the cerebral ventricles, the therapeutic outcome remains poor (Harbaugh et al. 1984; Mohs et al., 1985).

---

[1] Lafayette Clinic and Wayne State University School of Medicine, Detroit, MI 48207.

[2] New York State Psychiatric Institute and Columbia University, New York, NY 10032.

The failure of cholinergic agonists in the treatment of AD is in marked contrast to the clinically relevant improvements in PD patients following treatment with dopaminergic agents, and calls into question some of the underlying assumptions regarding our understanding of the cholinergic system in AD.

Two tacit assumptions underlying treatments with cholinomimetics have been that the function of muscarinic receptors remains normal in AD and that a hypoactivity of the central cholinergic system is invariably associated with this disorder. It is our contention that the currently available data do not allow any definitive statement either about the status of muscarinic receptor function or about central cholinergic activity in AD.

Muscarinic Receptor Responsivity in AD

A specific aspect of cholinergic function that has been overlooked is that the presynaptic cholinergic deficits may account only in part for the cholinergic dysfunction seen in AD, and that alterations in the functional responsivity of the remaining muscarinic receptors (M_1 and M_2) also may contribute to the pathophysiology of AD. To the extent that cholinergic transmission is reliant on the functional integrity of both pre- and postsynaptic components, the elucidation of muscarinic response in AD is of particular importance.

Although no significant reductions in the number of muscarinic receptors have been noted in AD (Bowen, 1983; Davies & Verth, 1978), the failure of these studies to observe a difference may by itself reflect some atypical characteristics of the cholinergic system. In contrast to lesions of the noradrenergic, dopaminergic, and serotonergic neuronal systems, which have been shown to be associated with receptor and behavioral supersensitivity (Creese et al., 1978; DeMontigny et al., 1980), lesions of the cholinergic system have not been shown consistently to produce either an upregulation of muscarinic receptors or denervation supersensitivity (Bracco et al., 1982; London et al., 1984; McKinney & Coyle, 1982). The failure to observe evidence for denervation supersensitivity in these animal experiments does not exclude the possibility that muscarinic denervation supersensitivity could occur in AD.

The results of these animal experiments do not permit definitive statements to be made on the impact of presynaptic cholinergic neuronal loss on the functional status of postsynaptic muscarinic receptors. Although most studies do not report a significant reduction in the number of muscarinic receptors in AD, the failure of these studies to find changes merely may reflect the inability of quinuclidinyl benzylate (QNB) binding, as it has been commonly applied, to distinguish pre- and postsynaptic receptors. Thus in AD, the loss of presynaptic receptors might not result in net decreases in QNB as a result of concomitant increases in postsynaptic muscarinic receptors. As far back as 1978, Davies and Verth speculated on the possibility of denervation supersensitivity to reconcile their findings of normal muscarinic receptor concentrations in the context of some loss of muscarinic cholinoceptive receptors in AD.

Recently, more direct proof for compensatory increases in postsynaptic muscarinic receptors was provided by Nordberg and colleagues (1983). These investigators noted that the number of muscarinic receptors, as measured by QNB binding in the hippocampus of Alzheimer brains, was significantly and inversely correlated with CAT activity. This suggests that, as the ascending cholinergic input to the hippocampus was lost, there was a compensatory increase in the number of postsynaptic muscarinic receptors.

In a more recent study, Mash et al. (1985) reported a selective decrease of presynaptic, M_2, muscarinic receptors in the cerebral cortex of AD brains which was positively correlated with the reduction in CAT activity. They reported no change in the M_1 postsynaptic receptors. However, this group of investigators, unlike Nordberg et al. (1983), did not report on the relationship between CAT activity and M_1 receptors. Without data on the relationship between CAT activity and M_1 postsynaptic receptors, compensatory changes in the M_1 receptors might not be detected.

Recently developed techniques for measuring receptor number are believed to be more selective and capable of distinguishing pre-

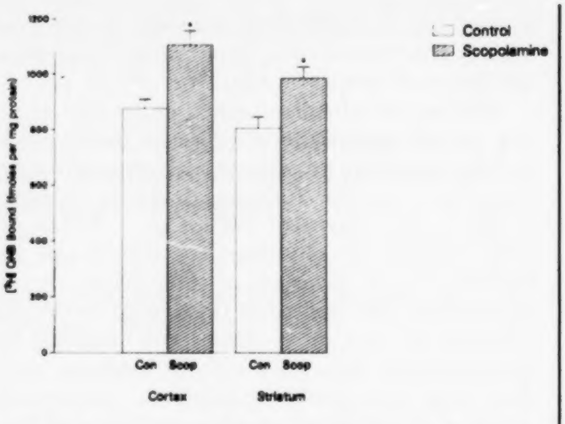


FIGURE 1. Chronic scopolamine increased the number of muscarinic receptors in rat brain as measured by QNB binding.

and postsynaptic muscarinic receptors. Nevertheless, these approaches may still not be adequate to differentiate receptors on more selectively damaged cholinergic pathways, i.e., those projecting from the nucleus basalis of Meynert, from receptors on intrinsic cortical cholinergic neurons and other non-cholinergic neuronal systems. Furthermore, the report of Mash and colleagues (1985) on the absence of upregulation of postsynaptic M_1 muscarinic receptors in AD does not address the larger question which concerns the functional status of the remaining muscarinic receptors.

Dissociations Between Muscarinic Receptor Number and Response

Changes in the functional response of muscarinic receptors are not necessarily reflected by alterations in static measures of receptor binding, i.e., number and affinity. This is illustrated in a number of animal experiments which have attempted to address this question directly.

Some studies report changes in the responsivity of muscarinic receptors that are in the direction anticipated from the change in number of muscarinic receptors as measured by QNB binding. For example, in a series of experiments conducted with rats by Lerer and colleagues (Lerer, 1985; Lerer & Sitaram, 1983), treatment with the muscarinic antagonist, scopolamine, led to an increase in the number of muscarinic receptors (Figure 1) which was accompanied by behavioral supersensitivity as measured by pilocarpine-induced catalepsy (Figure 2).

The same investigators (Lerer et al., 1983, 1984; Stanley & Lerer, 1985) found that the decrease in the number of muscarinic receptors that was produced by chronic electroconvulsive shock (ECS) (Figure 3) was accompanied by the anticipated decrease in responsivity (Figure 4).

However, this relationship between functional sensitivity and up- or down-regulation of corresponding receptors need not always be present. The same group of investigators demonstrated that while a single ECS caused no significant change in the number of QNB binding sites (Figure 5), it nevertheless induced a blunted cataleptic response to pilocarpine (Figure 6).

Data from a number of other investigators using a variety of experimental paradigms can be used to demonstrate similar dissociations between changes in receptor number and functional response (Lippa & Bartus, 1982; Marks et al., 1984; Pedigo et al., 1984).

Based on these animal data, the absence of a significant change in the number of muscarinic receptors in AD does not exclude the possibility of functional alterations in response. Both increases and decreases in functional response can occur in the absence of any change in the number of muscarinic receptors.

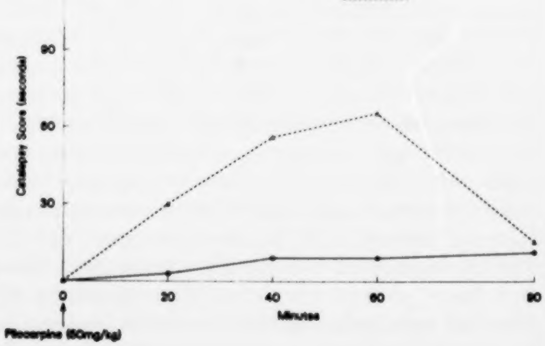


FIGURE 2. Chronic scopolamine increased pilocarpine induced catalepsy in accord with the increase in the number of muscarinic receptors.

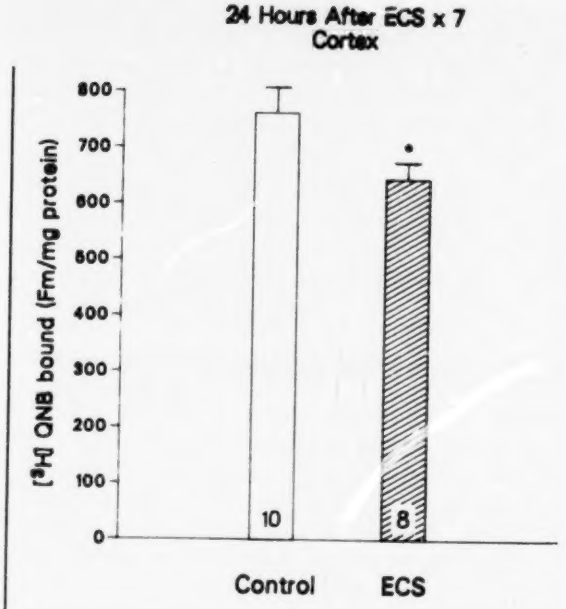


FIGURE 3. Chronic ECS decreased the number of muscarinic receptors in rat brain as measured by QNB binding.

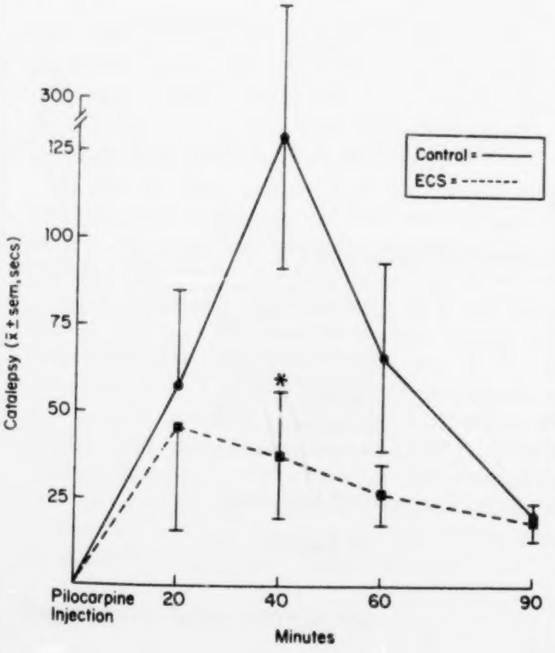


FIGURE 4. Chronic ECS decreased pilocarpine induced catalepsy in accord with the decrease in the number of muscarinic receptors.

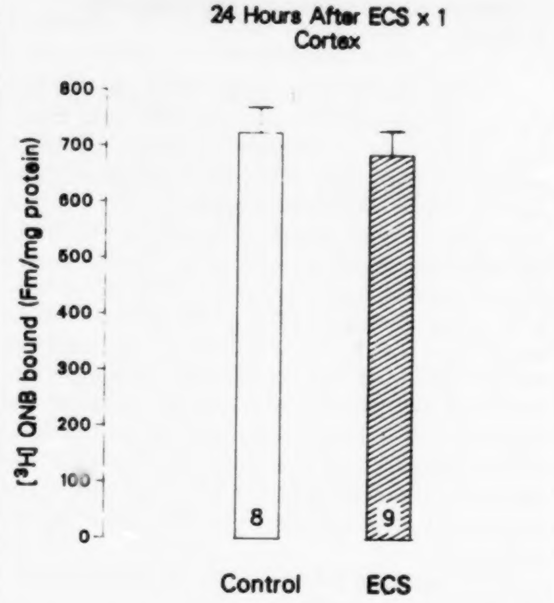


FIGURE 5. Acute ECS produced no significant change in the number of QNB binding sites.

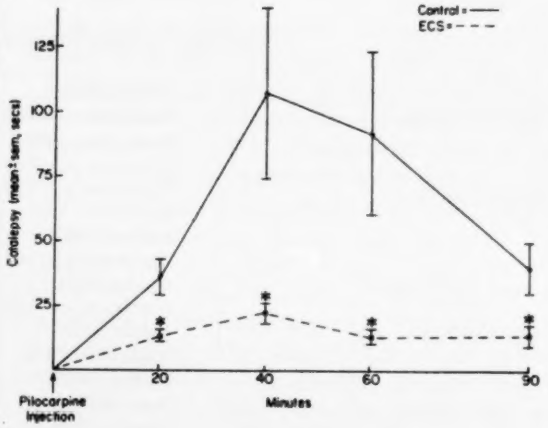


FIGURE 6. Acute ECS decreased pilocarpine induced catalepsy in rats even though muscarinic receptors, as measured by QNB binding, were not significantly altered.

Evidence for Cholinergic Hyperactivity in AD

In addition to a possible dissociation between changes in receptor number and function, there are a number of empirical findings in patients with AD which are more consistent with regional hyperactivity, rather than generalized hypoactivity of the cholinergic system. Patients with AD exhibit many abnormalities, e.g., hypercortisolemia, abnormal dexamethasone tests, depressive symptoms, and motor and memory dysfunction which also have been observed in major depression—a disorder for which a relative increase in cholinergic activity has been postulated (Janowsky et al., 1972, 1973). The Table presents some research findings which are consistent with cholinergic hyperactivity in AD.

Cortisol Hypersecretion

Cortisol hypersecretion, which has been reported in a significant number of patients with endogenous depression (Carroll et al., 1976, 1981; Fang et al., 1981; Sachar et al., 1973), also is found in a significant number of patients with Alzheimer-type dementia. There are at least three groups of investigators (Davis et al., 1983; Pomara et al., 1984; Raskind et al., 1982) that have reported high concentrations of plasma cortisol in individuals with AD. Davis et al. (1983) reported that the severity of dementia, as assessed by a number of rating scales, was correlated significantly with plasma cortisol concentration.

While a direct proof for the involvement of the cholinergic system in the development of hypothalamic-pituitary-adrenal axis hyperactivity in both depression and in AD is lacking, there are a number of observations that support such a role. Hypercortisolemia can be produced in both animals and man by administration of centrally acting cholinomimetics (Nurnberger et al., 1983; Pepper & Krieger, 1984). The administration of physostigmine, a centrally acting cholinesterase inhibitor, to normal individuals leads to the development of symptoms which mimic those found in depression. Additionally, physostigmine causes a reduction of manic symptoms in manic-depressive illness and an exacerbation of depressive symptoms in depressives (Davis et al., 1978; Janowsky et al., 1973; Risch et al., 1981). These findings suggest that central cholinergic activity may be increased in depression and may provide the basis for hypercortisolemia.

The only consistent neurochemical abnormality in AD which has been correlated with the clinical and neuropathological features of the disease has been the reduction in CAT activity. This has been interpreted as indica-

TABLE

Findings Consistent With Cholinergic Hyperactivity

	Alzheimer's Disease	Major Depression Study
Hypercortisolemia	Raskind et al., 1982 Davis et al., 1982 Pomara et al., 1984	Sachar et al., 1973 Carroll et al., 1976 Fang et al., 1981
Abnormal DSTs	Raskind et al., 1982 Davis et al., 1982 McKeith, 1984 Pomara et al., 1984	Carroll et al., 1976 Brown et al.,1979 Fang et al., 1981
Motoric Dysfunction	Pearce, 1974 Pomara et al., 1981	Wolff et al., 1985
Depressive Symptoms	Ziegler, 1954 Gustavson, 1975 Kendel, 1976 Roth, 1975 Epstein, 1976 Cawley, 1973	By definition
Cognitive and Memory Deficits	Reisberg, 1983	Weingartner et al., 1981
Dementia Syndrome	Reisberg, 1983	Folstein & McHugh, 1978 McAllister & Price, 1982

tive of a postulated decrease in central cholinergic activity. The finding of hypercortisolemia in AD patients is incompatible with the previously described animal and human studies in which more cortisol was released when central cholinergic activity increased. One would have predicted that the cholinergic deficiency in AD would have led to low cortisol levels. This contrasts with the increased incidence of hypercortisolemia reported in the AD patient population.

Abnormal Dexamethasone Suppression in AD Patients

Additional data that would be consistent with cholinergic hyperfunction are the numerous reports of abnormal dexamethasone suppression tests (DST) in individuals with Alzheimer-type dementia. At least four studies have reported significant increases in nonsuppression in patients with AD (Davis et al., 1983; McKeith, 1984; Pomara et al., 1984; Raskind et al., 1982). Further support for cholinergic hyperfunction as an underlying mechanism for dexamethasone non-suppression was provided by an experiment in which we induced an up-regulation of muscarinic receptors. This led to a significant degree of non-suppression which was not present in animals in whom muscarinic receptors were not up-regulated (Gershon et al., 1985).

A similar mechanism for abnormal dexamethasone responses in AD was suggested by the findings reported by Nordberg et al. (1983). They found a significant inverse correlation between CAT activity and the number of muscarinic receptors which suggested compensatory changes. Consistent with the interpretation of the findings of Nordberg et al.'s study, are the reports by Carroll et al. (1978) and Doerr and Berger (1983). These studies demonstrated that the usual suppression of cortisol after dexamethasone administration in normal subjects could be reversed by the administration of physostigmine.

Depressive Symptoms in AD

Also consistent with the hypothesis that major depression and AD may share some common pathophysiologic features which may be related to regional cholinergic hyperactivity, is the observation that a significant percentage of individuals with AD present with a depressive syndrome (Gustavson, 1975; Kendel, 1976; Ziegler, 1954). Similarly, many individuals with AD very often develop depressive symptoms in the course of their illness (Cawley, 1973; Epstein, 1976; Roth & Myers, 1975).

A primary depressive illness in the elderly can also lead to a dementia syndrome or to pseudodementia, a term which indicates its potential reversibility (Folstein & McHugh, 1978; McAllister & Price, 1982). These clinical entities are linked further by reports of cognitive and memory deficits in young depressives which are not qualitatively different from those found in early AD (Weingartner et al., 1981).

Motoric Dysfunction in AD and Depression

Motor activity is believed to be regulated in part by an interaction of dopaminergic and cholinergic neurons in the striatum. Extrapyramidal symptoms (EPS) in PD, a disorder associated with marked motor retardation, are believed to arise from an imbalance between dopaminergic and cholinergic tone in the striatum, i.e., the loss of dopaminergic function is believed to give rise to a relative increase in cholinergic tone. Supporting this hypothesis is the well-known observation that the administration of cholinergic antagonists leads to a diminution, whereas cholinomimetics cause an increase, in EPS.

A number of studies have reported EPS to be present in patients with AD (Pearce, 1974; Pomara et al., 1981). These observations support cholinergic hyperactivity in AD.

To our knowledge, there are no reports of EPS in depressive illness and there are no studies that have systematically evaluated the sensitivity of these patients to develop EPS in response to cholinomimetics. However, it is interesting to note that Wolff et al. (1985) recently found a significantly greater motor retardation in these patients during the depressive phase of their illness than during the euthymic or manic phases. Additionally, even during remission, individuals with affective illness showed lower motor activity than a control group.

Sleep EEG in Affective Illness and in AD

There are numerous studies that have implicated a role for the cholinergic system in the regulation of various components of sleep. Of particular interest is the finding that the induction of rapid-eye-movement (REM) sleep may be under partial cholinergic control (Sitaram & Gillin, 1979; Sitaram et al., 1984). This technique has been applied to study changes in muscarinic receptor sensitivity in individuals with affective illness. These individuals have been found to exhibit a shorter REM latency as compared to control subjects and a more rapid induction of REM sleep after administration of arecoline, a centrally acting muscarinic agonist (Jones et al., 1985; Sitaram et al., 1980, 1982).

Patients with Alzheimer-type dementia, as well as individuals with affective illness, also exhibit abnormalities in sleep architecture. On the other hand, when comparisons between the two disorders are made, they appear to be dissimilar with respect to baseline REM latency (Prinz et al., 1982). However, the important challenge tests using cholinergic agents such as arecoline will be needed to fully elucidate the extent to which these two illnesses are related.

Conclusion

The presynaptic cholinergic deficits that consistently have been observed in AD have been interpreted as indicative of a generalized cholinergic hypoactivity. However, there are a number of empirical data which have been reported in patients with AD which are best explained by regional cholinergic hyperactivity. The therapeutic strategies which have been applied in the treatment of AD, however, have been based exclusively on the underlying assumption of generalized cholinergic hypoactivity.

As we have pointed out in this review, there are a number of empirical findings about AD which may be better explained by cholinergic hyper- not hypoactivity. With this in mind, it may be useful to design treatment strategies that may explore the possibility of cholinergic hyperactivity as having a role in some of the behavioral symptoms observed in this illness.

However, one of the more basic but untested assumptions is that the remaining muscarinic receptors in AD when appropriately stimulated would result in a restoration of normal cholinergic function. To date, direct evidence in support of this contention is not available.

As we have recently reviewed elsewhere (Pomara & Stanley, in press), a presentation of receptor number in AD does not always serve as a reliable index of receptor response.

References

Bartus, R.T., Dean, R.L., Beer, B., and Lippa, A.S. The cholinergic hypothesis of geriatric memory dysfunction. *Science*, 217:408–417, 1982.

Bowen, D.M. Biochemical assessment of neurotransmitter and metabolic dysfunction and cerebral atrophy in Alzheimer's disease. In: Katzman, R. (ed.), *Biological Aspects of Alzheimer's Disease*. Cold Spring Harbor, N.Y.: Cold Spring Laboratory, 1983, pp. 219–31.

Bracco, L., Corradetti, R., and Amaducci, L. Acute subcortical lesions modify cortical muscarinic receptors in human brain. *Neurosci. Lett.*, 34:227–231, 1982.

Brown, W.A., Johnston, R., and Mayfield, D. The 24-hour dexamethasone suppression test in a clinical setting: Relationship to diagnosis, symptoms, and response to treatment. *Am. J. Psychiatry*, 136:543–547, 1979.

Carroll, B.J., Curtis, G.C., and Mendels, J. Neuroendocrine regulation in depression: II. Discrimination of depressed from non-depressed patients. *Arch. Gen. Psychiatry*, 33:1051–1058, 1976.

Carroll, B.J., Feinberg, M., Greden, J.F., et al. A specific laboratory test for the diagnosis of melancholia. *Arch. Gen. Psychiatry*, 38:15–22, 1981.

Carroll, B.J., Greden, J.F., Rubin, R.T., et al. Neurotransmitter mechanism of a neuroendocrine disturbance in depression. *Acta Endocrinol.*, (Suppl.) (KBH)220:14, 1978.

Cawley, R.H., and Whitehead, A. Barbiturate tolerance and psychological functioning in elderly depressed patients. *Psychol. Med.*, 3:39–52, 1973.

Creese, I., Burt, D.R., and Snyder, S.H. Dopamine receptor binding enhancement correlates with lesion-induced behavioral supersensitivity. *Science*, 197:596–598, 1978.

Davies, P., and Maloney, A.J.F. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet*, 2:1403, 1976.

Davies, P., and Verth, A.H. Regional distribution of muscarinic acetylcholine receptor in normal and Alzheimer's type dementia brains. *Brain Res.*, 138:385–392, 1978.

Davis, K.L., Berger, P.A., Hollister, L.E., and Defraites, E. Physostigmine in mania. *Arch. Gen. Psychiatry*, 35(1):119–122, 1978.

Davis, K.L., Davis, B., Greenwald, B.S., et al. Hypercortisolemia in Alzheimer's disease. APA Annual Meeting - New Research, New York, 1983.

DeMontigny, C.D., Wang, R.Y., Reader, T.A., and Aghajanian, G.K. Monoaminergic denervation of the rat hippocampus: Microiontophoretic studies on pre- and postsynaptic supersensitivity to norepinephrine and serotonin. *Brain Res.*, 200:363–376, 1980.

Doerr, P., and Berger, M. Physostigmine-induced escape from dexamethasone suppression in normal adults. *Biol. Psychiatry*, 18:261–268, 1983.

Drachman, D.A. Memory and cognitive function in man: Does the cholinergic system have a specific role? *Neurology*, 27:783–790, 1977.

Epstein, L.J. Depression in the elderly. *J. Gerontol.*, 3:278–287, 1976.

Fang, V.S., Tricou, J.B., Robertson, A., and Meltzer, H.Y. Plasma ACTH and cortisol levels in depressed patients. Relation to dexamethasone suppression test. *Life Sci.*, 29:931–938, 1981.

Folstein, M.F., and McHugh, P.R. Dementia syndrome of depression. In: Katzman, R., Terry, R.D., and Bick, K.L. (eds.), *Alzheimer's Disease: Senile Dementia and Related Disorders* (Series: *Aging*, Vol. 7). New York: Raven Press, 1978, pp. 87–93.

Gershon, S., McIntyre, I.M., Pomara, N., et al. Alterations in cholinergic receptors mediate the effects of dexamethasone on corticosterone. *Biol. Psychiatry*, 20:451–460, 1985.

Greenwald, B.S., and Davis, K.L. Experimental pharmacology of Alzheimer Disease. In: Mayeux, R., and Rosen, W.G. (eds.), *The Dementias*. New York: Raven Press, 1983, pp. 87–102.

Gustafson, L. Psychiatric symptoms in dementia with onset in the presenile period. *Acta Psychiatr. Scand.*, 257:9–35, 1975.

Harbaugh, R.F., Roberts, D.W., Coombs, D.W., et al. Preliminary report: intracranial cholinergic drug infusion in patients with Alzheimer's disease. *Neurosurgery*, 15(4):514–518, 1984.

Janowsky, D.S., Davis, J.M., El-Yousef, M.K., and Sekerke, H.J. A cholinergic adrenergic hypothesis of mania and depression. *Lancet*, 2:632, 1972.

Janowsky, D.S., Davis, J.M., El-Yousef, M.K., and Sekerke, H.J. Acetylcholine and depression. *Psychosom. Med.*, 35(5):459, 1973.

Janowsky, D.S., El-Yousef, M.K., Davis, J.M., and Sekerke, H.J. Parasympathetic suppression of manic symptoms by physostigmine. *Arch. Gen. Psychiatry*, 28:542–547, 1973.

Jones, D., Kelwala, S., Bell, J., et al. Cholinergic REM sleep induction response correlation with endogenous major depressive subtype. *Psychiatry Res.*, 14:99–110, 1985.

Kendel, R. The stability of psychiatric diagnosis. *Br. J. Psychiatry*, 124:352–356, 1976.

Lerer, B. Studies on the role of brain cholinergic systems in the therapeutic mechanisms and adverse effects of ECT and lithium. *Biol. Psychiatry*, 20:20–40, 1985.

Lerer, B., and Sitaram, N. Clinical strategies for evaluating ECT mechanisms: Pharmacological, biochemical and psychophysiological approaches. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 7:309–333, 1983.

Lerer, B., Stanley, M., Demetriou, S., and Gershon, S. Effect of electroconvulsive shock on muscarinic cholinergic receptors in rat cerebral cortex and hippocampus. *J. Neurochem.*, 41:1680–1683, 1983.

Lerer, B., Stanley, M., McIntyre, I., and Altman, H. Electroconvulsive shock and brain muscarinic receptors: Relationship to anterograde amnesia. *Life Sci.*, 35:2659–2664, 1984.

Lippa, A.S., and Bartus, R. Neurobiological aspects of geriatric cognitive dysfunction. In: Corkin, S., Davis, K.L., Growdon, J.H., and Wurtman, R.J. (eds.), *Alzheimer's Disease: A Report of Progress in Research.* (Series: *Aging*, Vol. 19). New York: Raven Press, 1982, pp. 223–233.

London, E.D., McKinney, M., Dam, M., et al. Decreased cortical glucose utilization after ibotenate lesion of the rat ventromedial globus pallidus. *J. Cereb. Blood Flow Metab.*, 4:381–390, 1984.

Marks, M.J., O'Connor, M.F., Artman, L.D., et al. Chronic scopolamine treatment and brain cholinergic function. *Pharmacol. Biochem. Behav.*, 20:771–777, 1984.

Mash, D.C., Flynn, D.D., and Potter, L.T. Loss of M2 muscarine receptors in the cerebral cortex in Alzheimer's disease and experimental cholinergic denervation. *Science*, 228(4703):1115–1117, 1985.

McAllister, T.W., and Price, T.R.P. Severe depressive pseudodementia with and without dementia. *Am. J. Psychiatry*, 139:626–629, 1982.

McKeith, I.G. Clinical use of the DST in a psychogeriatric population. *Br. J. Psychiatry*, 145:389–393, 1984.

McKinney, M., and Coyle, J.T. Regulation of neocortical muscarinic receptors: effects of drug treatment and lesions. *J. Neurosci.*, 2:97–105.

Mohs, R.C., Davis, B.M., Johns, C.A., et al. Oral physostigmine treatment of patients with Alzheimer's disease. *Am. J. Psychiatry*, 142:28–33, 1985.

Nordberg, A., Larsson, C., Adolfsson, R., et al. Muscarinic receptor compensation in hippocampus of Alzheimer patients. *J. Neural Transm.*, 56:13–19, 1983.

Nurnberger, J.I., Jimerson, D.C., Simmons-Alling, S., et al. Behavioral, physiological, and neuroendocrine responses to arecoline in normal twins and "well state" bipolar patients. *Psychiatry Res.*, 9:191–200, 1983.

Pearce, J. The extrapyramidal disorder of Alzheimer's disease. *Eur. J. Neurol.*, 12:94–103, 1974.

Pedigo, N.W., Minor, L.D., and Krumrei, T.N. Cholinergic drug effects and brain muscarinic receptor binding in aged rats. *Neurobiol. Aging*, 5:227–333, 1984.

Pepper, G.M., and Krieger, D.T. Hypothalamic-pituitary-adrenal abnormalities in depression: Their possible relation to central mechanisms regulating ACTH release. In: Post, R.M., and Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders.* Baltimore/London: Williams & Wilkins, 1984, pp. 245–270.

Perry, E.K., Tomlinson, B.E., Blessed, G., et al. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Br. Med. J.*, 2:1457–1459, 1978.

Pomara, N., and Stanley, M. The functional status of central muscarinic receptors in Alzheimer's disease: Assessment and therapeutic implications. In. Crook, T., Ferris, S., Bartus, R., and Gershon, S. (eds.), *Treatment Development Strategies for Alzheimer's Disease.* New Canaan, Conn.: Mark Powley Associates, Inc. (In press)

Pomara, N., Oxenkrug, G.F., McIntyre, I.M., et al. Does severity of dementia modulate response to dexamethasone in individuals with primary degenerative dementia? *Biol. Psychiatry*, 19(10):1481–1487, 1984.

Pomara, N., Reisberg, B., Albers, S., et al. Extrapyramidal symptoms in patients with primary degenerative dementia. *J. Clin. Psychopharmacol.*, 1:398–400, 1981.

Price, D.L., Whitehouse, P.J., Struble, R.G., et al. Basal forebrain cholinergic systems in Alzheimer's disease and related dementias. *Neurosci. Comment.*, 1(2):84–92, 1982.

Prinz, P.N., Vitaliano, P.P., Vitaliano, M.V., et al. Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. *Neurobiol. Aging*, 3:361–370, 1982.

Raskind, M., Peskind, E., Rivard, M.F., et al. Dexamethasone suppression test and cortisol circadian rhythm in primary degenerative dementia. *Am. J. Psychiatry*, 139:1468–1471, 1982.

Reisberg, B. Clinical diagnosis and differential diagnosis of Alzheimer's disease and related disorders. In: Reisberg, B. (ed.), *Alzheimer's Disease—The Standard Reference.* New York: The Free Press, 1983, pp. 173–187.

Risch, S.C., Cohen, P.M., Janowsky, D.S., et al. Physostigmine induction of depressive symptomatology in normal volunteer subjects. *J. Psychiatr. Res.*, 4:89–94, 1981.

Rossor, M.N. Neurotransmitters and CNS disease: dementia. *Lancet*, 2:1200–1204, 1982.

Roth, M., and Myers, D.H. The diagnosis of dementia. *Br. J. Psychiatry*, (Suppl. 9):87–89, 1975.

Sachar, E.J., Hellman, L., Roffwarg, H.P., et al. Disrupted 24 hour patterns of cortisol secretion in psychotic depression. *Arch. Gen. Psychiatry*, 28:19–24, 1973.

Sitaram, N., and Gillin, J.C. Acetylcholine: Possible involvement in sleep and analgesia. In: Berger, P., and Davis, K. (eds.), *Brain Acetylcholine and Neuropsychiatric Disease.* New York: Plenum Press, 1979, pp. 311–343.

Sitaram, N., Nurnberger, J.I., Gershon, E., and Gillin, J.C. Faster cholinergic REM sleep induction in euthymic patients with primary affective illness. *Science*, 208:200–202, 1980.

Sitaram, N., Nurnberger, J., Gershon, E., and Gillin, J.C. Cholinergic regulation of mood and REM sleep: A potential model and marker for vulnerability to depression. *Am. J. Psychiatry*, 139:571–576, 1982.

Sitaram, N., Gillin, J.C., and Bunney, W.E. Cholinergic and catecholaminergic receptor sensitivity in affective illness: Strategy and theory. In: Post, R.M., and Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders*, Baltimore/London: Williams & Wilkins, 1984, pp. 629–651.

Stanley, M., and Lerer, B. Electroconvulsive shock and brain cholinergic function: Role of striatal muscarinic receptors. *Convulsive Therapy*, 1:158–166, 1985.

Weingartner, H., Cohen, R.M., Murphy, D.L., et al. Cognitive processes in depression. *Arch. Gen. Psychiatry*, 38:42-47, 1981.

Wettstein, A., and Spiegel, R. Clinical trials with the cholinergic drug RS-86 in Alzheimer's disease and senile dementia of the Alzheimer type (SDAT). *Psychopharmacology*, 84:572–573, 1984.

Wolff, E.A., Putnam, F.W., and Post, R.M. Motor activity and affective illness. *Arch. Gen. Psychiatry*, 42:288–294, 1985.

Ziegler, D.K. Cerebral atrophy in psychiatric patients. *Am. J. Psychiatry*, 111:454–455, 1954.

Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia

CHAIRS: Carol Tamminga, M.D.
Maryland Psychiatric Research Center
Baltimore, Maryland

and Nina R. Schooler, Ph.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Ceruletide for Schizophrenia: A Review

Jeffrey A. Mattes, M.D.,[1] William Hom, M.D.,[1] and Joseph M. Rochford, M.D.

The majority of schizophrenics have residual symptoms, with functional and social impairment, despite an optimal regimen of neuroleptic medication. Additional treatment approaches, therefore, are needed. A compound recently reported to improve schizophrenics already on neuroleptics is ceruletide. Ceruletide, found in amphibians, is a decapeptide structurally nearly identical to the C-terminal amino acid sequence of cholecystokinin (CCK), a 33-amino acid polypeptide secreted by the duodenum to initiate contraction of the gall bladder during digestion (Morley, 1982).

As with other polypeptides (e.g., ACTH, vasopressin), CCK has been found to have central nervous system (CNS) effects apparently unrelated to its originally discovered hormonal effect. There is evidence that CCK is present in the brain (Beinfeld & Palkovits, 1981; Morley, 1982), acting as a neurotransmitter or neuromodulator (Snyder, 1980). Receptors for CCK have been found (Hays et al., 1982; Itoh et al., 1982; Saito et al., 1980). CCK in fact seems to be one of the most highly concentrated of the putative regulatory peptides in the brain (Noyer et al., 1980).

Relevant to schizophrenia, Hökfelt et al. (1980) discovered the coexistence of CCK and dopamine in mesolimbic, but not nigrostriatal, dopamine neurons. In addition, CCK has been reported to reduce dopamine turnover in the caudate nucleus and nucleus accumbens (Fuxe et al., 1980), to increase striatal dopamine release (Kovacs et al., 1981), to increase dopamine cell firing (Skirboll et al., 1981), to affect dopamine binding (Fuxe et al., 1981; Murphy & Schuster, 1982), and to modify dopamine receptor sensitivity (Hommer & Skirboll, 1983). Zetler (1983) found ceruletide to have neuroleptic-like activity in mice, Cohen et al. (1982) found that combining CCK-8 with haloperidol reduced signaled-avoidance behavior significantly more than either drug did alone, and van Ree et al. (1984) found ceruletide and other CCK analogues to be active in a number of behavioral test procedures in rats which predict antipsychotic activity; not all of these findings, however, have been consistently confirmed (Widerlov et al., 1983). Verbanck et al. (1984) recently reported reduced levels of CCK-8S in the cerebrospinal fluid of schizophrenics.

Moroji et al. (1982), in an open study, evaluated ceruletide in 20 schizophrenic patients refractory to neuroleptics. Results indicated

---

[1] Carrier Foundation, Belle Mead, NJ 08502.

improvement in both positive (e.g., hallucinations, delusions) and negative (e.g., withdrawal, blunted affect) symptoms after a single intramuscular (i.m.) injection of 0.3 or 0.6 mcg/kg to patients who were on stable dosages of neuroleptics for 3 weeks prior to the injection. The improvement was evident 2 hours after the dose, but peaked 1 week later. Moroji et al. found the higher dose, 0.6 mcg/kg, to be more beneficial than the lower. Side effects, slight abdominal pains, and borborygmus were minimal. Itoh et al. (1982), using a similar open design and comparable dosage, also reported benefit in 23 of 58 chronic schizophrenics; improvement was primarily in mood and spontaneity rather than in psychotic symptoms.

Nair and associates conducted two open trials of cholecystokinin (Nair et al., 1982, 1983a) and one open trial of the octapeptide CCK-8 (Bloom et al., 1983) in a total of 35 chronic schizophrenics, and also reported generally positive results. Nair et al. (1983b) subsequently conducted a placebo-controlled study of CCK in 17 schizophrenic inpatients, and reported positive effects on Brief Psychiatric Rating Scale (BPRS)-rated Anxiety-depression and Thought-disturbance 7 days after a single infusion, but the authors noted that the study was not truly double-blind since patients fairly consistently noted epigastric discomfort from the dose of CCK used. Peselow et al. (1983), in the second double-blind trial, using the octapeptide CCK-8, reported generally negative results. Nair et al. (1983b), however, found CCK-8 to show less striking results than CCK itself. Hommer et al. (1984), in a double-blind crossover study, found no benefit from ceruletide in 8 chronic schizophrenics, and no benefit from CCK-8 in 4 patients; however, the *N*s were small, and the use of a crossover design may have obscured drug-placebo differences, since the drug has been reported to act for up to 3 weeks (Moroji et al., 1982). Lostra et al. (1984), in another crossover study involving 9 drug-free schizophrenics (most other work has involved schizophrenics with residual symptoms stabilized on neuroleptics), also found no effect of ceruletide. In an additional double-blind study (Mattes et al., 1985), we administered two injections of ceruletide 0.6 mcg/kg or placebo to 17 chronic refractory schizophrenics and found no evidence of benefit.

Discussion

Five of six double-blind evaluations have not found beneficial effects of ceruletide in chronic schizophrenics. Given the previous positive reports from open studies, the samples, dosages, and evaluations used would appear to be more than adequate to demonstrate a positive effect; the most likely explanation for the discrepant results, therefore, is that positive reports reflected placebo responses.

There is still a question as to whether ceruletide crosses the blood-brain barrier (Cornford et al., 1978; Itoh et al., 1982). Analogues do affect sleep and appetite, but this may be through a peripheral mechanism, as some of these effects have been eliminated by vagotomy (Smith et al., 1981). The mechanisms of an apparent analgesic effect (Piazza et al., 1981) and of effects on dopamine receptors (Hommer & Skirboll, 1983) are unknown.

One would not expect that CCK analogues other than ceruletide would be more effective in schizophrenics; the CCK analogue found most in mammalian brains is the octapeptide CCK-8 (Cornford et al., 1978), but ceruletide has been found to be far more potent than CCK-8 in respect to CNS effects (Itoh et al., 1982). Also, ceruletide and CCK bind to the same receptors in all known receptor systems (Piazza et al., 1981).

Given the wide distribution and high concentration of CCK in the CNS, and its apparent interaction with dopamine and other neurotransmitters, it can be expected that CCK analogues and eventually CCK agonists and antagonists will continue to be of interest to psychiatrists. However, clinical relevance may depend on the development of analogues which more easily cross the blood brain barrier, or drugs structurally unrelated to CCK which nevertheless affect CCK receptors, synthesis, or release.

Acknowledgment: The authors wish to thank Sarah Robin, Mary Anne Hinz, and

Marie Magee Brown for their administrative assistance.

References

Beinfeld, M.C., and Palkovits, M. Distribution of cholecystokinin (CCK) in the hypothalamus and limbic system of the rat. *Neuropeptides*, 2:123–129, 1981.

Bloom, D.M., Nair, N.P.V., and Schwartz, G. CCK-8 in the treatment of chronic schizophrenia. *Psychopharmacol. Bull.*, 19(3):361–362, 1983.

Cohen, S.L., Knight, M., Tamminga, C.A., et al. Cholecystokinin-octapeptide effects on conditioned-avoidance behavior, sterotypy, and catalepsy. *Eur. J. Pharmacol.*, 83:213–222, 1982.

Cornford, E.M., Braun, L.D., Crane, P.D., et al. Blood-brain barrier restrictions of peptides and the lower uptake of enkephalin. *Endocrinology*, 103:1297–1303, 1978.

Fuxe, K., Agnati, L., Benfenati, F., et al. Modulation by cholecystokinins of $[^3H]$ spiroperidol binding in rat striatum: Evidence for increased affinity and reduction in number of binding sites. *Acta Physiol. Scand.*, 113:567–569, 1981.

Fuxe, K., Andersson, V., Locatelli, L.F., et al. Cholecystokinin peptides produce marked reduction of dopamine turnover in discrete areas in the rat brain following intraventricular injection. *Eur. J. Pharmacol.*, 67:329–331, 1980.

Hays, S.E., Beinfeld, M.C., Jensen, R.T., et al. Demonstration of a putative receptor site for cholecystokinin in rat brain. *Neuropeptides*, 1:53–62, 1982.

Hökfelt, T., Skirboll, L., Rehfeld, J.F., et al. A subpopulation of mesencephalic dopamine neurons projecting to limbic areas contains a cholecystokinin-like peptide: evidence from immunohistochemistry combined with retrograde tracing. *Neuroscience*, 5:2093–2124, 1980.

Hommer, D.W., Pickar, D., Roy, A., et al The effects of ceruletide in schizophrenia. *Arch. Gen. Psychiatry*, 41:617–619, 1984.

Hommer, D., and Skirboll, L. Cholecystokinin-like peptides potentiate opomorphine-induced inhibition of dopamine neurons. *Eur. J. Pharmacol.*, 91:151–152, 1983.

Itoh, H., Tanoue, S., Yagi, G., et al. Clinical study on the psychotropic effects of caerulein—an open clinical trial in chronic schizophrenic patients. *Keio J. Med.*, 31:71–95, 1982.

Kovacs, G.L., Szabo, G., Penke, B., et al. Effects of cholecystokinin octapeptide on the striatal dopamine metabolism and an apomorphine-induced sterotyped cageclimbing in mice. *Eur. J. Pharmacol.*, 69:313–319, 1981.

Lostra, F., Verbanck, P., and Mendlewicz, J. No evidence of antipsychotic effect of caerulein in schizophrenic patients free of neuroleptics: A double-blind cross-over study. *Biol. Psychiatry*, 19:877–882, 1984.

Mattes, J.A., Hom, W., Rochford, J.M., et al. Ceruletide for schizophrenia. *Biol. Psychiatry*, 20:533–538, 1985.

Morley, J.E. The ascent of cholecystokinin (CCK)—from gut to brain. *Life Sci.*, 30:479–493, 1982.

Moroji, T., Watanabe, N., Aoki, N., et al. Antipsychotic effects of ceruletide (caerulein) on chronic schizophrenia. *Arch. Gen. Psychiatry*, 39:485, 1982.

Murphy, R.B., and Schuster, D.I. Modulation of H^3-dopamine binding by cholecystokinin. *Peptides*, 3:539–543, 1982.

Nair, N.P.V., Bloom, D.M., and Nestoros, J.N. Cholecystokinin appears to have antipsychotic properties. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:509–512, 1982.

Nair, N.P.V., Bloom. D.M., Nestoros, J.N., et al. Therapeutic efficacy of cholecystokinin in neuroleptic resistant schizophrenic subjects. *Psychopharmacol. Bull.*, 19(1):134–136, 1983a.

Nair, N.P.V., Bloom, D.M., and Schwartz, G. Cholecystokinin and the treatment of chronic schizophrenia. Paper presented at the 36th Annual Meeting of the American Psychiatric Association, New York, May 1983b.

Noyer, M., Bui, N.D., Deschodt-Lanckman, M., et al. Postnatal development of the cholecystokinin-gastrin family of peptides in the brain and gut of rat. *Life Sci.*, 27:2197–2203, 1980.

Peselow, E.D., Angrist, B.M., Siekierski, J., et al. Cholecystokinin (CCK) in the treatment of chronic schizophrenic patients. Paper presented at NCDEU (New Clinical Drug Evaluation Unit) annual meeting, Key Biscayne, Florida, June 1983.

Piazza, E., Brambilla, M., Cattaneo, M.T., et al. Analgesic activity of ceruletide in cancer patients. In: Basso, N., Lexocke, E., Speronza, V., and Walsh, J.H. (eds.), International Symposium on Brain-Gut Axis, Abstracts. Florence, 1981.

Rehfeld, J.F. Immunochemical studies on cholecystokinin. *J. Biol. Chem.*, 253:4022–4027, 1978.

Saito, A., Sankaron, H., Goldfine, I.D., et al. Cholecystokinin receptors in the brain: Characterization and distribution. *Science*, 208:1155–1156, 1980.

Skirboll, L.R., Grace, A.A., Hommer, D.W., et al. Peptide-monoamine coexistence: Studies on the actions of cholecystokinin-like peptide on the electrical activity of midbrain dopamine neurons. *Neuroscience*, 16:2111–2124, 1981.

Smith, G.P., Jerome, C., Cushin, B.J., et al. Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. *Science*, 213:1036–1037, 1981.

Snyder, S.H. Brain peptides as neurotransmitters. *Science*, 209:976–983, 1980.

van Ree, J.M., Verhoeven, M.A., Brouwer, G.J., and de Weid, D. Ceruletide resembles antipsychotics in rats and schizophrenic patients. *Neuropsychobiology*, 12:4–8, 1984.

Verbanck, P.M.P., Lostra, F., Gilles, C., et al. Reduced cholecystokinin immuno-reactivity in the cerebrospinal fluid of patients with psychiatric disorders. *Life Sci.*, 34:67–72, 1984.

Widerlov, E., Agren, H., Wahlstrom, A., et al. Lack of interactions between cholecystokinin and dopamine in the central nervous system of rats and humans. *Psychopharmacol. Bull.*, 19(3):355–360, 1983.

Zetler, G. Behavioral pharmacology of CCK and analogs. *Psychopharmacol. Bull.*, 19(3):347–351, 1983.

Clinical Evaluation of Ceruletide in Schizophrenia: A Multi-Institutional Cooperative Double-Blind Controlled Study

Hitoshi Itoh, M.D.,[1] Yasuo Shimazono, M.D.,[2] Yukio Kawakita, M.D.,[3] Yoshio Kudo, M.D.,[4] Yorio Satoh, M.D.,[5] and Ryo Takahashi, M.D.[6]

Introduction

Since cholecystokinin (CCK) is present at high concentrations not only in the tissues of intestines but also in the cerebrum and other parts of the brain and exerts a variety of behavioral pharmacologic actions, it has been presumed that these peptides might have some important effects upon mental function. Having found in animal experiments that CCK-8 has sedative and various other central actions, S. Itoh (1980) speculated that CCK-8 or its homologues might have antipsychotic effects.

On May 2, 1981, the Japan Economic Journal carried a surprising piece of news as a scoop with the heading: "Highly effective schizophrenia drug is found by ex-Hokkaido professor." According to the article, Moroji, a psychiatrist who was a member of Dr. Itoh's study group, observed a marked improvement of such psychic symptoms as emotional disturbance, autism, auditory hallucination, and delusion in 16 of the 20 patients with chronic schizophrenia receiving a CCK-like compound (Moroji et al., 1982a).

In that clinical study, caerulein diethylamine was administered intramuscularly (i.m.) at doses of as low as 0.3 to 0.6 μg/kg and the patients became refreshed in mood 2 hours after injection. The above-mentioned various psychic symptoms abated most conspicuously 1 to 2 weeks after start of treatment and the effects remained sustained over the ensuing several weeks in some of the cases, according to the newspaper.

Caerulein diethylamine (ceruletide) is a polypeptide isolated from the skin of tree frogs, *Hyla caerulea*, in Australia. It is structurally analogous to CCK-8 and endowed with physiological effects on the gastrointestinal tract and central nervous system (CNS) similar to those of CCK-8. A synthetic preparation has been commercially available as a drug for testing the biliary tract and pancreatic function.

A synthetic product of Pharmitalia Co., Ltd., was used in early clinical studies in Japan, including the initial clinical trial by Moroji et al. (1982a). Since the development of a highly pure synthetic preparation of ceruletide at the Research Laboratories of Shionogi Pharmaceutical Co., Ltd., in Japan a few months later, the Japanese product has become clinically used in this country.

Since 1982, many investigators in various countries have reported results of evaluation of the antipsychotic effects of CCK and its CCK-like peptides chiefly in schizophrenia (Hommer et al., 1984; Lotstra et al., 1984; Nair et al., 1982).

In another study of Moroji et al. (1982b), 12 patients with schizophrenia were treated with 40 μg of ceruletide injected at 2-week intervals, and a long-sustained clinical effect for 1 year was evident in 11 of these cases. Follow-up studies to confirm their findings have been made by many psychiatrists in Japan.

Results of open trials conducted as early phase II studies were diverse. According to a report by Kudo (1983), a significant clinical improvement was observed in 36.6% of 292 cases of schizophrenia treated, as assessed by general improvement rating. It was inferred thereby that major indications for the drug would be chronic schizophrenics with manifest anxiety, blunted affect, and motor retardation.

---

[1] School of Medicine, Keio University, Tokyo, Japan. (Deceased)
[2] National Musashi Sanatorium, Tokyo, Japan.
[3] School of Medicine, Osaka City University, Osaka, Japan.
[4] Osaka Dai-ni Keisatsu Hospital, Osaka, Japan.
[5] Faculty of Medicine, University of Tokyo, Tokyo, Japan.
[6] School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan.

Furthermore, Kudo (1983) conducted a double-blind, matched-pair, placebo-controlled study in patients with schizophrenia who were ceruletide responders, with the results reconfirming the efficacy of the drug.

In double-blind controlled trials with a crossover design performed by Y. Satoh, I. Hasue, and K. Miyakawa (personal communication, 1982) and by K. Sugano (personal communication, 1984), there was no significant difference in clinical effects between ceruletide and placebo.

Nakamura et al. (1984) performed a double-blind crossover trial in which ceruletide (0.6 µg/kg) and a placebo were administered on five consecutive occasions each without any other concomitant antipsychotic drug medication. They reported that the study yielded positive results, namely, general improvement rates of 67% on ceruletide and 33% on placebo and aggravation rates of 11 and 22%, respectively.

In an open trial of the drug conducted in 1981–1982 by Itoh, one of the present authors, clinical improvement was noted in 19 (34%) of the 58 patients with chronic schizophrenia receiving neuroleptic medications concomitantly (Itoh et al., 1982). This improvement rate is by no means high, and the numbers of patients studied were rather small in the above-described double-blind trials reported in Japan. Thus, the data obtained therein seemed to be insufficient for drawing any conclusion as to clinical usefulness of ceruletide.

In view of this, the authors set out a multi-institutional cooperative double-blind study as a nationwide organization.

Experimental Methods

Subjects

The subjects studied were 265 psychiatric inpatients at 28 hospitals with the diagnosis of schizophrenia according to DSM-III (Diagnostic and Statistical Manual—3rd. ed., 1980). Patients meeting the following two inclusion criteria were admitted to the trial preferentially, i.e., 1) those whose principal clinical picture was hallucinatory-delusional, abulic-apathetic, neurasthenic, or depressive state, and 2) the clinical course was chronic defective, periodic defective, transitional, or periodic complete abatement type.

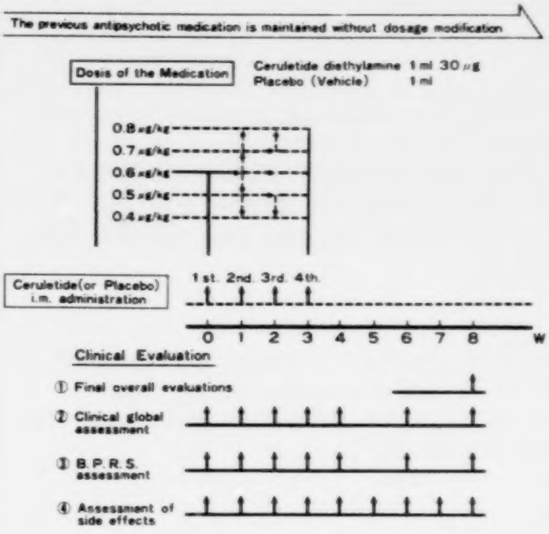

The previous antipsychotic medication is maintained without dosage modification
Dosis of the Medication
Ceruletide diethylamine 1 ml 30 µg
Placebo (Vehicle) 1 ml
0.8 µg/kg
0.7 µg/kg
0.6 µg/kg
0.5 µg/kg
0.4 µg/kg
Ceruletide(or Placebo) i.m. administration
1st. 2nd. 3rd. 4th.
0 1 2 3 4 5 6 7 8 W
Clinical Evaluation
① Final overall evaluations
② Clinical global assessment
③ B.P.R.S. assessment
④ Assessment of side effects

FIGURE 1. **Administration and evaluation schedule.**

Drugs and Administration

Patients were randomly allocated, in a double-blind manner, to ceruletide or a placebo (vehicle).

As shown in Figure 1, either drug was given at 7-day intervals on four occasions by i.m. injection. Ceruletide was administered on a fixed-flexible dosage schedule; it was begun at an initial dose of 0.6 µg/kg and the dosage was individualized thereafter at the investigator's discretion according to symptom. The maximum dose was 0.8 µg/kg.

Other antipsychotic drugs that had previously been instituted were continued without modification of dosage throughout the study treatment.

Methods of Evaluation

Clinical Global Assessment. Each patient was subjected to assessments by General Improvement Rating at Weeks 1, 2, 3, 4, 6, and 8 of treatment. The overall ratings were made by the physician on a 4-point scale, in categories of "markedly improved," "improved," "unchanged," or "deteriorated." At completion of the study treatment, Final General Improvement Rating was made on the same scale as described above.

Both the overall degree of side effects and of accompanying symptoms as a whole were assessed at the termination of study medication using a 4-point scale as the Overall Safety Rating.

Furthermore, Global Usefulness Rating for ceruletide or placebo was performed on each patient with reference to the Final General Improvement Rating and Overall Safety Rating, on a 5-point scale, i.e. "markedly useful," "moderately useful," "slightly useful," "not useful," or "undesirable."

Assessment of Symptoms. Patients were evaluated for degree of symptoms at Weeks 0, 1, 2, 3, 4, 6, and 8 of the study, using the Brief Psychiatric Rating Scale (BPRS) as a rating instrument.

Results

Background Characteristics of the Patients

A total of 265 patients received study treatment in the trial, of whom 135 received ceruletide and 130 received placebo. These two groups were remarkably comparable in practically all of the patient background characteristics. Analysis of these pretreatment data did not reveal any statistically significant difference between the two treatment groups as to any of the items.

Dosage and Trial Outcome

Inter-group comparison showed no noticeable difference with respect to mean dose per day, number of doses given, or dosing pattern.

There were 7 patients who were withdrawn from the ceruletide therapy group and 1 patient from the placebo therapy group.

The Final Evaluation

The Final General Improvement Rating. As seen in Figure 2, there were only 3 markedly improved cases in each treatment group. The cumulative percentage of improved to markedly improved patients was 29% with ceruletide and 24% with placebo. Analysis of the data by Mann-Whitney U-test showed no statistically significant inter-group difference in this respect.

The Overall Safety Rating. As assessed by Overall Safety Rating, the incidence of untoward effects was 38% in the ceruletide therapy group and 19% in the placebo group. The former was significantly higher (Figure 2).

The Global Usefulness Rating. No significant inter-group difference could be seen in the overall therapeutic benefit assessment by Global Usefulness Rating by the investigator, when data were analyzed using the U-test (Figure 2).

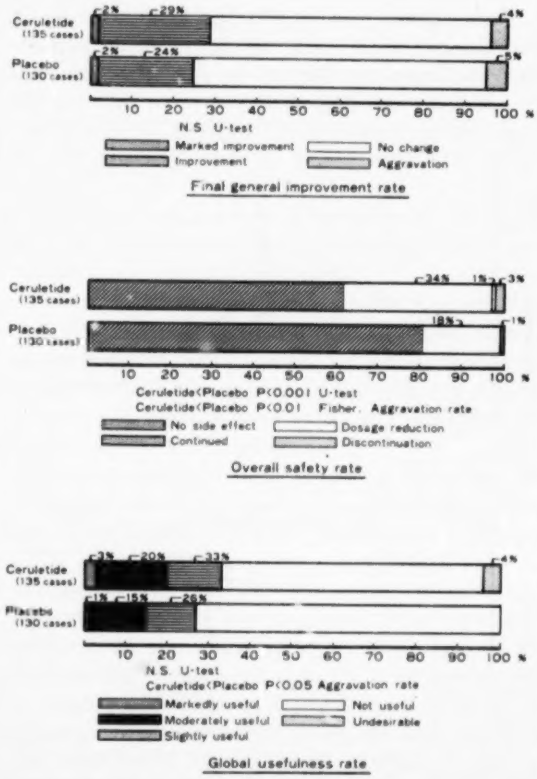


FIGURE 2. Final evaluation.

The cumulative percentage of patients in whom the study medication was evaluated as "markedly useful" to "moderately useful" was 20% in the ceruletide therapy group and 15% in the placebo therapy group. Percent of cases in which the medication was "slightly useful" to "markedly useful" was 33 and 27%, respectively. Thus, there were no significant differences between the two treatment groups.

The General Improvement Rating at Each Week. The results of Weekly General Improvement Ratings during the study treatment are presented in Figure 3. No significant inter-group difference was observed at any week during the course of the 8-week treatment.

Transition of the Total Scores of the BPRS. As a method to assess the general improvement, transition of the total scores of the two drug groups was examined at each week. As shown in Figure 4, the total scores of the ceruletide therapy group were significantly improved at the end of both week 3 and 4 in comparison to the initial score ($p<0.05$, Wilcoxon test). However, there were no statistically significant differences between the two groups throughout the course of the trial by means of the total BPRS scores (Mann-Whitney U-test).

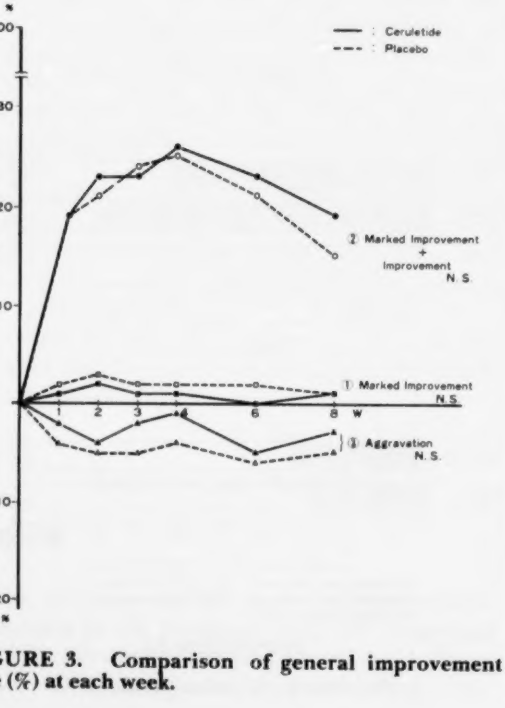


FIGURE 3. Comparison of general improvement rate (%) at each week.

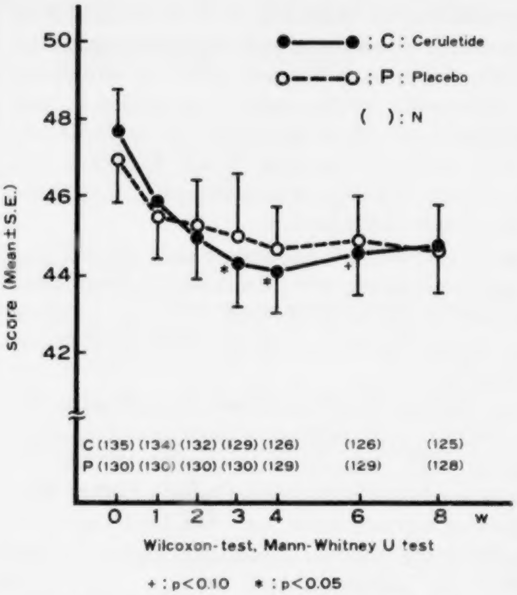


FIGURE 4. Comparison of changes of B.P.R.S. total score during the treatment.

Symptomatic Improvement Rating. From results of evaluation for degree of individual symptoms made at each week of treatment using the BPRS, improvement and aggravation rates were calculated by comparison with those at Week 0 and compared between the two treatment groups. The only symptom item for which ceruletide was significantly better was "Hostility" (Week 2, aggravation rate) whereas "Guilt feeling" was the only symptom item for which placebo was significantly superior (Week 1, aggravation rate).

Side Effects. The types and incidence of adverse effects encountered in the two treatment groups during the course of trial are shown in the Table.

Adverse reactions were significantly more frequent in the ceruletide therapy group ($p<0.001$, Fisher's test). The most common side effect was abdominal symptoms, occurring in 30 patients (41%) receiving ceruletide and in 9 patients (7%) receiving placebo; the incidence was significantly higher in the former ($p<0.001$, Fisher's test).

TABLE
Comparison of Main Side Effects

	Ceruletide (%)	Placebo (%)	Statist. analysis
Number of cases affected	49/135 (36)	21/130 (16)	$C<P^{***}$
Abdominal symptoms	41 (30)	14 (11)	$C<P^{***}$
Other symptoms	19 (14)	9 (7)	$C<P^{\dagger}$
Nausea	19 (14)	1 (1)	—
Vomiting	3 (2)	0 (0)	—
Borborygmus	5 (4)	1 (1)	—
Abdominal distension	1 (1)	2 (2)	—
Abdominal discomfort	8 (6)	2 (2)	—
Anorexia	3 (2)	2 (2)	—
Abdominal pain	10 (7)	2 (2)	$C<P^{*}$
Urgency to defecate	1 (1)	3 (2)	—
Diarrhea	6 (6)	3 (2)	—
Headache	4 (3)	0 (0)	—
Drowsiness	3 (2)	2 (2)	—
Insomnia	2 (1)	1 (1)	—
Malaise	3 (2)	0 (0)	—
Dizziness	2 (1)	0 (0)	—
Blurredvision	2 (1)	0 (0)	—

$C<P$: Ceruletide inferior to Placebo
*** : $P<0.001$, ** : $P<0.01$, * : $P<0.05$, † : $P<0.10$
Fisher's test

As for individual side effects, nausea and stomachache were significantly more frequent among patients receiving ceruletide.

Discussion and Conclusion

Since the first discovery by Moroji et al. (1982a), there have been some dozen clinical reports concerning the antipsychotic effect of CCK or ceruletide in the treatment of schizophrenia. According to reports with positive results, the treatment produced improvement of both positive and negative symptoms in chronic schizophrenics refractory to treatment with previously introduced drugs.

Schizophrenia is an illness which is so diverse in disease type, disease picture, and clinical course that it seems more or less difficult to deal with it as a single disease entity.

It is unclear from the data documented in the literature what particular type or types, clinical course pattern, and disease state features of schizophrenia correspond to responders to CCK or CCK-like peptides.

In the clinical trial reported herein, chronic schizophrenics with disease state features and clinical course patterns corresponding to those in the cases described to have been improved by ceruletide in the reports of Moroji et al. (1982a,b), and subsequent reports of open trials in Japan were selected as the case material, as described above.

It can be noted from the data obtained in the present series that a) there was no significant difference in percentage of improved cases between the ceruletide group and the placebo group; and b) the improvement rates were remarkably low, as assessed by Final General Improvement Rating. Only 2% of patients showed marked clinical improvements, and the cumulative rate of improved-to-marked-improved cases was as low as 29%. These are the lowest figures that have ever been found in clinical trials of antipsychotic drugs.

Gastrointestinal symptoms were encountered as side effects with significantly greater frequency in the ceruletide therapy group; 4 patients receiving the drug complained of nausea and/or abdominal pain that led to withdrawal. These manifestations were attributable to the pharmacologic actions of ceruletide. The data indicated that the incidence and severity of these side effects increased with increasing therapeutic dosage and dosing frequency of ceruletide, an undesirable condition from the therapeutic viewpoint.

Thus, the results of the present multiclinical cooperative, double-blind controlled trial conducted in 265 patients with schizophrenia failed to provide evidence for clinical effects that would qualify ceruletide as a drug for the treatment of schizophrenia.

The numerous new findings reported by investigators in various countries concerning the interrelation of the central actions of CCK and the psychic function are of profound interest and of great importance. Among them are investigations aiming at elucidation of the underlying mechanisms of action on the hypothesis that CCK or ceruletide is endowed with antipsychotic effects on schizophrenia. Furthermore, as described in the reports of Moroji et al. (1982a,b) and in several other papers, it may be probable, in fact, that some patients with chronic schizophrenia respond with some alterations in symptoms when treated with CCK or ceruletide injections.

It is concluded from the present cooperative trials that no evidence has been found to substantiate usefulness of ceruletide as a drug for the treatment of schizophrenia.

References

Hommer, D.W., Pickar, D., Roy, A., et al. The effects of ceruletide in schizophrenia. *Arch. Gen. Psychiatry*, 41:617–619, 1984.

Itoh, H., Tanoue, S., Yagi, G., et al. Clinical study on the psychotropic effects of caerulein—an open clinical trial in chronic schizophrenic patients. *Keio J. Med.*, 31:71–95, 1982.

Itoh, S. *Neuropeptides* (Japanese). Tokyo: Rikogaku-sha, 1980.

Kudo, Y. Clinical evaluation of ceruletide (883-S) on chronic schizophrenia. (Japanese) *Rinsho Seishinigaku*, 12:703–710, 1983.

Lotstra, F., Verbanck, P., Mendlewicz, J., and Vanderhaeghen, J.J. No evidence of antipsychotic effect of caerulein in schizophrenic patients free of neuroleptics: A double-blind crossover study. *Biol. Psychiatry*, 19:877–882, 1984.

Moroji, T., Watanabe, N., Aoki, N., and Itoh, S. Antipsychotic effects of ceruletide (Caerulein) on chronic schizophrenia. *Arch. Gen. Psychiatry*, 38(4):113–124, 1982a.

Moroji, T., Watanabe, N., Aoki, N., and Itoh, S. Antipsychotic effects of caerulein, a decapeptide chemically related to cholecystokinin octapeptide on schizophrenia. *Int. Pharmacopsychiatry*, 17(4):255–273, 1982b.

Nair, N.P.V., Bloom, D.M., and Nestoros, J.N. Cholecystokinin appear to have antipsychotic properties. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:509–512, 1982.

Nakamura, G., Nobuyama, M., and Kudo, Y. Antipsychotic effect of ceruletide as a sole agent. Presented at 14th C.I.N.P. Congress, Florence, June 1984.

Cholecystokinin: A Neuropeptide in the Treatment of Schizophrenia

Carol A. Tamminga, M.D.,[1] Robert L. Littman, M.D.,[1] and Larry D. Alphs, M.D.[1]

The distribution and functional activity of many peptidergic substances in the gastrointestinal system have been known for many years; more recently, a number of these have been found in the brain and are presumed to be neurally active. Cholecystokinin (CCK) is a member of this growing family of gut-brain peptides. It was first isolated from the gastrointestinal system in 1928 (Ivy & Oldberg, 1928), identified by its action on gall bladder smooth muscle, and sequenced as a 33-amino acid peptide in 1971 (Mutt & Jorpes, 1971). Not until 1975 was there evidence of a CCK-like substance in the brain (Dockray, 1976; Vanderhaeghen et al., 1975). Since that time various anatomic, biochemical, and behavioral studies have suggested a transmitter/modulator role for CCK in the brain (Beinfeld et al., 1981; Innes et al., 1979; Mueller et al., 1977; Rehfeld, 1978).

The predominant form of neuronal CCK is the carboxy-terminal octapeptide (CCK-8) (Mueller et al., 1977; Rehfeld, 1978). It derives from a polypeptide precursor synthesized in neuronal cell bodies, and modified by post-translational processing and cleavage during axonal transport down the neuraxis to form the octapeptide which remains stored in vesicles at the synapse (Eng et al., 1983; Schmitt et al., 1982). With depolarizing stimuli, CCK-8 is released from the nerve terminus to associate with specific receptors on postsynaptic neuronal surfaces. Inactivation of the peptidergic transmitter occurs by peptidase-mediated degradation rather than by reuptake into the presynaptic neuron. The initial catabolic step of CCK-8 degradation involves cleavage of the octapeptide into a C-terminal pentapeptide (Deschoht-Lanckman et al., 1981); subsequent steps produce the C-terminal di- and tri-peptide of CCK-8, which are relatively stable final products (Steardo et al., 1985). These intermediate and final catabolic products of CCK-8 are of interest because several of them show an affinity for the central CCK receptor and may have a functional interaction at the receptor (Knight et al., 1984). Thus, CCK, in addition to exerting an action itself at its receptor, may, after subsequent degeneration, continue to produce either agonist, partial agonist, or frank antagonist action at the same receptor through its peptide products.

CCK is known to produce characteristic hormonal effects in the body, which include stimulation of pancreatic enzyme secretion and gall bladder contraction. In addition, CCK has been associated with specific centrally mediated actions: appetite regulation, hyperglycemia, hypothermia, analgesia, central nervous system (CNS) depression, ptosis, catalepsy, and pituitary hormone modulation (Morley, 1982). CCK-8 produces what is described as satiety in rat, monkey, and man (Gibbs et al., 1973); it reduces conditioned avoidance responding in laboratory rodents (Cohen et al., in press), inhibits apomorphine-induced stereotypies (Zetler, 1983), and suppresses social behavior in mice (Crawley et al., 1981). These behavioral actions of CCK have been found after both central and systemic administration.

Interest in CCK for the treatment of schizophrenia was stimulated when CCK-8 was discovered to coexist with dopamine (DA) in certain mesencephalic neurons in the substantia nigra, area compacta, and in the ventral tegmental area (Hökfelt et al., 1980a). CCK-8 is found predominantly in those DA-containing neurons which project to the prefrontal and limbic cortex (Hökfelt et al., 1980b). Moreover, evidence suggests cholecystokinin may play a functional role in DA release (Markstein & Hökfelt, 1984), and in modulating neuronal metabolism in DA-dependent areas of cortex (Lucignani et al., 1984), even though this interaction remains difficult to consistently characterize

---

[1] Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, Baltimore, MD 21228.

(Widerlöv et al., 1983). Since psychotic symptoms of schizophrenia improve after a reduction in DA-mediated transmission, neurally active substances which modulate activity of DA neurons hold promise as being active in the treatment of schizophrenia. Since currently available treatments for schizophrenia have considerable limitations, without other known pharmacologic strategies being effective in modifying psychosis (Tamminga, 1982), additional, improved therapeutic strategies for the treatment of this illness are eagerly being pursued.

This theoretical rationale for the use of CCK-8 in the treatment of schizophrenia is supported by a number of open clinical studies which have reported symptomatic improvement in schizophrenia with CCK-8 administration and with the administration of its more potent analogue caerulein (Moroji et al., 1982; Nair et al., 1982). However, since these early studies were not carried out in a blind design, and because a subsequent replication study was negative (Hommer et al., 1984), we carried out a series of studies with caerulein in schizophrenia to test for potential antipsychotic activity (Tamminga et al., in press).

In the first of these studies, 5 schizophrenic subjects, who were free from all medication for at least 1 month, were given a 0.3 μg/kg dose of caerulein, intramuscularly, in a double-blind design with placebo. Patients were evaluated prior to drug administration and at 2 hours, 4 hours, and 24 hours after the drug by Brief Psychiatric Rating Scale (BPRS) assessment for evidence of a change in psychotic symptoms, in DA-mediated endocrine parameters (prolactin and growth hormone), and in visual-evoked potential pattern, after either the caerulein or placebo. This study was intended to evaluate any immediate or delayed effects of a single dose of caerulein on psychosis, endocrine function, or visual-evoked potential. The results showed no effect of caerulein on the level of psychosis in these schizophrenic patients (Table 1), or on plasma levels of prolactin or growth hormone. In addition, caerulein did not alter the brain electroencephalogram (EEG) pattern of visual-evoked response. Despite these negative clinical indices, significant increases in plasma levels of caerulein were demonstrated after drug administration; levels achieved a maximum in 20 to 30 minutes and largely disappeared by 60 minutes (Table 2). We concluded from this experiment that caerulein administration at the previously tested dose levels, despite demonstrable blood levels, has no effect on psychosis of an immediate or delayed nature.

TABLE 1

Effect of Caerulein on Psychosis

Total Score	0	4 hr	24 hr
PL	53.7 ± 15.5	49.5 ± 14.2	52.7 ± 15.2
CCK	53.3 ± 24.2	54.5 ± 26.3	53.0 ± 25.2
Psychosis Score			
PL	9.5 ± 6.7	8.8 ± 5.6	10.3 ± 5.2
CCK	9.5 ± 6.7	9.7 ± 6.1	9.0 ± 7.4

The mean ± SD of scores on BPRS: total score (Total) and psychosis subscale score (Psychosis) were collected after placebo (PL) and after 0.3 μg/kg caerulein (CCK), prior to drug administration (0), and at 4 hours (4 hr) and 24 hours (24 hr) following the drug. No significant differences were found between treatments or between treatments over time.

To evaluate the possibility that the previously administered dose levels were inadequate, increasing doses of caerulein from 0.3 μg/kg to 1.5 μg/kg were administered in a double-blind, placebo-controlled design to these same patients. The five drug-free schizophrenics received a 10-day course of daily medication: 5 days of active drug, and 5 days of placebo. The active drug was given in a rising dose sequence with single doses of placebo interspersed before, during, and after the caerulein sequence. Psychosis was evaluated at 0 time (prior to drug administration), at 4 hours, and 24 hours after caerulein and placebo administration. No patients showed an antipsychotic response to the peptide at any of the dose levels tested: 0.3 μg/kg, 0.6 μg/kg, 1.2 μg/kg, or 1.5 μg/kg. The

TABLE 2

Change In CCK-Li In Plasma After Caerulein Administration

	Minutes							
	0	5	10	15	20	30	45	60
Placebo	0	−1.7 (8.6)	−11.3 (10.1)	−9.0 (11.5)	1.0 (1.0)	−18 (15.9)	−7 (10.8)	3.7 (17.8)
Caerulein	0	50.3 (47.9)	48.3 (9.3)	66 (30.5)	65.8 (24.5)	53.7 (47.3)	22.8 (37.3)	15.5 (12.0)

Difference from basal values (mean SD) in CCK-like immunoreactivity (CCK-LI) (pg/ml plasma) after intramuscular administration of caerulein (0.3-0.6 μg/kg) or placebo to four human volunteers. Basal level of CCK-LI prior to placebo was 38.7 ± 18.0, and prior to caerulein was 35.3 ± 27.8.

upper dose of 1.5 µg/kg was limited by gastrointestinal side effects, chiefly mild pain and diarrhea.

Based on the suggestion from previous studies that a CCK-like drug would be active in neuroleptic-treated schizophrenic patients with a more chronic form of the illness, 6 chronically institutionalized patients, who were concurrently treated with stable doses of neuroleptic drugs, were given single doses of 0.3 µg/kg of caerulein or equivalent volumes of placebo in a parallel-group design. Their baseline psychosis level was established before they received the medication. Then, they were followed for psychosis change with the BPRS for 28 days after the single dose of drug administration. No patients who received the caerulein demonstrated improvement in their psychosis, nor did their response differ from those who received the placebo.

These studies provide no evidence for the hypothesis that systemic administration of caerulein, a potent CCK analogue, modifies schizophrenia, either by stimulating or reducing psychotic symptoms. Moreover, despite adequate caerulein drug levels in plasma, no definitive CNS effects of caerulein could be demonstrated: neither EEG patterns of visual-evoked potential changed nor plasma levels of prolactin were modified with caerulein, despite previous demonstration that intraventricular administration of CCK-8 elevates plasma prolactin in rats (Tanimoto et al., 1985).

While drawing a cautious conclusion because of the small number of patients tested, we would suggest that insufficient quantities of caerulein actually entered the CNS to produce a CCK-like effect. Thus, we would propose that the main hypothesis, namely that CCK-8 reduces psychosis through modifying DA-mediated neural transmission in the CNS, remains untested in schizophrenia at the present time.

We are pursuing the possibility of modifying CCK-8 levels in brain using other pharmacologic strategies, one being through inhibition of its degradation. CCK-8 is initially cleaved by a Mg^{++}-dependent metalloendopeptidase at the CCK^{3}/CCK^{1} bond (Steardo et al., in press). Blockade of this enzyme would be predicted to raise CNS levels of CCK-8 by inhibiting its breakdown and thereby producing a centrally mediated CCK agonist effect. Competitive and irreversible antagonists for this degradative enzyme are being synthesized. After establishing in vitro agonist effects of these compounds in laboratory animals, in vivo evidence of CCK-8 accumulation in the brain with systemic administration, and safety in human use, clinical evaluation in schizophrenia might be indicated. These kinds of alternate pharmacologic strategies will be necessary to test the hypotheses about the functional importance of CNS CCK systems in schizophrenia.

References

Beinfeld, M.D., Meyer, D.K., Eskay, R.L., et al. The distribution of cholecystokinin immunoreactivity in the central nervous system of the rat as determined by radioimmunoassay. *Brain Res.*, 212:51–57, 1981.

Cohen, S., Knight, M., Tamminga, C.A., and Chase, T.N. A comparison of peripheral and central effects of caerulein. *Br. J. Pharmacol.* (In press)

Crawley, J.N., Hayes, S.E., O'Donohue, T.L., and Paul, S.M. Neuropeptide modulation of social and exploratory behavior in laboratory rodents. *Peptides*, 2:123–219, 1981.

Deschoht-Lanckman, M., Bui, N.D., Noyer, M., and Christophe, J. Degradation of cholecystokinin-like peptides by a crude rat brain synaptosomal fraction: A study by high pressure liquid chromatography. *Regul. Pept.*, 2:15–30, 1981.

Dockray, G.L. Immunochemical evidence of cholecystokinin-like peptides in brain. *Nature*, 264:568–570, 1976.

Eng, J., Shiina, Y., Pan, Y-CE., et al. Pig brain contains cholecystokinin octapeptide and several cholecystokinin desoctapeptides. *Proc. Natl. Acad. Sci., USA*, 80:6381–6385, 1983.

Gibbs, J., Young, R.C., and Smith, G.P. Cholecystokinin elicits satiety in rats with open gastric fistulas. *Nature*, 245:323–325, 1973.

Hökfelt, T., Rehfeld, L., Skirboll, B., et al. Evidence for co-existence of dopamine and CCK in meso-limbic neurons. *Nature*, 285:476–478, 1980a.

Hökfelt, T., Skirboll, L., Rehfeld, J.F., et al. A subpopulation of mesencephalic dopamine neurons projecting to limbic areas contains a cholecystokinin-like peptide: Evidence from immunohistochemistry combined with retrograde tracing. *Neuroscience*, 5:2093–2124, 1980b.

Hommer, D.W., Pickar, D., Roy, A., et al. The effects of ceruletide in schizophrenia. *Arch. Gen. Psychiatry*, 41:617–622, 1984.

Innis, R.B., Correa, F.M.A., Uhl, G.R., et al. Cholecystokinin octapeptide-like immunoreactivity: Histochemical localization in rat brain. *Proc. Natl. Acad. Sci., USA*, 76:521–525, 1979.

Ivy, A.C., and Oldberg, E. A hormone mechanism for gall-bladder contraction and evaluation. *Am. J. Physiol.*, 86:599–613, 1928.

Knight, M., Tamminga, C.A., Steardo, L., et al. Cholecystokinin-octapeptide fragments: Binding to brain cholecystokinin receptors. *Eur. J. Pharmacol.*, 105:49–55, 1984.

Lucignani, G., Porrino, L.J., and Tamminga, C.A. Effects of systemically administered cholecystokinin-octapeptide on local cerebral metabolism. *Eur. J. Pharmacol.*, 101:147–151, 1984.

Markstein, R., and Hökfelt, T. Effect of cholecystokinin-octapeptide on dopamine release from slices of cat caudate nucleus. *J. Neurosci.*, 4:570–575, 1984.

Morley, J.E. The ascent of cholecystokinin from gut to brain. *Life Sci.*, 30:479–493, 1982.

Moroji, T., Watanabe, N., Aoki, N., and Itoh, S. Antipsychotic effects of ceruletide (caerulein) on chronic schizophrenia. *Arch. Gen. Psychiatry*, 39:485–486, 1982.

Mueller, J.E., Straus, E., and Yalow, P.S. Cholecystokinin and its COOH-terminal octapeptide in the pig brain. *Proc. Natl. Acad. Sci., USA*, 74:3035–3041, 1977.

Mutt, V., and Jorpes, J.E. Hormonal polypeptides of the upper intestine. *Biochem. J.*, 125:57–58, 1971.

Nair, N.P., Bloom, D.M., and Nestoros, J.N. Cholecystokinin appears to have antipsychotic properties. *Biol. Psychiatry*, 6:509–512, 1982.

Rehfeld, J.F. Immunochemical studies on cholecystokinin. *J. Biol. Chem.*, 253:4022–4030, 1978.

Schmitt, F.O., Bird, S.J., and Bloom, F.E. (eds.), *Molecular Genetic Neuroscience*. New York: Raven Press, 1982, pp. 171–188.

Steardo, L., Knight, M., Tamminga, C.A., and Chase, T.N. Products of cholecystokinin octapeptide proteolysis interact with central CCK receptors. *Neurosci. Lett.*, 54:319–325, 1985.

Steardo, L., Knight, M., Tamminga, C.A., et al. CCK_{26-33} degrading activity in brain and nonneural tissue: A metalloendopeptidase. *J. Neurochem.* (In press)

Tamminga, C.A. Atypical neuroleptics and novel antipsychotic drugs. In: Coyle, J.T., and Enna, S.J. (eds.), *Neuroleptics: Neurochemical, Behavioral, and Clinical Perspectives*. New York: Raven Press, 1982, pp. 281–295.

Tamminga, C.A., Littman, R.L., Alphs, L.D., et al. Neuronal cholecystokinin and schizophrenia: Pathogenic and therapeutic studies. *Psychopharmacology*. (In press)

Tanimoto, K., Tamminga, C.A., Knight, M., and Chase, T.N. Intraventricular cholecystokinin octapeptide elevates plasma prolactin. *Neurosci. Abstr.*, 1985.

Vanderhaeghen, J.J., Signeau, J.C., and Gepts, W. New peptide in the vertebrate CNS reacting with antigastrin antibodies. *Nature*, 257:604–605, 1975.

Widerlöv, E., Kalivas, P.W., Lewish, M.H., et al. Influence of cholecystokinin on central monoamine pathways. *Regul. Pept.*, 6:99–109, 1983.

Zetler, G. Neuroleptic-like effects of ceruletide and cholecystokinin octapeptide: Interactions with apomorphine, methylphenidate, and picrotoxin. *Eur. J. Pharmacol.*, 94:261–270, 1983.

Fenfluramine Therapy for Autism: Promise and Precaution

CHAIRS: Judith Rapoport, M.D.
Child Psychiatry Branch
National Institute of Mental Health
Bethesda, Maryland

and

Natalie Reatig
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Fenfluramine Treatment of Autism: UCLA Collaborative Study of 81 Patients at Nine Medical Centers[1]

Edward R. Ritvo, M.D.,[2] B.J. Freeman, Ph.D.,[2] Arthur Yuwiler, Ph.D.,[2] Edward Geller, Ph.D.,[2] Phillip Schroth, M.S.,[2] Alice Yokota,[2] Anne Mason-Brothers,[2] Gerald J. August, Ph.D.,[2] William Klykylo, M.D.,[2] Bennett Leventhal, M.D.,[2] Kay Lewis, M.D.,[2] Leonard Piggott, M.D.,[2] George Realmuto, M.D.,[2] E. Gene Stubbs, M.D.,[2] and Richard Umansky, M.D.[2]

Introduction

We recently reported that fenfluramine produced significant symptomatic improvements in patients with the syndrome of autism (Ritvo et al., 1984). These included increased social awareness, eye contact and attention to school work, decreased hyperactivity and repetitive behaviors such as hand flapping and spinning, and improved sleep patterns. No serious side effects, adverse drug reactions, or disruptions in growth or weight gain occurred. Significant positive correlations were found between good clinical response and high baseline IQ ($r = 0.80$, $p = <.001$), between good clinical response and low baseline blood serotonin concentration ($r = 0.57$, $p = <.05$), and between low baseline IQ and high initial blood serotonin concentration ($r = 0.72$, $p = <.01$). However, due to the small number of subjects, these correlations were only considered suggestive. Interestingly, the onset of symptomatic improvements varied from a few days to 2 months and relapses showed similar wide variations after patients returned to placebo. Similar findings have been reported on other small groups of patients (August et al., 1985; Klykylo et al., in press; Stubbs et al., in press).

To extend these preliminary findings, we designed a two-part multicenter study to obtain data from a much larger number of autistic patients. This report contains the results of the first part of this study, an ABA design utilizing 81 patients from nine medical centers. Our results confirm the previous findings that fenfluramine is a safe and effective treatment for some autistic patients (August et al., 1985; Klykylo et al., in press; Ritvo et al., 1984; Stubbs et al., in press).

---

[1] Supported by National Institute of Mental Health Grants MCT 927 and HD 46-12, Food and Drug Administration Grant 1 R01 FD 226-83-0023, Clinical Research Center for the Study of Child Psychosis Grant MH 30897, the Max and Lottie Dresher Fund, the Bennin Fund, the A.H. Robins Company, and the Veterans Administration Medical Research Service.

[2] Division of Mental Retardation and Child Psychiatry, Department of Psychiatry, University of California at Los Angeles, and the Neurobiochemistry Laboratory, Veterans Administration, Brentwood Medical Center, Los Angeles, and eight collaborating medical centers.

Reprint requests: Edward R. Ritvo, M.D., Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024.

The A.H. Robins Company supplied fenfluramine (Pondimin®) and placebo tablets.

Methods

1. *Patient selection.* Eighty-one patients (80% boys, ages 33 months to 24 years; mean 8.8 years, mode 5.9 years) were selected at nine medical centers throughout the United States (*see* Appendix for list of multicenter participants). They represented the entire clinical spectrum of patients with the syndrome of autism, from the mute and totally dependent to those living semi-independently. Each unequivocally met the DSM-III, 299.0 (APA Diagnostic and Statistical Manual—3rd Ed., 1980), and National Society for Children and Adults with Autism (NSAC) (Ritvo & Freeman, 1978) criteria for autism according to clinicians at each medical center. Furthermore, each patient's history was reviewed with the principal investigator at UCLA (E.R.R.) who concurred that they had manifested pathognomic symptoms and delays prior to 30 months of age. All patients had been free of central nervous system active medication for at least 3 months before the study and were either attending special education classes or rehabilitation programs specifically designed for autistic persons. None had other specific diagnosable neurological or medical conditions except one girl who was subsequently identified in Portland, Oregon, as having Retts' syndrome (Stubbs et al., in press). Two had electroencephalograph abnormalities and one of these had a seizure when younger.

2. *Human subject protection procedures and FDA approval.* Each participating institution obtained Human Subject Protection Committee approval and informed consent agreements. Since fenfluramine is approved by the FDA only as an anorexia agent in adults, a new drug application (NDA) was obtained for use in children and for autism (for fenfluramine #17,085 and for the placebo #16,935).

3. *Experimental protocol.* The study began with a 2-week training period using a known placebo to accustom patients to taking tablets and to assure parental compliance (stage 1). The double-blind phase then began with all patients receiving placebo for 1 month (stage 2), followed by 4 months of drug treatment (stage 3), and 2 months of placebo (stage 4). One investigator at each center was aware of the placebo-drug schedule during the study but did not participate in dispensing medication or in clinical assessments. All patients received tablets twice a day throughout the study (0.75 mg/kg body weight for a total daily dose of 1.5 mg/kg body weight).

4. *Biomedical monitoring.* General medical histories and weights were recorded at monthly intervals throughout the study. Blood serotonin levels were obtained at the initial visits and between stages of the experiment.

5. *Parental reports.* Parental interviews were conducted monthly to monitor each child's clinical status and to detect possible side effects. Parents kept diaries documenting daily medication administration, patient behaviors, appetite changes, and weekly body weights. They were requested to weigh their children on the same scales, in similar clothing, and at the same time of the day.

6. *IQ tests.* Psychologists blind to the drug protocol administered tests selected according to each patient's baseline developmental level. Patients who initially were younger than 4 years or had IQ < 45 were given the Merrill-Palmer Preschool Performance Test (Stutsman, 1948) and the Cattell (1960) or Stanford-Binet Intelligence Scale. Patients initially older than 4 years or with IQ > 45 were given a Wechsler Intelligence Scale (1967, 1974, 1981) appropriate for their age. A verbal IQ score was assigned for each patient by using the verbal score for the Wechsler Scales, the Cattell score, or the Stanford-Binet scale. A performance scale for each patient was also assigned by using the performance score of the Wechsler Scales or the Merrill-Palmer Preschool Performance Test.

7. *Alpern-Boll Developmental Profile* (Alpern et al., 1980). This standardized parental interview scale was administered to patients for whom it was age appropriate. It consists of five developmental scales (academic, communication, physical development, self-help, and social development).

8. *Ritvo-Freeman Real-Life Rating Scale for Autism* (Freeman et al., in press). This scale consists of 47 behaviors grouped in five categories (motor, affect, language, sensory, and social). Behaviors are coded on a 4-point scale (0 = never, 1 = rarely, 2 = frequently, and

3 = almost always). It was administered by raters blind to the drug protocol, who observed the patients for 45 minutes.

9. *Principal investigators' classification of strong, moderate, and nonresponders.* One month after each center completed its protocol the principal investigator was asked to list any patients in whom "strong clinical improvements were noted by themselves and the patients' parents and teachers." These were labeled "strong responders." Two weeks later each principal investigator was again contacted and asked to list patients who "they and the patients' parents and teachers agreed showed absolutely no changes." These were labeled "nonresponders." Strong responders, nonresponders, and moderate responders (defined as those not placed in one of the other two categories by the principal investigators) were then grouped for correlation analyses.

10. *Statistical analysis.* Mean scores for all patients at each visit were used in the statistical analyses. The statistical procedures for the Alpern-Boll Developmental Profile, IQ, and Ritvo-Freeman Real-Life Rating Scale were repeated-measures analyses of variance, with individual comparison of means using the Duncan multiple-range test. Program was procedure GLM, Statistical Analysis System (Ray, 1982). Serotonin blood levels and blood platelet counts were analyzed by percent changes from baselines.

Results

1. *Patient compliance.* Three patients were withdrawn during the course of the study (in one case the parents moved; in two cases parents complained of irritability, anorexia, weight loss, and insomnia). Despite the blind nature of the study, the majority of parents observed symptomatic improvements during the medication phase and a return of pathologic behaviors after the blind crossover back to placebo. Some wished to withdraw their child from the study and obtain active medication from their personal physicians. However, all were persuaded to continue through the study before again medicating their children.

2. *Parental reports.* The beneficial effects most often reported by parents were 1) decreased restlessness and hyperactivity; 2) decreased repetitive behaviors such as hand flapping, jumping, self-injury, and spinning; 3) increased social responsiveness and eye contact ("more tuned in"); 4) increased attention span and participation in school programs; and 5) improved speech and nonverbal communication. After the blind crossover back to placebo, the order of symptom return reported was similar. Hyperactivity and repetitive behaviors reappeared first, then withdrawal and social inappropriateness and, lastly, cognitive and communication skills decreased to pretreatment levels. Great variability in the time of onset of improvements and remissions was reported.

3. *Side effects.* No serious adverse reactions occurred. Lethargy and irritability were the most frequent side effects reported. The side effects observed and their incidences at all the centers are being systematically studied and will be reported upon separately (George Realmuto, M.D., personal communication) as are those at one center (Piggott et al., in press).

4. *Blood serotonin concentrations and platelet counts.* Blood serotonin concentrations were available on 62 of the 81 patients (77%). Since assays were conducted in different laboratories (Yuwiler et al., 1970), percent changes from baselines were used for statistical analyses. Average blood serotonin concentrations fell 46% from baseline after 2 months on drug, 57% from baseline after 4 months on drug, and rebounded to 5% over baseline 2 months after drug was replaced by placebo. These changes on drug were highly significant ($p = <.0001$). Platelet counts were available on 44 patients of the 81 total (54%). Percent changes from baseline were again used for analysis. The average of all counts fell 5% from baseline after 2 and 4 months on drug. These decreases approached significance ($p = <.0867$). Inspection of the data reveals that changes in serotonin concentrations and platelet counts were quite consistent across patients. Thus it appears that the dosage selected (1.5 mg/kg body weight/day) uniformly decreases serotonin concentrations approximately 50% regardless of the initial blood levels (*see* Figure 1 and Table 1).

5. *Appetite and weight changes.* Anorexia occurred initially in 16 patients (20%) with remission in all but 2 patients after 4 weeks. In these 2 cases, food prompting and supplements were sufficient to prevent weight loss.

6. *Wechsler Intelligence, Cattell, and Stanford-Binet Scales and the Merrill-Palmer Preschool Performance Test.* Data on these are shown in Table 1. Significant differences occurred between baseline and medication periods as indicated.

7. *Ritvo-Freeman Real-Life Rating Scale for Autism.* The mean values of the overall, motor, social, and sensory scales showed significant improvements between baseline and drug periods (*see* Figure 2 and Table 1). The affect and language scales trended in the direction of improvement but mean changes did not reach significant levels.

8. *The Alpern-Boll Developmental Profile.* The mean values for the communication, self-help, and overall scales showed significant improvement between the baseline and drug periods (*see* Figure 3 and Table 1). The academic age, social, physical development, and IQ scales trended in the direction of improvement but did not reach significant levels.

9. *Principal investigators' classification of strong, moderate, and non-responders.* The distribution (number and percent) of all 81 patients by center and sex is shown in Table 2. Twice as many patients were classified strong responders as nonresponders (33% vs. 15%). The percentage of strong, moderate, and nonresponders at various centers ranged from 0% to 100%, indicating wide variability within and among centers. The combined total of strong and moderate responders was far in excess of just nonresponders (85% to 15%), indicating that a consistent overall favorable clinical impression was created. Sex is not correlated with response. The sex distribution in the 81 patients (4:1) is similar within the principal response classifications (86% of males and 81% of females classified as strong and moderate responders vs. 14% males and 19% females as nonresponders). Within the strong responder category alone there was a nonsignificant higher percentage

TABLE 1

Effect of Fenfluramine on Laboratory and Clinical Measures

	No. of Pts.	Baseline	4 Mos. on Drug	2 Mos. on Placebo
Percent Serotonin	62	100%	−57%*	+5%*
Platelets	44	100%	− 5%	+2%
Verbal I.Q.	51	49.3	51.9*	51.3
Performance I.Q.	61	59.8	63.8*	65.8
Real Life Rating Scale	78			
Overall		.66	.55*	.60
Motor		.36	.26*	.38*
Social		1.06	.88*	.93
Sensory		.52	.39*	.44
Affect		.47	.36	.43
Language		.85	.84	.85
Alpern-Boll Profile	48			
Overall		39.9	44.9*	43.4
Communication		27.8	34.7*	34.4
Self-help		48.6	55.7*	54.0
Academic		38.7	43.9	42.9
Physical		49.1	53.5	50.3
Social		33.8	36.7	35.7

*Significant differences from prior period ($p < 0.05$).

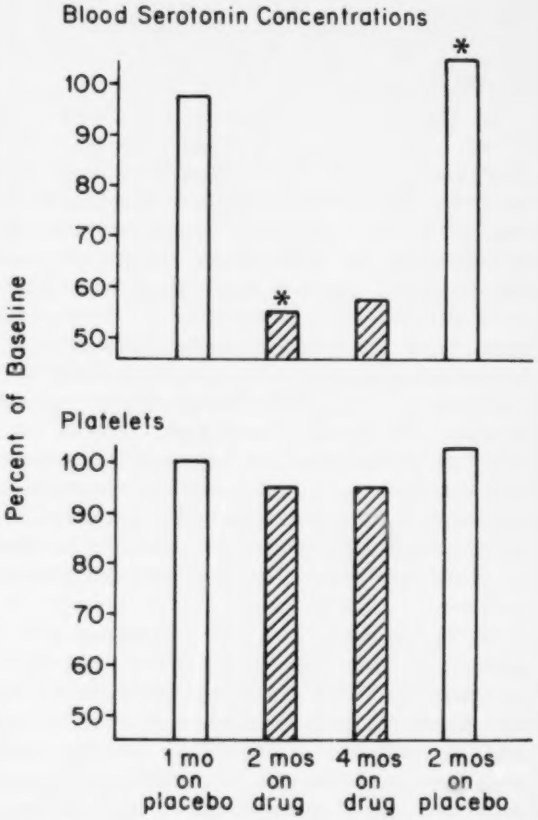


FIGURE 1. **Effects of fenfluramine on blood serotonin concentrations and platelet counts (percent changes from baselines). * = significant change from prior period ($p<.0001$).**

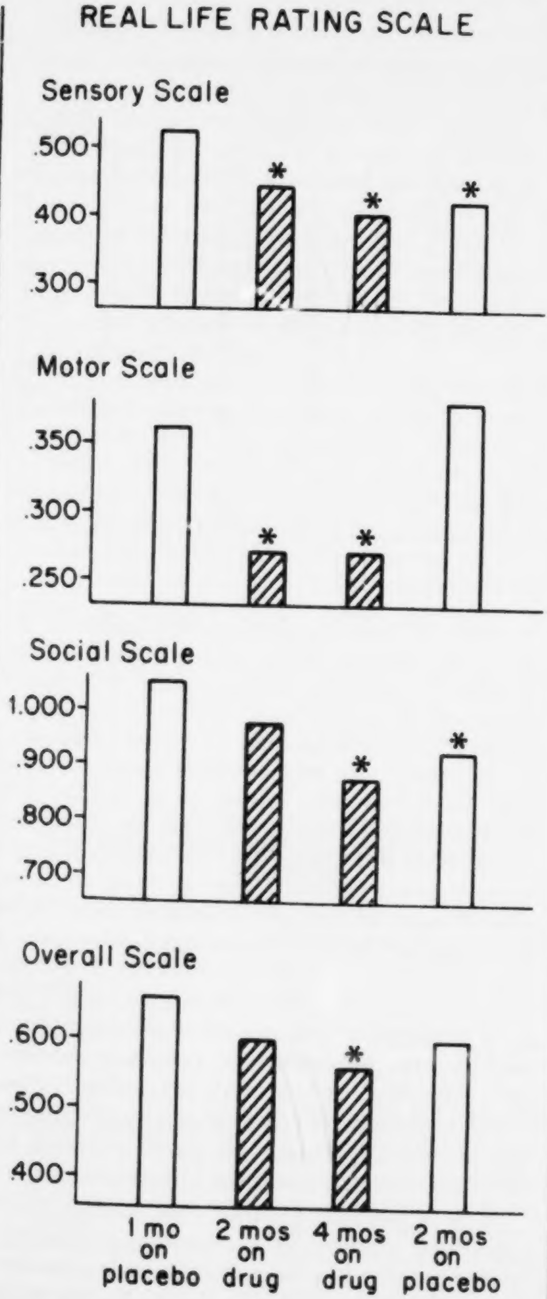


FIGURE 2. Ritvo-Freeman Real Life Rating Scale. * = significant difference from the initial placebo period (Sensory Scale $p < .0006$; Social Scale $p < .002$; Motor Scale $p < .006$; Overall Scale $p < .002$).

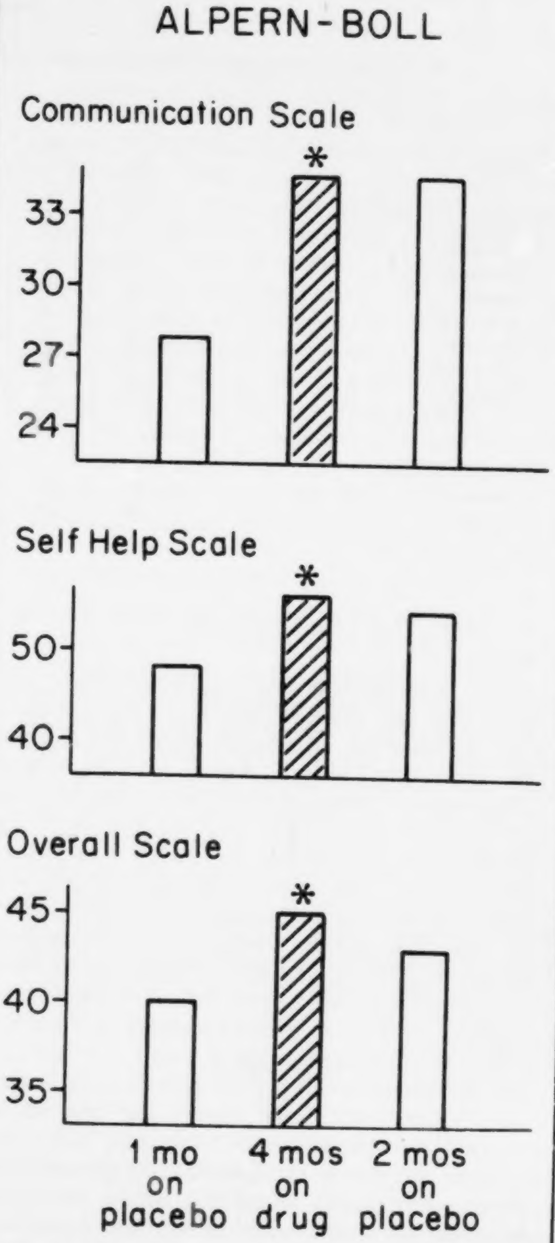


FIGURE 3. Effects of fenfluramine on the Alpern-Boll Developmental Profile. * = significant differences from the initial placebo period (Communication Scale $p < .001$; Self-help Scale $p < .01$; Overall Scale $p < .05$).

TABLE 2

Principal Investigators' Classification of Clinical Responses: Distribution by Center

			Strong Responders		Moderate Responders		Non-Responders	
I. Center	N	%[a]	N	%[b]	N	%[b]	N	%[b]
U.C.L.A.	14	17	6	43	8	57	0	0
Portland	8	10	2	25	6	75	0	0
Chicago	16	20	0	0	12	75	4	25
Oakland	7	9	2	29	2	29	3	42
Detroit	6	7	3	50	3	50	0	0
Minneapolis	3	4	0	0	3	100	0	0
Houston	13	16	10	77	3	23	0	0
Cincinnati	4	5	1	25	2	50	1	25
Galveston	10	12	3	30	3	30	4	40
Totals	81	100	27	33	42	52	12	15
II. Sex Distribution								
Males	65	80	24	37	32	49	9	14
Females	16	20	3	19	10	62	3	19

[a] Column percentage
[b] Row percentages

of males (37% of all males vs. 19% of all females).

10. *Correlations among baseline serotonin, IQ, behaviors, and clinical response.* The distribution by baseline laboratory and clinical data are shown in Table 3. Age is not correlated with response category, the means being only 13 months apart and the ranges showing great overlap. Baseline serotonin concentrations show a significant inverse correlation with clinical response categories, being lowest in the 11 strong responders measured (mean = .250), next higher in the 20 moderate responders measured (mean = .280), and highest in the 4 nonresponders measured (mean = .330) ($r = -.35$, $p < .05$). Verbal IQ and Performance IQ, Real Life Rating Scale, and Alpern-Boll Scale scores did not show significant correlations with any of the clinical response categories. Significant inverse correlations were also found between baseline serotonin concentrations and performance IQ ($r = -.57$, $p < .0025$) (*see* Table 3).

Discussion

The results indicate that fenfluramine is a safe and effective treatment for some autistic children and young adults, thus confirming earlier reports (August et al., 1985; Freeman et al., 1985; Geller et al., 1982; Klykylo et al., in press; Ritvo et al., 1983, 1984 Stubbs et al., in press). During the 4 months we administered it to children, only the same side effects observed in adults were noted. Any longer range effects will have to be studied separately. However, our prior report of administration for 12 months (Ritvo et al., 1984) and dozens of autistic patients we have learned about who have been on the medication for over 3 years indicate that at least in some children it can be well tolerated over these extended periods. Our anecdotal information also indicates that irritability, lethargy, anorexia, and other mild side effects usually last only during the first month of administration and can be eliminated by reducing the dosage. Although only a small percentage of patients experienced any side effects (Piggott et al., in press), certainly all parents should be informed of their potential appearance.

It is important to note that fenfluramine produced significant symptomatic improvements on both professionally administered scales (Ritvo-Freeman Real Life Rating Scale and the intelligence scales) as well as on the parent reported scales (Alpern-Boll). The improvements noted in the study of 81 patients were consistent with previous smaller sample studies in both the type and timing of onset after treatment began, and the return of symptoms after switching back to placebo.

This confirmation is particularly noteworthy, since the experimental design we utilized does not allow for assessing treatment order effect. However, such an effect should not confound the results of a study of autistic patients whose clinical courses are known to be stable over the span encompassed by this study (8 months) (Freeman et al., 1985). Nevertheless, a second experiment utilizing a design which mitigates treatment order effects is under way on an additional 99 patients at 14 medical centers.

IQ test scores showed slight but significant increases during the drug phase as was observed in our first two cases (Geller et al., 1982). The improvement in verbal scale scores probably reflects improved concentration and better relating to the examiner. The improved performance scale scores may have been due to these factors, combined with practice effects, as we have previously discussed (Ritvo et al., 1984).

The correlations that were found between baseline serotonin concentrations, IQ, and clinical response are consistent with earlier reports (Ritvo et al., 1984) and warrant further exploration.

TABLE 3

Principal Investigators' Classification of Clinical Responders and the Distribution of Baseline Measures

	Strong Responders	Moderate Responders	Non Responders
Number of patients	27	42	12
Percentages	33%	52%	15%
Age mean (months)	110	107	97
Range (months)	42–247	33–293	37–154
Serotonin mean*	.250	.280	.380
No. tested	11	20	4
Range	.140–.350	.090–.450	.230–.570
Real Life Rating Scale			
overall	0.60	0.69	0.68
Motor	0.29	0.40	0.36
Social	1.04	1.10	1.07
Sensory	0.46	0.59	0.51
Alpern-Boll overall	56	51	60
Communication	34	27	48
Self-help	48	48	57
IQ Verbal	51	48	45
No. tested	18	36	11
Range	20–100	15–126	24–138
IQ Performance**	58	63	60
No. tested	22	35	10
Range	9–130	16–127	36–131

*Significant correlation ($r =$ .57, p .0025) between baseline serotonin and performance IQ.

**Significant correlation ($r =$ .35, p .05) between response and baseline serotonin.

Several principal investigators reported their impressions that the medication produced differential effects in certain patients, depending upon their baseline verbal IQs. The clinical consensus was that patients with initially high verbal IQs (70 or higher) who responded showed mainly increased appropriate social responsiveness, lengthened attention spans, better concentration to cognitive tasks, and improved social conversation. They also showed, but to a lesser degree, decreased hyperactivity and repetitive behaviors. In contrast, patients with initially low IQs (50 or less) showed primarily decreased hyperactivity, improved sleep patterns, newfound ability to interrupt repetitive behaviors with appropriate training ("We had tried to get him to stop arm flapping before but it never worked"), and were "more tuned in."

The present results shed no light on such important issues as the method of action of fenfluramine or dose-response relationships. Hopefully, these and other relevant clinical and neurobiochemical issues will become of sufficient interest to be explored now that the efficacy and safety of fenfluramine as a treatment for some autistic patients has been more firmly established. Also remaining is the fascinating task of learning how to predict responders in advance, thus obviating the need for prolonged clinical trials of up to 8 months (Ritvo et al., 1984).

Appendix

The medical centers and personnel contributing to the research are (1) University of Texas Medical Branch, Department of Psychiatry and Behavorial Sciences, Galveston, Texas: Gerald J. August, Ph.D., Principal Investigator, Teresa D. Baerd, M.D., Naftali Raz, Ph.D., Louise Hsu, Ph.D.; (2) University of Cincinnati, Department of Psychiatry, Children's Hospital Medical Center, Cincinnati, Ohio: William Klykylo, M.D., Principal Investigator, Dorothyann Feldis, Ph.D., Donald O'Grady, Ph.D., Diana L. Ross, M.D., Charlotte Halloran, M.A.; (3) University of Chicago Pritzker School of Medicine and

Wyler Children's Hospital, Chicago, Illinois: Bennett Leventhal, M.D., Principal Investigator, Marolyn Morford-Boswell, M.A., Daniel X. Freedman, M.D. (presently at U.C.L.A.); (4) Texas Research Institute of Mental Health, Houston, Texas: Kay Lewis, M.D., Principal Investigator: (5) LaFayette Clinic, Detroit, Michigan: Leonard Piggott, M.D., Principal Investigator, Charles Gdowski, Ph.D., Charles Frohman, Ph.D., David Villanueva, M.D., Joseph Fischhoff, M.D.: (6) University of Minnesota, Division of Child and Adolescent Psychiatry, Medical School, Minneapolis, Minnesota: George Realmuto, M.D., Principal Investigator: (7) The Oregon Health Sciences University, Department of Psychiatry, Crippled Children's Division, School of Medicine, Portland, Oregon: E. Gene Stubbs, M.D., Principal Investigator, Sarojini Budden, M.D., Russell Jackson, Ph.D., Leif Terdal, Ph.D.: (8) Children's Hospital Medical Center, Oakland, California: Richard Umansky, M.D., Rosamond Gardner, Ph.D., Principal Investigators: (9) University of California at Los Angeles, Division of Mental Retardation and Child Psychiatry, Los Angeles, California: Edward R. Ritvo, M.D., Principal Investigator.

References

Alpern, G.D., Boll, T.J., and Shearer, M.S. *Developmental Profile II: Manual.* Aspen, Colo.: Psychological Development Publications, 1980.

August, G.J., Raz, N., and Baird, T.D. Effects of fenfluramine on behavioral, cognitive, and affective disturbances in autistic children. *J. Autism Dev. Disord.*, 15:97, 1985.

Cattell, P. *The Measurement of Intelligence of Infants and Young Children.* New York: The Psychological Corporation, 1960.

Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

Freeman, B.J., Ritvo, E.R., Yokota, A., et al. A scale for rating symptoms of patients with the syndrome of autism in real life settings. *J. Am. Acad. Child Psychiatry.* (In press)

Freeman, B.J., Ritvo, E.R., Needleman, R., et al. Stability of cognitive and linguistic parameters in autism. *J. Am. Acad. Child Psychiatry*, 24:459, 1985.

Geller, E., Ritvo, E.R., Freeman, B.J., et al. Preliminary observations on the effect of fenfluramine on blood serotonin and symptoms in three autistic boys. *N. Engl. J. Med.*, 307:165, 1982.

Klykylo, W.M., Feldis, D., O'Grady, D., et al. Clinical effects of fenfluramine in ten autistic subjects. *J. Autism Dev. Disord.* (In press)

Piggott, L.R., Gdowski, C.L., Villenueva, D., et al. Side effects of fenfluramine in autistic children. *J. Am. Acad. Child Psychiatry.* (In press)

Ray, E. (ed.). *SAS User's Guide: Statistics 1982.* Raleigh, N.C.: SAS Institute, 1982.

Ritvo, E.R., and Freeman, B.J. The National Society for Autistic Children definition of the syndrome of autism. *J. Am. Acad. Child Psychiatry*, 17:565, 1978.

Ritvo, E.R., Freeman, B.J., Geller, E., et al. Effects of fenfluramine on 14 outpatients with the syndrome of autism. *J. Am. Acad. Child Psychiatry*, 22:549, 1983.

Ritvo, E.R., Freeman, B.J., Yuwiler, A., et al. Study of fenfluramine in outpatients with the syndrome of autism. *J. Pediatr.*, 105:823, 1984.

Stubbs, E.G., Budden, S.S., Jackson, R.H., et al. Effects of fenfluramine on 8 outpatients with the syndrome of autism. *J. Am. Acad. Child Psychiatry.* (In press)

Stutsman, R. *Merrill-Palmer Scale of Mental Tests.* New York: Harcourt, Brace, and World, 1948.

Thorndike, R.L. *Manual for Stanford-Binet Intelligence Scale.* Boston: Houghton Mifflin, 1972.

Wechsler, D. *Manual for the Wechsler Preschool and Primary Scale of Intelligence.* New York: Psychological Corporation, 1967.

Wechsler, D. *Manual for the Wechsler Intelligence Scale for Children, Revised.* New York: Psychological Corporation, 1974.

Wechsler, D. *Manual for the Wechsler Adult Intelligence Scale, Revised.* New York: Psychological Corporation, 1981.

Yuwiler, A., Plotkin, S., Geller, E., et al. A rapid accurate procedure for the determination of serotonin in whole human blood. *Biochem. Med.*, 3:426, 1970.

Short-Term Efficacy and Safety of Fenfluramine in Hospitalized Preschool-Age Autistic Children: An Open Study[1]

Magda Campbell, M.D.,[2] Stephen I. Deutsch, M.D., Ph.D.,[2] Richard Perry, M.D.,[2] Barbara B. Wolsky, C.S.W.,[2] and Michael Palij, Ph.D.[3]

Introduction

Ritvo and associates (1983) reported encouraging results associated with administration of fenfluramine over a period of 4 months in 14 autistic subjects; decreases of certain symptoms and increases in IQ scores, with only a few side effects, were rated.

Structurally, fenfluramine is similar to amphetamine, though their mechanisms of action differ. Fenfluramine is a potent antiserotonergic drug (Costa et al., 1971). Some reports suggest that fenfluramine is a mild antidopaminergic drug with sedative or tranquilizing properties (Alphin et al., 1964; Franko et al., 1964; Jori et al., 1974), while others indicate that stimulating effects are dose dependent (Riley et al., 1969).

It has been demonstrated that about one-third of autistic children show elevated serotonin levels in blood, as compared to normal controls; this elevation of serotonin was found in those autistic children who were more retarded and who showed more florid symptomatology (Campbell et al., 1975). In the studies of Ritvo and his associates (1983, 1984), there was a marked decrease of serotonin levels following treatment with fenfluramine.

New and potentially therapeutically effective drugs, which are devoid of long-term untoward effects, are sought for the treatment of autistic children. D- and L-Amphetamine, dopamine agonists, had untoward effects in this population which often outweighed therapeutic effects (Campbell et al., 1972, 1976). Haloperidol, a potent antidopaminergic drug, was found to decrease significantly behavioral symptoms and to facilitate learning in the laboratory, in two large samples of autistic children, when administered under double-blind and placebo-controlled conditions at doses ranging from 0.5 to 4.0 mg/day (Anderson et al., 1984; Campbell et al., 1978). At these doses, haloperidol was a safe drug when given over a period of up to 3 months cumulatively. However, in a prospective study, when given over a longer period of time to 58 children, 22% developed tardive or withdrawal dyskinesias (Perry et al., 1985). There is no agreement about the therapeutic efficacy of L-dopa (Campbell et al., 1976; Ritvo et al., 1971), a drug which reduces serotonin levels.

The 14 subjects who participated in the study of Ritvo et al. (1983) were all outpatients exposed to a variety of educational programs and heterogeneous in regard to chronological age (3 to 18 years).

We wished to administer fenfluramine in an open fashion under close clinical and laboratory monitoring to a small sample of carefully diagnosed inpatients, with a relatively narrow age range.

Method

Subjects

Ten children, 7 males and 3 females, ages 3 to 5.75 years (mean, 4.15), participated in this pilot study. They were all inpatients in Bellevue Hospital, Psychiatric Division, Chil-

---

[1] This work was supported in part by USPHS Grant MH-32212 from the National Institute of Mental Health.

[2] Children's Psychopharmacology Unit, Department of Psychiatry, New York University Medical Center, New York, NY 10016.

[3] Department of Psychiatry and Behavioral Sciences, Health Sciences Center, State University of New York at Stony Brook, Long Island, NY 11794.

Address reprint requests to Magda Campbell, M.D., Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, NY 10016.

dren's Inpatient Service and all met the DSM-III (1980) criteria for Infantile Autism, Full Syndrome, as determined by at least 2 board-certified child psychiatrists independently. Following admission, baseline evaluations were performed: these included complete medical diagnostic workup as well as psychiatric observation; psychological, neurological, pediatric, hearing, and speech evaluations; and laboratory studies. Children with a known cause for autism were excluded from the study. Two children had seizure disorder (grand mal).

All children were withdrawn, displayed stereotypies, and had very short attention spans. In addition, 6 children had temper tantrums; 8 were very irritable and were screaming; 8 were hyperactive and, in 3 of these 8, hyperactivity alternated with hypoactivity. One child was exclusively hypoactive. Eight children were aggressive and, in 4 of these, aggression was also directed against self. In 2 children, self-injurious behavior resulted in prominent frontal bossing due to chronic severe head banging. Four children had insomnia. The children's intellectual functioning ranged from mildly to profoundly retarded.

Procedures

All children were free of psychoactive drugs for at least 2 weeks prior to the study.*

Ratings were done at fixed intervals, twice during the placebo baseline and during treatment, independently, by two child psychiatrists. Ratings were videotaped. The following rating scales were used: the Children's Psychiatric Rating Scale (CPRS), Clinical Global Impressions (CGI), and Abnormal Involuntary Movements Scale (AIMS) (*Psychopharmacology Bulletin*, 1985); the Simpson Abbreviated Dyskinesia Rating Scale (Simpson et al., 1979); and the Fenfluramine Untoward Effects Checklist.

Electrocardiogram (ECG) and laboratory studies (urinalysis, complete blood count, differential, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase, creatine phosphokinase, alkaline phosphatase, and electrolytes) were also done during the baseline period and at the end of each 4-week treatment period. Blood pressure and heart rate were taken daily, and weight weekly, at fixed times, adhering to a protocol.

Fenfluramine and identical matching placebo tablets were supplied by A.H. Robins Company. Following a placebo baseline period,** fenfluramine was started at a dose of 10 mg/day, in two divided doses, and increments occurred gradually at fixed intervals. Dosage was regulated individually, until positive or untoward effects were observed. Dosage was reduced when untoward effects emerged.

Results

Dosage

Optimal doses for the 10 children ranged from 15 to 30 mg/day or 1.093 to 1.787 mg/kg/day (mean, 1.413). The maximum dose explored, in two children was 60 mg/day (3.625 mg/kg/day).

Untoward Effects

The untoward effects necessitating dosage reduction consisted of drowsiness and lethargy ($N=9$), including falling asleep 4 1/2 hours after the administration of an 8 a.m. dose, loss of weight ($N=7$), excessive and uncontrollable irritability ($N=6$), body "rigidity," tension, and fidgetiness ($N=1$), sadness ($N=2$), increased aggressiveness against self or others ($N=2$), insomnia ($N=1$), increased withdrawal ($N=1$), and increase of stereotypies ($N=1$). These untoward effects occurred above optimal doses or during dosage regulation, on 1.23 to 3.625 mg/kg/day of fenfluramine. There were no untoward effects at optimal doses: the exception was a 46-

---

*The exception were two children with seizure disorder: one was receiving Tegretol, and the other Dilantin, throughout the study.

**Exception were two children who were placed as an emergency without placebo baseline on fenfluramine because of their extremely severe irritability, insomnia, or self-mutilating behavior with temper tantrums.

month-old boy, who showed only slight improvement on fenfluramine (1.787 mg/kg). As indicated above, 7 of the 10 children lost weight (from 0.02 to 1.70 kg) at the end of 1 month of fenfluramine administration. At the end of the second month, all but one* gained weight (from 0.23 to 0.91 kg). One child gained weight during the first month of fenfluramine administration (1.68 kg), and lost 1.11 kg at the end of second month. During the entire period of fenfluramine administration, only two children lost weight. No child developed dystonic reactions or dyskinesias during this study.

Laboratory Studies

Blood pressure and pulse rate remained essentially the same throughout the study; there was no change in ECG and in laboratory studies.

Rating Scales

Children's Psychiatric Rating Scale (CPRS). Of the first 28 items, only 14 were analyzed because the remaining 14 are usually rated as absent in autistic children. Although CPRS ratings were taken at four different times, that is, two baseline and one at 4 weeks on drug and 8 weeks on drug, the measures taken at 8 weeks on drug are not included. This was done because only five subjects had complete data for the four occasions, in contrast to the eight subjects for the three times listed in Table 1. Obviously, the sample with the larger number provides for more powerful statistical tests as well as better representation of the population of subjects.

The values reported in the fifth column of Table 1, labeled ANOVA F represents the F statistic and significance level from a one-way repeated measure (analysis of variance) for the three occasions of measurement. Five of the items (i.e., items 3, 4, 8, 10, and 28) produced F values which were significant at the traditional .05 level. Item 16 produced an F value of marginal significance ($p<.10$). The sum of the 14 items, when treated as a separate dependent variable, also produced a significant F value. In all instances, the rated severity for the items decreased after 4 weeks on drug.

Those items with significant F values were followed up with matched *t* tests. Only comparisons between the two baselines and 4 weeks on drug are presented (no significant differences were found between the baseline measures for any of the items). All of these comparisons showed a significant decrease in rated severity between the two baselines and 4 weeks on drug except for items 3 and 28. On item 3, fidgetiness, the decrease between the second baseline and 4 weeks on drug was not significant, apparently because the mean rating for the second baseline was lower than that of the first baseline (though not significantly). On item 28, rhythmic motions, the decrease between the first baseline and 4 weeks on drug is only marginally significant. These comparisons should be interpreted with caution appropriate to the number of comparisons performed.

Clinical Global Impressions (CGI). Table 2 contains the ratings for the three items on the CGI for various combinations of times of measurement. The last column contains the F values from one-way repeated measures ANOVA. Each of the items are presented in two ways: first, analyses based on the largest sample possible for the smallest number of meaningful times of measure and, second, analyses based on a smaller sample size but representing all times of measurement.

Item 1, the rated severity of illness, indicated a significant decrease in rated severity from baseline to measures made while on drug. Row 1(a) contains values based on the same subjects represented by the CPRS ratings in Table 1. The two baseline measures did not differ from each other but both were significantly higher than the rating made at 4 weeks on drug (both $p<.05$). Row 2(a) contains the second drug measurement made at 8 weeks after drug treatment began. Here, again, the two baseline measures did not differ, nor did the two ratings made while on drug. Ratings made on baseline were both significantly higher than either rating made on drug (one $p=.07$, others $p<.05$).

Item 2, improvement in the child relative to first interview by the clinician, shows only a marginal improvement from the second

---

*One child received fenfluramine only for 31 days.

TABLE 1

Children's Psychiatric Rating Scale (CPRS) Items at First and Second Baseline and at 4 Weeks on Fenfluramine*

CPRS Items	B1 First Baseline	B2 Second Baseline	D1 Four Weeks on Drug	ANOVA F Value	Posthoc Comparisons: t values B1 vs D1	Posthoc Comparisons: t values B2 vs D1
2. Underproductive speech	5.87 (2.23)	5.87 (2.10)	5.12 (2.17)	ns	—	—
3. Fidgetiness	4.00 (0.76)	3.50 (0.76)	1.87 (1.25)	22.13 ($p<.001$)	6.06 ($p<.01$)	1.53 ns
4. Hyperactivity	3.12 (1.55)	3.50 (1.29)	1.25 (0.71)	7.84 ($p<.01$)	2.61 ($p<.05$)	4.33 ($p<.01$)
5. Hypoactivity	1.87 (1.25)	1.62 (1.77)	1.37 (1.06)	ns	—	—
7. Abnormal object relationships	4.75 (2.19)	4.50 (2.07)	3.50 (1.60)	ns	—	—
8. Withdrawal	6.12 (0.99)	6.12 (1.13)	4.75 (1.16)	6.67 ($p<.01$)	2.99 ($p<.05$)	2.99 ($p<.05$)
10. Negative, uncooperative	4.00 (1.31)	4.37 (1.77)	1.75 (1.49)	6.96 ($p<.01$)	3.81 ($p<.01$)	2.90 ($p<.05$)
11. Angry affect	3.37 (1.77)	3.25 (2.37)	1.87 (1.81)	ns	—	—
16. Unspontaneous relation to examiner	7.00 (0.00)	7.00 (0.00)	5.75 (2.05)	2.97 ($p<.10$)	—	—
20. Lability of affect	2.25 (1.91)	3.12 (2.29)	1.75 (2.12)	ns	—	—
24. Low voice	1.37 (0.74)	1.75 (1.03)	1.00 (0.00)	ns	—	—
25. Loud voice	1.75 (1.49)	2.12 (1.81)	1.37 (1.06)	ns	—	—
27. Other speech deviance	4.62 (2.56)	4.00 (2.33)	3.75 (3.01)	ns	—	—
28. Rhythmic motions (Stereotypie)	5.38 (1.41)	5.00 (0.93)	3.87 (1.73)	3.74 ($p<.05$)	2.05 ($p<.10$)	2.55 ($p<.05$)
Sum of above 14 items	55.50 (8.50)	56.87 (11.08)	40.62 (9.30)	9.14 ($p<.01$)	3.40 ($p<.05$)	3.25 ($p<.05$)

*Means and standard deviations (in parenthesis) are based on eight subjects. Items are rated on a 7-point scale where 1 means not present, 2 means very mild, and so on to 7 which means extremely severe. Degrees of freedom for the repeated measures ANOVA are 2 and 14 and 7 for the matched *t* test used in the posthoc comparisons.

baseline to 4 weeks on drug. When the second drug measure is included, the repeated measures ANOVA is nonsignificant even though there is a steady improvement from baseline.

Item 3, the efficacy of the drug treatment, a rating which is to reflect the relative benefit of a drug given the number of side effects that are observed, shows a significant therapeutic effect of fenfluramine at 4 weeks on drug relative to baseline measures [row 3(a)]. When the second drug measure is included, we still obtain a significant F value from the repeated measures ANOVA. Though the two ratings made on drug did not differ from each other, both were significantly higher than the baseline measure ($p = .06$ and $p = .02$).

Conclusions

In this open-label study, a variety of positive stimulating and tranquilizing effects of fenfluramine were observed: the most consistent and striking effects were increased relatedness and animated facial expression, decreases of irritability, temper tantrums, aggressiveness, self-mutilation, hyperactivity, and improved sleep pattern. Ritvo et al.

TABLE 2

Clinical Global Impressions (CGI) Ratings for Two Baselines, 4 Weeks, and 8 Weeks on Fenfluramine[1]

CGI Items	Placebo Baseline 1	Baseline 2	Fenfluramine Treatment 4 Weeks	8 Weeks	ANOVA F
1(a) Severity of Illness	5.75	6.12	4.12	—	10.62**
	(1.03)	(0.83)	(0.99)	—	
	$N=8$	$N=8$	$N=8$		
1(b) Severity of Illness	5.80	6.20	4.20	4.00	6.62**
	(0.84)	(0.84)	(1.09)	(1.58)	
	$N=5$	$N=5$	$N=5$	$N=5$	
2(a) Global Improvement	—	4.44	2.67	—	4.41$+$
	—	(1.94)	(1.41)	—	
		$N=9$	$N=9$		
2(b) Global Improvement	—	3.67	3.00	2.67	ns
	—	(1.97)	(1.55)	(1.21)	
		$N=6$	$N=6$	$N=6$	
3(a) Efficacy (Drug Effect)	—	0.77	2.47	—	19.28**
	—	(0.44)	(1.75)	—	
		$N=9$	$N=9$		
3(b) Efficacy (Drug Effect)	—	0.83	2.71	2.33	6.40*
	—	(0.41)	(1.27)	(1.21)	
		$N=6$	$N=6$	$N=6$	

[1] Means, standard deviations (in parentheses), and sample size.

$+ = .05<p<.10$

$^{*} = p<.05$

$^{**} = p<.01$

(1983) and August et al. (1985) also reported improvements in sleep pattern, attention, and social relatedness, as well as decreases in hyperactivity and stereotypies. Marked global improvement was observed in 4 children; 2 had moderate and 4 showed minimal or no change. However, in 2 children, the level of initial improvement could not be sustained over a 2-month period of active medication. Therapeutic effects occurred as early as 2 days after medication was started.

Major untoward effects included drowsiness and lethargy, excessive and uncontrollable irritability, and a transient weight loss at the end of 1 month (followed by weight gain at the end of the second month). While Ritvo did not find weight loss a problem, August et al.'s (1985) findings are in agreement with ours. Ritvo states that weight monitoring may have been flawed in his study. We used the same scale throughout the study and adhered to a strict protocol. Untoward effects seemed to be dose-dependent as they disappeared upon dosage reduction. While in the previous reports children adapted to sedation after a few days (August et al., 1985; Ritvo et al., 1983), this was not true for our patients. Actually, no child adapted to behavioral toxicity.

In conclusion, we learned the following from this open clinical trial of fenfluramine, when administered at the specified doses over a period of up to 2 months to hospitalized preschool-age autistic children under the present conditions (100% compliance and 24-hour a day careful monitoring):

1. Flexible, and not a fixed dosage schedule should be employed since the range of optimal doses was wide: 1.1 to 1.8 mg/kg/day; mean, 1.4.

2. Onset of therapeutic effects was as early as 2nd day of treatment; one child fell asleep 4 1/2 hours after the morning dose.

3. Stimulating and calming properties of drug were reflected in both therapeutic and in untoward effects.

4. The most consistent and striking therapeutic effects were increased relatedness and animated facial expression, and decreases of irritability, temper tantrums, aggressiveness, self-mutilation, hyperactivity, and improved sleep pattern.

5. Four of the 10 children showed dramat-

ic improvement: all 4 had low IQs. All 4 failed to respond to haloperidol and to special education.

6. In some children, therapeutic effects are transient.

7. In a subsample of 7 children who received separate trials of both fenfluramine and of haloperidol, 3 responded to haloperidol and not to fenfluramine; 4 responded to fenfluramine but not to haloperidol.

8. Untoward effects with fenfluramine occurred mainly above therapeutic doses and there was a good therapeutic margin. Major untoward effects were drowsiness, uncontrollable irritability, and transient weight loss.

The observed effects in our study could be attributed to antiserotonergic or amphetamine-like, or antidopaminergic properties of fenfluramine.

However, while in our previous studies of D- and L-amphetamine the potentiating effects on stereotypies were striking in most autistic children, with fenfluramine only one child showed increases of stereotypies on 3.625 mg/kg/day, a dose which was above optimal (1.787 mg/kg/day). On therapeutic doses, there was reduction of stereotypies. This observation is consistent with the preclinical literature demonstrating that fenfluramine can antagonize apomorphine-induced stereotypies in rats (Jori et al., 1974), although in our sample the reduction of stereotypies was only mild.

While the literature (Alphin & Ward, 1969) indicates that fenfluramine has mild antidopaminergic-tranquilizing properties, in our patients calming effects were pronounced: decreases of aggressiveness, temper tantrums, hyperactivity, and insomnia were observed at therapeutic doses and, at higher doses, 9 of the 10 patients were drowsy or fell asleep.

Future well-designed, carefully planned, and placebo-controlled studies involving large samples of hospitalized autistics who are homogeneous with respect to age are needed to assess critically the efficacy and the safety of fenfluramine in this disorder.

We have recently begun such a study: in this double-blind, placebo-controlled parallel group's clinical trial we will assess the effects of fenfluramine on both behavioral symptoms and on discrimination learning.

References

Alphin, R.S., Funderburk, W.H., and Ward, J.W. Anorexigenic activity of N-ethylmethyl-3-trifluoromethylphenethylamine hydrochloride (AHR-965), a non-CNS stimulant. *Toxicol. Appl. Pharmacol.*, 6:340, 1964.

Alphin, R.S., and Ward, J.W. Anorexigenic effects of fenfluramine hydrochloride in rats, guinea pigs and dogs. *Toxicol. Appl. Pharmacol.*, 14:182–191, 1969.

Anderson, L.T., Campbell, M., Grega, D.M., et al. Haloperidol in infantile autism: Effects on learning and behavioral symptoms. *Am. J. Psychiatry*, 141 (10): 1195–1202, 1984.

August, G.J., Raz, N., and Baird, T.D. Brief report: Effects of fenfluramine on behavioral, cognitive, and affective disturbances in autistic children. *J. Autism Dev. Disord.*, 15(1):97–107, 1985.

Bowers, M.B., Jr., Swigar, M.E., Jatlow, P.I., and Goicoechea, N. Plasma catecholamine metabolites and early response to haloperidol. *J. Clin. Psychiatry*, 45:248–251, 1984.

Campbell, M., Anderson, L.T., Meier, M., et al. A comparison of haloperidol, behavior therapy and their interaction in autistic children. *J. Am. Acad. Child Psychiatry*, 17(4):640–655, 1978.

Campbell, M., Fish, B., David, R., et al. Response to triiodothyronine and dextroamphetamine: A study of preschool schizophrenic children. *J. Autism Child Schizophr.*, 2(4):343–358, 1972.

Campbell, M., Small, A.M., Collins, P.J., et al. Levodopa and levoamphetamine: a crossover study in young schizophrenic children. *Curr. Ther. Res.*, 19(1):70–86, 1976.

Costa, E., Groppetti, A., and Revuelta, A. Action of fenfluramine on monoamine stores of rat tissues. *Br. J. Pharmacol.*, 41:57–64, 1971.

Franko, B.V., Garber, J.L., and Hudson, B.H. Cardiovascular effects of N-ethylmethyl-3-trifluoromethylamine hydrochloride (AHR-965), an appetite suppressant lacking CNS-stimulating activity. *Fed. Proc.*, 23:330, 1964.

Jori, A., Cecchetti, G., Ghezzi, D., and Samanin, R. Biochemical and behavioral antagonism between fenfluramine and apomorphine in rats. *Eur. J. Pharmacol.*, 26:179–183, 1974.

Perry, R., Campbell, M., Green, W.H., et al. Neuroleptic-related dyskinesias in autistic children: A prospective study. *Psychopharmacol. Bull.*, 21(1):140–143, 1985.

Psychopharmacol. Bull. Rating scales and assessment instruments for use in pediatric psychopharmacology research. Vol. 21 (4), 1985.

Riley, I., Carson, J., Haider, I., and Oswald, I. Fenfluramine overdosage. *Lancet*, II: 1162–1163, 1969.

Ritvo, E.R., Yuwiler, A., Geller, E., et al. Effects of L-dopa in autism. *J. Autism Child Schizophr.*, 1:190–205, 1971.

Ritvo, E.R., Freeman, B.J., Geller, E., and Yuwiler, A. Effects of fenfluramine on 14 outpatients with the syndrome of autism. *J. Am. Acad. Child Psychiatry*, 22:549–558, 1983.

Ritvo, E.R., Freeman, B.J., Yuwiler, A., et al. Study of fenfluramine in outpatients with the syndrome of autism. *J. Pediatr.*, 105(5):823–828, 1984.

Simpson, G.M., Lee, J.H., Zoubok, B., and Gardos, G. A rating scale for tardive dyskinesia. *Psychopharmacology (Berlin)*, 64(2):171–179, 1979.

Fenfluramine: Neurotoxicity[1]

Charles R. Schuster, Ph.D.,[2] Marilyn Lewis,[3] and Lewis S. Seiden, Ph.D.[4]

Fenfluramine [(M-trifluoromethyl)-N-ethyl-amphetamine)], a secondary amine, is structurally similar to its analog the primary amine, amphetamine, and shares its anorectic effects but not its stimulant effects (Le Douarec & Neveu, 1970). Its anorectic actions are based upon its ability to release and block reuptake of serotonin from neurons (Fuxe et al., 1975: Trulson & Jacobs, 1976). Our interest in the neurotoxic effects of fenfluramine was generated in the course of investigating currently marketed anorectic drugs as part of a program of research conducted at the Drug Abuse Research Center at the University of Chicago. We investigated the efficacy, dependence potential, and possible neurotoxicity of structurally related anorectic drugs. We have established that methylamphetamine, as well as certain other related anorectics, produce long-term possibly irreversible damage to one or more monoaminergic systems in the brain (Ricaurte et al., 1982: Schuster & Johanson, 1984: Seiden et al., 1976: Wagner et al., 1979). We report here that fenfluramine is different from most other anorectic drugs because it produces evidence of long-term, possibly irreversible, changes in serotonergic neurons at comparatively low doses compared to those which suppress food consumption.

Several investigators have reported that brain serotonin levels in rats were significantly lowered several hours after the administration of fenfluramine (Duhault & Verhavainne, 1967; Opitz, 1967). Costa et al. (1971) showed that serotonin (5-hydroxytryptamine, 5-HT) brain concentrations were depleted at maximum between 2 and 5 hours after a low interperitoneal injection (10 μmol/kg) of fenfluramine and returned to only 80% of normal 48 hours post-injection. Subsequently, a number of investigators reported that the fenfluramine-induced depletions of brain 5-HT in rats lasted for weeks after drug administration was stopped (Clineschmidt et al., 1978; Harvey & McMaster, 1975; Harvey et al., 1975; Sanders-Bush et al., 1975). In these studies, brain levels of serotonin were found to gradually return to near-normal levels over a 30- to 60-day period. In addition to demonstrating a long-lasting effect upon serotonin brain levels, these investigators also demonstrated long-lasting decreases in the rate limiting enzymatic activity of tryptophan hydroxylase, serotonin uptake, and production of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA). These neurochemical changes are similar to those produced by 5,6-dihydroxytryptamine (5,6-DHT), a toxin known to act on 5-HT neurons. This suggests that fenfluramine also produces a degeneration of serotonergic nerve terminals. The return of serotonin levels to near-normal in most areas suggested that the terminal degeneration was not sufficient for death of the neuron and that sprouting occurred with the formation of new nerve terminals. In addition to this neurochemical evidence for toxic effects on serotonergic nerve terminals, Harvey reported in 1975 that fenfluramine produced morphologic changes in the cell bodies of serotonergic neurons located in the ventral tegmentum of the rat brain, but not in the dorsal or median raphe nuclei (Harvey & McMaster, 1975; Harvey et al., 1975). Although this morphological evidence of cytotoxic effects of fenfluramine is controversial, it suggests that fenfluramine has two types of toxic effects on serotonergic neurons in the rat: 1) on the terminals of 5-HT neurons in general regions of the brain, and 2) on cell bodies in a restricted region.

---

[1] This work was supported in part by NIDA Grant DA-00085. C.R. Schuster is the recipient of a RSA Award DA-00024. L. S. Seiden is the recipient of a RSA Award MH-10562.

[2] The University of Chicago, Drug Abuse Research Center, Department of Psychiatry, Chicago, IL 60637.

[3] The University of Chicago, Department of Behavioral Sciences, Chicago, IL 60637.

[4] The University of Chicago, Department of Pharmacological and Physiological Sciences, Chicago, IL 60637.

Studies from our laboratory have found that the dose of fenfluramine necessary to reduce food intake by 50% in the rat is 5.0 mg/kg subcutaneous (s.c.) (Schuster & Johanson, 1984). To investigate the possible neurotoxic effects of fenfluramine, two s.c. injections per day were given for 4 days over a range of doses from 6.25 to 50 mg/kg/injection. Two weeks after the last injection, rats were killed and their brains rapidly removed, dissected, and assayed for neurochemical changes as described by Heffner et al. (1980) and Ricaurte et al. (1981). In the caudate hippocampus, and cortex-limbic system, caudate serotonin was depleted by approximately 50% by all dose levels of fenfluramine. In contrast, the levels of dopamine and norepinephrine were not significantly different than controls.

To investigate the neuronal changes responsible for the depletions, we assessed the uptake of tritiated 5-HT into synaptosomal preparations of cortical cells from rats 2, 4, or 8 weeks after the 4-day administration regimen of fenfluramine. When fenfluramine was given twice daily at a dose of 6.25 mg/kg/injection for 4 consecutive days, the number of uptake sites (V_{max}) is decreased by approximately 50% of control values at 2 weeks, but is less affected at 4 weeks and is at control levels by 8 weeks post-fenfluramine. The decrease in the number of uptake sites suggests that fenfluramine damaged the terminals of serotonergic neurons, but that there was a gradual recovery over an 8-week period.

When the effects of fenfluramine were examined at 2, 8, and 16 weeks after two 12.5 mg/kg injections per day for 4 days, it was found that 5-HT levels in the caudate and cortex-limbic system fractions showed a gradual return to control levels over the 16-week period. In contrast, hippocampal 5-HT levels continued to show 50% depletions up to and including the 16-week period. The fact that the 5-HT depletion is longer lasting in the hippocampus than that found in other brain regions confirms previous findings by Harvey et al. (1975). It should be noted that the 5-HT uptake studies cited above were done with synaptosomes from 5-HT nerve terminals from the cortex, a region in which 5-HT levels show a return to normal. We presume that 5-HT uptake into synaptosomes from the hippocampus would continue to be low since the levels of 5-HT show little trend towards returning to control levels over the 16-week period. We may conclude from these studies that at a dose approximately equal to that necessary to produce a significant decrease in food intake (50%), fenfluramine produces long-term changes in 5-HT neurons. It remains to be determined whether the changes induced by fenfluramine in hippocampal 5-HT nerve terminals are irreversible.

Guinea Pigs

Fenfluramine is metabolized in the rat to norfenfluramine which has been shown to cause the release of 5-HT from neurons and to produce long-term depletions of brain levels of 5-HT (Clineschmidt et al., 1978; Sterenka & Sanders-Bush, 1979). In the guinea pig, however, fenfluramine is not changed into an active metabolite (Beckett et al., 1973). This difference in the metabolism of fenfluramine in the guinea pig allows the determination of whether the parent compound alone can produce long-term depletions of 5-HT in the brain.

Four groups of guinea pigs were used in this investigation. Group I was given 6.25 mg/kg/injection twice daily for 8 days. Group II was given 6.25 mg/kg/injection twice daily for 4 days and then 12.5 mg/kg/injection for an additional 4 days. Group III was given 12.5 mg/kg/injection twice daily for 4 consecutive days. Group IV was given saline injections twice daily for 8 consecutive days. Fourteen days after the last injection, animals were killed and the levels of 5-HT in the hippocampus determined. Animals treated with fenfluramine showed a significant dose-related depletion of 5-HT. At the higher dosage level (Groups II and III) these depletions were approximately 50%.

This study indicates that fenfluramine does not have to be metabolized to norfenfluramine in order to produce long-term depletions of brain levels of 5-HT. A similar conclusion was reached by Garattini et al. (1975) who blocked the metabolism of fenfluramine to norfenfluramine in the rat by pretreatment with SKF 525-A.

Rhesus Monkeys

In order to strengthen the prediction of neurotoxicity from animal studies to humans, it is necessary to use a number of species. It is particularly important to determine whether neurotoxicity found in rodents can be replicated in primates. Data on the long-term neurochemical effects of fenfluramine in the rhesus monkey have begun to be collected by our laboratories.

Rhesus monkeys were administered either saline ($N = 2$) or fenfluramine ($N = 4$) at doses of 10 mg/kg/injection by a s.c. route twice daily for 14 consecutive days. Two and 8 weeks later, one of the control animals and two of the fenfluramine-treated monkeys were sacrificed for neurochemical studies. Levels of 5-HT were markedly lower in the fenfluramine-treated animals in caudate, hippocampus, and somatosensory cortex at both 2 and 8 weeks postdrug. In addition, studies of the uptake of tritiated 5-HT into synaptosomal preparations from the cortex showed that 2 weeks after the last injection of fenfluramine there was a 51% decrease in the number of uptake sites (V_{max}) but no change in the affinity (K_m). This is in accord with the results of the studies in rats and suggests that in both species fenfluramine destroys 5-HT nerve terminals.

Before any conclusions can be drawn about the degree and duration of the neurotoxicity produced by fenfluramine in rhesus monkeys, a larger number of animals must be studied. Nevertheless, the concordance in the data from the rat, guinea pig, and rhesus monkeys strengthens the prediction that fenfluramine probably produces similar long-term effects on 5-HT neurons in humans. This conclusion is given support by the findings of Chase and Shoulson (1975) who demonstrated that cerebrospinal fluid (CSF) levels of 5-HIAA were significantly decreased 24 hours after a 7-day treatment regimen with fenfluramine. It would be of great significance to determine the duration of such changes in 5-HIAA levels after fenfluramine administration is stopped. Even if 5-HIAA levels return to normal in the CSF, it does not guarantee that fenfluramine does not produce irreversible changes in 5-HT neurons in restricted brain regions. Our findings in the rat that hippocampal levels of 5-HT are still significantly lower 16 weeks after the last injection of fenfluramine is in accord with previous reports of long-term depletions by Harvey et al. (1975). This suggests that certain 5-HT neurons may be more sensitive to the neurotoxic effects of fenfluramine.

The question remains: What are the implications of this pre-clinical laboratory evidence regarding long-term changes in 5-HT neurons for clinicians? When fenfluramine is used in the treatment of obesity, one must ask whether the therapeutic benefits gained warrant even the slightest risk that long-term changes in 5-HT neurons are being produced. At the very least, clinicians should be aware of this possibility in order to make a decision as to whether the drug should be prescribed. In the case of the possible benefits of fenfluramine for the treatment of autism, the problem is somewhat different. This disease may be sufficiently devastating and intractable to warrant the possible risks of long-term changes in 5-HT neurons. It is even conceivable that such depletions might be therapeutic for some autistic patients.

Before clinicians can make an appropriate analysis of the cost/benefit ratio for fenfluramine in the treatment of autism, more research is needed. At the present time, however, the findings from animal studies strongly suggest that the therapeutic benefits produced by fenfluramine must be sizable and durable in order to outweigh the potential risk of long-term, possibly irreversible, changes in 5-HT neurons in the brain.

References

Beckett, A.H., Coutts, R.T., and Ogunbona, F.A. N-ethyl-a-methyl-a-(m-trifluoromethylbenzyl)nitrone—the major in vitro metabolic product of fenfluramine in guinea-pig liver microsomal fractions. *J. Pharm. Pharmacol.*, 24:190–192, 1973.

Chase, T.M., and Shoulson, I. Behavioral and biochemical effects of fenfluramine in patients with neurologic disease. *Postgrad. Med. J.*, 51(1):105–109, 1975.

Clineschmidt, B.V., Zacchei, A.G., Totaro, J.A., et al. Fenfluramine and brain serotonin. *Ann. NY Acad. Sci.*, 305:222–241, 1978.

Costa, E., Groppetti, A., and Revuelta, A. Action of fenfluramine on monoamine stores of rat tissue. *Br. J. Pharmacol.*, 41:57–64, 1971.

Duhault, J., and Verdavainne, C. Modification du taux de serotonine cerebrale chez le rat par le trifluoromethyl-phenyl-2-ethyl-aminopropane (Fenfluramine 768 S). *Arch. Int. Pharmacodyn. Ther.*, 170:276, 1967.

Fuxe, K., Farnebo, L.O., Hamberger, B., and Ogren, S.O. On the in vivo and in vitro actions of fenfluramine and its derivatives on central monoamine neurons, especially 5-hydroxytryptamine neurons, and their relation to the anorectic activity of fenfluramine. *Postgrad. Med. J.*, 51(1):35–45, 1975.

Garattini, S., Buczko, W., Jori, A., and Samanin, R. The mechanism of action of fenfluramine. *Postgrad. Med. J.*, 51(1):27–35, 1975.

Harvey, J.A., and McMaster, S.E. Fenfluramine: Evidence for a neurotoxic action on midbrain and a long-term depletion of serotonin. *Pharmacol. Commun.*, 1:217-228, 1975.

Harvey, J.A., McMaster, S.E., and Yunger, L.M. P-Chloroamphetamine: Selective neurotoxic action in brain. *Science*, 187:841–843, 1975.

Heffner, T.G., Hartman, J.A., and Seiden, L.S. A rapid method for the regional dissection of the rat brain. *Pharmacol. Biochem. Behav.*, 13:453–456, 1980.

Le Douarec, P., and Neveu, C. Pharmacology and biochemistry of fenfluramine. In: Costa, E., and Garattini, S., (eds.), *Amphetamine and Related Compounds*. New York: Raven Press, 1970, pp. 75–105.

Opitz, K. Anoroxigene phenylalkylamine und serotoninstoffwechsel. *Naunyn-Schmied. Arch. Exptl. Pathol. Pharmacol.*, 259:56–65, 1967.

Ricaurte, G.A., Guillery, R.W., Seiden, L.S., et al. Dopamine nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain. *Brain Res.*, 235:93–103, 1982.

Ricaurte, G.A., Schuster, C.R., and Seiden, L.S. Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: A regional study. *Brain Res.*, 193:153–163, 1980.

Sanders-Bush, E., Bushing, J.A., and Sulser, F. Long-term effects of P-chloroamphetamine and related drugs on central serotonergic mechanism. *J. Pharmacol. Exptl. Ther.*, 192(1):33–41, 1975.

Schuster, C.R., and Johanson, C.E. Efficacy, dependence potential, and neurotoxicity of anorectic drugs. In: Seiden, L.S., and Balster, R.L. (eds.), *Behavioral Pharmacology The Current Status*. Vol. 13. New York: Alan R. Liss, Inc., 1984, pp. 263–280.

Seiden, L.S., Fischman, M.W., and Schuster, C.R. Long term methamphetamine-induced changes in brain catecholamines in tolerant rhesus monkeys. *Drug Alcohol Depend.*,1(3):215–219, 1976.

Sterenka, L.R., and Sanders-Bush, E. Species differences in the rate of disappearance of fenfluramine and its effects on brain serotonin neurons. *Biochem. Pharmacol.*, 28:3103–3107, 1979.

Trulson, M.E., and Jacobs, B.L. Behavioral evidence for the rapid release of CNS serotonin by PCA and fenfluramine. *Eur. J. Pharmacol.*, 36:149–154, 1976.

Wagner, G.C., Schuster, C.R., and Seiden, L.S. Methamphetamine induced changes in brain catecholamines in rats and guinea pigs. *Drug Alcohol Depend.*, 4:435–439, 1979.

Fenfluramine Treatment of Childhood Attention Deficit Disorder With Hyperactivity: A Preliminary Report

Maureen Donnelly, M.D.,[1] Judith L. Rapoport, M.D.,[1] and Deborah R. Ismond, M.A.[1]

Attention Deficit Disorder With Hyperactivity (ADD-H) is a common childhood disorder, with significant morbidity and a chronic course (Weiss, 1985). Pharmacotherapy with stimulant medications has been the mainstay of drug treatment (Gittelman, 1980). However, limitations of stimulant therapy—such as lack of response in about 20% of individuals, inconvenience of multiple daily dosing, possible rebound effects, abuse potential, and adverse effects such as growth suppression—have led to the investigation of alternative drug treatments (Rapoport et al., 1985).

Fenfluramine is a halogen-substituted phenethylamine derivative, presumed to act in part through serotonergic mechanisms. Acutely and at low doses, it increases central nervous system (CNS) serotonin (5-HT) activity, via 5-HT release, reuptake inhibition, and weak receptor agonist action. At high doses or with chronic use, it depletes brain 5-HT (Garattini et al., 1975; Mueller et al., 1984; Reuter et al., 1975).

Clinical and preclinical studies suggest that CNS 5-HT systems might be altered in ADD-H and that serotonergic activity might mediate stimulant drug effect (Solanto, 1984). In rats, increased 5-HT activity, by various means, is associated with decreased locomotor activity (Warbritton et al., 1978) and perhaps acquisition of behavioral inhibitory responses (McElroy et al., 1982). In autistic children, fenfluramine has been reported to decrease hyperactive behaviors (Ritvo et al., 1984). Other pharmacotherapeutic agents thought to enhance CNS 5-HT activity—namely, L-tryptophan (Brown, personal communication, 1984), chlorimipramine (Garfinkel et al., 1983), and clorgyline (Zametkin et al., 1985) have shown some beneficial effects in hyperactive populations.

This study evaluates behavioral, cognitive, and motor activity response of boys with ADD-H in a randomized, double-blind, crossover trial of fenfluramine, amphetamine, and placebo.

Method

Ten boys (mean age 8±2 years) with DSM-III diagnoses of ADD-H, Conners Teacher Rating Scale (Goyette et al., 1978) Factor IV baseline ratings greater than two standard deviations above age means, and Wechsler Intelligence Scale for Children–Revised (WISC-R) full scale IQ scores of 80 or above (mean 104±12) participated in a 10-week, double-blind, placebo-controlled day-hospital study. Six boys also met diagnostic criteria for Conduct Disorder and four met Developmental Learning or Language Disorder criteria. All subjects were medication-free for at least 4 weeks.

After a 1-week baseline assessment period, subjects received 3 weeks of placebo, 3 weeks of D-amphetamine (0.5 mg/kg/day in two doses), and 3 weeks of fenfluramine (week 1: (low dose) 0.6 mg/kg/day; week 2: 1.3 mg/kg/day; week 3: (high dose) 2.0 mg/kg/day, in two doses) in randomized counterbalanced order.

The children also attended school and participated in a structured group activities program while at the hospital.

The classroom teacher rated behavior daily using the 10-item Conners Abbreviated Rating Scale (Conners, 1976). Sustained attention was measured at the end of weeks 1 and 3 of each drug phase with a modified version of the Continuous Performance Test (CPT) (Rosvold et al., 1956). Daytime ward motor activity was recorded daily with an acceleration sensitive activity monitor (Colburn et al.,

---

[1] Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20892.

1976). In addition, weekly weights and side effects complaints (using the Subject's Treatment Emergent Symptom Scale) (ECDEU, 1976) were obtained.

Results

Data were analyzed with three- or four-way repeated measure analysis of variance (ANOVA) for drug, time (week, hour), and treatment × time interaction. Significant effects by Greenhouse Geisser probability of .05 or less were then examined by Bonferroni *t* tests.

A significant drug effect ($F = 12.76$; df 1,7; $p = .009$) was found for motor activity, though not for drug × week interaction. Motor activity significantly decreased on amphetamine ($p<.05$) compared to fenfluramine and to placebo. The latter two conditions did not differ. Figure 1 illustrates drug effects for weeks 2 and 3 of each treatment.

Behavioral ratings improved significantly with amphetamine, as opposed to placebo, treatment ($p<.05$). Fenfluramine, however, did not differ from amphetamine or placebo, indicating perhaps a weak response. Though ANOVA showed significant drug and week effects ($F = 4.80$; *df* 2,18; $p = .03$ and $F = 3.95$; *df* 2,18; $p = .05$, respectively), there was no medication × time interaction. Therefore, behavioral response to "low-dose" and "high-dose" fenfluramine did not differ. Figure 2 illustrates mean behavioral rating scores for week 3 of each medication phase.

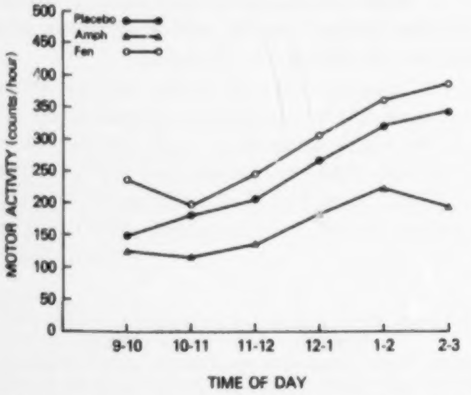
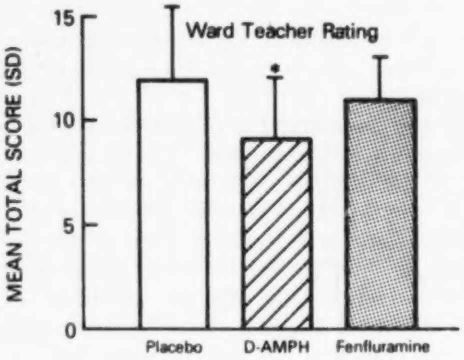


FIGURE 1. Weeks 2 and 3: Effects of fenfluramine, D-amphetamine and placebo on Ward motor activity of hyperactive boys ($N=8$) (means for weeks 2 and 3 of each treatment).



*p< .05 *vs.* placebo

FIGURE 2. Ward behavioral ratings for hyperactive boys ($N=10$) on week 3 of placebo, D-amphetamine (.5 mg/kg) and fenfluramine (mean 60 mg/day).

Performance on the CPT, a measure of vigilance, for commission errors, omission errors, and interstimulus interval did not significantly change on any drug at any time. This is an unexpected finding, as improved performance on the CPT is usually found with amphetamine treatment.

Analysis of group data for side effects showed no significant problems with either medication. One child showed clinically significant sedation for the first 3 days on fenfluramine, which disappeared thereafter.

Children's weights did not change significantly from admission to discharge from the study. Only one child had significant weight loss (2.5 kg) during the fenfluramine phase, necessitating a decrease in drug dosage. This subject's weight subsequently returned to baseline by the end of his hospitalization.

Discussion

Clinically, these results are disappointing as fenfluramine, which has less abuse potential than stimulants, does not appear to be an effective agent for the treatment of ADD-H. It had no beneficial effects on hyperactivity, classroom behavior, or attention. Though statistically there was an insignificant trend toward behavioral improvement with fenfluramine, this is probably not clinically significant.

If the assumptions of low dose and acute treatment, extrapolated from animal and adult data, have been met by the low dose (0.6 mg/kg/day) fenfluramine trial of 1 week, then these findings suggest that a serotonergic mechanism does not mediate stimulant or other drug efficacy in ADD-H. The findings also suggest that if fenfluramine is found effective in autism, then this is not secondary to a nonspecific antihyperactive action.

References

Colburn, T., Smith, B., Guarini, J., et al. An ambulatory activity monitor with solid-state memory. *ISA Trans.*, 15: 149-154, 1976.

Conners, C. Rating scales for use in drug studies with children. *Psychopharmacol. Bull.* (Special Issue), 59-60, 1976.

Early Clinical Drug Evaluation Unit Assessment Manual. Rockville, Md: National Institute of Mental Health, 383-395, 1976.

Garattini, S., Buczko, W., Jori, A., and Samanin, R. The mechanism of action of fenfluramine. *Postgrad. Med. J.*, 51 (Suppl. 1):27-35, 1975.

Garfinkel, B., Wender, P., Sloman, L., and O'Neill, I. Tricyclic antidepressant and methylphenidate treatment of attention deficit disorder in children. *J. Am. Acad. Child Psychiatry*, 22:343-348, 1983.

Gittelman, R. Childhood disorders. In: Klein, D., Gittelman, R., Quitkin, F., and Rifkin, A. (eds.), *Drug Treatment of Adult and Childhood Psychiatric Disorders.* New York: Williams & Wilkins, 1980.

Goyette, C., Conners, C., and Ulricr, R. Normative data on revised Conners Parent and Teacher Rating Scales. *J. Abnorm. Child Psychol.*, 6:221-236, 1978.

McElroy, J., DuPont, A., and Feldman, R. The effects of fenfluramine and fluoxitine on the acquisition of a conditioned avoidance response on rats. *Psychopharmacology*, 77:356-359, 1982.

Mueller, E., Siever, L., and Murphy, D. Neuroendocrine responses to serotonin agonists as possible markers of the functional state of serotonergic neurotransmission in psychiatric disorders. In: Beckmann, H., and Biederer, P. (eds.), *Pathochemical Markers of the Psychoses.* Berlin: Springer Verlag, 1984.

Rapoport, J., Zametkin, A., Donnelly, M. and Ismond, D. New drug trials in attention deficit disorder. *Psychopharmacol. Bull.*, 21(2):232-236, 1985.

Reuter, C. A review of the CNS effects of fenfluramine, 780SE and norfenfluramine on animals and man. *Postgrad. Med. J.*, 51 (Suppl.1):18-27, 1975.

Ritvo, E., Freeman, B., Yuwiler, A., et al. Study of fenfluramine in outpatients with the syndrome of autism. *J. Pediatr.*, 105:823-828, 1984.

Rosvold, H., Mirsky, A., Sarason, I., et al. A continuous performance test of brain damage. *J. Consult. Clin. Psychol.*, 20:343-350, 1956.

Solanto, M. Neuropharmacological basis of stimulant drug action in attention deficit disorder with hyperactivity: A review and synthesis. *Psychol. Bull.*, 95:387-409, 1984.

Warbritton, J., Stewart, M., and Baldessarini, R. Decreased locomotor activity with intraventricular infusion of serotonin in the rat. *Brain Res.*, 143:372-382, 1978.

Weiss, G. Followup studies on outcome of hyperactive children. *Psychopharmacol. Bull.*, 21(2):169-177, 1985.

Zametkin, A., Rapoport, J., Murphy, D., et al. Treatment of childhood attention deficit disorder with hyperactivity with monoamine oxidase inhibitors. *Arch. Gen. Psychiatry.* (In press)

The Effects of Fenfluramine on Suicidal Behavior[1]

Elaine Meyendorff, M.D.,[2] Anil Jain, M.D.,[2] Lil Träskman-Bendz, M.D., Ph.D.,[2] Barbara Stanley, Ph.D.,[2] and Michael Stanley, Ph.D.[3]

Suicidal behavior is one of the few mental health problems for which no pharmacologic treatment aimed specifically at the behavior itself has been developed. Instead, this behavior is treated as a symptom of other illnesses, usually depression. However, several reports have indicated that in addition to affective illness, attempted and completed suicide occurs in other diagnostic groups, including schizophrenia and personality disorders (Barraclough et al., 1974; Dorpat et al., 1960; Robins et al., 1959).

In addition to behavioral studies which provide evidence that suicide occurs across diagnosis, there is also evidence that there may be a common biochemical deficit associated with suicide and attempted suicide.

In a series of postmortem studies evaluating the levels of biogenic amines in various brain regions of suicide victims, it was noted that the most consistent finding was that 5-HT or 5-HIAA levels were reduced in suicides compared with non-suicide controls (Lloyd et al., 1974; Pare et al., 1969; Shaw et al., 1967). Subsequent to these reports, recent studies which have examined the status of serotonergic receptors in the brains of suicide victims have indicated changes in binding which are consistent with the above reported reductions in 5-HT and 5-HIAA (Paul et al., 1984; Perry et al., 1983; Stanley et al., 1982, 1983).

In addition to postmortem studies, there have been a large number of studies which have examined the cerebrospinal fluid (CSF) levels of 5-HIAA in individuals who have attempted suicide. In these CSF studies, 5-HIAA levels from those having a history of a suicide attempt included individuals from various diagnostic groups (e.g., schizophrenia, personality disorders, and depression) (Åsberg et al., 1976; Brown et al., 1979; Van Praag, 1983). In the majority of these studies, lower levels of 5-HIAA were reported for those with a history of a suicide attempt.

The diagnostic heterogeneity of those who attempt suicide, as well as the common biochemical deficit in 5-HT they are reported to manifest, led to our decision to investigate the effects of fenfluramine on suicidal behavior. Fenfluramine has been shown to promote the release of 5-HT and to block its reuptake. Chronic exposure to fenfluramine causes a reduction in the number of 5-HT_2 binding sites in the brain. This latter effect, the reduction of 5-HT_2 binding, is apparently a common pharmacologic property of antidepressant drugs of a variety of classes. Furthermore, the time course of 5-HT_2 binding reduction parallels clinical response, it may relate to the therapeutic mode of action of these compounds (Peroutka & Snyder, 1982).

Methods

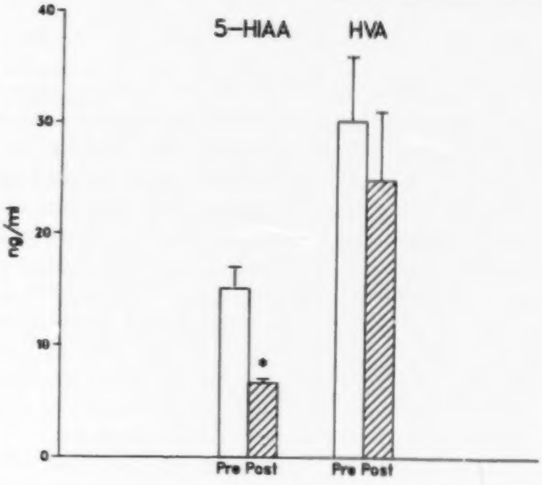
Eight suicidal patients from various diagnostic categories with a history of suicide attempts were entered into the study. All patients were free of major medical illness. Two patients had a diagnosis of bipolar disorder, depressed phase; one patient, bipolar disorder mixed; two patients, major depression with psychotic features; one patient, major depression; one patient, schizoaffective disorder; and one patient had a diagnosis of chronic undifferentiated schizophrenia. Subjects were inpatients ranging in age from 21 to 47 years, with a mean age of 35 years. Diagnosis was determined by interview performed according to the Schedule for Affective Disorders and Schizophrenia (SADS), and was established according to DSM-III criteria.

---

[1] This study was supported in part by USPHS Grant MH-40048 from the National Institute of Mental Health.

[2] Lafayette Clinic, Wayne State University, Detroit, MI 48207.
[3] New York State Psychiatric Institute, New York, NY 10032.

Address all correspondence to Michael Stanley, Ph.D., Department of Psychiatry, Columbia University, New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032.



* $p<0.05$

FIGURE 1. CSF levels of 5-HIAA and HVA before and after chronic fenfluramine treatment.

Supplemental information for Axis II diagnosis was obtained with the Schedule for Interviewing Borderlines, and psychological testing including a Rorschach.

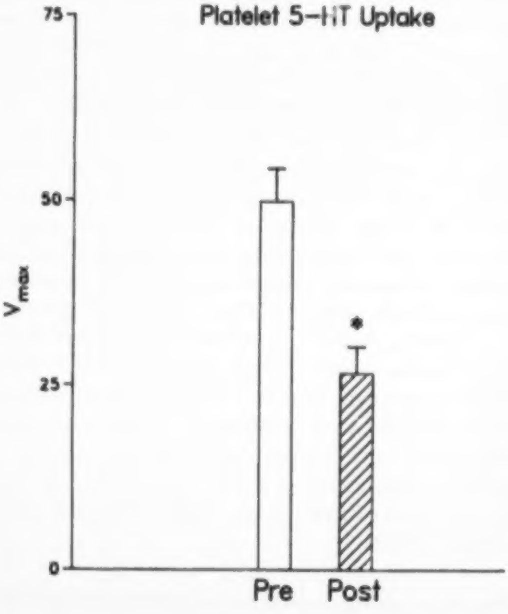
Patients were maintained free of active medication for 2 to 3 weeks. During the third week they received fenfluramine placebo. This was followed by 4 weeks of treatment with active fenfluramine. Acetominophen, diazepam, or chloral hydrate were occasionally administered for relief of anxiety, insomnia, or other acute symptoms. Fenfluramine was administered in an open-dose ranging fashion with an initial dose of 20 mg orally three times daily, up to a maximum dosage of 60 mg three times daily.

Weekly measures of psychopathology and suicidality, designed to assess treatment response, were performed. These included the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression and Anxiety Scales, the Scale for Suicide Ideation (SSI), and the Suicide Assessment Scale (SAS) (Stanley et al., 1986), a scale designed specifically to assess suicidal and related behaviors.

During the drug-free period, participants had routine chemistries performed, and blood was drawn in EDTA-treated tubes for determination of platelet tritiated imipramine binding, and platelet serotonin uptake. At the end of the final week of medication a plasma sample was drawn for determination of platelet tritiated imipramine binding and serotonin uptake. Subjects received a lumbar puncture prior to the study following a drug-free period for measures of 5-HIAA and homovanillic acid (HVA). To minimize the effects of movement and diet upon CSF 5-HIAA levels, lumbar punctures were performed between the hours of 8 to 10 a.m., after the subject had had nothing by mouth and had been resting supine for 8 hours. In several subjects enrolled in the study, a second lumbar puncture was performed 24 hours after the last dose of medication.

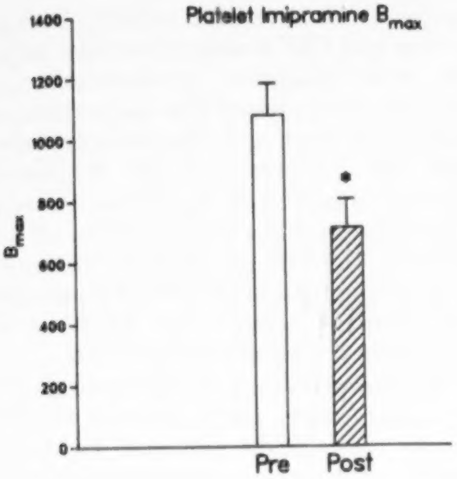
Isolation of platelets from whole blood was performed according to Briley et al. (1980). Tritiated imipramine binding was analyzed as described in Raisman et al. (1982). Serotonin uptake was determined by methods described by Tuomisto (1980). 5-HIAA and HVA were assayed in spinal fluid with high performance liquid chromatography.

Statistical analysis was done using paired *t* tests and analysis of variance.



$p<0.01$

FIGURE 2. Platelet serotonin uptake before and after chronic fenfluramine treatment.



p<0.1

FIGURE 3. Platelet imipramine binding before and after chronic fenfluramine treatment.

Results

Biochemical Findings

Chronic treatment with fenfluramine caused a significant reduction in the concentration of 5-HIAA in the CSF when compared with the values obtained prior to treatment. The 66% decrease in 5-HIAA is in contrast to the nonsignificant 18% decrease seen in HVA levels for the same patients (Figure 1).

Reductions in platelet 5-HT uptake and imipramine binding were also observed following treatment with fenfluramine. V_{max} values for platelet 5-HT uptake were reduced from 49.8±4.44 to 26.6±3.61 (pmol/10^8 platelets/min) ($p<0.005$) (Figure 2). Platelet imipramine binding was decreased from 1078±104 to 711±92.9 (fmol/mg protein) ($p<0.10$) (Figure 3).

Behavioral Ratings: Suicidal Behavior

Both scales used in this study to assess suicidality reflected a time-dependent decrease in the severity of this behavior. SSI scores were reduced to their lowest point after 4 weeks of fenfluramine treatment (Figure 4). Similarly, SAS scores were lowest after 4 weeks of fenfluramine (Figure 5). The downward trend observed for both of these measures was reversed immediately upon discontinuation of fenfluramine (Figures 4 and 5).

Measures of Psychopathology

In contrast to the uniform effect fenfluramine treatment exerted on the above measures of suicidality, it had a differential effect on psychotic and depressive symptoms. Hamilton depression scores showed a time-dependent reduction maximal at 5 weeks. However, psychotic symptoms, as assessed by the BPRS, reflected virtually no change over the entire treatment period (Figures 6 and 7).

Side Effects

With regard to side effects, subjects demonstrated a net weight loss of approximately 3 lbs, including one patient who lost 12 lbs, 4 patients who lost 4 to 5 lbs, one patient who lost 1 lb, one who gained 1 lb, and one patient gained 8 lbs. There were no clinically significant changes in either blood pressure or pulse rate throughout the active treatment

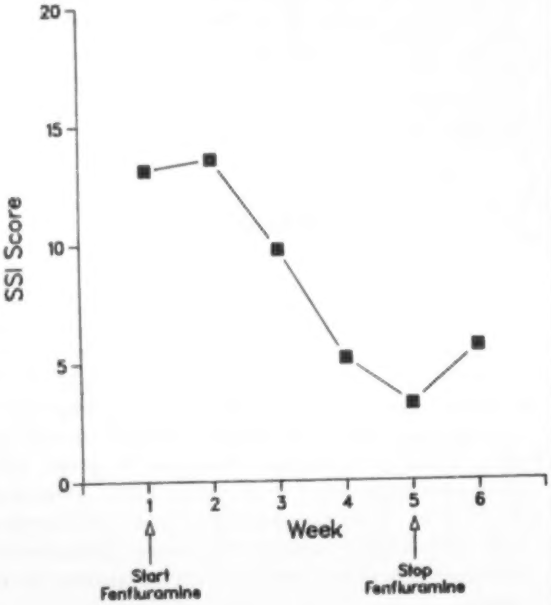


FIGURE 4. Effect of 4 weeks of fenfluramine treatment on Scale for Suicide Ideation Scores.

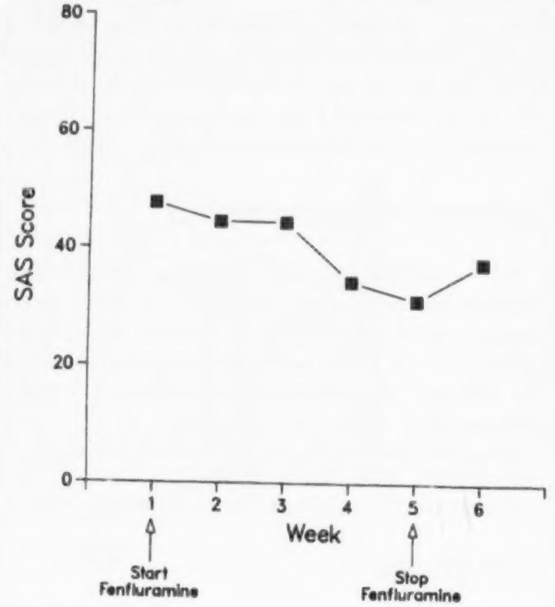


FIGURE 5. Effect of 4 weeks of fenfluramine treatment on Suicide Assessment Scale Scores.

phase of the study. No dystonia or other adverse effect was observed. Two patients with a diagnosis of bipolar disorder became manic during the treatment phase, and one patient with a diagnosis of bipolar disorder and another with a diagnosis of borderline personality became manic after discontinuation of the drug. Whether the drug induced the symptoms, or this was coincidental emergence of symptoms which were unaffected by fenfluramine, was unclear.

Discussion

The findings of this preliminary study parallel both the behavioral and biochemical findings reported for individuals who either attempt or complete suicide. The behavioral changes observed in this mixed diagnostic group indicate a consistent change in ratings of suicidality whereas changes in gross psychopathology were not consistently affected. Psychotic symptomatology was unchanged and depressive symptoms were diminished throughout the course of fenfluramine treatment.

The biochemical findings of this study were also consistent with the biochemical changes which have been noted in both postmortem and CSF studies of suicidal patients. The most consistent biochemical change which has been observed in studies of suicidal patients has been with the neurotransmitter 5-HT. In the present study, fenfluramine treatment resulted in significant reductions in peripherial and central indices of 5-HT function. The CSF measures further indicated the changes observed in 5-HT metabolism were relatively specific for 5-HT, as HVA values were not significantly altered.

The interpretations of the findings of this preliminary study are supportive of the hypothesis that suicidal behavior may be independent of diagnostic categorization and are also consistent with a serotonergic deficit. However, it must be noted that these results are of a very preliminary nature. Further, the study was conducted in a dose-ranging and open design on a relatively small patient sample. Accordingly, future studies of fenfluramine treatment of suicidal behavior should employ a larger patient sample and consider the use of a double-blind experimental design.

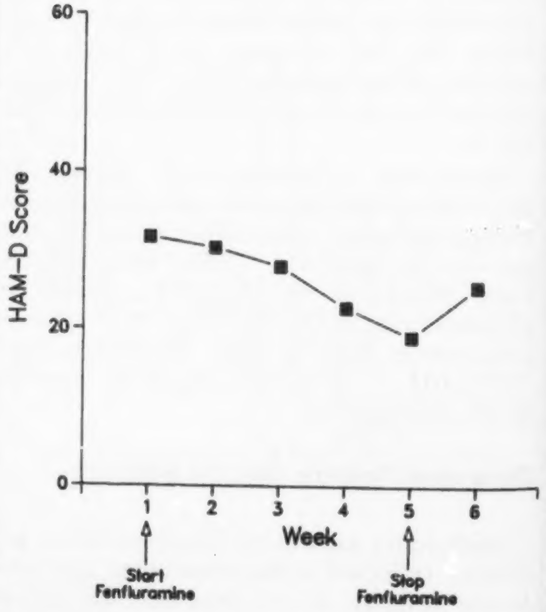


FIGURE 6. Effect of 4 weeks of fenfluramine treatment on Hamilton Depression Scale Scores.

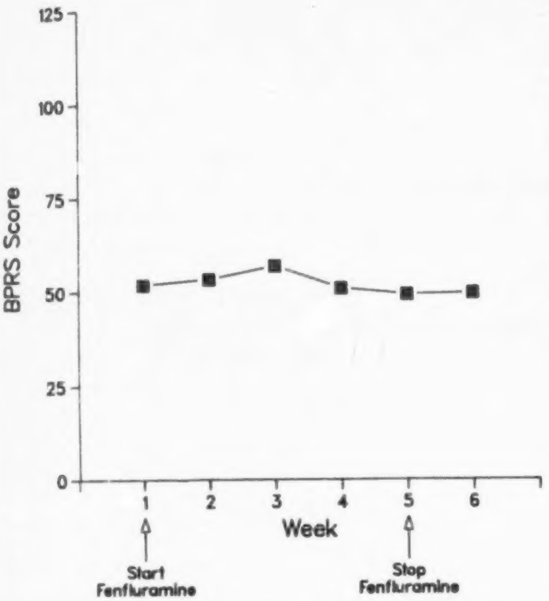


FIGURE 7. Effect of 4 weeks of fenfluramine treatment on Brief Psychiatric Rating Scale Scores.

References

Åsberg, M., Thorén, P., and Träskman, L. "Serotonin depression"—A biochemical subgroup within the affective disorders? *Science*, 191:478, 1975.

Barraclough, B., Bunch, J., Nelson, B., et al. A hundred cases of suicide: Clinical aspects. *Br. J. Psychiatry*, 125:355–373, 1974.

Briley, M., Langer, S.Z., and Raisman, R. Tritiated imipramine binding sites are decreased in platelets of untreated depressed patients. *Science*, 209:303, 1980.

Brown, G.L., Goodwin, F.K., Ballenger, J.C., et al. Aggression in human correlated with cerebrospinal fluid amine metabolites. *Psychiatry Res.*, 1:131–139, 1979.

Dorpat, T.L., and Ripley, H.S. A study of suicide in the Seattle area. *Compr. Psychiatry*, 1(6):349–359, 1960.

Lloyd, K.G., Farley, I.J., Deck, J.H.N., et al. Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brainstem of suicide victims and control patients. In: Costa, E., Gessa, G.L., and Sandler, M. (eds.), *Serotonin*. New York: Raven Press, 1974, pp. 389–397.

Pare, C.M.B., Yeung, D.P.H., Price, K., et al. 5-Hydroxytryptamine, noradrenaline, and dopamine in brainstem, hypothalamus, and caudate nucleus of controls and outpatients committing suicide by coal-gas poisoning. *Lancet*, ii:133–135, 1969.

Paul, S.M., Rehavi, M., Skolnick, P., and Goodwin, F.K. High-affinity binding of antidepressants to biogenic amine transport sites in human brain and platelet: Studies in depression. In: Post, R.M., and Ballenger, J.C. (eds), *Neurobiology of Mood Disorders*. Baltimore: Williams & Wilkins, 1984, pp. 846–853.

Peroutka, S.J., and Snyder, S.H. Different synaptic location of mianserin and imipramine binding sites. *Science*, 215:1112–1115, 1982.

Perry, E.K., Marshall, E.F., Blessed, G., et al. Decreased imipramine binding in the brains of patients with depressive illness. *Br. J. Psychiatry*, 142:188–192, 1983.

Raisman, R., Briley, M., Bouchami, F., et al. [^{3}H]-Imipramine binding and serotonin uptake in platelets from untreated depressed patients and control volunteers. *Psychopharmacology*, 77:332–335, 1982.

Robins, E., Murphy, G.E., Wilkinson, R.H., et al. Some clinical considerations in the prevention of suicide based on a study of 134 successful suicides. *Am. J. Publ. Health*, 49:888–889, 1959.

Shaw, D.M., Camps, F.E., and Eccleston, E.G. 5-Hydroxytryptamine in the hind brain of depressive suicides. *Br. J. Psychiatry*, 114:1407–1411, 1967.

Stanley, M., and Mann, J.J. Increased serotonin-2 binding sites in frontal cortex of suicide victims. *Lancet*, ii:214–216, 1983.

Stanley, M., Virgilio, J., and Gershon, S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science*, 216:1337–1339, 1982.

Stanley, B., Träskman-Bendz, L., and Stanley, M. The Suicide Assessment Scale: A scale evaluating change in suicidal behavior. *Psychopharmacol. Bull.*, 22(1): 200–205, 1986.

Tuomisto, J. Platelet uptake of serotonin in pathological conditions. In: Angrist, B., Burrows, G.D., Lader, M., et al. (eds.), *Recent Advances in Neuropsychopharmacology*. New York: Pergamon Press, 1980.

Van Praag, H. CSF-5HIAA and suicide in nondepressed schizophrenics. *Lancet*, i:977–978, 1983.

Free Communications—Session A

CHAIRS: Paul Leber, M.D.
Food and Drug Administration
Rockville, Maryland

and

Jack D. Blaine, M.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

The Relationship of Antiobsessional and Antidepressant Effects of Tricyclic Antidepressants[1]

Matig Mavissakalian, M.D.,[2] Samuel M. Turner, Ph.D.,[2] Larry Michelson, Ph.D.,[2] and Rolf Jacob, M.D.,[2]

Antidepressant medications, primarily clomipramine, have been found effective in treating obsessive-compulsive disorder (OCD) although the relationship between their well-established antidepressant action and their antiobsessional effects remains an open question (Ananth et al., 1981; Insel & Murphy, 1981; Insel et al., 1983; Marks et al., 1980; Mavissakalian, 1982, 1983; Montgomery, 1980; Thorén et al., 1980). Observations made in 8 OCD patients treated with either clomipramine or imipramine (Mavissakalian & Michelson, 1983) revealed synchronous patterns of change in depression, anxiety, and obsessive-compulsive symptoms which, coupled with the tendency for responders to have higher initial depression ratings, tentatively supported Marks' contention (Marks, 1983; Marks et al., 1980) that antidepressant drugs may not have an antiobsessional effect independent of their antidepressant properties. However, in a more recent placebo-controlled study of 12 OCD patients (Mavissakalian et al., 1985), it was found that OCD symptoms improved significantly more with clomipramine compared to placebo, while outcome of depression was equivalent in the two groups. The discrepancy between the fate of depression and obsessive-compulsive symptomatology in the placebo group was interesting and suggested that change in these symptom dimensions can occur independently from each other. The aim of this presentation is to further explore the relationship between the antidepressant and antiobsessional effects of tricyclic drugs in the combined sample of 15 primary OCD patients who were treated with clomipramine or imipramine in the aforementioned studies.

Subjects

Table 1 presents the individual characteristics of the 15 patients who were uniformly selected to be part of two consecutive mul-

---

[1] Supported by Grants M2323K and M2964K from Ciba-Geigy and Grant MH-34177 from the National Institute of Mental Health.

[2] Department of Psychiatry, University of Pittsburgh, School of Medicine, Pittsburgh, PA 15213.

Reprint requests to Matig Mavissakalian, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

TABLE 1

Patient and Treatment Characteristics of the Sample

Drug Condition	Age	Sex	Type of Ritual	Duration of Illness	Dosage	Response
Clomipramine						
1	23	M	Checking	4 years	200 mg	NR
2	51	F	Washing/Checking	8 years	200 mg	NR
3	65	M	Checking	38 years	100 mg	R
4	45	F	Washing/Checking	13 years	300 mg	R
5	43	M	Washing/Obsessional Fears	10 years	250 mg	NR
6	32	M	Compulsive Touching/ Counting/Washing	20 years	200 mg	NR
7	36	F	Washing/Obsessional Fears	13 years	150 mg	NR
8	20	F	Washing/Ruminations (Counting)	5 years	200 mg	R
9	35	F	Washing/Checking/ Obsessional Fears	10 years	200 mg	R
10	29	F	Washing	2 years	300 mg	NR
$\bar{X}$	37.9	60%		12.3 years	210 mg	40% R
(SD)	(13.54)	(F)		(10.43)	(61.46)	
Imipramine						
1	23	M	Obsessional Fears	2 years	300 mg	NR
2	26	F	Washing/Checking	16 years	200 mg	R
3	54	F	Washing/Checking	34 years	300 mg	R
4	20	F	Washing/Checking	6 years	250 mg	NR
5	39	F	Obsessional Fears/ Checking	18 years	200 mg	R
$\bar{X}$	32.4	80%		15.2 years	250 mg	60% R
(SD)	(14.06)	(F)		(12.46)	(50.0)	
Overall Sample						
N = 15	36.1	67%		13.3 years	223.3 mg	47% R
	(13.48)	(F)		(10.78)	(59.35)	

ticenter projects sponsored by Ciba-Geigy (Mavissakalian & Michelson, 1983; Mavissakalian et al., 1985). Inclusion criteria included: 1) DSM-III diagnosis of primary OCD; 2) a score of at least 56 on the Obsessive-Compulsive Neurotic Scale (*see* Assessment); and 3) a psychotropic medication-free and alcohol-free period of at least 2 weeks. Exclusionary criteria included: 1) diagnosis of primary affective disorder or major depressive episode with melancholic features, schizophrenia, and organic brain syndrome and 2) presence of physical illness precluding the use of antidepressants either because of the illness itself or because of treatment necessary for that illness.

Patients were randomly assigned to double-blind clomipramine or imipramine in the respective protocols. Initial drug dose was 50 mg/day in the first week with gradual increases to the largest tolerable level or a maximum of 300 mg/day. In order to remain in the study, patients had to be on at least a 100 mg/day regimen. Patients were seen weekly up to 6 weeks and then at 8 and 12 weeks of treatment at which time the trial ended. The tone of these sessions was supportive, and patients were encouraged to tolerate obsessions without engaging in compulsive behavior. The maximum stable dosage for the individual patients is presented in Table 1.

Major assessments included a uniform battery of tests which were administered at pretreatment, and at 4, 8, and 12 weeks posttreatment. The Obsessive-Compulsive Neurotic Scale (OCNS), a 25-item questionnaire covering commonly encountered obsessive-compulsive symptoms, was used as the patient-rated measure of change. Each item was rated on 4-point scales where 1 = none or little of the time; 2 = some of the time; 3 = a good part of the time; and 4 = most or all of the time (range 25 to 100). In addition, clinician-rated 5-point obsessive-compulsive scales were used to assess 1) frequency of obsessive thoughts (OCRS-O), 2) distress-anxiety caused by obsessive thoughts (OCRS-A), 3) frequency of compulsive behaviors (OCRS-C), and 4) interference with everyday life due to compulsive behavior (OCRS-I). On these scales, 0 = absent or none; 1 = infrequent or mild; 2 = moderate frequency or severity; 3 = very frequent or severe; and 4 = almost constant or extremely severe, incapacitating. These measures were also utilized to classify patients into responders (posttreatment ratings of ≤ 1 on at least 3 out of 4 criteria). Depression (HD-17) and anxiety (ZAS) measures consisted of the first 17 items of the Hamilton Depression Rating Scale (Hamilton, 1960) and the Zung Self-Rating Anxiety Scale (Zung, 1971), respectively.

Results

There were no significant differences on any demographic and clinical variables or pretreatment dependent measures between patients recruited from the two different studies. Nor did analysis of variance reveal significant pretreatment and improvement differences between the 5 imipramine- and the 10 clomipramine-treated patients (*see* Figure 1). For the purposes of investigating the relationship between the antidepressant and antiobsessional effects of tricyclic drugs among OCD patients, therefore, pooling of data across the two studies and the two drugs seemed justified.

Two-tailed *t* tests comparing pretreatment mean group scores and 4th week, 8th week, and posttreatment assessments, respectively, revealed significant improvement ($p<.05$) on all measures at all occasions in the samples as a whole. As shown in Table 1, 7 (47%) patients were classified as responders. Figure 2 illustrates the contrasting patterns of change between them and the nonresponders. Two-tailed *t* tests did not reveal significant differences at pretreatment. Significant differences on depression and anxiety were present only at posttreatment while differences on all obsessive-compulsive measures were significant at 4 and 8 weeks of treatment and ostensibly at posttreatment. Figure 2 also indicates an overall synchronous pattern of change between all three symptom dimensions.

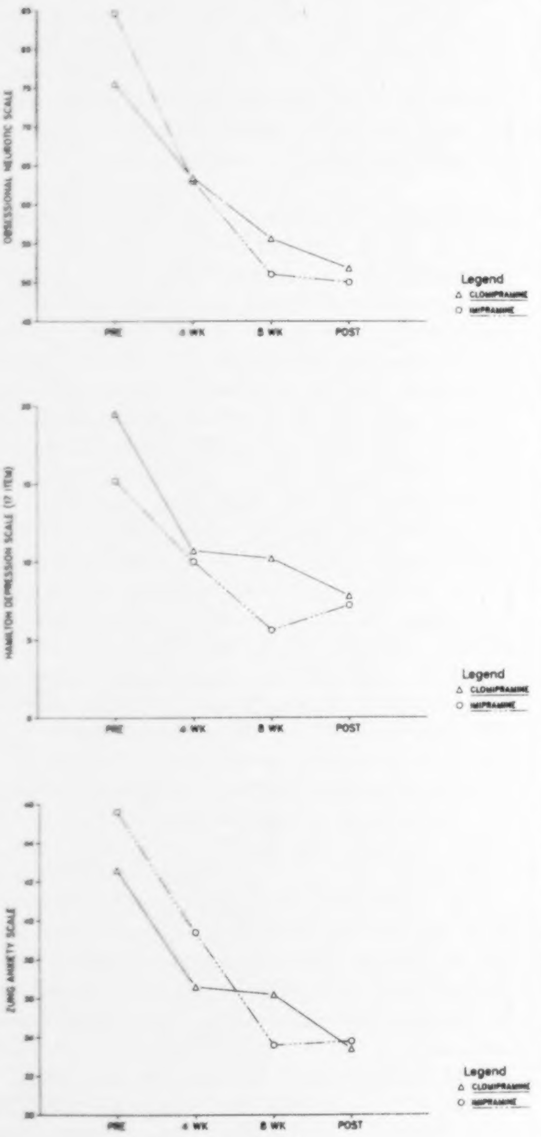


FIGURE 1. Differential improvement of obsessive-compulsive, depressive, and anxiety symptoms with clomipramine ($N = 10$) and imipramine ($N = 5$).

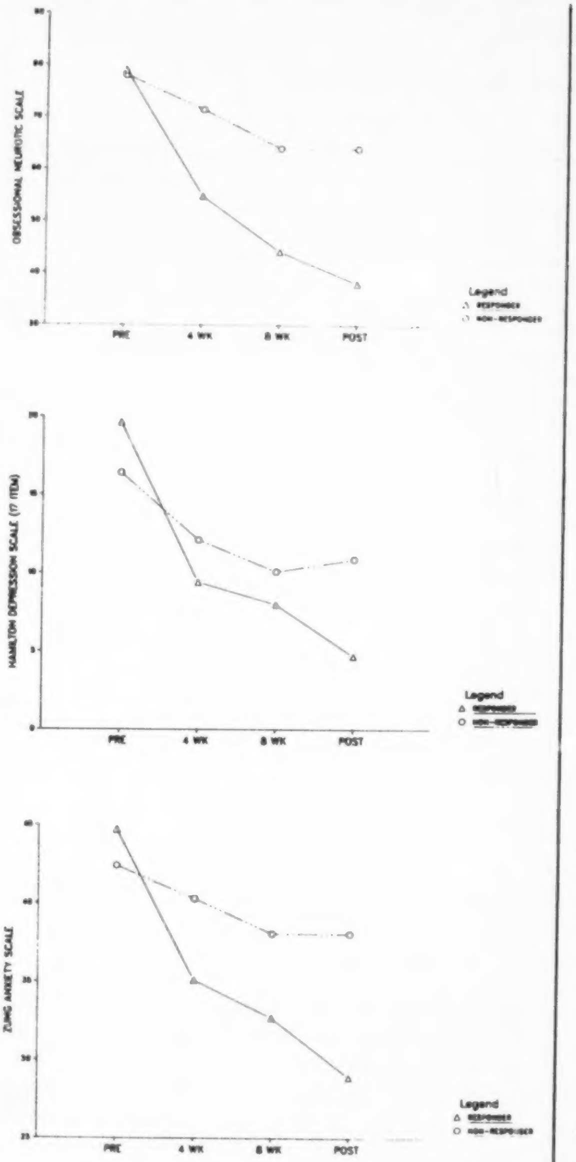


FIGURE 2. Differential improvement of obsessive-compulsive, depressive, and anxiety symptoms between responders ($N = 7$) and nonresponders ($N = 8$).

To assess the degree of association between the antidepressant and antiobsessional effects, change scores in depression were correlated with change scores in obsessive-compulsive symptoms. For this purpose, the 4 clinician-rated scales were combined into a total measure (OCRS-T) to reduce the quantity of analysis required and to make its range (0 to 16) more comparable with the other scales. As shown in Table 2, there were significant correlations at Week 4, but these had decreased in strength by the 8th week and had become inconsistent at posttreatment.

TABLE 2

Pearson Correlations Between Change in Depression and Obsessive-Compulsive Symptoms at Various Phases of Treatment

	Obsessive-Compulsive Symptoms	
Depression	OCNS	OCRS-T
4 Weeks		
HD-17	.53*	.50*
8 Weeks		
HD-17	.37	.38
12 Weeks		
HD-17	.30	.70**

*$p < .05$
**$p < .001$

Finally, the 5 patients with the lowest depression scores ($\overline{X} = 9.6$, range 4–14, s.d. = 5.18) were compared with the 5 patients who were most depressed ($\overline{X} = 25.6$, range 23–28, s.d. = 2.61). *T*-test comparisons of absolute and change scores at each assessment did not reveal significant ($p < .05$) differences on the anxiety or any of the obsessive-compulsive measures. Figure 3 illustrates the overall similarity in improvement of obsessive-compulsive symptoms in these two subgroups.

Discussion

The present findings suggest that the antiobsessive effect of tricyclic antidepressants may be at least partially independent of their antidepressant mechanisms. Although correlational analyses suggested that improvement in depression and obsessive-compulsive symptoms co-vary, most consistently in the earlier phases of treatment, and despite the overall synchronous pattern of change between these symptom dimensions, the comparison between low- and high-depressed subgroups was compelling evidence that an antidepressant effect is not a prerequisite to the antiobsessional effects of clomipramine or imipramine. Because the study was not prospectively designed to compare OCD patients with high

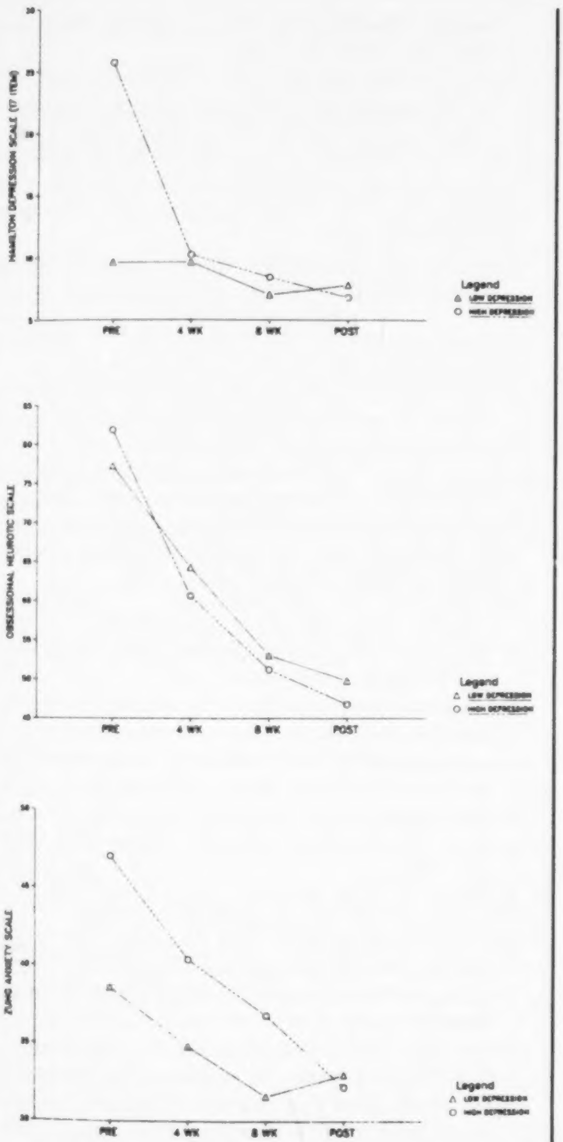


FIGURE 3. Differential improvement of obsessive-compulsive, depressive, and anxiety symptoms between high ($N=5$) and low ($N=5$) depressed subgroups.

and low initial depression levels, however, the findings warrant cautious interpretation. Indeed, 12 of the 15 patients had Hamilton depression scores ≥14, a level of dysphoria incurring high probability for an antidepressant effect in depressed outpatients (Stewart et al., 1983). Nevertheless, the categorization of the low depressed group appeared satisfactory not only because of the low initial levels, but also because of the very minimal and inconsequential changes in dysphoria over the course of treatment. Still, for more definitive data in this regard, placebo-controlled studies in OCD patients without appreciable dysphoria would be needed.

Several points of clinical and research interest warrant brief comment. First, and in contrast to the near maximal improvement of depression noted at 4 weeks, improvement in obsessive-compulsive symptoms continued throughout the 12 weeks suggesting that robust antiobsessional effects require long periods of treatment. Second, in this study, both obsessions and compulsions improved in a clinically significant degree with 56% and 48% pre-post reduction on their respective clinician-rated scores (details available upon request). Although it would be plausible to suggest that some of the improvement noted was due to the encouragement to apply the behavioral principles of exposure-response prevention (Foa et al., 1985), none of the 5 placebo patients treated under similar conditions (Mavissakalian et al., 1985) had improved to a level of virtual freedom from obsessive-compulsive symptoms as compared to nearly half of the sample treated with the active drugs. Thus, at the very least, it seems reasonable to conclude that clomipramine and impramine had significant facilitatory interactive effects with behavioral instructions. From a clinical vantage point, studies of the relative and combined effectiveness of pharmacological and behavioral treatments of OCD seem warranted.

Third, the equivalent improvement noted with clomipramine and imipramine is particularly interesting inasmuch as the investigation of a specific antiobsessional effect has primarily concerned clomipramine, and some studies have suggested superior clinical effects with clomipramine in comparison to other antidepressants (Ananth, 1983). The similar effects observed, on the other hand, are not entirely surprising given that, in addition to their close chemical structure, imipramine and clomipramine undergo parallel pharmacokinetic changes which control their neurobiochemical activities, i.e., they are mostly serotonergic while their active desmethyl metabolites are mostly noradrenergic (Risch et al., 1979). Although the small numbers do not permit confident generalizations, the finding has practical significance since clomipramine is still unavailable for clinical use in the United States.

Conclusion

The present data add to the literature suggesting that clomipramine, and probably imipramine, may be specific antiobsessional agents independently from their antidepressive properties. On the other hand, it is clear that a complex association exists between the antiobsessional and antidepressant effects of these drugs which may not be easily elucidated by symptom rating scales alone. A more promising approach is suggested by findings implicating clomipramine's serotonergic action in the control of obsessive-compulsive symptoms and the drug's noradrenergic action in the control of depressive symptoms (Stern et al., 1980; Thorén et al., 1980). Newer pharmacological agents with more selective action on neurotransmitter systems (Lapierre, 1983) can therefore be used to dissect the broad spectrum clinical effects of clomipramine and imipramine and to explore the neurobiological basis of OCD (Insel & Mueller, 1984; Richelson, 1983).

References

Ananth, J. Clomipramine in obsessive-compulsive disorder: A review. *Psychosomatics*, 24(8):723-727, 1983.

Ananth, J., Pecknold, J.C., van den Steen, N., and Engelsmann, F. Double-blind comparative study of clomipramine and amitriptyline in obsessive-neurosis. *Prog. Neuro-Psychopharmacol.*, 5:257-262, 1981.

Foa, E.B., Steketee, G.S., and Ozarow, B.J. Behavior therapy with obsessive-compulsives—From theory to treatment. In: Mavissakalian, M., Turner, S.M., and Michelson, L. (eds.), *Obsessive-Compulsive Disorder: Psychological and Pharmacological Treatment*. New York: Plenum Press, 1985, pp. 49-129.

Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry*, 23:56-62, 1960.

Insel, T.R., and Mueller, E.A. The psychopharmacologic treatment of obsessive-compulsive disorder. In: Insel, T.R. (ed.), *New Findings in Obsessive-Compulsive Disorder*. Washington, D.C.: American Psychiatric Press, Inc., 1984, pp. 72-88.

Insel, T.R., and Murphy, D.L. The psychopharmacological treatment of obsessive-compulsive disorder: A review. *J. Clin. Psychol.*, 1(5):304-311, 1981.

Insel, T.R., Murphy, D.L., Cohen, R.M., et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline. *Arch. Gen. Psychiatry*, 40:605-612, 1983.

Lapierre, Y.D. New antidepressant drugs. *J. Clin. Psychiatry*, 44(8):41-44, 1983.

Marks, I. Are there anticompulsive or antiphobic drugs? Review of the evidence. *Br. J. Psychiatry*, 143:338-347, 1983.

Marks, I.M., Stern, R.S., Mawson, D., et al. Clomipramine and exposure for obsessive-compulsive rituals: I. *Br. J. Psychiatry*, 136:1-25, 1980.

Mavissakalian, M. Pharmacological treatment of anxiety disorders. *J. Clin. Psychiatry*, 43:487-491, 1982.

Mavissakalian, M. Antidepressants in the treatment of agoraphobia and obsessive-compulsive disorder. *Compr. Psychiatry*, 24(3):278-284, 1983.

Mavissakalian, M., and Michelson, L. Tricyclic antidepressants in obsessive-compulsive disorder: Antiobsessional or antidepressant agents? *J. Nerv. Ment. Dis.*, 171(5):301-306, 1983.

Mavissakalian, M., Turner, S.M., Michelson, L., and Jacob, R. Tricyclic antidepressants in obsessive-compulsive disorder: Antiobsessional or antidepressant agents?—II. *Am. J. Psychiatry*, 142(5):572-576, 1985.

Montgomery, S.A. Clomipramine in obsessional neurosis: A placebo controlled trial. *Pharm. Med.*, 1:189-192, 1980.

Richelson, E. Are receptor studies useful for clinical practice? *J. Clin. Psychiatry*, 44(9):4-9, 1983.

Risch, S.C., Huey, L.Y., and Janowsky, D.S. Plasma levels of tricyclic antidepressants and clinical efficacy: Review of the literature—Part II. *J. Clin. Psychiatry*, 40:58-69, 1979.

Stern, R.S., Marks, I.M., Mawson, D., and Luscombe, D.K. Clomipramine and exposure for compulsive rituals: II. Plasma levels, side effects and outcome. *Br. J. Psychiatry*, 136:161-166, 1980.

Stewart, J.W., Quitkin, F.M., Liebowitz, M.R., et al. Efficacy of desipramine in depressed outpatients: Response according to research diagnostic criteria diagnoses and severity of illness. *Arch. Gen. Psychiatry*, 40:202-207, 1983.

Thorén, P, Åsberg, M., Bertilsson, L., et al. Clomipramine treatment of obsessive-compulsive disorder. *Arch. Gen. Psychiatry*, 37:1289-1294, 1980.

Thorén, P., Åsberg, M., Cronholm, B., et al. Clomipramine treatment of obsessive-compulsive disorder. *Arch. Gen. Psychiatry*, 37:1281-1285, 1980.

Zung, W.W.K. A rating instrument for anxiety disorders. *Psychosomatics*, 12:371-379, 1971.

A Comparison of Alprazolam and Imipramine in the Treatment of Agoraphobia and Panic Disorder

Ross Rizley, Ph.D.,[1] Richard J. Kahn, M.D.,[1] Douglas M. McNair, Ph.D.,[1] and Laura M. Frankenthaler, B.A.[1]

McNair and Kahn (1981) reported the results of a double-blind clinical trial showing greater efficacy of imipramine (IMI) over relatively high dosages of chlordiazepoxide (CDZ) in the treatment of agoraphobia, panic disorder, and mixed panic-phobic syndrome. The antipanic effects of IMI were not attributable to its antidepressant effects. However, they were somewhat late in onset (6 to 8 weeks), and the level of unpleasant early side effects was fairly substantial. The effects of IMI on the agoraphobic syndrome component were complicated. There were drug interactions with initial levels of both depression and phobia which could not be unconfounded. Differences in outcome as a function of depression and phobia were substantial on IMI but relatively small on CDZ. IMI-treated subjects who were both more depressed and more phobic at baseline showed the greatest reduction of phobic symptoms.

Recently, a class of triazolo-benzodiazepines, represented by alprazolam (APZ), have shown promise in relieving both anxiety and depression. Strong evidence shows that APZ is well tolerated and effective in the treatment of anxiety (Cohn, 1981), and considerable evidence suggests its effectiveness for depression (Feighner et al., 1983). Thus, a trial of APZ for the panic-phobic syndrome seemed warranted.

Reported here are the results from a 12-week, double-blind, independent group comparison of APZ with IMI for the treatment of panic-phobic disorder. Among the questions asked were: are there differences in their relative efficacy, speed of onset, presence of side effects, and specificity of effects?

Method

Recruitment and Screening

Subjects were symptomatic volunteers recruited through newspaper advertisements, pre-screening procedures, and intensive screening interviews and workups. To be screened, respondents had to score at least two standard deviations above normative means on the Hopkins Symptom Checklist (HSCL) anxiety factor (Lipman et al., 1979), be 18 to 60 years of age, not be in psychiatric treatment, and have no contraindicated medical condition. At screening, they had medical and psychiatric examinations and self-rating assessments to ascertain that they met selection criteria including DSM-III criteria for agoraphobia, panic disorder, or study criteria for panic attacks with mixed phobias. The last group was diagnostically similar to DSM-III agoraphobics with panic in that their phobias included situations such as elevators, tunnels, bridges, or places from which escape would be difficult, but differed in that they did not clearly include the interpersonal components such as fear of crowds and leaving home alone. Accepted subjects had a 1-week placebo (PBO) washout period followed by 12 weeks of randomly assigned, double-blind, active drug plus supportive treatment with weekly visits the first month and biweekly visits for 2 months.

Measures

At baseline and repeatedly during the trial, subjects completed the Profile of Mood States (POMS) (McNair et al., 1971), an 80-item version of the HSCL providing eight syndrome cluster scores, a 7-point Global Improvement Scale, and daily, weekly, or biweekly ratings of panic and agoraphobia on scales described below. Psychiatrists repeatedly completed the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959), the Hamilton Depression Scale (HAM-D) (Hamilton, 1967), the Treatment Emergent Signs and Symp-

---

[1] Clinical Psychopharmacology Laboratory, Boston University, Boston, MA 02114.

toms Inventory (TESS) (Guy, 1976), a doctor version of the HSCL, and a 7-point Global Improvement Scale. Vital signs were recorded at each visit.

Attrition

Of 126 patients screened, 51 (40%) were accepted and began the PBO period, 7 dropped out while on PBO, and the remaining 44 were randomly assigned to an active agent by a computer program designed to balance the two groups as closely as possible for severity of phobic and panic symptoms, severity of depression, sex, and age (in that order of priority). Six of the 44 who began the active phase continued less than 1 week, and their response after baseline could not be assessed.

Completion rates for the entire 12 weeks of active treatment were 58% for IMI and 60% for APZ. However, 90% of the APZ patients completed at least 4 weeks of active treatment compared with only 71% of the IMI group. The IMI dropouts were due to side effects more often than those on APZ (4 vs. 0), with most such attrition occurring the first month.

Completer vs. Endpoint Samples

Thirty-five of the 44 patients beginning active treatment completed 4 or more weeks. This group was designated as the Endpoint Sample ($N=35$). The Completer Sample consisted of 26 patients treated the entire 12 weeks. Efficacy and related analyses were conducted separately on each sample. Both types of analyses yielded similar results except that there were fewer significant findings favoring APZ in the Endpoint analysis despite the larger *N*. The most likely reason for the less conclusive patterns seemed to be that APZ subjects who discontinued treatment between 4 and 8 weeks did not improve and differed from those who completed the trial, while this was far less true for IMI. Data from the Completer Sample were used for the principal comparisons reported below.

TABLE 1

Sample Characteristics
($N=26$)

Current Age	37.9
Age First Episode	19.5
Women	62%
Education	Some college
Duration Current Episode	2 to 3 years
Prior Psychotropic Treatment	73%
Diagnosis	
Agoraphobia Without Panic	8%
Agoraphobia With Panic	42%
Mixed Phobia With Panic	38%
Panic Disorder	12%

Sample

Table 1 displays the major clinical and demographic characteristics of the Completer Sample at baseline, just prior to beginning active medication. They are very similar to the groups studied by McNair and Kahn (1981) and by Zitrin et al. (1976). Diagnostically, over 90% reported panic attacks and over 85% reported substantial phobic and avoidance behavior. Table 2 displays mean scores at screen and after PBO on the HAM-A, HAM-D, and *t*-scores on the POMS tension-anxiety and depression-dejection factors. Psychometrically and clinically, depressive symptom levels were low. Drug groups were very similar at baseline.

Medication

During the PBO period, all subjects received 1 capsule twice a day (b.i.d.). During the 12-week active phase, they received matching capsules containing either 25 mg IMI or 0.5 mg APZ. Dosage actually taken is in Table 3. Based on counts of returned med-

TABLE 2

Sample Means Pre and Post Placebo Washout

	Pre	Post
Hamilton Anxiety	14.7	12.8
Hamilton Depression	10.5	9.0
POMS Normative T Scores		
Tension-Anxiety	59.0	54.0
Depression-Dejection	53.0	49.0

TABLE 3

Dosage
(mg daily)

Week	Alprazolam	Imipramine
2	1.5	70.0
4	2.3	112.5
6	2.5	127.5
8	2.7	132.5
10	2.6	130.0
12	2.8	132.5

ication, compliance with prescribed dosage was above 95%. Maximum protocol daily dosages were 4.5 mg APZ and 225 mg IMI. The mean daily IMI dosage of 132.5 mg during the final 2 weeks was almost identical to that in the IMI versus CDZ study reported by McNair and Kahn (1981). Five IMI cases required low dose (10 mg) capsules, but no low dose APZ was required.

Efficacy Results

One-way analysis of covariance (ANCOVA) was the principal statistical procedure, with the pre-active, post-PBO score as the covariate. Because the groups were well matched for initial severity, interpretation of the ANCOVA results was straightforward.

Panic Cluster

Self-ratings on a Daily Panic measure consisting of two HSCL items ("Suddenly scared for no reason" and "Spells of terror or panic") scored on a 0 to 3 point scale were completed each evening and phoned in the next day. The results showed a trend toward lower panic levels in the APZ group by the latter half of week 1 ($p<.10$). By week 4, the APZ group was significantly lower on Daily Panic ratings than the IMI group with a trend continuing through week 5. The superiority of APZ to IMI during the early weeks suggests faster onset of action. The IMI group changed relatively little until after 5 weeks, when they appeared to catch up with the APZ-treated patients.

Weekly and biweekly Panic Cluster self-ratings included the two items from the Daily Panic measure plus three items from the POMS ("Desperate," "Terrified," and "Panicky"), scored on a 0 to 4 point scale. The results indicated comparable improvement in the two drug groups although there was a trend at week 4 in favor of APZ. This is consistent with results from the Daily Panic measure suggesting faster relief with APZ.

A slightly modified version of Klein and Zitrin's Acute Panic Inventory focused primarily on distress during the past month from signs and symptoms of panic attacks. Obtained at baseline and at 12 weeks, the Panic Distress subscale results showed that APZ subjects improved significantly more than those on IMI ($p<.05$). Thus, convergent evidence from the daily, weekly, and pre-post panic measures indicated more rapid and greater efficacy for APZ in reducing the distress from panic symptoms.

Agoraphobia

Daily and weekly Agoraphobia Distress measures were collected in the same manner as for Panic. The 5-item cluster is shown in Table 4. Except for one item (fear of fainting in public), it is identical to the HSCL phobic-anxiety factor.

On both the Daily and the Weekly Agoraphobia Distress measures, there was a trend at week 4 favoring APZ ($p<.10$). However, doctor ratings of agoraphobic symptom severity on a global 7-point scale failed to discriminate between the active agents. Overall, there was little evidence of a differential drug effect.

Anxiety

There were no significant differences between groups on self-rated anxiety on a daily measure (composed of 5 of the 12 items from the HSCL anxiety factor), on the weekly

TABLE 4

Agoraphobia Cluster (HSCL-80)

Feeling afraid in open spaces or on streets
Feeling uneasy in crowds, shops, or movies
Fear of going on buses, subways, or trains
Being afraid to go out of house alone
Feeling nervous when left alone

POMS tension-anxiety factor, or on the weekly, full HSCL anxiety factor. However, psychiatrists' ratings of anxiety on both a 7-point global HSCL anxiety scale and on the HAM-A showed early differences favoring APZ. The more striking results were from the HAM-A (Figure 1). By the first week, and continuing through the first month, the APZ group was rated as significantly less anxious.

Global Improvement

Doctors and patients independently rated Global Improvement "since beginning medication" on 7-point rating scales. In both cases, the results favored APZ, although the pattern of significant treatment effects differed. Psychiatrists saw the clear APZ advantage as early as 2 weeks ($p<.05$), and it continued during the first month. Patient Global Improvement showed APZ to be more effective at 4 weeks and during the final month (Figure 2).

Depression

The subjects were not highly depressed. Baseline POMS depression means were at the 50th percentile relative to unselected college student norms and at the 24th percentile compared with psychiatric outpatient admission norms. HAM-D means also were low relative to the minimum scores of 18 to 21 often required for outpatient antidepressant drug trials, and no patient in the Completer sample had HAM-D scores greater than 15 after washout. However, results from several measures of depressive symptomatology were of interest. At 2 weeks, psychiatrists rated the APZ group as significantly less depressed on the HAM-D ($p<.01$), although there were no further significant differences. It is well known that the HAM-D includes components of both anxiety and depression, and the result may only reflect decreased anxiety. Given the growing body of evidence suggesting APZ is effective in decreasing depression, it is also possible that there was a small but genuine decrease in subclinical depression.

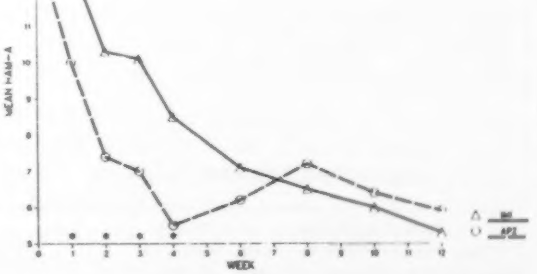


FIGURE 1. Hamilton anxiety ratings (*$p<.05$).

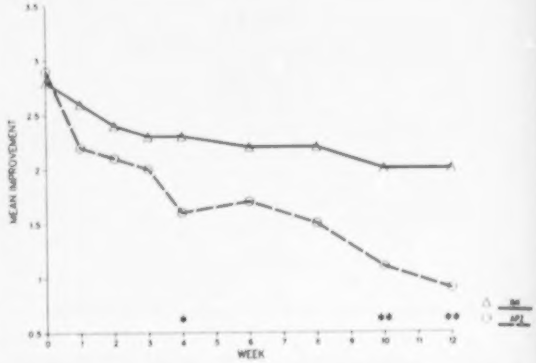


FIGURE 2. Patient global improvement ratings (*$p<.05$; **$p<.01$).

Self-ratings on two depression measures consistently favored APZ at every visit. Results from the POMS depression-dejection factor showed the APZ group to be significantly less depressed at week 2 ($p<.05$), but not thereafter. Stronger evidence was found in increased POMS elation scores, where significant findings favored APZ at 2, 6, and 12 weeks ($p<.05$).

Other Effects

The POMS vigor factor, a measure of general alertness and arousal, showed the APZ group to be more alert, efficient, and vigorous after 2 weeks ($p<.01$). Subsequent differences on vigor continued to favor APZ, but not significantly (although there were trends at 10 and 12 weeks).

Psychiatrists rated patients' anger-hostility using the global HSCL scale. The IMI group was less angry by week 8 ($p<.10$) and significantly less so by week 12 ($p<.05$). It is important to note that the APZ Completers did not show increased anger over the 12-week trial, but simply a smaller decrease than IMI-treated subjects.

Endpoint and Completer samples were analyzed for subjects' self-ratings of HSCL anger-hostility. There were no significant differences between the two Completer groups, but there were interesting relative differences between the Completer and Endpoint groups for each drug. Results from the Completer and Endpoint samples were virtually identical for IMI, but not for APZ. APZ patients who terminated the study between 4 and 8 weeks had increases on this measure relative both to their baseline and to the Completers. It is possible that APZ exacerbated anger-hostility in a subgroup of patients, but it is unclear whether this reaction was a reason for their premature termination.

Side Effects

A majority of patients in both groups reported drowsiness, but significantly more IMI cases reported dizziness, constipation, sweating, and dry mouth ($p<.05$). IMI significantly elevated supine diastolic blood pressure relative to APZ by the first week, and the elevation continued throughout (Figure 3). McNair and Kahn (1981) also reported that IMI elevated diastolic blood pressure relative to CDZ.

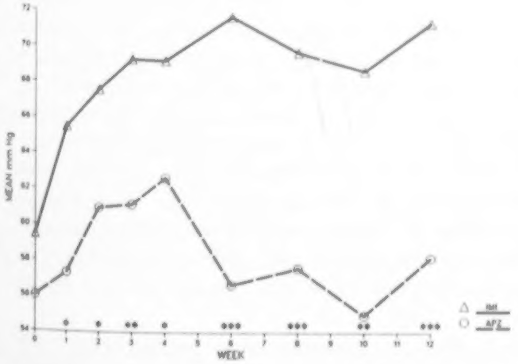


FIGURE 3. Supine diastolic blood pressure (*$p<.05$; **$p<.01$; ***$p<.001$).

Relation Between Anti-Panic and Anti-Agoraphobic Action

While there was evidence that the APZ group improved on both panic and agoraphobia, there was no indication that improvement occurred earlier in one component than the other. Actually, in neither group was there evidence of differential speed of onset of action for panic versus agoraphobia. This is also consistent with the results of the earlier IMI-CDZ trial (McNair & Kahn, 1981).

Summary

These results appear to replicate the earlier study by McNair and Kahn (1981) demonstrating the efficacy of IMI in the treatment of panic-phobic disorder. In addition, they support the efficacy of the newer benzodiazepine, APZ, in the treatment of this syndrome. Moreover, APZ showed significantly earlier onset of action and fewer side effects than IMI. In addition to the anti-panic effects, there may be a significantly greater and faster boost in feelings of well-being (elation and vigor) even when pre-treatment levels of depression are low. Finally, there may be some advantage of IMI over APZ in reducing anger. The findings also suggest a small proportion of patients fail to respond well to APZ after 4 to 8 weeks of treatment, but the number of such patients in this trial was too small to clearly characterize.

References

Aden, G.C., and Thein, S.G. Alprazolam compared to diazepam and placebo in the treatment of anxiety. *Br. J. Psychiatry*, 41:245-248, 1980.

Cohn, J.B. Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J. Clin. Psychiatry*, 42:347-351, 1981.

Feighner, J.P., Aden, G.C., Fabre, L.F., et al. Comparison of alprazolam, imipramine, and placebo in the treatment of depression. *JAMA*, 249(22):3057-3064, 1983.

Guy, W. *ECDEU Assessment Manual for Psychopharmacology*. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (ADM) 76-338, Washington, D.C.,: U.S. Government Printing Office, 1976

Hamilton, M. The assessment of anxiety states by rating. *Br. J. Med. Psychol.*, 32:50-55, 1959.

Hamilton, M. Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychol.*, 6:278-296, 1967.

Lipman, R.S., Covi, L., and Shapiro, A.K. The Hopkins Symptom Checklist (HSCL). *J. Affective Disord.*, 1:9-24, 1979.

McNair, D.M., and Kahn, R.J. Imipramine compared with a benzodiazepine for agoraphobia. In: Klein, D.F., and Rabkin, J. (eds.), *Anxiety: New Research and Changing Concepts*. New York: Raven Press, 1981, pp. 69-78.

McNair, D.M., Lorr, M., and Droppleman, L.F. *Manual for the Profile of Mood States*. Educational and Industrial Testing Service, San Diego, Calif., 1971.

Zitrin, C.M., Klein, D.F., Lindemann, C., et al. Comparison of short-term treatment regimens in phobic patients. In: Spitzer, R.L., and Klein, D.F. (eds.), *Evaluation of Psychological Therapies*. Baltimore: Johns Hopkins University Press, 1976, pp. 233-250.

Taper Withdrawal Studies With Alprazolam in Patients With Panic Disorder and Agoraphobia

John C. Pecknold, M.D.,[1] and Richard P. Swinson, M.D.[2]

Introduction

Since the introduction of chlordiazepoxide in the 1960's, the benzodiazepines have become the major therapeutic modality in the treatment of anxiety and insomnia. New work indicates that the triazolobenzodiazepine alprazolam is also effective in the treatment of panic disorder (Klerman et al., 1986). Most authors focus primarily on efficacy and patient acceptance. However, the problems of tapering and discontinuing medication have become increasingly important. Physical dependence on high doses of chlordiazepoxide has been described by Hollister et al. (1961) and later by Covi et al. (1973). Since then, withdrawal reactions have been described with virtually all current benzodiazepines (Swinson et al., in press).

Evaluation of phenomena associated with the stopping of anxiolytic medication requires careful differentiation among physical dependency, rebound phenomena, and the return of the pre-existing condition. The cessation of pharmacological treatment in chronically anxious or insomniac patients and in those for whom the existing crisis has not been resolved may result in the return of the pre-existing syndrome. A rebound phenomenon implies the recurrence of pre-existing symptoms in an exaggerated way with greater intensity than before treatment. A withdrawal syndrome implies that tolerance has developed to the drug and that the presenting symptoms are pharmacologically derived in a direction opposite to the pharmacological action of the drug. Dependence on the compound thus derives from a physiological basis. This particular syndrome has also been referred to as the onset of new symptoms (Lapierre, 1981).

The present study is a careful assessment of patients who have been on an 8-week trial of either alprazolam or placebo for the treatment of panic disorder with agoraphobia and who were followed on a 4-week taper and a 2-week post-taper weekly assessment schedule.

Methods

As part of the cross-national collaborative panic disorder study, subjects with panic disorder and agoraphobia or limited phobic avoidance were enrolled in five centers in the United States, two in Canada, and one in Australia. Those meeting the DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) criteria modified for the study were randomly assigned to either alprazolam or placebo for an 8-week period of treatment. All patients then underwent a 4-week gradual tapering of medication and a final 2 weeks in which they were assessed. During the taper period, medication was withdrawn no faster than 1 mg in every 3 days and, for the most part, 4 weeks were taken to accomplish that. During the 2 weeks post-taper, patients were permitted to take placebos on an as-needed basis. The two Canadian sites at St. Mary's Hospital in Montreal and the Toronto General Hospital in Toronto studied the taper withdrawal phenomenon according to the following protocol. In addition to the time and dosage schedule mentioned above, patients were assessed on a weekly basis with the following instruments: the Panic Attack Scale, the Disability Scale (DISS), the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D), the Sheehan Patient-Rated Anxiety Scale (SPRAS), the Sheehan Clinical Rated Anxiety Scale (SCRAS), the Patient's Global Im-

---

[1] St. Mary's Hospital, McGill University, Montreal, Quebec, Canada.

[2] University of Toronto, Toronto General Hospital, Toronto, Ontario, Canada.

provement, the Physician's Global Improvement, the Symptoms and Side Effect Checklist, the Phobia Scale, the Benzodiazepine Withdrawal Checklist (BWCL), the Merz, and the SCL-90. These assessments were done weekly during the entire 14-week period with the exception of the BWCL and Merz which were done at baseline, at week 8, and then weekly during the taper and post-taper. In addition, patients completed a diary on a weekly basis which itemized the numbers of panic attacks, whether they were situational or spontaneous, their intensity and duration, as well as their outings and the intensity of discomfort on their outings.

Population

Of the 61 evaluable patients originally placed on alprazolam after a 1-week washout, 58 patients completed the 8-week trial but only 33 completed the withdrawal study. All patients were eventually tapered off alprazolam.

Of the 58 evaluable patients who initially enrolled on placebo, 49 patients completed the drug trial but only 21 patients completed the withdrawal study. Table 1 shows the demographic variables of patients who completed not only the 8-week active treatment but also the 6 weeks of taper withdrawal. Statistical analysis was completed using analysis of variance and a regression analysis for the Panic Attack Scale.

Results

Panic Attacks: Combined situational and spontaneous panic attack data are presented as derived from the daily patient diaries and the Weekly Panic Attack Scale. The group as a whole is presented in Figure 1. In the group as a whole the problem is that we are offering data during the withdrawal period only from those patients on placebo who were able to continue on medication, and they represent only a fraction of the starting group.

TABLE 1

Demographic Data by Drug Group (Post-Taper Week 2 Completers)

	Alprazolam	Placebo
Number of patients	32	21
Mean age (S.D.)	31.8 (10.7)	32.3 (8.5)
Female	59.4%	57.1%
Male	40.6%	42.9%

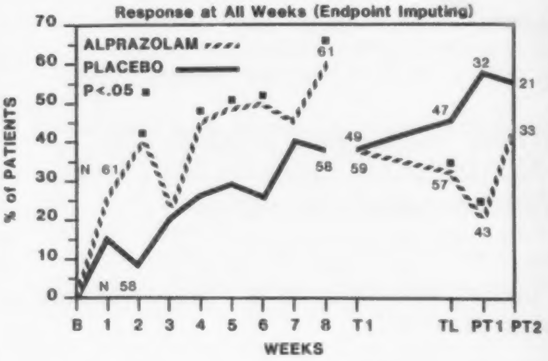


FIGURE 1. Percentage of patients with "o" panic attacks.

Rebound Panic: The criteria for rebound were set at the following: a 50% increase over baseline values and a change of at least three panic attacks. In 28% of alprazolam patients rebound is shown to occur; one patient on placebo (a nonresponder) also had a rebound.

The Figures show the response for the group as a whole with all available data (Figure 2).

Rebound Anxiety: The criteria for rebound anxiety on the HAM-A were an increase of 50% over the baseline levels and a change in score of 3. Twenty-two percent of patients on

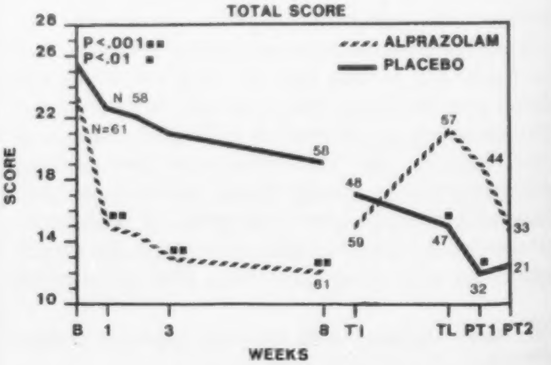


FIGURE 2. Hamilton anxiety scale.

alprazolam had rebound; 2 patients on placebo also had rebound.

Severity of phobias overall shows a similar pattern to the HAM-A with significant decrease in the alprazolam group only after 1 week of medication and thereafter, and a return of phobia during the taper with a drop to previous gains by the end of post-taper week 2. Work and Social Disability scales showed a similar pattern to the severity of phobias.

Benzodiazepine Withdrawal Checklist (BWCL): Our criteria for the emergence of new symptoms included the definition that the patients had never before had the symptoms, that they were seen to occur on the BWCL, and they had to occur during the final taper and withdrawal period. They divided into the percentage who had no new symptoms, the percentage who had mild new symptoms, and the percentage who had severe new symptoms. On the BWCL there was a significant drop in symptoms for the alprazolam versus placebo group during the 8 weeks of study representing primarily the various symptoms of anxiety. During the withdrawal period, the last week of taper and the first post-taper week, the trial score rose to above baseline level (significantly higher than placebo patient group) but returned to nonsignificant levels by the end of post-taper week 2. Table 2 shows the syndromes in four alprazolam patients.

TABLE 2

Benzodiazepine Withdrawal Checklist (New Symptoms — Last Taper/First Post-Taper Weeks: Patients With Three or More New Symptoms)

Patients	Last Taper Week	First Post-Taper Week
#203 Alprazolam	Blurred vision Clouded sensorium* Dysosmia*	Muscle cramps* Blurred vision
#38 Alprazolam	Tremor Paresthesias Dysosmia* Muscle cramps*	Tremor
#49 Alprazolam	Blurred vision Headaches Paresthesias Muscle cramps*	(nothing)
#36 Alprazolam	(nothing)	Blurred vision Heightened sensory perceptions Paraesthesias Muscle cramps*

*Patient not asked about symptom during weeks 1-7 of acute study.

Conclusion

We report that despite a 4-week taper period, many patients have a symptomatic withdrawal. Very few of the patients on alprazolam were able to continue through this period without a return of symptoms. This occurred despite the excellent therapeutic success during the 8-week active treatment. Furthermore, we document the presence in a proportion of patients of panic rebound. The measurement, namely the Panic Attack Scale, is backed up by a daily diary questionnaire which gives a behavioral measurement of the occurrence of the panic attacks. The findings on the panic are different from those observed with the HAM-A. Twenty-five of our 60 patients had rebound; of panic (50%), of anxiety (32%), and both panic and anxiety (20%). Most of the patients with panic disorder did not have panic rebound but rather had a gradual return of the original syndrome. There is, however, a peaking during the latter end of the taper and the beginning of the drug-free period that shows rebound. This is proportional in fact to the onset and dosage schedule during the efficacy period.

The behavior of the placebo responders also shows a return of symptoms after discontinuation of the medication which documents a kind of psychological worsening. However, none of these patients had the type of rebound found in the active alprazolam group.

A small minority of patients have the development of new symptoms despite the tapering. This is related to the high dosage levels of medication and may be found with most benzodiazepine withdrawal studies.

Two important clinical questions are addressed by this withdrawal data: the first is the adequacy of the length of trial. Our patients were treated for an 8-week period with a 4-week taper and then discontinued. There was a considerable relapse. This finding was also seen in the study of Solyom et al. (1981) in which phenelzine was the drug used in comparison with placebo. Perhaps panic disorders are similar in some respect to depressive disorders in terms of length of treatment required. Certainly, more detailed comparison of short-term treatment period, namely 8 weeks, and a longer-term treatment period, namely 6 months, is required. It is very likely that patients with panic disorder and agoraphobia require a minimum of 6 months' medication, and a premature discontinuation of medications may trigger a relapse.

The second question has to do with the taper. Our patients had a 4-week period in which their medication was tapered mostly at 1 mg reduction every 3 days. Furthermore, at the end of the period the medication went from 1 mg to 0. The taper schedule should perhaps be much more prolonged with decrements in the dosage but a continual division over time, inasmuch as the pharmacokinetics of alprazolam tend to require divided dosages. This taper perhaps should be accomplished over a more prolonged period, possibly a 2-month period rather than a 4-week period. Nonetheless, a proper study of taper after a prolonged 6-month trial of the drug would be informative.

Finally as to the issue of tolerance and dependency, it appears that our patients do not have a tendency to increase the dosage and this is confirmed by other withdrawal schedules (Dupont & Pecknold, 1985). My impression is that the dependency resides more in the development of new symptoms and rebound and that the gravity of those symptoms is more likely to cause a prolonged period of drug taking. Once again, it is likely that a proper therapeutic interval, namely 6 months, would result in an easier period of taper and withdrawal. Certainly further studies comparing a short-term administration period with a longer-term administration period are required. Furthermore, a more prolonged taper appears to be highly desirable.

References

Covi, L., Lipman, R.S., Pattison, J.H., et al. Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. *Acta Psychiatr. Scand.*, 49:51-64, 1973.

Dupont, R.L., and Pecknold, J.C. Symptoms after stopping alprazolam: Withdrawal or relapse? Presented at the Annual Meeting of the American Psychiatric Association, Dallas, Texas, May 18-24, 1985.

Hollister, L.E., Motzenbecker, F.P., and Degan, R.O. Withdrawal reactions from chlordiazepoxide (Librium). *Psychopharmacologia*, 2:63-68, 1961.

Klerman, G.L., Coleman, J.H., and Purpura, R.P. The design and conduct of the Upjohn cross-national collaborative panic study. *Psychopharmacol. Bull.*, 22(1):59–64, 1986.

Lapierre, Y.D. Benzodiazepine withdrawal. *Can. J. Psychiatry*, 26(2):93-95, 1981.

Solyom, C.L., Lapierre, Y., Pecknold, J.C., and Morton, L. Phenelzine and exposure in the treatment of phobias. *Biol. Psychiatry*, 16:239-247, 1981.

Swinson, R.P., Pecknold, J.C., and Kirby, M.E. Benzodiazepine dependence. (In press)

Amitriptyline and Haloperidol in Unstable and Schizotypal Borderline Disorders[1]

Paul H. Soloff, M.D.,[2] Anselm George, M.D.,[2] Swami Nathan, M.D.,[2] Patricia M. Schulz, M.S.W.,[2] Richard F. Ulrich, M.S.,[2] and James M. Perel, Ph.D.[2]

Empirical study of the borderline syndrome delineates two statistically independent but overlapping dimensions to this disorder, defining a spectrum of symptoms with affective instability at one extreme and mild thought disorder at the other. Separated in DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) into an unstable borderline personality disorder (BPD) and a schizotypal personality disorder (SPD), the two dimensions co-exist in over half of clinically defined borderline patients (Spitzer & Endicott, 1979; Spitzer et al., 1979). The heterogeneity of symptoms presented by borderline patients confounds efforts to define a single treatment of choice. The affective, schizotypal, and impulsive-behavioral symptoms characteristic of these patients are treated with a wide variety of antidepressants, major and minor tranquilizers, and even anticonvulsants, without systematic proof of efficacy or empirically defined guidelines. Treatment is further complicated by a lack of agreement on the target symptoms for chemotherapy, on the delineation of state from trait manifestations of the disorder, and on the responsiveness of each to chemotherapy. To address these issues, we are conducting a first double-blind, placebo-controlled study of antidepressant and neuroleptic medication in acutely symptomatic, criteria-defined borderline patients. Our objectives are twofold: 1) to determine the differential efficacy of an antidepressant (amitriptyline: AMI) and a neuroleptic (haloperidol: HAL) medication against the affective, schizotypal, and impulsive-behavioral presentations of acutely symptomatic borderline patients; and 2) to test the hypothesis that medication response can define clinically meaningful borderline subtypes. Following current clinical prejudice, we predicted preferential responsiveness of schizotypal borderlines (SPD) to haloperidol and unstable borderlines (BPD) to amitriptyline.

Method

Patients for this study were referred from both inpatient and outpatient divisions of the Western Psychiatric Institute and Clinic of the University of Pittsburgh. Following informed consent, and a thorough medical and psychiatric evaluation, Gunderson's Diagnostic Interview for Borderlines was used to define a study sample with a cut-off score of 7 or greater required for inclusion (Kolb & Gunderson, 1980). A DSM-III subtype diagnosis of BPD, SPD, or Mixed BPD/SPD was made on the basis of direct patient interviews. Exclusion criteria for chronicity, medical disorders, and organicity were adopted from Gunderson et al. (1975). Co-morbidity on Axis I was defined by the Schedule for Affective Disorders and Schizophrenia (SADS) interviews with exclusion for schizophrenic disorders, major depression with psychosis, and bipolar related disorders in either current (SADS) or lifetime (SADS-L) experience. Major depression without psychosis is reported in 14% to 50% of borderline patients and was not an exclusionary criterion but was coded for separate statistical analysis (Kroll et al., 1981; Pope et al., 1983). Following a medication-free period of at least 7 days, patients were required to demonstrate continuing symptom severity defined by the Global Assessment Scale (GAS≤50) and *either* the Hamilton Rating Scale for Depression-24 item (HAM-D≥17) *or* the Inpatient Multidimensional Psychiatric Rating Scale (IMPS≥66).

---

[1] This work was supported by NIMH Grant #35392 and MHCRC #30915.

[2] Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

Patients were randomly assigned to haloperidol (HAL) (2 mg), amitriptyline (AMI) (25 mg), or placebo (PLC) (tablets) with titration in 1 week up to a daily maximum of HAL 12 mg, AMI 150 mg, and PLC 6 tablets. (Early experience prompted a reduction in the daily maximum haloperidol dose to 6 mg.) Medication trials lasted 5 weeks with weekly self- and observer-rated measures of mood [HAM-D-24, Beck Depression Inventory (BDI)], schizotypal symptoms [Inpatient Multidimensional Psychiatric Rating Scale (IMPS), Schizotypal Symptom Inventory (SSI)], and global functioning [Global Anxiety Scale (GAS), Symptom Checklist-90 (SCL-90), and Ward Scale of Impulse Action]. Two of these scales, the SSI and the Ward Scale, were adapted from other sources for this study. The SSI is a symptom checklist with an associated severity scale which incorporates all eight of Spitzer's DSM-III Schizotypal criteria (Spitzer et al., 1979), seven of Khouri's discriminating symptoms for Schizotypal disorder (Khouri et al., 1980), and three of Meehl's diagnostic criteria for schizotypy (e.g., ambivalence, anhedonia, pan-anxiety) (Meehl, 1964). The Ward Scale of Impulse Action is derived from the Impulse Action section of Gunderson's Diagnostic Interview for Borderlines (DIB) and lists 12 behavioral items (with an associated severity scale) which are characteristic of borderline patients in long hospital stays (e.g., self-mutilation, manipulation of staff, suicidal threat, etc.). The Ward Scale is scored weekly by the patient's primary nurse while all other observer measures are scored by two raters (P.H.S., P.M.S., or A.G.) during a weekly research interview. Weekly plasma levels were drawn and analyzed for HAL and for the AT+NT metabolites of AMI to allow for control for systemic exposure.

Statistical Analysis

Specific tests for medication effects and differences between groups were performed by Analysis of Covariance (ANCOVA) using Week 1 (baseline) as the covariate and the average of Weeks 5 and 6 as outcome. Our study hypothesis predicted that patients with a preponderance of affective symptoms would respond preferentially to AMI while those with more schizotypal symptoms would do better on HAL—and both would improve more on medication than on PLC. Because of the heterogeneity of affective and schizotypal symptoms presented by these patients, we felt it desirable to have a composite measure of change which reflects overall symptom severity and direction of change (i.e., between affective and schizotypal poles). To address our study hypothesis and complement the conventional ANCOVA for specific medication effects, a composite measure of overall change was constructed from a factor analysis of rating scales reflecting affective or schizotypal pathology. These included the HAM-D-17; Beck Depression Inventory; SCL-90: Hostility and Psychoticism Subscales; IMPS: Intropunitiveness, Hostility, Paranoia, and Perceptual Distortion Subscales; SSI; and GAS.

Taking the unrotated factors of these selected scores defined the first two components of variation, namely, an overall measure of severity and a subsequent bipolar factor which presumably contrasts affective and schizotypal symptoms. The existence of a severity factor and a bipolar factor is the standard result of factoring among a set of measures that are all positively correlated. The first factor provides a robust measure of severity to be used to test the multivariate hypothesis of symptom differences favoring a group. The second factor provides a bipolar measure of affective vs. schizotypal symptom pattern. Constructed as a contrast of two equally weighted extremes, the second factor will be less robust than the severity factor, owing to measurement issues. With care, it can be used to test for the hypothesized interaction of medication and symptom polarity (e.g., affective vs. schizotypal). Finally, using both the severity factor score and baseline scores as covariates, a separate ANCOVA can be performed on each of the outcome scales to "partial out" the effects of severity to see if treatment has any unique effect independent of severity.

TABLE 1

Overview of Pharmacotherapy Outcomes

Outcome Measures	Med Effects 3-Way	Hal vs PLC	AMI vs PLC	AMI vs HAL
	Analysis of Covariance[a]			
	(F)	(F)	(F)	(F)
Global Assessment Scale	1.14	2.04	0.65	0.44
Hamilton Rating Scale-17	0.81	0.54	1.76	0.18
Beck Depression Inventory	3.09†	4.69* (H>P)	3.24† (A>P)	0.49
Schizotypal Symptom Inventory	1.76	3.10† (H>P)	0.26	1.57
Ward Scale of Impulse Action Patterns	1.64	3.47† (H>P)	0.00	2.90
SCL-90 Factors				
Somatization	3.63*	5.22* (H>P)	2.83	0.76
Obsessive-Compulsive	3.00†	5.34* (H>P)	0.33	2.78
Interpersonal Sensitivity	6.40**	12.15*** (H>P)	2.22	2.90† (H>A)
Depression	1.85	3.11† (H>P)	0.50	1.56
Anxiety	4.26*	6.34* (H>P)	0.34	5.55* (H>A)
Hostility	7.75***	12.73*** (H>P)	1.83	5.65* (H>A)
Phobic Anxiety	2.79†	4.93* (H>P)	1.25	2.10
Paranoid Ideation	5.03**	8.61** (H>P)	0.59	5.78* (H>A)
Psychoticism	3.80*	5.86* (H>P)	3.00† (A>P)	0.87
Additional Items	3.03†	2.52	5.98* (A>P)	0.53
General Severity Index	5.39**	8.03** (H>P)	1.39	3.74† (H>A)
IMPS Factors				
Excitement	1.94	2.64	3.63† (A>P)	0.08
Hostile Belligerence	2.33	3.73† (H>P)	2.08	0.67
Paranoid Projection	1.68	2.79	0.28	1.66
Grandiose Expansiveness	0.04	0.19	0.13	0.00
Perceptual Distortions	1.07	1.62	0.67	0.47
Anxious Intropunitiveness	0.93	0.65	0.20	2.44
Retardation-Apathy	0.72	0.86	0.12	0.65
Disorientation	1.84	1.81	0.95	1.97
Motor Disturbances	0.99	1.26	0.07	1.23
Conceptual Disorganization	1.05	3.07† (H>P)	0.31	1.60
Total	0.87	1.54	0.80	0.12

*$p < .05$
**$p < .01$
***$p < .001$
†$p < .1$
(two-tailed tests) N: HAL = 21, AMI = 20, PLC = 20
[a] Baseline scores are covariates. Greater improvement noted as X>Y.

Factor analyses were performed each week separately for Weeks 1, 5, and 6. The results were quite similar at each. Factors were operationalized by giving equal weights to variables loading on a factor, and were standardized across all periods to have an overall mean of 50 and a standard deviation (s.d.) of 10, scoring across all data. Change on this standardized measure is in s.d. units (×10). Higher scores indicate greater severity on the first factor and an excess of affective traits on the second.

Results

Sixty-four patients have entered protocol to date, 49 women and 15 men, with an age range of 16 to 53 (median age 25 years). Among this sample were 51 inpatients recruited from consecutive acute admissions and 13 outpatients who met all inclusion, exclusion, and continuation criteria but refused or did not require hospitalization. By DSM-III criteria, 43.8% are diagnosed as "pure" borderline disorder, 50% as mixed borderline and schizotypal disorder, and 6.2% as "pure" schizotypal disorder. (The "pure" SPD patients are included in the mixed BPD/SPD sample for analysis. It should be noted that these are DIB-defined borderline patients with prominent schizotypal symptoms in the context of otherwise typical borderline affect, impulse, and interpersonal relatedness. These patients are *not* the isolated affectless schizotypes related to the schizophrenia spectrum) (Soloff & Millward, 1983).

Random assignment resulted in 23 HAL trials, 20 AMI trials, and 21 PLC trials. Average daily medication dosage by Day 42 was 7.24±3.19 mg for HAL and 147.62±13.47 mg for AMI. Analysis of plasma levels indicated a mean (±s.d.) of 11.87 (±11.68 ng/ml) for HAL and 244.74 (±73.07 ng/ml) for AT+NT by Day 35 (i.e., after 4 weeks of treatment). Assuming a minimum therapeutic range of 160 ng/ml–200 ng/ml for AT+NT, all but one inpatient achieved minimum therapeutic range by Day 35.

Three patients terminated the study before completing 2 full weeks of medication (Day 21) which was defined as the minimum duration required for inclusion of data. Two patients terminated for adverse medication effects: extrapyramidal side effects in one inpatient, unwitnessed hives in an outpatient, both on HAL. One inpatient on PLC terminated the study before Day 21 for reasons of personal convenience and left the hospital despite remaining symptomatic. These three trials are not included in end-point analyses, reducing the sample to 61. An overview of preliminary pharmacotherapy outcomes is given in Table 1.

Significant medication effects (i.e., $p<.05$) with baseline scores as covariates were found exclusively on self-rated measures: SCL-90 Somatization, Interpersonal Sensitivity, Anxiety, Hostility, Paranoid Ideation, Psychoticism factors, and the SCL-90 General Severity Index. Near significance ($p<.1$) was achieved on SCL-90 Obsessive Compulsive, Phobic Anxiety and Additional factors, and the BDI. It is noteworthy that the *observer-rated* measures of depression, psychoticism, and global functioning—i.e., the HAM-D, IMPS, SSI, and GAS—did not demonstrate significant medication effects.

Between-group comparisons produced clear differences. HAL was significantly superior to PLC (i.e., $p<.05$) on a broad spectrum of symptom patterns including SCL-90 Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism factors; the SCL-90 General Severity Index; and the BDI. (Trends were apparent on SCL-90 Depression; IMPS: Hostile Belligerence and Conceptual Disorganization; the SSI; and the Ward Scale of Impulse Action.) In contrast, AMI proved significantly superior to PLC only on one scale, the ill-named SCL-90 Additional factor, a scale defined largely by depression items (e.g., poor appetite, trouble falling asleep, early morning awakening, guilt, and thoughts of death and dying). Changes favoring AMI but short of significance were found on the BDI, SCL-90 Psychoticism, and IMPS Excitement factors. The SCL-90 Psychoticism factor contains several items common to depression (e.g., the idea that you should be punished for your sins, or feeling lonely with other people) while IMPS Excitement highlights arousal behavior (e.g., loud, overactive, hurried speech), perhaps responsive to the sedative effects of AMI.

Randomization resulted in no significant differences in severity or polarity factor scores across the three medication groups at baseline (Table 2). Following treatment, patients in the HAL group improved significantly more on the composite severity measure than those receiving AMI or PLC, with no difference between AMI and PLC. Posttreatment polarity factor scores reflect a trend toward differences among groups attributable to an increase in affective polarity in the PLC group and a decrease in affective polarity among patients treated with AMI. These effects are independent of severity.

In the comparison of severity and polarity factor scores by borderline subtype, increased severity is attributed to the mixed BPD/SPD group while increased affective polarity is associated with the pure BPD patients (Table 3). There was no significant interaction of medication group with polarity of symptom pattern (affective vs. schizotypal) on overall severity, leaving unsupported the hypothesis of significant differential efficacy

TABLE 2

Medication Effects on Severity and Polarity Scores[a]

Outcome Factor	AMI *N* = 18	HAL *N* = 20	PLC *N* = 17	ANCOVA *F*	 *p*
Severity, Pretreatment	54.78	58.65	56.29	1.322	n.s.
Severity, Posttreatment[b]	49.57***	44.45***	51.87†	3.993	.024
Polarity, Pretreatment	50.67	53.10	48.47	1.041	n.s.
Polarity, Posttreatment[c]	48.28	49.84	54.24†	2.768	.073

***$p < .001$ †$p < .1$ Pre- vs. Posttreatment, within group. Two-Tailed *t* test.

[a] *N* decreased by six cases with inadequate data to compute factor scores (2 AMI, 1 HAL, 3 PLC).

[b] Pretreatment Severity as Covariate

Posttreatment Severity: HAL vs. PLC (*F* 5.782, *p* .022); AMI vs. PLC (*F* 0.713, n.s.)
AMI vs. HAL (*F* 3.974, *p* .054).

[c] Pretreatment Polarity, Posttreatment Severity as Covariates

Posttreatment Polarity: HAL vs. PLC (*F* 2.547, n.s.); AMI vs. PLC (*F* 6.687, *p* .015)
AMI vs. HAL (*F* 0.481, n.s.)

of medication by affective or schizotypal dimensions. Analysis of medication effect by borderline subtype produced similar results. There was no significant interaction of medication group with subtype diagnosis (BPD vs. BPD/SPD) on overall severity. Using this statistical strategy, we were unable to demonstrate a pharmacologic behavioral dissection of medication responsive borderline subtypes. To identify unique effects of medication independent of severity, the severity scores were factored out in an ANCOVA. With composite severity "partialled out," significant medication effects remained in measures of hostility (IMPS, SCL-90) and paranoid ideation (SCL-90) suggesting a specific effect for HAL, and on the Additional Factor of the SCL-90, reflecting an antidepressant effect for AMI. The pattern of change over time was striking—with most improvement occurring by Day 21 (e.g., 7 days med-free followed by 2 weeks of medication). This is well illustrated in the Figure indicating the course of response over the study on the self-rated General Severity Index of the SCL-90.

TABLE 3

Severity and Polarity Factors
by Borderline Subtype
AMI vs. HAL vs. PLC (*N* = 55)

	DSM-III BPD (*N*-24)	DSM-III BPD/SPD (*N*-31)	*F*/*p*
Severity, Pretreatment	53.57	59.02	7.381, <.01
Severity, Posttreatment[a]	48.93	48.02	0.137, n.s.
Polarity, Pretreatment	54.41	48.13	5.797, <.05
Polarity, Posttreatment[a]	51.55	50.02	0.467, n.s.

[a] ANCOVA: Pretreatment severity, pretreatment polarity as covariates; higher score implies greater severity/more affective polarity.

Summary

Although these are preliminary results of a study in progress, several important observations arise from our data. Significant medication effects are found consistently in self-rated measures—not interview based ratings. The sensitivity and relevance of our interview based measures to specific borderline symptoms warrant further study. There is a need for measures of change more relevant to this disorder. We are unable to determine

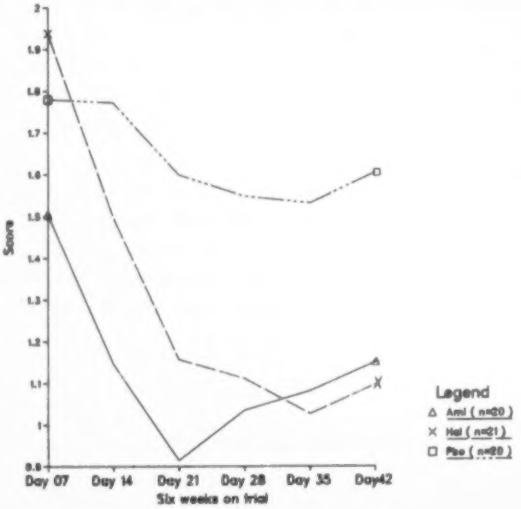


FIGURE. Comparison of SCL–GSI across three treatments.

if interviewer bias plays a role in minimizing reported effects, since expectation of clinical change is understandably modest given the degree of chronic impairment. Similarly, the interview setting may affect patients' willingness to report change.

The disappointing response to AMI in patients with strong depressive symptoms suggests that more attention be given to the atypical pattern of depressive presentations in borderline patients as a possible indication for future research with monoamine oxidase inhibitor antidepressants.

Despite these limitations, our preliminary results support the use of low-dose neuroleptics in borderline disorder and demonstrate significant efficacy against a broad range of symptoms including hostility, paranoia, anxiety, and depression. Despite the prevalence of affective symptoms in this population, AMI is no better than HAL against depression and little better than PLC against a wide range of associated borderline symptoms. Medication effects are modest in magnitude, generally attributable to decreased severity and occur early in the treatment course. Both unstable and schizotypal borderline patients demonstrate some improvement. We are unable to separate borderline subtypes by medication response or support the clinical prejudice predicting selective efficacy for HAL in schizotypal patients and AMI in unstable borderlines. Rather, we have shown that HAL is broadly effective while AMI adds little to the treatment of borderline disorder.

References

Gunderson, J.G., Carpenter, W.T., and Strauss, J.S. Borderline and schizophrenic patients: A comparative study. *Am. J. Psychiatry*, 132:1257–1264, 1975.

Khouri, P.J., Haier, R.J., Rieder, R.D., et al. A symptom schedule for the diagnosis of borderline schizophrenia: A first report. *Br. J. Psychiatry*, 137:140–147, 1980.

Kolb, J.E., and Gunderson, J.G. Diagnosing borderline patients with a semi-structured interview. *Arch. Gen. Psychiatry*, 37:37–41, 1980.

Kroll, J., Sines, L., Martin, K., et al. Borderline personality disorder: Concept validity of the concept. *Arch. Gen. Psychiatry*, 38:1021–1026, 1981.

Meehl, P.E. *Manual for Use with Checklist of Schizotypal Signs*. Psychiatric Research Unit, University of Minnesota, 1964.

Pope, H.G., Jr., Jonas, J.M., Hudson, J.I., et al. The validity of DSM-III borderline personality disorder: Phenomenologic, family history, treatment response, and long-term follow-up study. *Arch. Gen. Psychiatry*, 40:23–30, 1983.

Soloff, P.H., and Millward, J.W. Psychiatric disorders in the families of borderline patients. *Arch. Gen. Psychiatry*, 40:37–44, 1983.

Spitzer, R.L., and Endicott, J. Justification for separating schizotypal and borderline personality disorders. *Schizophr. Bull.*, 5:95–104, 1979.

Spitzer, R.L., Endicott, J., and Gibbon, M. Crossing the border into borderline personality and borderline schizophrenia: The development of criteria. *Arch. Gen. Psychiatry*, 36:17–24, 1979.

Open Trial of Buspirone in the Treatment of Major Depressive Disorder

Edward E. Schweizer, M.D.,[1] Jay Amsterdam, M.D.,[1] Karl Rickels, M.D.,[1] Myron Kaplan, D.O.,[1] and Marian Droba, M.D.[1]

The pharmacologic treatment of depression and anxiety rests on the clinical judgment, often difficult to make, as to which diagnosis is primary. Confidence in the essential therapeutic importance of this decision has been undermined recently by studies suggesting anxiolytic properties for antidepressants (Klein, 1964; Sheehan et al., 1980), and antidepressant properties for benzodiazepines (Rickels et al., 1985). Buspirone is a newer anxiolytic with a novel chemical structure and an atypical profile of pharmacologic activity (Riblet et al., 1982). It has demonstrated an anxiolytic efficacy comparable to the benzodiazepines (Goldberg & Finnerty, 1979; Rickels, 1981), despite having no apparent activity at the Bz-GABA receptor. The side-effect profile of buspirone, at doses in the anxiolytic range of 15 to 30 mg, compares favorably with benzodiazepines, with significantly less sedation (Newton et al., 1982).

Several studies (Feighner et al., 1982; Goldberg & Finnerty, 1979) using buspirone in anxious patients have noted concomitant improvement in associated depressive symptoms. This led us to undertake an open-label study of the efficacy of buspirone in major depression.

Methods

Thirty patients meeting DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) criteria for Major Depressive Disorder were entered in an open-label treatment protocol. Eligibility criteria required a score of at least 18 on the Hamilton Depression Scale (HAM-D), and at least 9 on the Raskin Depression Scale, with the Covi Anxiety Scale scoring less than the Raskin scale. Excluded from the study were patients with personality disorders, organic brain syndrome, schizophrenia, alcohol, drug abuse, or acute or unstable medical conditions. Also excluded were pregnant or lactating women, or women of child-bearing potential not taking birth control precautions. Concomitant medications were not permitted. A 1-week, single-blind placebo washout was employed prior to entry into a 4-week acute treatment phase. Initial dosing with buspirone was begun at 15 or 30 mg, given on a three-times-a-day (t.i.d.) schedule. Dosage adjustments were made every 3 to 4 days to a maximum dose of 90 mg, as tolerated by the patient and in light of clinical indications. At the end of 4 weeks' acute treatment, the patient had the option of entering a 3-month maintenance phase.

TABLE 1

Clinical Characteristics of Patients ($N = 30$)

Major Depression Subtype	No.	Sex	Age ($\bar{X}$ Yrs)	Duration of Illness ($\bar{X}$ Mos)	No. Previous Antidepressant Trials
Melancholic	10	F = 7 M = 3	48.0	17.0	3.0
Non-Melancholic	20	F = 9 M = 11	41.6	14.4	2.2

Participation in the study was voluntary and written informed consent was given. Table 1 shows the clinical characteristics of the patients. Notable are the duration of current illness, which averaged over 1 year for both melancholic and non-melancholic subtypes;

TABLE 2

Reasons for Attrition

Reasons	Melancholic	Non-Melancholic
Unimproved	6	3
Side Effects		
Therapy Refused	1	2

---

[1] University of Pennsylvania Hospitals, Philadelphia, PA 19104.

TABLE 3

Buspirone Side Effects
($N = 30$)

Side Effect	Mild (%)	Mod-Severe (%)
1. Lightheadedness/Dizziness	23	16
2. Restlessness/Agitation	6	26
3. "Spacey" Feeling	6	13
4. Nausea	6	10
5. Paresthesias	10	3
6. Insomnia	3	10
7. Drowsiness/Tiredness	10	3
8. Hot Flashes/Sweating	6	3

also the fact that most patients had had more than one previous trial of antidepressant treatment. Ten patients met melancholic criteria while 20 were non-melancholic. At intake, the mean HAM-D score for melancholics was 28.1±3.5, and for non-melancholics, it was 20.6±3.6. Weekly HAM-D, Hopkins Symptom Checklist, and a 6-point physician- and patient-rated global improvement scale were used to assess treatment outcomes.

Results

Of the 30 patients entering treatment, 18 completed the 4-week acute phase (3 melancholic and 15 non-melancholic). As indicated in Table 2, attrition was higher for the melancholic than for the non-melancholic group. Lack of therapeutic effect was most frequently cited as the reason for drop out.

Table 3 indicates percentages of patients reporting a given side effect. Overall, 11 patients complained of none or mild side effects and 19 complained of moderate to severe side effects. These figures must be understood in light of a dosing strategy that, in the absence of a known antidepressant dose range, called for incremental increases to 90 mg, or until significant side effects developed, whichever came first. As a result, the mean maximal dose for buspirone was 78 mg, which was well above the usual anxiolytic range. In retrospect, a dose of 40 to 60 mg appeared sufficient to produce the desired antidepressant effect and was well tolerated.

TABLE 4

Global Treatment Outcome
($N = 30$)

Major Depression	Marked–Moderate	Mild	None
Melancholia (Includes two Bipolar II)	0	1	9*
Non-Melancholic	11	4	5

Fishers Exact Test

Marked–moderate vs. mild, none = $p < .03$

Marked–moderate, mild vs. none = $p < .01$

*Includes two patients with only 1 week's data because of side effects.

Table 4 gives the results for physician rated global improvement at the end of acute treatment. Moderate to marked improvement was seen for 55% of non-melancholic depressives as opposed to none of the melancholics. This is a significant treatment effect for non-melancholics (moderate and marked improvement vs. mild, none) at $p < .05$. There was virtual identity between patients evincing moderate to marked improvement, and those deciding to continue the trial of buspirone into a maintenance phase.

Tables 5 and 6 show the HAM-D scores for melancholic vs. non-melancholic patients at each of the study weeks, presented in two different ways. Table 5 presents "endpoint" data in which final HAM-D scores of dropouts are carried forward to final Week 4. This corrects for the artifactual improvement in HAM-D scores that results from deleting dropouts, who frequently have higher scores

TABLE 5

Weekly Endpointer HAM-D Scores (Mean ±SD)
Repeated Measures Analysis

	Week				
	0	1	2	3	4
Melancholic ($N = 10$)	28.1 ± 3.54	27.1 ± 7.3	27.8 ± 7.36	28.6 ± 5.27	28.7 ± 6.18
Non-Melancholic ($N = 20$)	20.6 ± 3.65	17.7 ± 4.18	15.8 ± 6.28	14.0 ± 7.18	11.6 ± 7.59

Treatment Group × Time: F (Linear) = 13.38, df 1,28, $p < .001$

TABLE 6

Weekly Completer HAM-D Scores (Mean ± SD)
Repeated Measures Analysis

	Week 0	1	2	3	4
Melancholic ($N = 3$)	25.0 ± 3.46	23.0 ± 5.20	20.7 ± 5.51	24.7 ± 2.52	25.0 ± 7.55
Non-Melancholic ($N = 15$)	19.8 ± 3.43	17.1 ± 4.13	14.3 ± 5.31	11.5 ± 6.16	8.30 ± 5.12

Treatment Group × Time: F (Linear) = 8.53, df 1,16, $p < .01$.

and have failed to respond to treatment. To counterbalance this approach, Table 6 presents weekly HAM-D data on "completers" of the 4-week active treatment protocol. Repeated measures analysis of variance, conducted on endpoint and completer data, demonstrated a significant improvement in HAM-D scores over the 4 weeks of the study for the non-melancholic, but not the melancholic, subgroup.

To address the question of whether baseline levels of anxiety would predict treatment response, baseline Covi anxiety scores were examined in treatment responders vs. nonresponders. As can be seen (Table 7), baseline levels of anxiety were not significantly different for treatment responders vs. nonresponders.

Conclusion

A preliminary study of buspirone in the treatment of DSM-III Major Depression suggests a significant antidepressant effect for this novel compound for a non-melancholic subgroup. Further, antidepressant efficacy did not appear to be merely the result of an anxiolytic "halo" effect, since treatment response was not predicted by baseline levels of anxiety or its reduction. A daily dose in the range of 40 to 60 mg of buspirone appears sufficient to produce an antidepressant effect. The open-label nature of the study obviously makes any conclusions highly tentative. But given these preliminary results, and the favorable side-effect profile, a well-controlled, double-blind trial of buspirone in the treatment of non-melancholic depression would appear to be indicated.

TABLE 7

Baseline Anxiety

Depression Subtype	Treatment Response	Covi Score
Melancholic ($N = 10$)	Nonresponders	7.8
Non-Melancholic ($N = 11$)	Responders	5.9
Non-Melancholic ($N = 9$)	Nonresponders	6.0

References

Feighner, J.P., Merideth, C.H., and Hendrickson, G.A. A double-blind comparison of buspirone and diazepam in outpatients with generalized anxiety disorder. *J. Clin. Psychiatry*, 43(2):103–107, 1982.

Goldberg, H.L., and Finnerty, R.J. The comparative efficacy of buspirone and diazepam in the treatment of anxiety. *Am. J. Psychiatry*, 136:1184–1187, 1979.

Klein, D.J. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia (Berlin)*, 5:397–408, 1964.

Newton, R.E., Casten, G.P., Alms, D.R., et al. The side-effect profile of buspirone in comparison to active controls and placebo. *J. Clin. Psychiatry*, 43(2):100–102, 1982.

Riblet, L.A., Taylor, D.P., Eison, M.S., and Stanton, H.C. Pharmacology and neurochemistry of buspirone. *J. Clin. Psychiatry*, 43(2):11–16, 1982.

Rickels, K. Recent advances in anxiolytic therapy. *J. Clin. Psychiatry*, 42(2):40–44, 1981.

Rickels, K., Feighner, J.P., and Smith, W.T. Alprazolam, amitriptyline, doxepin, and placebo in the treatment of depression. *Arch. Gen. Psychiatry*, 42:134–141, 1985.

Sheehan, D.V., Ballenger, J., and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. *Arch. Gen. Psychiatry*, 37:51–59, 1980.

A Review of Controlled Studies of Adinazolam Mesylate in Patients With Major Depressive Disorder

John P. Feighner, M.D.[1]

Introduction

At the NCDEU Annual Meetings in 1982 and 1984, some results of the dose-finding studies with adinazolam mesylate (DERACYN® Tablets, The Upjohn Company) in depressed patients, and two subsequent placebo-controlled antidepressant trials using the new triazolobenzodiazepine, were presented. Since then, a total of five studies controlled with placebo have been completed, and four larger studies controlled with both placebo and an active standard have also been completed or nearly completed. The latter were 6-week trials comparing adinazolam with imipramine in depressed outpatients and with amitriptyline in depressed inpatients. The purpose of this paper is to review the clinical data obtained in these Phase II and III trials.

In animal studies using assays known to predict anxiolytic activity, e.g., pentylenetetrazol antagonism, adinazolam was effective at doses similar to those for diazepam (Hester et al., 1980). Yet, in assays known to predict antidepressant activity, e.g., yohimbine toxicity potentiation, adinazolam was effective at doses similar to those for imipramine (Hester et al., 1980). Works by others also indicate that adinazolam shows typical antidepressant-like activities in animals. For instance, in rats, adinazolam inhibited reserpine-mediated upregulation of cortical β-adrenergic receptors (Lahti et al., 1984) and sensitized forebrain hippocampal neurons to applied serotonin (Turmel & deMontigny, 1984). The apparent key to the novel dual activity was the addition of a tertiary amino group to the 1-position of the triazolobenzodiazepine ring system.

The first clinical trials with adinazolam were done in patients hospitalized for severe depression. These trials indicated antidepressant activity with little or no anticholinergic activity. Perhaps greater novelty, however, rested in the rapidity of the responses. About half those responding to adinazolam responded markedly within 2 to 7 days after starting the new drug (Pyke et al., 1983).

Methods

The five Phase II double-blind, placebo-controlled studies with adinazolam were conducted in patients with DSM-III Major Depression. The two inpatient studies required a total score of greater than 25 on the 21-item Hamilton Rating Scale for Depression (HAM-D); the three outpatient studies required HAM-D scores greater than 20. In all five studies, patients had to be more depressed than anxious on Raskin and Covi scores, respectively.

The Phase III double-blind, placebo- and tricyclic-controlled studies also treated DSM-III Major Depression. Three studies required outpatients with HAM-D total scores of greater than 19; one study required inpatients with Melancholia and HAM-D total scores greater than 25.

Patients under age 18 or over age 65 were excluded, as were women not using reliable contraceptive methods. Patients with uncontrolled physical illness or those taking concomitant psychotropics, patients with a history of substance abuse or benzodiazepine sensitivity, and patients who had been treated with electroconvulsive therapy or investigational drugs within a month of the study were excluded. Patients with DSM-III diagnoses of bipolar, dysthymic, or atypical depression were also excluded, but bipolar II subjects

---

[1] Feighner Research Institute, La Mesa, CA 92041.

(atypical bipolar major affective disorder) were allowed in one Phase II outpatient study (6310, Dunner).

Study Design

During screening, for which up to 7 days were allowed, a placebo was given three times a day while physical examinations and diagnostic workup were completed. Patients who fulfilled entrance criteria were then randomized to receive either adinazolam or placebo tablets for 6 weeks. In Phase III studies, an additional group of patients received either imipramine (outpatients) or amitriptyline (inpatients).

Follow-up evaluations were conducted on day 3 or 4 and at weeks 1, 2, 4, and 6 after medication was initiated. Efficacy judgments were made on the basis of the rating scales shown in Tables 1 and 2. These included the HAM-D total score, the Physician's Global Impressions, and, at final evaluation, a Patient's Drug Evaluation Form. Tolerance was rated through a modification of the Treatment-Emergent Symptoms and Side Effects (TESS) Form (Guy, 1980). For analyses, all medical events were added to the TESS results.

Results

Phase II Studies

A total of 172 patients were treated with adinazolam and 171 patients were treated with placebo; of these, 164 adinazolam-treated patients and 158 placebo-treated patients completed more than 5 days of study medication and were considered evaluable. An analysis of patient enrollment and results by study is given in Tables 1 and 2. Except for study 6306 (Cohn), which predominantly enrolled males, female enrollees outnumbered males in Phase II by 64% to 36%.

Adinazolam (30 to 90 mg daily) was significantly superior to placebo on most or all measures in four of the studies (6306, Smith; 6309, Cohn and Feighner; 6310, Dunner), which cumulatively treated 140 patients with adinazolam and 140 patients with placebo. Of these, more than twice as many adinazolam-treated patients (63%) completed the 6-week study as compared with placebo-treated patients (31%). The predominant reason for dropping out was inefficacy of the placebo. The combined incidence of moderate or marked therapeutic effect at final evaluation in these four studies was 61% with adinazolam and 29% with placebo. The final incidence of 50% or greater decrease in HAM-D

TABLE 1

Incidence of Success Measured by Primary Efficacy Variables
Inpatient Studies

	Protocol No. 6306			
	Cohn		Smith	
	Adinazolam	Placebo	Adinazolam	Placebo
Total Enrolled	32	31	40	40
Evaluable Patients*	28	24	40	40
Completers	14 (50%)	9 (38%)	25 (63%)**	15 (38%)
Physician's Global: Much or very much improved since admission	17 (61%)	9 (38%)	25 (63%)**	14 (35%)
Physician's Global: Moderate or marked therapeutic effect of drug	13 (48%)	9 (38%)	25 (63%)**	15 (38%)
Hamilton Depression Scale: Total score decrease ≥50% of initial	7 (26%)	8 (33%)	24 (60%)**	15 (38%)
Patient's Drug Evaluation Form: Felt drug helped moderately, much, or very much	15 (54%)**	6 (25%)	24 (60%)**	12 (30%)

*Patients were required to complete at least 5 days of study medication to be considered evaluable.

**Significant difference from placebo ($p<0.05$) using one-tailed Fisher's exact test.

TABLE 2

Incidence of Success Measured by Primary Efficacy Variables
Outpatient Studies

	Protocol No. 6309				Protocol No. 6310	
	Cohn		Feighner		Dunner	
	Adinazolam	Placebo	Adinazolam	Placebo	Adinazolam	Placebo
Total Enrolled	40	40	20	20	40	40
Evaluable Patients*	36	36	20	18	40	40
Completers	24 (67%)**	7 (19%)	12 (60%)**	5 (28%)	24 (60%)**	15 (38%)
Physician's Global: Much or very much improved since admission	28 (78%)**	7 (19%)	11 (55%)**	2 (11%)	22 (55%)	15 (38%)
Physician's Global: Moderate or marked therapeutic effect of drug	24 (67%)**	7 (19%)	12 (60%)**	4 (22%)	21 (53%)	15 (38%)
Hamilton Depression Scale: Total score decrease ≥50% of initial	22 (61%)**	6 (17%)	12 (60%)**	3 (17%)	24 (60%)**	15 (38%)
Patients Drug Evaluation Form: Felt drug helped moderately, much, or very much	26 (72%)**	6 (17%)	12 (60%)**	3 (17%)	21 (53%)**	12 (30%)

*Patient's were required to complete at least 5 days of study medication to be considered evaluable.
**Significant difference from placebo ($p < 0.05$) using one-tailed Fisher's exact test.

total score was 60% with adinazolam and 28% with placebo.

The Figure shows the Physician's Global Impression of the therapeutic effect of the drug relative to length of treatment combining the two outpatient studies done under the same protocol (6309, Cohn and Feighner). Only those with a moderate or marked therapeutic effect are counted. By one-tailed Fisher's exact test, the difference between groups is already significant by day 2, the first follow-up evaluation. More than half of the eventual responders to adinazolam did so by day 4, and three-fourths, by day 7.

The only study not significantly favoring adinazolam on most measures was a study of 63 Veterans Administration Hospital patients, 32 given adinazolam and 31 given placebo (6306, Cohn). The results in this study were not significantly different for the two treatments except in response to the Patient's Drug Evaluation Form; significantly more patients (54%) who had taken adinazolam felt that the drug helped them moderately, much, or very much, as compared with patients who had taken placebo (25%).

Table 3 shows the side effects observed in 10% or more of the patients in either treatment group in the largest compilation made to date, that for studies 6306 (Cohn) and 6309 (Cohn and Feighner). The side effects reported at incidences higher with adinazolam than with placebo were mainly drowsiness, followed by lightheadedness, dizziness,

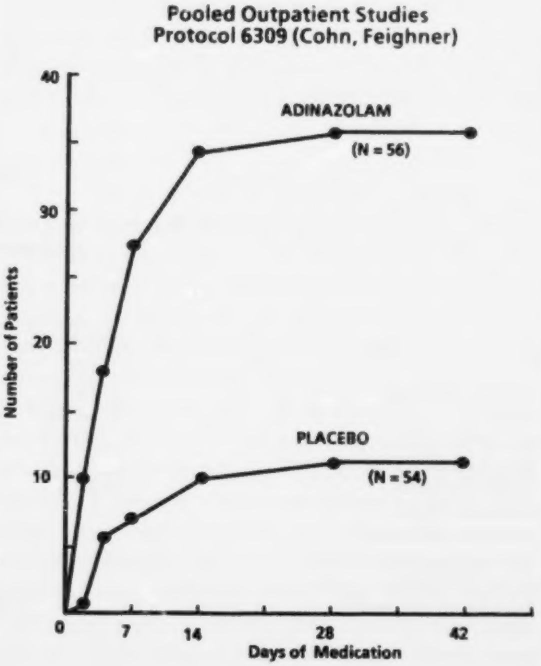


FIGURE. Number of patients with a Physician's Global Impression rating of moderate or marked therapeutic effect of the study drug.

or faintness; excessive dreaming was also more frequent with adinazolam than placebo, but only in one of the three studies. No hypomanic episodes, even in the bipolar II subjects, and no significant anticholinergic effects were observed.

Phase III Studies

Four 6-week comparisons with placebo and a tricyclic antidepressant, each with 40 subjects or more per treatment group, have been analyzed. Three single-center studies involved outpatients who were required to have DSM-III Major Depression and a HAM-D total score greater than 19; one multicenter study involved inpatients, required to have DSM-III Major Depression with Melancholia and a HAM-D total score greater than 25. The interim results from these Phase III studies are shown in Table 4.

In the outpatient studies, adinazolam (30 to 90 mg daily) was compared with imipramine (75 to 225 mg daily) and with placebo. Approximately 40 patients were enrolled per treatment per center; a majority of the patients enrolled completed the study in each treatment group at each center. Across the centers, the final incidence of moderate or marked therapeutic effect was 64% with adinazolam, 55% with imipramine, and 38% with placebo. The final incidence of 50% HAM-D total score reduction was 47% with adinazolam or imipramine and 30% with placebo.

The inpatient studies compared adinazolam (30 to 120 mg daily) with amitriptyline (75 to 300 mg daily) and with placebo in eight participating centers. Interim results with 54 patients given adinazolam, 46 given amitriptyline, and 41 given placebo, indicate that a majority of the patients completed treatment with adinazolam or amitriptyline (59% and 61%, respectively), but only 39% completed treatment with placebo. The incidence of moderate or marked therapeutic effect (50%, 56%, and 27%, respectively), that of HAM-D total score decrease to eight or less (30%, 33%, and 15%, respectively), and perhaps that of 50% symptom reduction on HAM-D (39%, 52%, and 27%, respectively), indicate that adinazolam is an effective antidepressant in severe depression, also.

The only side effects seen significantly more with adinazolam than with placebo in any Phase III study have been drowsiness and some confusion, decreased memory, etc., which were transient. Again, no significant anticholinergic effects were seen.

Discussion

In Phase II trials adinazolam was active as an antidepressant; it was superior to placebo in almost all measurements. It had a rapid onset of action, providing a significant antidepressant effect after 2 to 7 days in most eventual responders. Little dose titration was

TABLE 3

Side Effects or Medical Events in≥10% of Patients
Adinazolam Studies 6306 (Cohn) and
6309 (Cohn, Feighner)

	Adinazolam (*N* = 92)					Placebo (*N* = 91)
	Mild	Moderate	Severe	Total	%	%
Drowsiness***	25	31	5	61	66.3	16.5
Lightheadedness, dizziness, or faintness*	13	8	1	22	23.9	5.5
Vivid dreams or dreaming*	8	6	0	14	15.2	1.1
Dry mouth or decreased salivation	8	2	0	10	10.9	8.8
Headache	4	4	2	10	10.9	7.7

Asterisks: Incidence significantly higher with drug than with placebo in:
*** = each of the three studies and * = one study
No Asterisk: No significant differences in the incidence from placebo

best copy available

TABLE 4

Interim Analysis of Adinazolam Phase III Antidepressant Trials
Incidence of Success

	R-6318 Outpatients[a]			R-6329 Inpatients[b]		
	Adinazolam	Imipramine	Placebo	Adinazolam	Amitriptyline	Placebo
Evaluable Patients	122	120	120	54	46	41
Completers	67%	62%	58%	59%	61%	39%
Physician's Global:						
Moderate or marked therapeutic effect of drug	64%	55%	38%	50%	56%	27%
Hamilton Total Score:						
≥50% decrease	47%	47%	30%	39%	52%	27%
Final score≤8				30%	33%	15%

[a] DSM-III diagnosis: Major depression. Interim analysis across three studies.

[b] DSM-III diagnosis: Major depression with melancholia. Interim analysis across eight centers.

needed before the onset of efficacy (an initial dose of 30 mg daily was titrated to a final dose median of 45 to 80 mg daily).

Adinazolam alleviated the core symptoms of depression in these studies, as measured using HAM-D cluster scores, and it appeared useful in severe (inpatient) or moderate (outpatient) Major Depression, in chronic or relatively acute depression, and in drug-resistant depression. In addition, in studies done by Dr. David Dunner, 21 outpatients with bipolar II depression were given adinazolam with outcomes similar to those in patients with unipolar illness; none became hypomanic or manic. Since these were 6-week studies, only limited conclusions may be drawn regarding safety in bipolar II subjects.

Adinazolam was well-tolerated; the Phase II dropout rate for side effects was 4%, compared with 3% for placebo. The typical side effects observed were moderate and usually transient. Drowsiness was the most common and dizziness was the next most common. Anticholinergic effects were absent or equal to placebo. A tapered withdrawal period served to decrease side effects reported after extended use of benzodiazepines.

In the Phase III trials, interim analysis of the studies with larger enrollment appears to support the conclusion that adinazolam is an active antidepressant that is useful in both outpatients and inpatients. The side effects seen in Phase III were similar to those seen in the Phase II trials.

The overdose profile of adinazolam has so far been completely benign. Five suicide attempts using up to 500 mg produced no cardiovascular toxicity; in these patients cognitive impairment and oversedation were the only effects observed and these were rapidly reversible without neurologic sequelae.

In conclusion, adinazolam is a new triazolobenzodiazepine that appears to be an effective antidepressant, even for hospitalized patients with Major Depression with Melancholia. The therapeutic index of this drug appears to be extremely promising and warrants further study.

Acknowledgment: While my center performed two of these studies and is currently participating in a third, the other studies reviewed herein were performed under the supervision of Drs. G.C. Aden, S.C. Bhatia, J.D. Carman, J.B. Cohn, D.L. Dunner, W.E. Fann, R.H. Gerner, B. Hubbard, M. Morphy, E. Robins, W.T. Smith, S. Thein, and C.C. Weise. The editorial assistance of M.M. Wesley is also appreciated.

References

Guy, W. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, Md.: U.S. Department of Health, Education, & Welfare, 1976.

Hester, J.B., Jr., Rudzik, A.D., and VonVoigtlander, P.F. 1-(Aminoalkyl)-6-aryl-4H-s-triazolo [4,3-a] [1,4] benzodiazepines with antianxiety and antidepressant activity. *J. Med. Chem.*, 23:392–402, 1980.

Lahti, R.A., Pyke, R.E., and Sethy, V.H. Adinazolam, a triazolobenzodiazepine antidepressant. Preclinical and clinical data. In: *IUPHAR 9th International Congress of Pharmacology.* London: The Macmillan Press Ltd., 1984 (abstract 1983P).

Pyke, R.E., Cohn, J.B., Feighner, J.P., and Smith, W.T. Open-label studies of adinazolam in severe depression. *Psychopharmacol. Bull.*, 19(1):96–98, 1983.

Turmel, A., and deMontigny, C. Sensitization of rat forebrain neurons to serotonin by adinazolam, an antidepressant triazolobenzodiazepine. *Eur. J. Pharmacol.*, 99:241–244, 1984.

Chronic Depression: Demographic and Clinical Characteristics[1]

James H. Kocsis, M.D.,[2] Carlyle Voss, M.D.,[3] J. John Mann, M.D.,[2] and Allen Frances, M.D.[2]

Interest in states of chronic depression has recently been raised because of observations that these conditions may represent unrecognized and/or poorly treated forms of affective disorder (Weissman & Klerman, 1977) and do share clinical, familial, biological, and treatment response characteristics with acute or episodic affective illnesses (Akiskal et al., 1980, 1981; Kocsis et al., 1985; Rounsaville et al., 1980; Ward et al., 1979). Prior to 1980, patients having chronic depression tended to be seen as suffering primarily from personality disorders, and their chronic depression was viewed as an aspect of, or complication of, character pathology (Diagnostic and Statistical Manual—2nd ed., 1968; Schildkraut & Klein, 1975). Recently, Akiskal et al. (1980) proposed a reclassification of "chronic characterologic depressions" into two major subgroups, one which shares many features of typical affective disorders including response to antidepressant medication and a second, medication unresponsive type, with "unstable" personality disorders. An extension of this reconceptualization of chronic depressions was placement in DSM-III (1980), under the term Dysthymic Disorder, in the Affective Disorder section of that classification.

Chronic depression has been regarded variously as a complication of personality disorders, an attenuated form of affective disorder, or as a reaction to chronic stress (DSM-III, 1980). However, there have been few empirical studies which have reported data pertinent to these theories. Validation of meaningful subtypes of chronic depression along the suggested theoretical lines remains a goal of research.

The current study was undertaken for the purpose of systematic collection of data about concomitant affective and personality diagnoses, presence of psychosocial stressors, and family history of psychiatric disorders in a sample of patients with chronic depression and a comparison group of outpatients having episodes of acute depression.

Methods

Description of the Study: The study was conducted in two outpatient clinics (Department of Psychiatry, Maine Medical Center and Department of Psychiatry, New York Hospital-Cornell Medical Center) according to identical protocols and selection criteria. Patients were interviewed by research psychiatrists utilizing a semi-structured interview designed to elicit information which would allow diagnosis according to the DSM-III. Based on this interview, clinicians rated DSM Axis I, II (Personality Disorders), and IV (Psychosocial Stressors). Systematic inquiry about demographic material and family history of psychiatric disorders was also done and results were recorded at this time. Clinical symptom profile and severity were rated by use of the 24-item version of the Hamilton Scale for Depression (HAM-D; 1960). Information about prior treatments with psychotherapy or drugs was recorded and informed consent was obtained from all subjects.

Selection of Patients and Depressive Controls: Two patient groups were sampled, both drawn from the Affective Disorders clinics of the New York Hospital or Maine Medical Center. The chronic depression patients were included if they met DSM-III criteria for Dysthymic Disorders, i.e., had depressed or dysphoric mood for longer than 2 years and at least three associated symptoms of depression. Presence or absence of current Major Depression or Melancholia was systematically determined but patients were included

---

[1] This study was supported in part by USPHS Grant MH-37103 from the National Institute of Mental Health.

[2] Department of Psychiatry, New York Hospital-Cornell Medical Center, New York, NY 10021.

[3] Department of Psychiatry, Maine Medical Center, Portland, ME 04102.

The authors wish to thank Carmen Fontanes for her help in the preparation of this manuscript.

whether or not they had these associated or superimposed conditions. Patients with nonaffective DSM-III Axis I diagnosis (e.g., schizophrenia, drug or alcohol dependence, or organic brain syndromes) were excluded, as were patients with severe chronic or acute medical illness.

The sample of acute depressive controls included 26 age- and sex-matched patients who participated in one of two outpatient psychopharmacology studies of acute depression in the Affective Disorders clinic of New York Hospital. All had durations of the current episode under 1 year. They received the same battery of diagnostic and clinical evaluations at baseline with the exception of the evaluation of family psychiatric history.

Results

Comparisons of demographic and clinical characteristics between patients with chronic depression and the acute depressive control group are shown in Table 1. Age and sex did not differ significantly between the two groups. Significantly fewer acute depressives had ever married.

Thirty-seven of 39 (95%) chronic depressives fulfilled DSM-III criteria for Major Depressive Disorder in addition to their Dysthymic Disorder, and 23 (59%) also met criteria for Melancholia. Forty-seven percent of depressives were rated as having an Axis II diagnosis. Personality disorder diagnoses included: Dependent (*N* = 9), Avoidant (*N* = 4), Narcissistic (*N* = 3), Schizotypal (*N* = 3), Compulsive (*N* = 2), and five others which were given once each.

Axis I and Axis II diagnoses were similar for the acute depressive controls. All had Major Depressive Disorder by definition, 73% met criteria for Melancholia, and 40% were given an Axis II diagnosis. Moderate to severe psychosocial stress tended to be more prevalent in the acute depressives (62% vs. 47%). There was no significant difference in severity of illness in the two groups as measured by the 24-item HAM-D total score.

TABLE 1

Demographic and Clinical Characteristics of Chronic Depressives and Acute Depressive Controls

Characteristic	Chronic (*N* = 39)	Acute (*N* = 26)
$\bar{X}$ Age (Years)	40.1	42
Male	11	8
Female	27	18
Never Married	10	16*
Married	18	5
Divorced, Separated, or Widowed	10	5
% Current Major Depression	95	100
% Current Melancholia	59	73
% Current DSM-III Axis II Dx	47	40
$\bar{X}$ HAM-D Total Score	26.2	28
% FH Depression	55	–
% FH Mania	11	–
% Onset Before Age 25	65	42**
% Prior Psychotherapy	76	–
% Prior Antidepressant Drug Rx	18	50*
% Prior Psychiatric Hospitalization	13	15
% Prior Suicide Attempt	19	10
% DSM-II Axis IV = 4 (Moderate)	47	62

* $p < .01$

** $p < .1$

By definition, all patients in the chronic depressive sample had durations of illness greater than 2 years. In fact, this group reported remarkable chronicity of their depression. Fifty percent stated that depression had been continually present for more than 10 years. The chronic group showed a trend for earlier age of onset, with 65% reporting onset prior to age 25, as compared to 42% of the acute depressives.

Profiles of clinical symptoms as rated on the HAM-D in the two patient groups are compared in Table 2. Although chronic and acute depressives had similar frequencies of most items, acute depressives had significantly higher frequencies of four symptoms: loss of productivity, general somatic complaints of fatigue and body pains, diurnal variation of mood with morning worsening, and feelings of worthlessness. A history of suicide attempts was found in 19% of chronic and 10% of acute depressives. Only one patient had a history of more than one attempt.

Systematic family history data was collected in the chronic depressive sample. Fifty-five percent reported a history of depression in a first-degree relative, and 11% reported a history of mania.

A significant difference was noted in history of prior psychiatric treatment between

TABLE 2

Frequency of Occurrence of Individual HAM-D Symptoms*

Item	% Occurrence Chronic ($N = 39$)	 Acute ($N = 26$)
Depressed Mood	92	100
Guilt	41	54
Suicide	54	50
Early Insomnia	28	46
Middle Insomnia	33	46
Late Insomnia	23	31
Work and Interests	77	100**
Retardation	15	15
Agitation	0	8
Psychic Anxiety	77	88
Somatic Anxiety	54	42
GI Symptoms	15	12
General Somatic	51	81**
Genital	38	42
Hypochondrias	38	35
Weight Loss	15	27
Insight	0	0
AM Mood Worsening	21	46**
Depersonalization	13	15
Paranoia	3	4
Obsessions	0	8
Helplessness	28	50
Hopelessness	46	50
Worthlessness	51	80**
$\bar{X}$ Total Score	26.2	28.4

*Item score higher than one.

**Acute > Chronic $p < .05$

chronic depressive and controls. Fifty percent of the acute depressives had received at least one prior adequate trial of antidepressant medication, compared to only 18% of chronic patients. Seventy-six percent of chronic depressives had received prior treatment by psychotherapy. No comparison data were available for acute depressives.

Discussion

We report results of a study of clinical and demographic characteristics in 39 outpatients with Chronic Depression (DSM-III—Dysthymic Disorder). A group of 26 patients with acute Major Depressive Disorder was used as a comparison group.

Thirty-seven of the 39 chronic depressives also fulfilled DSM-III criteria for Major Depression and 59% also fulfilled criteria for Melancholia. Therefore, in this sample of patients there was clearly a good deal of symptomatic overlap between chronic depression and typical acute affective disorders as defined in DSM-III. The relationship between chronic depression and affective illness is further emphasized by the few differences seen in these two groups in other clinical and demographic characteristic and similarities in profiles of symptoms. These results and the high incidence of affective illness reported by the chronic depressives in their first-degree relatives support the notion recently advanced by Akiskal (1983) and Akiskal et al. (1980, 1983) that many states of chronic depression seen in psychiatric outpatients may represent attenuated or alternative forms of typical, acute affective disorders. Our previously reported preliminary results from a placebo-controlled trial of imipramine treatment conducted in this same chronic depression sample also supports similarity to acute forms of depression (Kocsis et al., 1985).

Another issue which has been raised by Akiskal et al. is the relationship of Dysthymic Disorders to Bipolar Illness (1981). In our sample of chronic depressives we indeed saw a larger than expected family incidence of bipolar illness, and one of our patients did develop a possible episode of drug-induced hypomania. Further data will be needed to address the relationship between these disorders, but it appears that a subgroup of dysthymic patients may be "sub-bipolar."

It has previously been suggested that some forms of chronic depression may result from the chronic presence of severe psychosocial or other kinds of stress (Schildkraut & Klein, 1975). The current study found a nonsignificant trend toward more current psychosocial stress in the acute depressives. However, prior studies have found interactions between stress, chronicity of depression, and non-response to antidepressant medications (Akiskal, 1982; Kocsis et al., 1984). We have not yet accumulated sufficient data to address such interactions in our chronic depressive sample. Some anecdotal experience suggests that chronic depression related to severe psychosocial stress may be a particular indication for psychotherapy or a combined treatment. It remains to be determined whether a meaningful subgroup of chronic depressives exists having chronic stress, a distinct clinical picture, and differential response to treatment.

Because of a long history of interest in relationships between chronic depression and personality disorder and the possibility that some forms of chronic depression may represent either a class of or complication of personality disorders, we have also examined the frequency of Personality Disorders in the two groups. Axis II diagnoses were given in 47% of chronic depressives and 40% of acute depressives, a nonsignificant difference. Because personality characteristics are known to be markedly influenced in a state-dependent fashion by depression (Akiskal et al., 1983; Liebowitz et al., 1979), evaluation of personality diagnosis in depressed patients is fraught with uncertainty. There may, in fact, not be an excess of personality disorders in chronic depressions and the apparent association may have resulted from the presence of depression itself on a chronic basis. However, further evidence that these patients have been seen previously by health professionals as being characterologic rather than affective is provided by our findings that chronic depressives have received frequent prior psychotherapy and little prior adequate antidepressant drug therapy. This has obvious important clinical implications in light of the increasing evidence that a substantial proportion of chronic depressions may respond to antidepressant drugs (Akiskal et al., 1980; Kocsis et al., 1985; Rounsaville et al., 1980; Ward et al., 1979).

References

Akiskal, H.S. Factors associated with incomplete recovery in primary depressive illness. *J. Clin. Psychiatry*, 43:266–271, 1982.

Akiskal, H.S. Dysthymic disorder: Psychopathology of proposed chronic depressive illness. *Am. J. Psychiatry*, 140:11–20, 1983.

Akiskal, H.S., Hirschfeld, R.M.A., and Yerevanian, B.I. The relationship of personality to affective disorders. *Arch. Gen. Psychiatry*, 40:801–810, 1983.

Akiskal, H.S., King, D., Rosenthal, T.L., et al. Chronic depressions. I. Clinical and familial characteristics in 137 probands. *J. Affect. Dis.*, 3:297–315, 1981.

Akiskal, H.S., Rosenthal, T.L., Haykal, R.F., et al. Characterologic depressions: Clinical and sleep EEG findings separating "subaffective dysthymias" from "character spectrum disorders." *Arch. Gen. Psychiatry*, 37:777–783, 1980.

Diagnostic and Statistical Manual of Mental Disorders, 2nd Ed. (DSM-II), American Psychiatric Association, Washington, D.C., 1968.

Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. (DSM-III), American Psychiatric Association, Washington, D.C., 1980.

Hamilton, M. A rating scale for depression. *J. Neuro. Neurosurg. Psychiatry*, 25:56–62, 1960.

Kocsis, J.H., Butler, T., and Mason, B. Psychosocial stress predicts tricyclic antidepressant response. *Am. Psychiatr. Assoc.*, New Research Abstracts, 1984.

Kocsis, J.H., Frances, A., Mann, J.J., et al. Imipramine for the treatment of chronic depression. *Psychopharmacol. Bull.*, 21(3):698–700, 1985.

Liebowitz, M.R., Stallone, F., Dunner, D.L., et al. Personality features of patients with primary affective disorders. *Acta Psychiatr. Scand.*, 60:214–224, 1979.

Rounsaville, B.J., Sholomskas, D., and Prusoff, B.A. Chronic mood disorders in depressed outpatients. *J. Affective Disord.*, 2:73–88, 1980.

Schildkraut, J.J., and Klein, D.F. The classification and treatment of depressive disorders. In: Shader, R.I. (ed.), *Manual of Psychiatric Therapeutics*, Chapt. 3. Boston: Little Brown Co., 1975.

Ward, N.G., Bloom, V.L., and Friedel, R.O. The effectiveness of tricyclic antidepressants in chronic depression. *J. Clin. Psychiatry*, 40:49–52, 1979.

Weissman, M.M., and Klerman, G.L. The chronic depressive in the community: Unrecognized and poorly treated. *Compr. Psychiatry*, 18:523–531, 1977.

Self-Rating of Personality Characteristics and Their Relationship to Treatment Response in Recurrent Unipolar Depressives: A Pilot Study[1]

Ellen Frank, Ph.D.,[2] David J. Kupfer, M.D.,[2] David B. Jarrett, M.D., Ph.D.,[2] and Miriam Jacob, ACSW[2]

Introduction

In their review of the relationship of personality to affective disorders, Akiskal et al. (1983) point out that personality variables have been hypothesized to relate to affective illness in at least four ways: 1) as predisposing factors to affective episodes, 2) as modifiers of affective episodes, 3) as a complication of affective illness, and 4) as an attenuated expression of affective illness. These authors point out that the predisposing factors hypothesis suggests that personality pathology may be etiologic with respect to affective illness. When personality variables are considered as modifiers of affective episode, there is no etiologic speculation, simply the observation that personality characteristics may have an effect on clinical presentation, course, treatment response, and outcome. Personality pathology may also be viewed as a complication of affective illness; it may be either state-dependent (i.e., present during the episode), or it may represent either a short-term or long-term complication observed following the remission of affective symptoms. Finally, personality pathology may represent an attenuated expression of affective illness. In this view, both personality features and affective episodes are considered to be expressions of the same underlying genetic or constitutional endowment.

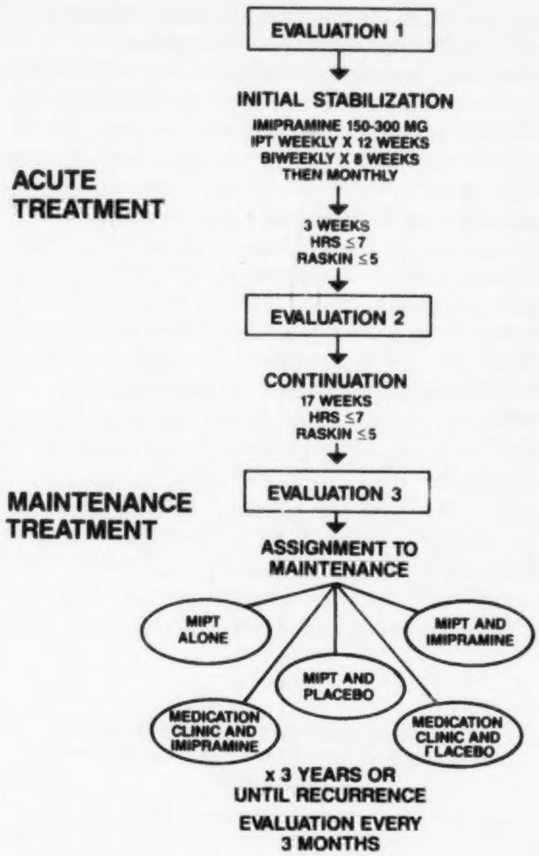
Study Design

When we began the Maintenance Therapies in Recurrent Depression Study, we had no particular bias as to which of these views might be correct. However, we thought it would indeed be important to measure characteristics of personality in the patients being studied. The design of the Maintenance Therapies in Recurrent Depression Study has been described in detail elsewhere (Frank et al., 1984). Briefly, however, the study involves acute treatment of recurrent unipolar patients who present in at least their third episode of major depressive disorder. Patients must have a single-rater Hamilton ≥15 and a Raskin of ≥7. Prior to entering the study, all patients are evaluated with respect to sleep electroencephalograph (EEG) and neuroendocrine parameters after a 2-week drug-free period. Self-report and interview measures of clinical state and social functioning are taken at that time; however, personality is not assessed at baseline. Acute treatment combines imipramine (150 to 300 mg) and Interpersonal Psychotherapy offered weekly for 12 weeks, biweekly for 8 weeks, and then monthly. Patients remain in acute treatment until they achieve a Hamilton of ≤7 and a Raskin of ≤5 for 3 consecutive weeks. At this time, sleep EEG and all night neuroendocrine studies are repeated and self-report measures of personality are administered. Patients then enter a continuation treatment phase of 17 weeks, during which their symptoms are expected to remain stable and no changes are made in the treatment regimen. Following this 17-week period, patients receive a third evaluation including sleep EEG, neuroendocrine, and personality measures. They are then assigned on a random basis to one of five maintenance treatments (*see* Figure) which are continued for 3 years or until the patient experiences a recurrence of illness.

---

[1] This work is supported by NIMH Grants MH-29618 and MH-30915 and the John D. and Catherine T. MacArthur Foundation.

[2] Western Psychiatric Institute and Clinic, Pittsburgh, PA 15213.


ACUTE TREATMENT
EVALUATION 1
INITIAL STABILIZATION
IMIPRAMINE 150-300 MG
IPT WEEKLY X 12 WEEKS
BIWEEKLY X 8 WEEKS
THEN MONTHLY
3 WEEKS
HRS ≤7
RASKIN ≤5
EVALUATION 2
CONTINUATION
17 WEEKS
HRS ≤7
RASKIN ≤5
MAINTENANCE TREATMENT
EVALUATION 3
ASSIGNMENT TO MAINTENANCE
MIPT ALONE
MIPT AND IMIPRAMINE
MIPT AND PLACEBO
MEDICATION CLINIC AND IMIPRAMINE
MEDICATION CLINIC AND PLACEBO
x 3 YEARS OR UNTIL RECURRENCE
EVALUATION EVERY 3 MONTHS

Subjects

The present report is based on the first 95 patients to finish the first 16 weeks of the Maintenance Therapies in Recurrent Depression protocol. The patient group consisted of 23 males and 72 females with a mean age of 40.6 ±10.8 years. The average length of the index episode was 23 weeks and the median was 19 weeks. Typically, age of onset was young (mean = 27.2±9.8 years; median = 24.0 years). Although the protocol requires only two previous episodes, the mean number of prior episodes was 6.1±5.8 and the median was 4.0. As we have reported elsewhere (Frank et al., 1984), a little over one third of the patients entering the Maintenance Therapies study have the expected treatment response. That is, they achieve remission within the first 7 to 8 weeks and remain well throughout the continuation period. A second third shows a more variable response, taking up to 16 weeks to achieve a stable remission. Finally, one third of the patients studied show only a partial response to the combined pharmacotherapy/psychotherapy treatment regimen. An algorithm was developed for assigning patients to these response categories on the basis of absolute Hamilton scores and percent change in Hamilton scores from baseline (Frank et al., 1984). When these three treatment response groups were examined, no differences were observed among them on age, sex, length of index episode, age at onset of illness, or number of previous episodes of affective illness. However, differences were observed in terms of baseline biological characteristics with the normal responders showing the most biological disturbance.

When we examined this larger cohort of 95 patients, we continued to observe the same kinds of differences between normal and slow responders in terms of sleep EEG and neuroendocrine changes. The present paper focuses on the differences in self-ratings of personality between the normal ($N = 35$) and the slow ($N = 32$) responders, and on the relationship between biological variables measured prior to treatment and personality variables measured once remission was achieved. The Hirschfeld-Klerman Personality Battery, a 436-item self-report inventory made up of a total of 17 scales taken from the Guilford-Zimmerman Temperament Survey, the Interpersonal Dependency Inventory, the Lazare-Klerman-Armor Personality Inventory (short version), the Maudsley Personality Inventory, and the Ego Control and Ego Resiliency Scales of the Minnesota Multiphasic Personality Inventory (MMPI), was used to assess personality.

Results

Since we had obtained personality ratings on patients at both Evaluation II (end of the 3-week stabilization period) and Evaluation III (end of continuation treatment) which, by design, are separated by 17 weeks, we examined the stability of scores on the Hirschfeld-Klerman battery over that time period.

TABLE 1

Hirschfeld-Klerman Battery: Normal Versus Slow Responders

Scale	*t*
Ascendance (GZTS)	2.51*
Sociability (GZTS)	2.27*
Emotional Stability (GZTS)	3.97***
Objectivity (GZTS)	3.36***
Lack of Self-Confidence (IDI)	2.56*
Orality (LKA)	3.65***
Neuroticism (MPI)	4.24***

*$p<.05$
***$p<.001$

Abbreviations: GZTS = Guilford-Zimmerman Temperament Survey
IDI = Interpersonal Dependency Inventory
LKA = Lazare-Klerman-Armor Personality Inventory
MPI = Maudsley Personality Inventory

Test-retest correlation coefficients for the 17 scales ranged from .61 to .86, all $p<.001$.

When we compared normal responders with slow responders in terms of their personality characteristics, we found that on 7 of the 17 scales, normal responders showed significantly less personality pathology than did the slow responders. On no scale was the reverse true; the remaining 10 scales revealed no statistically significant differences between the two response types (*see* Table 1).

When comparisons were made between baseline biological characteristics and scores on the Hirschfeld-Klerman battery once patients had achieved remission, a complementary pattern emerged. Table 2 illustrates this pattern of relationships, indicating a dissociation between biological pathology and personality pathology.

Discussion

These pilot data suggest four preliminary conclusions. First, among outpatients with a history of recurrent unipolar illness, personality variables appear to remain relatively stable when the affective illness is in remission. Second, there appears to be a striking dissociation between biological disturbance (as measured when the patient is acutely ill) and the personality disturbance (as measured in remission). That is, the more disturbed the patient's baseline biology the less disturbed the patient's personality, and vice versa. Third, when recurrent unipolar patients are offered combined pharmacotherapy and psychotherapy as an acute treatment, those who show a relatively rapid response appear to have clear-cut biological disturbance, at least in terms of EEG sleep and neuroendocrine parameters, and little personality disturbance. Those who respond relatively slowly to this treatment regimen have little biological disturbance and considerably more personality pathology. Finally, with respect to the four hypotheses of Akiskal et al. (1983), whatever else personality may be, it does appear to function as a modifier of the affective episode in terms of the rapidity of response to combined pharmacotherapy/psychotherapy.

These preliminary studies suggest a number of interesting directions for further exploration. First, it would seem to be important to explore the personality characteristics of that group classified as partial responders, keeping in mind that this group needs to be subdivided further into those patients who ultimately went on to have a rapid response

TABLE 2

Relationship Between Baseline Biological Variables and Hirschfeld-Klerman Scores in Remission

	r
Cortisol nadir with	
Sociability (GZTS)	.37*
Emotional Stability (GZTS)	.28*
Thoughtfulness (GZTS)	–.32*
Hysterical Pattern (LKA)	–.31*
Orality (LKA)	–.30*
Neuroticism (MPI)	–.37*
Extraversion (MPI)	.34*
Cortisol latency with	
Hysterical pattern (LKA)	.31*
Ego Control (MMPI)	.29*
Sleep maintenance with	
Emotional Stability (GZTS)	–.46***
Objectivity (GZTS)	–.45***
Emotional Reliance (IDI)	.38**
Assertion of Autonomy (IDI)	.25*
Hysterical pattern (LKA)	.42***
Orality (LKA)	.36**
Neuroticism (MPI)	.46***
REM latency with	
Restraint	–.23*

*$p<.05$
**$p<.01$
***$p<.001$

Abbreviations: GZTS = Guilford-Zimmerman Temperament Survey
LKA = Lazare-Klerman-Armor Personality Inventory
MPI = Maudsley Personality Inventory
MMPI = Minnesota Multiphasic Personality Inventory
IDI = Interpersonal Dependency Inventory

to another treatment regimen (typically monoamine oxidase inhibitors) and those patients who, after being tried on several treatment regimens, continued to show only partial remission of their symptoms. Second, it will be important to explore the clinician ratings of personality features collected using the Personality Assessment Form at the same evaluation points as those used to administer the Hirschfeld-Klerman battery. Third, since the Maintenance Therapies in Recurrent Depression protocol also includes the evaluation of significant others using von Zerssen Personality Inventory (in press), it will be possible to examine the relationship between personality characteristics as perceived by a patient's significant other and the patient's biology and response to treatment. The questions of greatest interest, however, are how these biological and personality parameters might influence the risk of recurrence in a population at high risk for another affective episode and how each of these parameters interact with each of the five maintenance treatment conditions being studied. The answers to these final questions will have to await the completion of the 3-year maintenance phase.

References

Akiskal, H.S., Hirschfeld, R.M.A., and Yerevanian, B.I. The relationship of personality to affective disorders. *Arch. Gen. Psychiatry*, 40:801–810, 1983.

Frank, E., Jarrett, D.B., Kupfer, D.J., and Grochocinski, V.J. Biological and clinical predictors of response in recurrent depression. A preliminary report. *Psychiatry Res.*, 13:315–324, 1984.

von Zerssen, D. Clinical self-rating scales (CSr-S) of the Munich psychiatric information system (Psychis Munchen). In: Sartorius, N., and Ban, T.A. (eds.), *Assessment of Depression*. (In press)

The Suicide Assessment Scale: A Scale Evaluating Change in Suicidal Behavior[1]

Barbara Stanley, Ph.D.,[2,4] Lil Träskman-Bendz, M.D., Ph.D.,[3] and Michael Stanley, Ph.D.[4]

Introduction

Evidence increasingly points to a biochemical deficit associated with suicidal behavior (Åsberg et al., 1976; Stanley et al., 1982). As this body of evidence grows, it becomes more likely that pharmacologic studies designed to alter suicidal behavior will be conducted. In order to perform these studies, adequate means of evaluating change in levels of suicidality must be utilized. However, available measures of psychopathology and suicidality are inappropriate in this regard. There are several reasons for this lack of suitability. First, existing scales (Beck et al., 1979) focus principally on suicide ideation only. For treatment studies, it is vital that evaluation be linked to more than ideation, since ideation relies solely on verbal report. Suicidal thoughts can be denied or distorted and, thus, a rating that relies only on the patient's report can be faulty. While scales measuring other forms of psychopathology may have similar problems, this problem is particularly acute in assessing suicidality where patients may have greater motivation to conceal suicidal thoughts than other forms of symptomatology.

In addition to scales which evaluate suicidal ideation, another group of scales focuses on the prediction of suicide (Zung, 1974). These scales seek to identify individuals at risk for committing suicide and often combine demographic information with an assessment of psychopathology. These measures are also unsuitable for pharmacologic treatment studies because they focus on identification of future behavior. For purposes of treatment studies, current status and fluctuations in this status over time are of prime importance.

Some of the more widely used suicide scales which, while valid in many settings, would be limited in pharmacologic studies, include the following:

1. Scale of a Suicidal Ideation (SSI) (Beck et al., 1979)—This is a 19-item rating scale designed to assess suicidal ideation and includes items such as the wish to die;
2. Suicide Intent Scale (SIS) (Beck et al., 1974a)—This is a 20-item scale designed to characterize and describe a suicide attempt;
3. Index of Potential Suicide (IPS) (Zung, 1974)—The IPS is a 50-item scale combining psychopathology ratings with an index of level of social support to predict suicide potential;
4. Hopelessness Scale (Beck, 1974b)—This is a 20-item scale designed to evaluate pessimism in outlook toward life;
5. Reasons for Living Inventory (Linehan, 1983)—This is a 48-item scale which identifies reasons that individuals have to prevent them from committing suicide. It has been shown to differentiate suicide attempters from non-attempters.

An alternative to using suicide ideation scales would be to consider suicidal behavior as a symptom of a larger diagnostic entity. In most traditional psychiatric conceptualizations of suicide, suicidal ideation is viewed as a manifestation of depression. In this case, standard scales for depression treatment studies such as the Hamilton Depression Scale (HAM-D) (Hamilton, 1976) could be used. However, since both epidemiological and biochemical studies of suicide appear to point to a deficit that cuts across diagnoses

---

[1] This study was supported in part by USPHS Grant No. 40048 from the National Institute of Mental Health.

[2] Department of Psychology, City University of New York, John Jay College, 445 West 59th Street, New York, NY 10019.
[3] Karolinska Institute, Stockholm, Sweden.
[4] New York State Psychiatric Institute, New York, NY 10032.

(Robins, et al., 1954), diagnosis-linked scales would be of only limited value.

Given that available scales were inappropriate for suicide treatment studies, the Suicide Assessment Scale, a scale assessing suicidality and related factors, was developed. Several criteria were established for this scale: 1) it was to evaluate both observable and reported symptomatology associated with suicidality: 2) the scale would not be linked to a specific diagnosis or weighted more heavily toward one diagnosis: and 3) the scale would be designed to evaluate current levels of suicidality and would be sensitive to change in suicide-related symptoms.

Method and Results

Scale Description

The Suicide Assessment Scale (SAS) contains 20 items each rated on a 5-point Likert-type scale. The ratings are performed in the course of a semi-structured clinical interview similar to an interview for the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1976). The interview requires approximately 20 to 30 minutes to conduct. The items were developed by reviewing the relevant literature on differentiating suicidal and non-suicidal individuals. In addition, the authors of the scale independently generated items. Those items on which there was agreement among the raters as well as the literature were included in the scale. The scale items tend to be grouped in five areas: affect, bodily states, control and coping, emotional reactivity, and suicide thoughts and behavior. Table 1 shows the items on the scale.

Items 16 through 20 are the suicide ideation and behavior items. Item 1: sadness and despondency, Item 2: hostility, Item 9: anxiety, Item 12: low self esteem, conceptualized as a sense of failure, and Item 13: hopelessness are the items related to affect. Items 3: anergia, 8: tension, and 10: somatic concern are the bodily states items. Emotional reactivity is evaluated on items 4: hypersensitivity, 5: emotional withdrawal, and 14: inability to feel. The last grouping of items clusters around control and coping. These items are resourcefulness (6), perceived loss of control (7), impulsivity (11), and poor frustration tolerance (15).

Scale Development

In evaluating interrater reliability for total SAS scores, correlations among three raters (two for each patient evaluation) on a set of 37 ratings were computed. Interrater reliability was found to be adequate ranging from .78 to .88. In attempting to examine the validity of the SAS, we administered the scale to a group of 62 suicide attempters and 47 non-attempters who were hospitalized on a psychiatry service (Table 2).

The groups were matched for age and education. We had a higher proportion of males in the non-attempter category, principally as a consequence of the patient population at the time of data collection. Diagnosis did not differ significantly between the groups.

In examining the construct validity of the SAS, a comparison of scores for suicide attempters and non-attempters was made (Table 3). The results show suicide attempters scored significantly higher than non-attempters.

Table 4 differentiates between attempters and non-attempters on the other scales administered. The SSI, the HAM-D Scale, and the suicide item which assesses current suicidal state on the Hamilton Scale distinguished attempters from non-attempters. The BPRS and the Hamilton Anxiety (HAM-A) scale did not.

Table 5 shows the SAS scores for the three diagnostic groups represented in the study: Major Affective Disorder, Schizophrenia, and Personality Disorder. The diagnostic groups do not differ in SAS scores. This is consistent with the finding that suicide cuts across psychiatric diagnoses. Table 6 shows the correlation of the SAS with other scales. As can be seen, the SAS correlates moderately with depression as reflected by the HAM-D scores and moderately with suicide ideation as reflected by the SSI and the suicide item on the HAM-D. The scale shows somewhat of a correlation with psychotic symptomatology as measured by the BPRS. Furthermore, we find that the presence of suicide ideation within the past week and recent attempt in the past 6 months correlates with SAS scores.

TABLE 1

Suicide Assessment Scale

Item	Symptoms
1. Sadness and Despondency	Sad mood; low spirits; feels miserable
2. Hostility	Hostile; angry; belligerent; antagonistic; provoked to rage; easily provoked
3. Anergia	Lack of energy; weariness; tired; fatigued; worn down; harried; sense of weakness
4. Hypersensitivity	Sensitive to criticism; easily hurt; feels easily rejected; easily offended; touchy; takes things personally; suspicious; distrustful
5. Emotional Withdrawal	Lack of emotional contact; socially isolated; retreating; insulated; distrustful
6. Resourcefulness	Inability to solve problems effectively; lack of flexibility in coping with problems; sees few options and alternatives
7. Perceived Loss of Control	Feels lack of control over self or own destiny; feels at mercy of external events; feeling of lacking influence over environment
8. Tension	Physically tense; nervous; ill at ease; inability to relax; jumpy (exclude autonomic symptoms)
9. Anxiety	Worry; overconcern for present or future; fearfulness; dread; uneasiness (exclude autonomic symptoms)
10. Somatic Concern	Concern over physical health; preoccupation with physical symptoms (including aches and pains; sleeplessness; gastrointestinal and cardiovascular symptoms); generalized worries or delusions about body
11. Impulsivity	Acts on impulses; acts without planning or considering consequences; has irresistable urges; acts on spur of moment
12. Low Self Esteem	Low self esteem; feelings of worthlessness and inferiority; feels like a failure
13. Hopelessness	Feels hopeless and despairing; gloomy outlook; pessimistic; feels that the worst will happen, nihilistic thoughts
14. Inability to Feel	Depersonalization; lack of feelings; inability to feel emotions (not lack of empathy)
15. Poor Frustration Tolerance	Easily frustrated or irritated; readily discouraged
16. Suicidal Thoughts	Preoccupied with suicidal thoughts; thinks about being dead; thinks of reactions of others to suicide; finds it difficult to think of anything other than suicide
17. Purpose of Suicide	Suicide is a solution to the problem; suicide is the only alternative to problems; wants to relieve others of burden; reunion with someone who is deceased (as opposed to suicide attempt as attention-seeking and manipulative)
18. Wish to Die	Strong desire to die; feels that he/she doesn't deserve to live; feels that life isn't worth living
19. Lack of Reasons for Living	Feels that there is no one to live for; feels that no one cares; feels that there is no purpose to life
20. Suicidal Actions	Actively plans method for committing suicide; has written a note or informed others; needs to be supervised to prevent attempt

TABLE 2

Demographic Characteristics of Suicide Attempters and Non-Attempters

	Suicide Attempters ($N = 62$)	Non-Attempters ($N = 47$)	Significance Test[a]
Age $\bar{X}$	33.1 ± 10.5	30.3 ± 7.6	1.53^{NS}
Education			
$\bar{X}$	12.3 ± 2.2	12.94 ± 2.0	1.45^{NS}
Sex			
% Male	46.8	70.2	5.98^*
Diagnosis (%)			
Bipolar, Manic	19.4	23.4	
Bipolar, Depressed	3.2	2.1	
Unipolar, Depressed	24.2	8.5	5.37^{NS}
Schizophrenia	29.0	38.3	
Personality	21.0	21.3	
Other	3.2	6.4	

[a] For age and education variables, a t-test for independent groups was performed; for sex and diagnosis, a χ^2 test.

$^*p < .05$

NS = Nonsignificant

Lethality and seriousness of the most recent attempt did not correlate with SAS scores nor did the level of aggressive behavior in the patient's past.

Table 6 shows the decline in SAS scores for a group of 8 suicidal patients who took part in a study using fenfluramine to treat suicidality. Although not a significant decline, possibly due in part to the small sample size, it appears that the scale will be sensitive to change and can reflect the effect of drugs on patients' conditions.

Discussion

The SAS is a measure that is designed to assess changes in level of suicidality for use in pharmacologic studies as well as other studies of suicidal behavior. The SAS may be useful to investigators studying suicidal behavior when it is important to use a rating that evaluates observable as well as reported symptomatology. The inclusion of observable symptoms on a suicide rating scale is particularly important for inpatient studies of suicidal behavior because suicidal ideation can be readily denied. Patients in psychiatric hospitals may be more motivated to deny suicidal thoughts than other psychiatric symptoms, since hospital privileges (e.g., passes) are often linked to a lack of suicidal ideation.

TABLE 3

SAS Scores for Suicide Attempters and Non-Attempters

	Suicide Attempters ($N = 62$)	Non-Attempters ($N = 47$)	
SAS† $\bar{X}$	29.5 ± 13.2	17.3 ± 9.7	5.34^*

$^*p < .01$

† possible range = 0-80

Furthermore, the development of the SAS represents an effort to identify and assess symptomatology associated with suicidal behavior (e.g., impulsivity and poor frustration tolerance) that go beyond suicidal ideation and diagnosis-specific symptoms. This effort parallels other scales that are commonly used in pharmacologic studies. These scales include the BPRS and the HAM-D and HAM-A scales.

The present study reports preliminary findings on the utility and validity of the SAS. Findings indicate that a high degree of reliability can be achieved in overall ratings. Furthermore, the scale appears to have construct validity, in that it correlates with suicidal ideation. In addition, those patients who have previously attempted suicide and are not cur-

TABLE 4

Comparison of Psychopathology Scores for Suicide Attempters and Non-Attempters

	Suicide Attempters ($N = 62$)	Non-Attempters ($N = 47$)	t
SSI (range = 0–38) $\bar{X}$	7.2 ± 9.5	1.7 ± 4.7	3.62*
BPRS (range = 18–126) $\bar{X}$	42.4 ± 10.2	38.6 ± 9.7	1.94^{NS}
HAM-A† (range = 0–56) $\bar{X}$	27.4 ± 12.6	25.2 ± 18.6	.56^{NS}
HAM-D (range = 0–64) $\bar{X}$	22.5 ± 8.9	16.8 ± 7.4	3.53*
Suicide Item (range = 0–4) $\bar{X}$	1.6 ± 1.3	.34 ± .8	5.73*

*$p < .01$
NS = Nonsignificant
†sample size = 47, NA = 18

rently suicidal tend to obtain somewhat higher scores on the SAS. This difference between those with and without a history of a suicide attempt may indicate that the scale is detecting some behavioral trait difference between suicide attempters and non-attempters. It may also be that patients with a previous history of a suicide attempt may be more likely to be hospitalized again for suicide-related reasons although not currently suicidal. While these speculations may be valid, additional research needs to be conducted to determine the reasons for the difference between those with and without a history of a suicide attempt.

In addition, several other analyses need to be performed on the scale to determine its usefulness. First, a large-scale follow-up study of suicidal patients over the course of their hospitalization should be performed. This analysis will determine whether the scale reliably detects changes in suicidality.

TABLE 5

Comparison of SAS Scores Across Diagnostic Classification

Diagnosis	$\bar{X}$, SD	t
Major Affective Disorders ($N = 45$)	23.7 ± 13.5	.60^{NS}
Schizophrenia ($N = 36$)	23.8 ± 13.4	
Personality Disorders ($N = 23$)	27.4 ± 12.5	

NS = Nonsignificant

Secondly, a factor analysis of the scale items is yet to be performed. While the scale has been grouped by item clusters on an a priori basis, a factor analysis is required to determine whether the statistical analysis yields the same factor grouping.

The data for these analyses are in the process of being collected and, thus, the current findings on the SAS are preliminary. At this point, the SAS appears to be a promising instrument for use in evaluating the efficacy of pharmacologic treatments of suicidal behavior.

TABLE 6

Correlation Between the SAS and Other Measures of Psychopathology

Other Measures	SAS
Overall Psychopathology	
Brief Psychiatric Rating Scale ($N = 109$)	.543*
Depression and Anxiety	
Hamilton Depression Scale ($N = 109$)	.655*
Hamilton Anxiety Scale ($N = 65$)	.332*
Suicidal Thoughts and Behavior	
Suicidality (HAM-D item) ($N = 109$)	.708*
Scale of Suicidal Ideation ($N = 106$)	.682*
Ideation within 1 week of SAS ($N = 109$)	−.587*
Total Number of Attempts in Past ($N = 109$)	.418*
Attempt within 6 months of SAS ($N = 109$)	−.304*
Seriousness of Recent Attempts ($N = 91$)	.173^{NS}
Medical Lethality of Recent Attempt ($N = 91$)	.175^{NS}
Aggression	
Aggression History Total Score ($N = 66$)	.118^{NS}

*$p < .01$
NS = Nonsignificant

References

Asberg, M., Träskman, L., and Thorén, P. 5-HIAA in the cerebrospinal fluid: A biochemical suicide predictor? *Arch. Gen. Psychiatry*, 33:1193–1197, 1976.

Beck, A.T., Kovac, M., and Weisman, A. Suicidal intention: The scale for suicidal ideation. *Consult. Clin. Psychol.*, 47:343–352, 1979.

Beck, A.T., Schuyler, D., and Herman, I. Development of suicide intent scales. In: Beck, A.T., Resnik, H.L.P., and Lettieri, D. (eds.), *The Prediction of Suicide*. Baltimore, Md.: Charles Press Publishers, Inc., 1974, pp. 45–56.

Beck, A.T., Weissman, A., Lester, D., and Trexler, L. The measurement of pessimism: The hopelessness scale. *J. Consult. Clin. Psychol.*, 42(6):861–865, 1974b.

Hamilton, M. Hamilton Depression Scale. In: Guy, W. (ed.), *ECDEU Assessment Manual for Psychopharmacology*. Washington, D.C., DHEW Publ. No. (ADM) 76-338, 1976, pp. 180–192.

Linehan, M. Reasons for Living Inventory. Suicidal Behaviors Research Clinic, Washington, D.C., 1983.

Overall, J.E., and Gorham, D.R. Brief Psychiatric Rating Scale. In: Guy, W., (ed.), *ECDEU Assessment Manual for Psychopharmacology*, Washington, D.C., DHEW Publ. No. (ADM) 76-338, 1976, pp. 158–169.

Robins, E., Murphy, G.E., Wilkinson, R.H., Jr., et al. Some clinical considerations in the prevention of suicide based on a study of 134 successful suicides. *Am. J. Public Health*, 49:889, 1959.

Stanley, M., Virgilio, J., and Gershon, S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science*, 216:1337–1339, 1982.

Zung, William. Index of Potential Suicide. In: Beck, A., Resnik, H., and Lettieri, D. (eds.), *The Prediction of Suicide*. Baltimore, Md.: Charles Press Publishers, Inc., 1974.

A Retrospective Clinical Analysis of the Overall-Rhoades Classification of Hamilton Depression Scale Profiles

Robert H. Lenox, M.D.,[1] Lelon A. Weaver, Ph.D.,[1] James E. Shipley, M.D.,[1] and Stephen Cohen, M.D.[1]

Introduction

Overall and Rhoades (1982a,b) described an empirical method of classifying depressed patients based on the profile of ratings on the Hamilton Depression Rating Scale (HAM-D). The profiles of 420 patients selected for participation in antidepressant medication trials were subjected to cluster analysis. Five phenomonological subtypes, designated "Anxious," "Suicidal," "Vegetative," "Paranoid," and "Somatizing" were identified. Discriminant functions were calculated to maximize the separation of the subtypes, resulting in five sets of weights for each Hamilton item. Classification was achieved by multiplying each Hamilton rating by these weights, summing algebraically within subtype, and assigning the patient to the subtype with the greatest positive sum. Rating profiles which result in only negative sums cannot be classified, i.e., the score profile does not fit any of the subtypes. No clinical validation data were included in their original publications.

The purpose of this study was to examine the distribution of the Overall-Rhoades classifications in the pre- and posttreatment data from depressed patients participating in clinical investigations of major depressive disorder. We examined two such groups of patients: an Inpatient population treated in our Clinical Research Center, and an Outpatient group followed in the ambulatory care setting at the University of Vermont College of Medicine.

Methods

Patients

The Inpatient group consisted of 24 patients, 7 males and 17 females, with an age range of 28 to 73 years; mean ±SEM = 53.8±3.0 years (Table 1). All patients were diagnosed as Major Depressive Disorder, Endogenous Subtype, in accordance with Research Diagnostic Criteria (Spitzer et al., 1977). This group was screened from a much larger sample of depressed patients referred for treatment to the psychiatric unit of a general hospital. All were returned to the community following treatment.

The Outpatient study group consisted of 13 patients, 4 males and 9 females, with an age range of 21 to 59 years; mean ± S.E.M. = 38.2±2.8 years (Table 1). These patients are selected from a larger group of physician and self-referrals. All were diagnosed as Major Depression according to DSM-III criteria. All patients completed the prescribed course of treatment without significant complications.

Measures

In both groups each patient was administered a battery of clinical assessment instruments. For our present purpose, the data for the pre- and posttreatment HAM-D and the

TABLE 1

Demographic Data for the Inpatient and Outpatient Study Groups

	Inpatient			Outpatient		
	N	Mean	SE	*N*	Mean	SE
Age Group	24	53.8	3.0	13	38.2	2.8
Male	7	50.4	6.7	4	37.0	2.1
Female	17	55.2	3.3	9	38.7	4.0
Duration Prior to Treatment (wks)		19.4	4.5		66.8	17.3
History of Previous Manic Depressive Disorder			50%			92%

---

[1] Department of Psychiatry, College of Medicine, University of Vermont, Burlington, VT 05405.

Physician's Global Impressions (PGI) scales will be considered. The latter instrument contains a 7-category scale (ranging from 1 = "Normal, not at all ill" through 7 = "Among the most extremely ill patients"). We have defined a patient as "Improved" if a final PGI rating of 1 or 2 ("Normal" or "Borderline ill") was given. In the Inpatient study, the ratings on both scales are the mean of two independent raters. The interrater correlations were +.91 for the HAM-D data and +.89 for the PGI. In the Outpatient study, all ratings on both scales were carried out by a single psychiatrist who did not participate in the Inpatient study and who was unacquainted with the Overall-Rhoades classification system.

Results

The first step was to determine the appropriate classification for each patient on the pre- and posttreatment Hamilton profiles according to the method detailed by Overall and Rhoades (1982b). Table 2 contains a sample output from our Inpatient group in which the highest positive score is underlined to indicate the category to which the patient was assigned. Thus, patient #629 was classified "Vegetative" during the pretreatment period and "Anxious" at posttreatment with an overall improvement of 67% in the HAM-D. On the other hand, patient #275 was classified "Suicidal" for both pre- and posttreatment with an overall improvement in the HAM-D of only 17%.

The results of the application of the method to our data are summarized in Table 3 which contains the distribution of the Inpatient and Outpatient groups across the six possible classifications for both the initial and final ratings. For ease of comparison, frequency data has been converted into group percentages. On the initial rating, the Inpatient group was heavily represented in the Vegetative and Suicidal classes with very modest frequencies in the other four categories. Following treatment, the final ratings showed a substantial increase in the Anxious and Not-Classifiable categories. These results are consistent with expectations for a group of moderately to severely ill patients, only some of whom responded to treatment.

For the Outpatient group, the initial (pretreatment) data showed a preponderance of patients classified in the Anxious category, some in the Vegetative, and a minor representation in the others; again consistent with expectations for a less severely ill group of patients. The final rating was heavily concentrated in the Not-Classifiable category, due largely to the reduction in the total HAM-D score and the substantial number of items rated zero.

A classification table using the Overall-Rhoades categories assigned to each patient for both initial and final Hamilton profiles was constructed. Each patient could be assigned to only one cell. In Table 4, the cell entries are the mean total Hamilton scale scores for the initial and final ratings of the Inpatient group. Each pair of entries represents a single patient. The table may be read as follows: The patient classified as Vegetative initially and Anxious finally had an initial Hamilton score of 30.0 and a final Hamilton score of 10.0.

There were 11 patients initially classified as Vegetative with a mean HAM-D rating of 30.1. At the time of final rating (posttreatment), 3 of the original 11 remained in the Vegetative category, while the others had shifted into Anxious (3) or Not-Classifiable categories (5). Here again, it is apparent that patients in the Inpatient study shifted from predominantly Vegetative/Suicidal/Somatizing categories pretreatment to Anxious/Not-Classifiable posttreatment. It is clear that those shifting into the Not-Classifiable category represented the patients showing the most improvement with a mean overall reduction in HAM-D of 81%.

Table 5 utilizes the identical format and contains the data for the Outpatient group. Three patients were initially classified as Vegetative with a mean HAM-D score of 24.8. Two of the three patients shifted into the Non-Classifiable category during the posttreatment rating with an overall reduction in HAM-D of 84%. As indicated in Table 2, the preponderance of patients were initially classified as either Anxious or Vegetative with the majority of these (77%) classified as Not-

TABLE 2

Sample Output of the Overall-Rhoades Classification Function Program Using Pre- and Posttreatment Hamilton Depression Rating Scale Profiles

		Overall-Rhoades Classification Functions						
Patient No.	Phase	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not Classifiable	Total Hamilton Score
275	Pre	-6.82	8.03	-5.99	-9.72	-2.75		27.00
	Post	-5.81	2.22	-5.36	-8.81	1.93		22.50
678	Pre	-1.60	-0.56	-4.23	-9.11	-1.08	•	23.50
	Post	0.96	-3.02	-3.51	-7.26	-0.45	•	7.00
363	Pre	3.12	-1.88	-5.80	-6.33	-5.05		26.00
	Post	-2.13	-1.20	-3.68	-8.32	-0.69	•	1.50
269	Pre	5.24	-1.14	-7.07	-6.57	-7.24		24.50
	Post	-0.07	2.69	-5.52	-6.63	-0.22	•	17.00
604	Pre	-0.92	-5.63	3.88	-6.28	-7.06		41.00
	Post	-3.72	-3.48	-3.46	4.05	-1.27		22.50
161	Pre	0.78	-4.94	-3.15	-10.99	2.80		19.00
	Post	-2.65	-2.87	-3.04	-11.76	2.77		11.00
965	Pre	-3.32	4.75	-6.24	-10.49	-2.76		31.50
	Post	-2.81	-2.03	-4.94	-5.44	1.22		11.00
629	Pre	1.36	-3.63	-5.05	-10.68	0.42		30.00
	Post	0.84	-4.54	-3.08	-6.78	0.57		10.00

Classifiable following treatment, with a mean score of 5.8.

Data shown in Tables 6 and 7 utilize the same format to show the initial and final PGI ratings for the Inpatient and Outpatient groups classified according to the Overall-Rhoades system. Patients were placed in the same cells as in Tables 4 and 5. A final rating that is underlined indicates that the patient was judged clinically "improved." Of the five patients in the Inpatient group classified as Vegetative or Suicidal both initially and finally, only one was rated as "improved" on the final PGI rating. Inspection of the HAM-D data (Table 4) for these patients indicated that this patient had the lowest final HAM-D rating, well below the mean of the other four patients. Similarly, only one patient initially classified as Vegetative and finally as Anxious showed significant improvement on the PGI, and the HAM-D rating reflected this improvement. Consistent with our findings in Tables 4 and 5, all patients found Not-Classifiable on the final HAM-D were found to be improved according to the PGI.

As part of the design of the original inpatient study, the dexamethasone suppression test (DST) was administered to all patients pre- and posttreatment. Patients were administered the DST as described previously (Lenox et al., 1985). At the initial (pretreatment) period there were 11 suppressors and 13 non-

TABLE 3

Summary of Pre- and Posttreatment HAM-D Profile Classification by Groups

Overall-Rhoades Classification	Inpatient (*N* = 24) Initial	Inpatient (*N* = 24) Final	Outpatient (*N* = 13) Initial	Outpatient (*N* = 13) Final
Vegetative	46	17	24	8
Suicidal	33	8	8	0
Somatizing	12	0	8	8
Paranoid	0	4	0	0
Anxious	4	29	54	8
Not-Classifiable	4	42	8	76

(Cell Entries Are in Percent of Patient Groups)

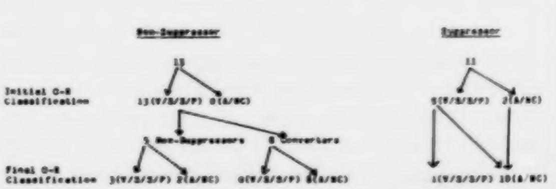


FIGURE. Flow diagram of changes in status on the DST as related to the Overall-Rhoades (O-R) classification system. Patients were administered the DST both during the pretreatment period (initial) and following at least 3 weeks of treatment (final). At the same time, HAM-D ratings were carried out and the O-R classifications were determined. (*See* text for definition of abbreviations.)

TABLE 4

The Overall-Rhoades Classification of the Inpatient Group on the Initial and Final Administration of the HAM-D

			Final					
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	36.0/22.5				30.0/10.0	27.5/8.5	11	30.1/12.4
	33.0/13.0				39.5/23.0	28.5/5.5		
	24.5/17.0				35.0/26.0	26.0/1.5		
						20.0/0.0		
						31.0/9.0		
Suicidal		27.0/22.5			31.5/11.0	39.0/8.0	8	29.0/16.0
		34.0/21.0			26.0/30.0	28.5/5.5		
					22.0/24.0	24.0/6.0		
Somatizing	45.0/28.5			41.0/22.5		36.0/3.5	3	40.7/18.2
Paranoid							0	
Anxious					19.0/11.0		1	19.0/11.0
Not-Classifiable						23.5/7.0	1	23.5/7.0
N	4	2		1	7	10	24	
Mean	34.6/20.2	30.5/21.7		41.0/22.5	29.0/19.3	28.4/5.4		30.3/14.0

(Cell entries are the initial and final HAM-D ratings for each patient)

suppressors (*see* Figure). At the posttreatment (final) evaluation, of the 13 patients classified as non-suppressors pretreatment, 8 normalized while 5 continued to be non-suppressors. The 11 original DST suppressors remained suppressors at the final evaluation. For the purpose of examining the relationship of Overall-Rhoades classifications, we created two category groups, Vegetative/Suicidal/Somatizing/Paranoid (V/S/S/P) and Anxious/Not-Classifiable (A/N-C). It may be remembered that the Vegetative and Suicidal categories contain 19 of the 24 Inpatients classified during the pretreatment period. All 13 of the initial DST non-suppressors and 9 out of the 11 suppressors were found in the V/S/S/P categories while only 2 of the 24 fell into A/N-C group. Of the five patients designated DST non-suppressors posttreatment, 3 remained in the V/S/S/P classification and 2 in the A/N-C category. All 8 patients who normalized the DST posttreatment were in the A/N-C category. Of the 9 suppressors who were initially categorized in the V/S/S/P, 8 shifted into the A/N-C category at final posttreatment evaluation.

TABLE 5

The Overall-Rhoades Classification of the Outpatient Group on the Initial and Final Administration of the HAM-D

			Final					
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	26.0/17.0					22.5/5.0	3	24.8/8.3
						26.0/3.0		
Suicidal						19.0/3.0	1	19.0/3.0
Somatizing						22.0/3.0	1	22.0/3.0
Anxious	23.0/10.0				24.0/18.0	19.5/4.0		
						23.0/1.0		
						25.0/0.0	7	24.9/6.0
						34.0/7.0		
						26.0/2.0		
Paranoid							0	
Not-Classifiable						21.5/11.0	1	21.5/11.0
N	2				1	10	13	
Mean	24.5/13.5				24.0/18.0	23.8/4.0		24.0/6.50

(Cell entries are the initial and final HAM-D ratings for each patient)

TABLE 6

The Relationship Between the Overall-Rhoades Classification and the PGI Ratings for the Inpatient Group.

			Final					
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	6.0/5.5 6.0/$\underline{2.0}$ 5.0/5.5				4.0/$\underline{2.0}$ 5.0/4.0 6.0/6.0	4.0/$\underline{2.0}$ 6.0/$\underline{2.0}$ 5.5/$\underline{2.0}$ 5.0/$\underline{1.0}$ 5.0/$\underline{2.0}$	11	5.3/3.2
Suicidal		6.0/5.0 5.5/4.5			6.0/3.0 5.0/5.0 4.0/4.0	4.0/$\underline{2.0}$ 5.0/$\underline{2.0}$ 5.0/$\underline{2.0}$	8	5.1/3.6
Somatizing	7.0/6.5			6.0/6.0		6.5/$\underline{1.5}$	3	6.5/4.7
Paranoid							0	
Anxious					4.0/$\underline{2.0}$		1	4.0/2.0
Not-Classifiable						4.5/2.0	1	4.5/2.0
N	4	2	0	1	7	10	24	
Mean	6.0/4.9	5.8/4.8		6.0/6.0	4.9/3.7	5.1/1.8		5.3/3.4

(Cell entries are initial and final PGI ratings. Underlining of final rating indicates patient was considered "improved")

Discussion

First, it is important to point out that these data were collected as part of a psychopharmacological research program and hence cannot be regarded as a designed prospective validation study. Rather, it represents a retrospective study of the distribution of the Overall-Rhoades classification in pre- and post-treatment data from two groups of patients with diagnosis of major depressive disorder. Both Inpatient and Outpatient studies were carried out independently of each other and the Overall-Rhoades classification scheme.

We have noted several problems incidental to the Overall-Rhoades classification system which are worthy of discussion. It will be remembered that each HAM-D item rating is multiplied by a different positive or negative weight in each of the categories. The algebraically summed categories will thus be either positive or negative and the patient assigned to the category with the highest positive sum. But since the same item may have

TABLE 7

The Relationship Between the Overall-Rhoades Classification and the PGI Ratings for the Outpatient Group.

			Final					
	Vegetative	Suicidal	Somatizing	Paranoid	Anxious	Not-Classifiable	*N*	Mean
Vegetative	5/3					6/$\underline{1}$ 6/$\underline{1}$	3	5.7/1.7
Suicidal						3/$\underline{1}$	1	3.0/1.0
Somatizing						4/1	1	4.0/1.0
Paranoid							0	
Anxious	4/$\underline{2}$				4/$\underline{1}$	4/1 6/3 4/$\underline{1}$ 5/4 7/4	7	4.9/2.3
Not-Classifiable						6/2	1	6.0/2.0
N	2				1	10	13	
Mean	4.5/2.5				4.0/1.0	5.1/1.9		4.9/1.9

(Cell entries are initial and final PGI ratings. Underlining of final rating indicates patient was considered "improved") both positive and negative weights in the several categories, a patient rated high on several different items may cancel out the patterns, resulting in a high HAM-D total but fitting no specific category.

A still unresolved problem concerns the number of HAM-D items which are required to produce a valid categorization. The effectiveness of the discrimination of classification types depends upon the presence of both positive and negative weights; thus, if only a few items are non-zero rated, it is probable that no positive profile will emerge. Such a result, i.e., a finding of Not-Classifiable, is acceptable in logic, but a more serious question arises when a positive classification does emerge when only a few items are rated, since a chance combination of loaded items becomes more likely. This usually results when one or more of the rated items has a high positive loading in one category. Thus, even a rating of 1 on the HAM-D items #1 (Depressed Mood) and #4 (Early Insomnia) would ensure an Anxious categorization. Part of the problem is the dearth of negative offsetting scores when a large percentage of the items are rated zero. We have addressed these issues in this study by applying two decision rules:

1. If a profile results in "Not-Classifiable," it stands without regard to the number of items rated.
2. If a profile is categorized, the HAM-D must have at least one-third non-zero ratings for the categorization to be accepted as valid. If less than one-third of the items were rated, the profile was considered "Not-Classifiable."

The basic question is whether the Overall-Rhoades classification system results in clinically relevant data. Overall and Rhoades originally noted that the Vegetative type loaded onto items with symptoms of sleep disturbance, weight loss, and diurnal variation, consistent with endogenous features most responsive to somatic treatment intervention (tricyclics, ECT, etc.). The Anxious type is weighted for early (but not middle or late) insomnia, and psychic anxiety consistent with anxious depression or minor depression with anxiety, often responding to anxiolytics and thought to have a higher placebo response. The suicidal type was weighted heavily in the suicide item while the paranoid type was weighted heavily for paranoid symptoms and lack of insight. Both our Inpatient and Outpatient studies attempted to exclude psychotic depressions, but we would expect that the more seriously ill Inpatients would classify into the "sicker" categories, Vegetative and Suicidal. As shown in Table 3, 79% were so classified with high initial HAM-D (29.6) and PGI (5.2) ratings. Thus, the Overall-Rhoades classification did reflect the known severity of symptomatology in a carefully selected Inpatient group.

The Outpatient sample was not as severely ill as the Inpatient group since they were judged not to require hospitalization. There was a significant difference between the mean initial HAM-D scores of the Inpatient and Outpatient groups; 30.3 vs. 24.0, respectively. It is important to note that the same total score on the HAM-D can be produced by high ratings on different sets of items. From Table 3 it is apparent that this in fact occurred. Contrasting the Inpatient and Outpatient groups on the initial classification, the Vegetative and Suicidal categories comprised 78% of the Inpatient group but only 32% of the Outpatient group. For the Anxious and Not-Classifiable categories, the respective percentages were 8% and 62%. It can be concluded that the two groups of patients clinically judged to be different demographically (Table 1) and in degree of illness were differentially and properly categorized by the Overall-Rhoades classification.

Another question concerns the ability of the Overall-Rhoades classification scheme to reflect a change in clinical status. If a patient is judged to have improved significantly in terms of clinical criteria, this change should be reflected in posttreatment categorization. As noted in Table 3, the Inpatient group underwent a marked shift from Vegetative/Suicidal categories to Anxious/Not-Classifiable categories, with a similar shift occurring in the Outpatient group from Anxious to Not-Classifiable. The predominant shift in the Inpatient group would appear to be consistent with the suggestion of an affective spectrum, i.e., that patients with Vegetative/Suicidal depression profiles may pass through the stage described as an "Anxious Depression" prior to clinical recovery. These data might also suggest that some of the patients designated "Anxious" during pretreatment in the Outpatient study may represent an early stage of the Vegetative/Suicidal disorders treated in the Inpatient group.

Inspection of Table 4 shows that the final HAM-D rating of the patients remaining in the Vegetative/Suicidal categories did not differ from those moving into the Anxious category. Those moving into the Not-Classifiable category, however, had a significantly lower final HAM-D rating. There is, of course, an element of circularity present; patients with low HAM-D ratings are likely to fall into the Not-Classifiable category since there may not be enough non-zero item ratings to permit establishment of any pattern. However, inspection of the detailed PGI data of Table 6 confirmed the HAM-D data; all eight patients with a final classification of Not-Classifiable were judged "Improved" on the PGI scale. While it may be argued that since the HAM-D and PGI ratings were carried out by the same raters, agreement is only to be expected; cell-by-cell comparisons of the HAM-D and PGI ratings on the same patients showed numerous discrepancies.

It is concluded that the Overall-Rhoades classification reflects the clinical changes seen in both the HAM-D and PGI ratings. A shift into the Anxious category is not necessarily accompanied by a significant change in the HAM-D but movement into the "Not-Classifiable" is. Clinical improvement on the PGI is no more frequent in the Anxious category than in any other, but all patients rated "Not-Classifiable" showed significant clinical improvement. The data for the Outpatient group shows substantially the same trend.

We examined the possibility that the DST response might segregate according to the Overall-Rhoades classification scheme. Our findings would seem to indicate that patients classified into the "sicker" categories of Vegetative/Suicidal/Somatizing/Paranoid were as likely to be suppressors as non-suppressors. However, there was an indication that patients showing improvement by shifting into Anxious or Not-Classifiable categories were more likely to be the same patients whose DST converted to suppression. These data would be consistent with evidence showing a link between clinical improvement and DST conversion (Greden et al., 1980; Nemeroff & Evans, 1984). However, one must be cautious in light of our recent report that normalization of DST may be dependent upon long-term factors affecting the ability of the hypothalamic-pituitary-adrenal axis to revert to normal homeostatic control (Lenox et al., 1985).

In a recent study reported by Overall (1984), he examined the classification of patients enrolled in a series of 11 studies examining the clinical efficacy of nomifensine. Interestingly, while the initial classification type did not predict response reliably, it was apparent that patients in the Somatizing category appeared to be more responsive to placebo. However, the investigators did not study changes in classification profile as a function of treatment response.

The utility of the Overall-Rhoades classification scheme to prospectively screen and follow patients in psychopharmacological/behavioral/or even psychotherapeutic studies requires further investigation. These studies might address the early exclusion of placebo responders from major drug trials; the predictive value of suicidal classification; or the selection of patients more likely to respond to psychotherapy versus pharmacotherapy. Since the HAM-D is an instrument widely accepted and utilized in clinical studies, the potential application of this classification system requires further study.

References

Greden, J., Albala, A., Haskett, R., et al. Normalization of Dexamethasone Suppression Test: A laboratory index of recovery from endogenous depression. *Biol. Psychiatry*, 15:449–458, 1980.

Lenox, R., Peyser, J., Rothschild, B., et al. Failure to normalize the dexamethasone suppression test: Association with length of illness. *Biol. Psychiatry*, 20:333–337, 1985.

Nemeroff, C., and Evans, D. Correlation between the dexamethasone suppression test in depressed patients and clinical response. *Am. J. Psychiatry*, 141(2):247–249, 1984.

Overall, J. Efficacy of nomifensine in different depressive syndromes. *J. Clin. Psychiatry*, 45:85–89, 1984.

Overall, J., and Rhoades, H. Refinement of phenomenological classification in clinical psychopharmacology research. *Psychopharmacology*, 77:24–30, 1982a.

Overall, J., and Rhoades, H. Use of the Hamilton Rating Scale for classification of depressive disorders. *Compr. Psychiatry*, 23:370–376, 1982b.

Spitzer, R., Endicott, J., and Rabins, E. Research diagnostic criteria for a selected group of functional disorders, 3rd ed. New York: New York Biometrics Research Division, New York State Psychiatric Institute, 1977.

Understanding the Response Lag to Tricyclics. I. Application of Pulse-Loading Regimens With Intravenous Clomipramine[1]

Bruce G. Pollock, M.D.,[2,3] James M. Perel, Ph.D.,[3] Michael Shostak, M.D.,[3] Seymour M. Antelman, Ph.D.,[3] Barbara Brandom, M.D.,[4] and David J. Kupfer, M.D.[3]

The slow, gradual therapeutic onset of tricyclic antidepressants (TCAs) is difficult to explain by their reuptake-blocking properties alone, because these effects occur acutely. Recent research on the mode of action of TCAs has focused primarily on chronic modification of rat postsynaptic β-adrenergic receptors manifesting decreases in density (Sulser, 1983) and dopamine autoreceptors displaying subsensitivity (Chiodo & Antelman, 1980). These time-dependent phenomena may help to explain the enigma of the therapeutic delay in antidepressant treatment. Conversely, the explanation might be pharmacokinetic. Retrospective analyses of plasma level/response data have revealed that optimal effects are observed within 5 days after attaining adequate steady-state levels of orally administered antidepressants (Perel, 1983). Furthermore, it has been found that continuous intravenous infusions of TCAs in rats produce β-receptor downregulation within 16 to 48 hours as opposed to intraperitoneal (i.p.) or oral routes which produce changes after 10 days (Sethy & Day, 1985).

The variable, extensive hepatic pre-systemic clearance and relatively long half-lives of TCAs militate against the rapid achievement of therapeutically effective steady-state blood levels via the oral route. Intravenous (i.v.) medication circumvents this limitation and, in addition, provides an opportunity to test whether continuous medication is necessary after the administration of a sufficiently large initial dose. The relative contribution of pharmacokinetic versus pharmacodynamic factors in the therapeutic onset of TCAs was examined using a pulse-loading dose strategy with i.v. clomipramine (CMI). I.V. clomipramine is a commonly employed treatment in many European centers. Treatment, however, is typically initiated with 25 to 50 mg in a morning dose, and gradually increased to 150 to 200 mg over a 7- to 10-day period, with an attendant therapeutic lag, thereby precluding observations of more rapid onset of action. Pulse-loading may be defined as the rapid attainment of transient therapeutic plasma concentrations.

Methods

Those studied were inpatients on the Clinical Research Unit at Western Psychiatric Institute and Clinic. All patients had a minimum duration of their current illness of 2 weeks and a maximum current episode duration of 1 year prior to hospitalization. A psychiatric interview and physical examination were carried out at admission, and collateral information was obtained from the families and records of prior treatment. During a 2-week drug-free period, patients underwent routine tests, including blood chemistry, EEG, and EKG, and any other tests suggested by their history and physical examination. They were then evaluated by two independent psychiatrists to ensure criteria of the Diagnostic and Statistical Manual (3rd ed.) for either Major Depressive Episode with Melancholia or Bipolar Disorder, Depressed, were met. If patients met these diagnostic criteria and were not delusional, were physically

---

[1] This study was supported in part by USPHS Grant No. MH-30915 from the National Institute of Mental Health.

[2] Centennial Fellow, Medical Research Council of Canada.

[3] Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213.

[4] Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA 15213.

healthy, had a minimum rating of 15 on the 17-item Hamilton Depression Rating Scale (HAM-D) at the end of the 2-week drug-free period, and gave written informed consent, they entered the protocol.

An overview of the protocol is shown in the Table. EEG sleep and cardiac rhythm were recorded via remote cable while patients slept in their own rooms on 11 nights during the protocol. The first 2 nights of EEG sleep were considered as facilitating adaptation to the procedure while data for the next 2 nights were averaged and represent baseline sleep. EEG sleep was recorded on the nights of clomipramine or saline infusions and 7, 8, and 10 nights after the infusions and for 2 nights at the start of any additional infusions. All sleep records were scored independently without knowledge of the clinical diagnosis or drug status of the patient. In addition to the standard classification of sleep into stages, automated delta analyses were performed according to methods previously described (Kupfer et al., 1981a). Patients were rated by an independent observer with the HAM-D at the start of the protocol, the day following the second infusion of CMI or saline, and twice weekly thereafter.

On the fifth evening of the protocol, at 9:30 p.m., 75 mg of CMI diluted in 250 cc of normal saline was administered via a butterfly cannula. This procedure lasted approximately 45 minutes. The following evening 200 mg of CMI in 500 cc of saline was administered over a 90-minute period. No additional medication was given for 11 days. Ten patients completed the above protocol. Four patients received i.v. saline only, in a double-blind fashion, on protocol nights 5 and 6. These patients were then offered active CMI infusions on nights 11 and 12. A minimum of six timed plasma samples were taken up to 80 hours after the second CMI infusion for pharmacokinetic analysis and twice weekly thereafter. Plasma samples were analyzed by radioimmunoassay and high performance liquid chromatography using methods developed in our laboratory (Stiller et al., 1985). Pharmacokinetic treatment of plasma level data was performed utilizing curve fitting by our version of the computer program ESTRIP (Brown & Manno, 1978) for the Hewlett Packard 9836, followed by nonlinear regression analysis (Yamaoka et al., 1981). Half-lives were calculated using a modification of a program written by Niazi (1977). Paired *t*-tests and Wilcoxon's signed rank test (two-tailed) were used in the statistical analyses.

Results

One male and 9 females (mean age 40.6 s.d. ± 11.2 years) with an average duration of illness of 7.5 months, were admitted to and completed the protocol. The infusions of clomipramine were well tolerated. All patients experienced a pleasant sedation during these infusions, but were kept awake until the infusions were completed because of the sleep studies. Six patients experienced mild to moderate nausea on receiving the first infusion of 75 mg CMI, while 3 of these patients subsequently had milder nausea with the second infusion of 200 mg. Two patients experienced myoclonic jerks and 4 complained of a transient restlessness shortly after the initation of the infusions. Three patients complained of mild headache on the morning af-

TABLE

I.V. Clomipramine Protocol Schedule

Day**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
EEG Sleep Studies	X	X	X	X	X	X							X	X		X	X *	X			
I.V. Dose in mg: CMI or placebo 9:30-11:00 p.m.					25 50	200															
Blood Levels			X		X	X	X X	X X	X X	X X			X			X			X		X
Clinical Ratings			X				X			X			X			X			X		X

*If placebo is given on Days 5 and 6, I.V. CMI was offered here.
**Days represent period following 2 weeks medication-free in hospital.

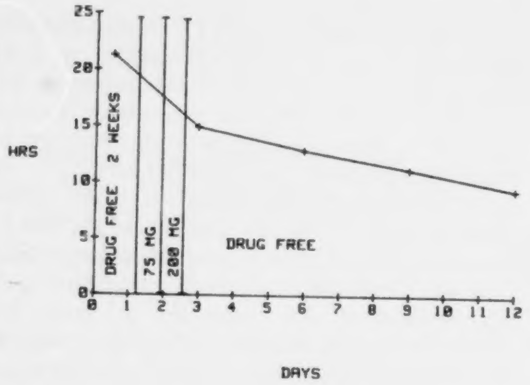


FIGURE 1. Mean Hamilton rating scale for 10 patients treated with IV clomipramine pulse-loading.

ter the second infusion. There was one report of blurred vision and three of dry mouth from patients receiving CMI, while 2 patients who received saline initially also complained of these side effects. Blood pressure remained stable throughout the infusions and there were no cardiographic changes post-infusion.

The HAM-D means changed over the course of the protocol as shown in Figure 1.

The mean HAM-D for the 10 patients just prior to the first CMI infusion was 21.5±SEM 2.8, as compared to 14.8±SEM 3.9 on the day (protocol day 7) following the second infusion ($p = .02$, Wilcoxon's signed rank test). Ten days after the second infusion of CMI (protocol day 16), the mean HAM-D had dropped further to 9.5±SEM 3.5 ($p < .02$ relative to protocol day 7). The immediate reduction in the HAM-D after the second infusion was primarily due to all patients reporting an improvement in their sleep. Eight patients, however, continued to report attenuation of their depressive symptoms over the ensuing 10 days. This progressive improvement occurred despite the fact that no additional medication was administered over this time. Only 2 of the 10 patients failed to clinically improve after the CMI infusions. Interestingly, one of these nonresponders became worse when sleep deprived for a pre-protocol EEG. At the conclusion of this study period, patients were placed on differing regimens of tricyclic therapy (either CMI or imipramine). Two of the 8 patients who had achieved near remission of their depression with i.v. CMI relapsed on oral CMI but improved again when lithium was added.

To control for the increased attention and nonspecific effects due to the procedures, 4 patients initially received two infusions of i.v. saline in a double-blind fashion. As shown by Figure 2, their mean HAM-D score slowly changed by 19% over a 10-day period following the second saline infusion. When these patients then received two CMI infusions, in an open fashion, their mean HAM-D score dropped rapidly by 43.4% within the ensuing 10 days.

Changes in EEG sleep were remarkable. The first REM period latency, after 2 weeks drug-free in hospital, was short (mean 40.5 SD±32.1 minutes): and sleep efficiency, the ratio of the time spent asleep to the total recording period, was less than expected for this age group (mean 73.5 SD±22.9%). Both these parameters are stigmata of moderate depression. Rapid-eye-movement (REM) sleep was completely suppressed on the 2 nights CMI was infused and then returned to the pre-infusion baseline over the ensuing 8 nights (Figure 3).

There was no significant change in sleep efficiency with the two CMI infusions ($p > .2$, $< .3$, paired t-test). This suggests that the considerable improvement which all patients reported in their sleep, after the CMI infusions, was due to a fundamental change in the quality of their sleep, rather than merely due to sedation. Delta sleep, subsequent to the CMI infusions, was not significantly altered.

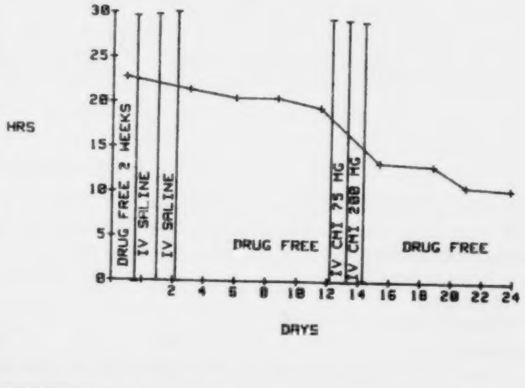


FIGURE 2. Mean Hamilton rating scale for 4 patients treated initially with IV saline.

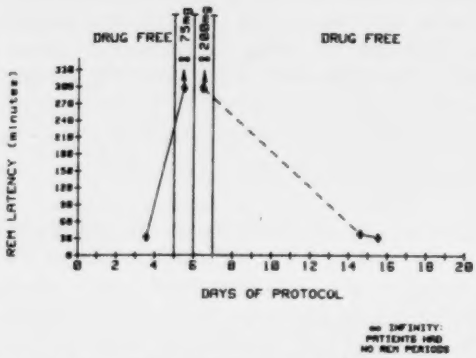


FIGURE 3. REM latency before and after treatment with IV clomipramine pulse-loading.

The saline infusions did not induce any significant changes in EEG sleep parameters.

Withdrawal pharmacokinetics performed after the second CMI infusion revealed a mean elimination half-life of 34 SD±3 hours. Concentration of zero time was 353 SD±127 ng/ml. Importantly, no significant amounts of desmethylclomipramine (>20 ng/ml) could be detected after the second infusion of CMI for at least 36 hours.

Discussion

Routine oral treatment with TCA's requires a minimum of 2 to 3 weeks at substantial doses to manifest optimal therapeutic effect (Hollister, 1983). It is well known that the extensive hepatic first-pass metabolism of orally administered TCAs prevents the rapid achievement of therapeutically effective blood levels (Evans et al., 1980). It is thus puzzling, as Klein et al. (1980) have noted, that there is such a paucity of studies on parenteral administration of these drugs. With respect to the i.v. administration of CMI, there have been several anecdotal reports and open studies attesting to its safety and superior efficacy in depression (Collins, 1970; Escobar et al., 1976; O'Flanagan, 1973; Symes, 1973), refractory depression (Dudley, 1980), and obsessive-compulsive disorder (Warneke, 1984).

There have been two double-blind controlled studies published in the English literature, comparing oral and i.v. routes of administration (Escobar, 1973; Faravelli, 1983). Both of these studies failed to show a significant difference in percent reduction in Hamilton ratings between i.v. and oral treatment groups. There is some cause, however, for caution in interpreting both of these studies. In the case of Escobar's 1973 study, there was considerable heterogeneity of diagnoses, e.g., only 43% of the i.v. group were diagnosed as suffering from endogenous depression versus 76% of the oral group. In spite of this, the authors concluded that there was a mean onset of action of 4 days for the i.v. group and 5 days for the oral. The same researchers in a subsequent paper (Escobar et al., 1976) commented on the importance of diagnostic criteria, and concluded "The results of this open trial, where specific diagnostic criteria were used, suggest i.v. administration of CMI to be a safe and feasible procedure, providing rapid therapeutic effects almost exclusively on unipolar and bipolar depressions, and a poor response in secondary affective disorders."

With regard to the more recent Faravelli paper, patients were begun at .5 mg/kg CMI, in a single a.m. dose, and raised to a maximum dose of 2 mg/kg after 10 days. At the end of 4 weeks, 30% of the patients had not achieved steady-state; combined plasma levels for CMI and its desmethyl metabolite were the same for both i.v. and oral groups and, thus, it is perhaps not entirely surprising that therapeutic response was equivalent. The authors suggest that a minimum, mean combined plasma level of 175 ng/ml is necessary for therapeutic improvement. Since it took 3 weeks to achieve these minimum levels in both groups of their patients, the important question still remained: If therapeutic levels are reached earlier, do patients improve earlier? Our data would appear to answer this question in the affirmative.

The evidence for impaired indoleaminergic functioning in subtypes of depressed patients, while not conclusive, remains as a highly viable hypothesis (Van Praag, 1984a). CMI, of all the TCAs, has consistently been shown to be the most potent inhibitor of the serotonin carrier pump in vitro (Tuck & Punell, 1973) and in vivo (Åsberg et al., 1977). Clinically, however, the significance of this has been obscured by the fact that the major metabolite of CMI, desmethylclomipramine (DCMI), is usually present in much greater concentrations (DCMI/CMI = 2.0–5.0) than CMI after oral administration and is a potent inhibitor of noradrenaline uptake (Mulgirigama et al., 1977). It has been suggested that increasing the serotonicity of orally administered CMI through the addition of 5-HTP and a peripheral decarboxylase inhibitor may shorten the latent period before a therapeutic response is observed (Van Praag, 1984b). Pulse-loading with i.v. CMI creates a system of moderate serotonicity, through the virtual absence of DCMI, and with extensive bioavailability to the central nervous system. It is also of interest to compare the results achieved by giving oral CMI at a dose of 225 mg/day (Van Praag, 1984b) as opposed to a total i.v. dose of 275 mg (Figure 4). Although there are obvious limitations to such a comparison, the effect nonetheless is striking and impels us to further investigation.

The magnitude of suppression of REM sleep by antidepressants may be predictive of clinical response (Kupfer et al., 1981b). Consistent with earlier preliminary work (Lacey et al., 1977), we found a profound suppression of REM sleep with parenteral CMI. The return of REM parameters to their pre-infusion state during the drug-free interval may herald an impending worsening of the patient's clinical status, which was aborted by initiating maintenance treatment. Alternatively, as has been suggested in sleep deprivation studies (Vogel et al., 1980), the buildup of REM pressure, i.e., rebound itself, may be associated with clinical improvement. Of considerable interest is the finding that patients who respond to sleep deprivation have a greater likelihood of response to CMI infusions (Wirz-Justice, 1976). It is possible that this procedure may delineate a group of patients requiring serotonergic agents (Fahndrich, 1983).

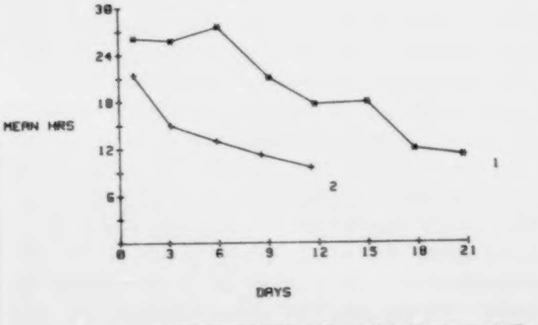


FIGURE 4. Comparative response of oral versus IV clomipramine.

Eight of the 10 patients in our pilot study began to evidence clinical improvement after achieving transient supra-therapeutic plasma levels of clomipramine, while their plasma levels were, in fact, declining. This paradox may be a manifestation of the activation of a time-dependent cellular process, as has been suggested for similar findings in animals (Chiodo & Antelman, 1980). Alternatively, it may represent a well-articulated pharmacodynamic process, anticlockwise hysteresis (Holford & Sheiner, 1981). This process occurs when there is an equilibration delay between systems (blood) concentrations and the effects (receptor) sites. The pattern of response observed in our patients seems to mirror that seen after the achievement of steady-state levels in patients treated with imipramine (Perel, 1983). This leads to the tentative conclusion that pharmacokinetic processes occuring in TCA therapy are mostly, but not entirely, the major determinants controlling the response lag time. Definition of the role of each factor awaits findings from a large-scale study currently underway.

References

Asberg, M., Ringberger, V., Sjöqvist, F., et al. Monoamine metabolites in cerebrospinal fluid and serotonin-uptake inhibition during treatment with chlorimipramine. *Clin. Pharmacol. Ther.*, 21:201–207, 1977.

Brown, R., and Manno, J. ESTRIP: A basic computer program for obtaining initial polyexponential parameter estimates. *J. Pharm. Sci.*, 67:1687–1691, 1978.

Chiodo, L.A., and Antelman, S.M. Repeated tricyclics induce a progressive dopamine autoreceptor subsensitivity independent of daily drug treatment. *Nature*, 287:451–454, 1980.

Collins, G.H. I.V. Clomipramine in the treatment of severe depression. *Br. J. Psychiatry*, 117:211–212, 1970.

Dudley, D.D., Volberding, N., and Loebel, J.P. Intravenous chlorimipramine and refractory depression. *Gen. Hosp. Psychiatry*, 2:61–64, 1980.

Escobar, J.I., Flemenbaum, A., and Schiele, B.C. Chlorimipramine: A double-blind comparison of intravenous versus oral administration in depressed patients. *Psychopharmacologia*, 33:111–116, 1973.

Escobar, J.I., Teeter, R.R., Tuason, V.B., et al. Intravenous chlorimipramine and depressive subtypes. *Dis. Nerv. Syst.*, 37:325–328, 1976.

Evans, L.E., Bett, J.H., Cox, J.R., et al. The bioavailability of oral and parenteral chlorimipramine. *Prog. Neuro-Psychopharmacol.*, 4:293–302, 1980.

Fahndrich, E. Effect of sleep deprivation as a predictor of treatment response to antidepressant medication. *Acta Psychiatr. Scand.*, 68:341–344, 1983.

Faravelli, C., Broadhurst, A.D., Ambonetti, A., et al. Double-blind trial with oral versus intravenous clomipramine in primary depression. *Biol. Psychiatry*, 18:695–706, 1983.

Holford, N.H.G., and Sheiner, L.B. Understanding the dose-effect relationships: Clinical application of pharmacokinetic-pharmacodynamic models. *Clin. Pharmacokinet.*, 6:429–453, 1981.

Hollister, L.E. *Clinical Pharmacology of Psychotherapeutic Drugs*, 2nd Ed. New York: Churchill Livingston, 1983, p. 94.

Klein, D.F., Gittelman, R., Quitkin, F., and Rifkin, A. *Diagnosis and Drug Treatment of Psychiatric Disorders*. 2nd Ed. Baltimore, Md.: Williams & Wilkins, 1980, p. 275.

Kupfer, D.J., Shaw, D.H., Ulrich, R., et al. Application of automated delta analysis. *Sleep Res.*, 10:173, 1981a.

Kupfer, D.J., Spiker, D.G., Coble, P.A., et al. Sleep and treatment prediction in endogenous depression. *Am. J. Psychiatry*, 138:429–434, 1981b.

Lacey, J.H., Crisp, A.H., Crutchfield M., et al. Chlorimipramine and sleep. A preliminary communication. *Post Grad. Med. J.*, 53:35–40, 1977.

Mulgirigama, L.D., Pare, C.M., Turner, P., et al. Tyramine pressor responses and plasma levels during tricyclic antidepressant therapy. *Postgrad. Med. J.*, (Suppl.4):30–34, 1977.

Niazi, S. Application of a programmable calculator in data fitting according to one and two compartment open models in pharmacokinetics. *Comput. Prog. Biomed.*, 7:41, 1977.

O'Flanagan, P.M. A Clomipramine (Anafranil) infusion unit. *J. Int. Med. Res.*, 1:375–381, 1973.

Perel, J.M. Tricyclic antidepressant plasma levels, pharmacokinetics, and clinical outcome. In: Grinspoon, L. (ed.), *Psychiatry Update*, Vol. 2. Washington, D.C.: American Psychiatric Press, 1983, pp. 491–511.

Sethy, V.H., and Day, J.S. Down-regulation of beta-adrenergic receptors within 24 hr after intravenous infusion of antidepressants. Abstract presented at the meeting of Society of Neuroscience, 1985.

Stiller, R.L., Perel, J.M., Pollock, B.G., and Foglia, J. Quantitative analysis of clomipramine. (In preparation, 1985).

Sulser, F. Mode of action of antidepressant drugs. *J. Clin. Psychiatry*, 44:14–20, 1983.

Symes, M.H. Oral and intravenous clomipramine (anafranil). *J. Int. Med. Res.*, 1:352–360, 1973.

Tuck, J.R., and Punell, G. Uptake of (^{3}H)5-hydroxytryptamine and (^{3}H)noradrenaline by slices of rat brain incubated in plasma from patients treated with chlorimipramine, imipramine or amitriptyline. *J. Pharm. Pharmacol.*, 25:573–374, 1973.

Van Praag, H.M. Depression, suicide, and serotonin metabolism in the brain. In: Post, R.M., and Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders*. Baltimore, Md.: Williams & Wilkins, 1984a, pp. 601–618.

Van Praag, H.M. In search of the mode of action of antidepressants: 5-HTP/tyrosine mixtures in depression. In: Usdin, E., Åsberg, M., Bertilsson, L., and Sjöqvist, F. (eds.), *Frontiers in Biochemical and Pharmacological Research in Depression*. New York: Raven Press, 1984b, pp. 301–314.

Vogel, G.W., Vogel, F., McAbee, R.S., and Thurmond, A.J. Improvement of depression by REM sleep deprivation. *Arch. Gen. Psychiatry*, 37:247–253, 1980.

Warneke, L.B. The use of intravenous chlorimipramine in the treatment of obsessive compulsive disorder. *Can. J. Psychiatry*, 29:135–141, 1984.

Wirz-Justice, A., Puhringer, W., and Hole, G. Sleep deprivation and clomipramine in endogenous depression. *Lancet*, 23:912, 1976.

Yamaoka, K., Tanigawara, Y., Nakagawa, T., and Uno, T. Pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobiodyn.*, 4:879–885, 1981.

Pharmacology of Combined Antidepressant/H_2-Blocking Drug Therapy

Stephen H. Curry, Ph.D.,[1] C. Lindsay DeVane, Pharm.D.,[1] and M. Michael Wolfe, M.D.[1]

Introduction

It has been observed that before the advent of antagonists of histamine-induced gastric acid secretion (H_2 blocking drugs), the treatment of ulcers with centrally acting drugs was common: nowadays, with H_2 blocking drugs available there is a tendency to treat psychiatric conditions with cimetidine. While this statement is clearly too broad to be universally true, it reflects increasing interest in two-pronged attack on human disease, and the combination of tricyclic antidepressants, and H_2 blocking drugs is an important component of this approach (Abernathy et al., 1984a: Somogyi & Gugler, 1979).

Little is currently known about the effects of individual tricyclic antidepressants and H_2 blocking drugs on each other. This is in spite of the well established fact that cimetidine inhibits hepatic microsomal enzymes and reduces hepatic blood flow (Puuronen & Pelkonen, 1979). Cimetidine is known to affect a wide variety of other drugs, including oral anticoagulants (Hetzel et al., 1979: Silver & Bell, 1979: Wallin et al., 1979: Willoughby, 1979), antipyrine (Roberts et al., 1981), phenytoin (Hetzel et al., 1981), ethanol (Feely & Wood, 1981), diazepam (Klotz & Reimann, 1980), chlordiazepoxide (Desmond et al., 1980), caffeine (May et al., 1982), theophylline (Campbell et al., 1981: Reitberg et al., 1981: Roberts et al., 1981), propranolol (Feely et al., 1981: Reimann et al., 1981), and lidocaine (Feely et al., 1982). In contrast, ranitidine appears less likely to affect other drugs (Abernathy et al., 1984a).

In one study with two oral antidepressants, administered separately, cimetidine decreased maximum plasma levels of imipramine, which is primarily metabolized by demethylation, but had no effect on plasma concentrations of nortriptyline, which is primarily metabolized by hydroxylation (Henauer & Hollister, 1984). With imipramine, the area under the curve of plasma levels against time was increased by cimetidine, implying inhibited metabolism. In another study, with imipramine only, after intravenous doses the elimination half-life of imipramine was increased, with no change in volume of distribution (Abernathy et al., 1984b). There was also no change in protein binding. After oral doses, the peak concentration, the area under the curve, and the half-life were all increased by cimetidine.

Methods

A recent study conducted at the University of Florida involved pretreatment with cimetidine or placebo for 2 days, amitriptyline test doses of 25 and 50 mg, blood samples for assay of amitriptyline and nortriptyline, measurement of blood pressure and pulse rate, and application of a digit symbol substitution test and a battery of visual analogue scales. Plasma concentrations were evaluated for time of maximum recorded concentration (T_{max}), maximum recorded concentration (Cp_{max}), half-life from 8 to 48 hours past amitriptyline dosage ($T_{1/2}$), and area under the curve (AUC). The AUC for amitriptyline included extrapolation to infinity using the formula $Cp_{(48)}/\beta$ where $Cp_{(48)}$ is the 48-hour concentration and β is the terminal phase rate constant for amitriptyline (AUC_{∞}). This was not done for nortriptyline, for which $AUC_{(0\text{-}48)}$ was calculated. Statistical analysis employed analysis of variance designed to identify differences between treatments, times, and subjects, and t tests for unrelated samples to determine significant differences between means. A level of $p<0.05$ was taken

---

[1] Colleges of Pharmacy and Medicine, University of Florida, Gainesville, FL 32610.

to indicate significance throughout. The methods and results of this work are presented in detail in two papers submitted for publication (Curry et al., in press: submitted, 1985).

Results

In a pilot experiment, it was shown that Cp_{max} and AUC were linearly related to amitriptyline dose for both amitriptyline and nortriptyline, with both measurements higher after higher doses. T_{max} and $T_{1/2}$ were similar for both 25 and 50 mg doses. Digit symbol substitution showed a dose-dependent depression in performance, with the greater depression after the 50 mg dose. Visual analogue scales recording sedation were similarly affected, but with no difference at the two dose levels.

In the interaction experiment, pretreatment with cimetidine apparently doubled Cp_{max} and AUC for amitriptyline, but halved these two measurements for nortriptyline. T_{max} and $T_{1/2}$ data were not affected. Mean concentration data are in the Table. Digit symbol substitution results correlated with plasma amitriptyline changes, and visual analogue scale data correlated with plasma nortriptyline changes. Blood pressure and pulse rate changes were consistent with plasma amitriptyline changes.

Discussion

At the commencement of this experiment, a cimetidine-induced slowing of amitriptyline metabolism was anticipated, and this was expected to affect plasma concentrations of amitriptyline and nortriptyline. The observations support this hypothesis. There was no reason to expect changes in volumes of distribution, protein binding, or rate of transfer of amitriptyline from the gastrointestinal tract to the general circulation. Furthermore, there was no reason to expect a detectable effect on nortriptyline kinetics. Since T_{max} and $T_{1/2}$ stayed unchanged, and Cp_{max} and AUC were much affected, we consider that this impairment is primarily of presystemic metabolism of amitriptyline (first-pass effect) such that the fraction of the dose reaching the general circulation as unmetabolized amitriptyline increased.

Since this study was conducted with single doses in healthy volunteers, caution must be exercised in extrapolation to long-term treatment in patients. However, it is reasonable to predict that this interaction will occur in patients, with doubled steady-state amitriptyline concentrations and halved steady-state nortriptyline concentrations predicted. This clearly has implications for patient management, especially in regard to plasma level monitoring, and a need for a clinical study of the importance of this interaction is indicated.

Acknowledgments: We are grateful to our subjects for their participation in this project, to the staff of the Clinical Research Center of the J. Hillis Miller Health Center of the University of Florida for their supervision of dosing and blood sampling, and to Mrs. Sandy Sundlof and Mr. Ron Miller for their skilled technical assistance in the drug assays.

TABLE

Plasma Concentrations (ng/ml) of Amitriptyline and Nortriptyline After Single Doses of Amitriptyline (25 mg) With and Without Cimetidine Pretreatment

Pretreatment	Compound Measured	Time After Amitriptyline Dose (hours)													
		0	1	2	3	4	5	6	8	10	12	24	30	36	48
Placebo	Amitriptyline	0	4.1	10.0	13.7	9.8	8.7	7.1	5.4	4.8	3.8	2.7	2.0	1.9	1.0
		(-)	(1.2)	(1.9)	(1.8)	(1.1)	(1.1)	(0.9)	(0.7)	(0.7)	(0.6)	(0.4)	(0.3)	(0.4)	(0.3)
	Nortriptyline	0	0.3	2.1	4.2	4.6	6.2	4.8	4.4	3.8	4.4	2.4	2.8	2.5	1.6
		(-)	(0.2)	(1.0)	(1.0)	(1.1)	(2.1)	(1.3)	(1.1)	(0.9)	(1.4)	(0.7)	(0.6)	(0.6)	(0.4)
Cimetidine	Amitriptyline	0	3.6	13.9	18.8	15.9	13.3	12.8	9.5	7.5	7.6	6.2	5.7	3.9	1.9
		(-)	(1.0)	(2.1)	(2.9)	(2.4)	(1.7)	(2.6)	(1.9)	(1.2)	(1.8)	(1.9)	(1.7)	(1.1)	(0.7)
	Nortriptyline	0	0	1.0	2.2	2.1	2.1	3.1	1.9	1.2	2.0	1.5	1.8	1.7	1.0
		(-)	(-)	(0.9)	(1.6)	(1.2)	(1.1)	(1.3)	(0.8)	(0.7)	(0.5)	(0.5)	(0.4)	(0.5)	(0.4)

(Figures are means with S.E.M. in brackets)

References

Abernathy, D.R., Greenblatt, D.J., Eshelman, F.N., and Shader, R.I. Ranitidine does not impair oxidative or conjugative metabolism: Noninteraction with antipyrine, diazepam, or lorazepam. *Clin. Pharmacol. Ther.*, 35:188–192, 1984a.

Abernathy, D.R., Greenblatt, D.J., and Shader, R.I. Imipramine-cimetidine interaction: Impairment of clearance and enhanced absolute bioavailability. *J. Pharmacol. Exp. Ther.*, 229:702–705, 1984b.

Campbell, M.A., Plachetka, J.R., Jackson, J.E., et al. Cimetidine decreased theophylline clearance. *Ann. Intern. Med.*, 95:68–69, 1981.

Curry, S.H., DeVane, C.L., and Wolfe, M.M. Hypotension and bradycardia induced by amitriptyline in healthy volunteers. *Eur. J. Clin. Pharmacol.* (In press)

Curry, S.H., DeVane, C.L., and Wolfe, M.M. Hypotension and bradycardia induced by amitriptyline in healthy volunteers. *J. Clin. Psychopharmacol.* (Submitted, 1985)

Desmond, P.V., Patwardhan, R.V., Schenker, S., and Speeg, K.V., Jr. Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. *Ann. Intern. Med.*, 93:266–268, 1980.

Feely, J., and Wood, A.J. Effects of cimetidine interaction on the elimination and actions of ethanol. *JAMA*, 43:66–69, 1982.

Feely, J., Wilkinson, G.R., McAllister, C.B., and Wood, A.J.J. Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann. Intern. Med.*, 96:592–594, 1982.

Feely, J., Wilkinson, G.R., and Wood, A.J.J. Reduction in liver blood flow and propranolol metabolism by cimetidine. *N. Engl. J. Med.*, 304:692–695, 1981.

Henauer, S.A., and Hollister, L.E. Cimetidine interaction with imipramine and nortriptyline. *Clin. Pharmacol. Ther.*, 35:183–187, 1984.

Hetzel, D.J., Birkett, D., and Miners, J. Cimetidine interaction with warfarin. *Lancet*, 2:639, 1979.

Hetzel, D.J., Bochner, F., Hallpike, J.R., et al. Cimetidine interaction with phenytoin. *Br. Med. J.*, 282:1512, 1981.

Klotz, U., and Reimann, I. Delayed clearance of diazepam due to cimetidine. *N. Engl. J. Med.*, 302:1012–1014, 1980.

May, D.C., Jarboe, C.H., Van Bakel, A.B., and Williams, W.M. Effects of cimetidine on caffeine disposition in smokers and nonsmokers. *Clin. Pharmacol. Ther.*, 31:656–661, 1982.

Puurunen, J., and Pelkonen, O. Cimetidine inhibits microsomal drug metabolism in the rat. *Eur. J. Pharmacol.*, 55:335–336, 1979.

Reimann, I.W., Klotz, U., Siems, B., and Frohlich, J.C. Cimetidine increases steady-state plasma levels of propranolol. *Br. J. Clin. Pharmacol.*, 12:785–790, 1981.

Reitberg, D.P., Bernhard, H., and Schentag, J.J. Alteration of theophylline clearance and half-time by cimetidine in normal volunteers. *Ann. Intern. Med.*, 95:582–585, 1981.

Roberts, R.K., Grice, J., Wood, L., et al. Cimetidine impairs the elimination of theophylline and antipyrine. *Gastroenterology*, 81:19–21, 1981.

Silver, B.A., and Bell, W.R. Cimetidine potentiation of the hypoprothrombinemic effect of warfarin. *Ann. Intern. Med.*, 90:348–349, 1979.

Somogyi, A., and Gugler, R. Drug interactions with cimetidine. *Clin. Pharmacokinet.*, 7:23–41, 1982.

Wallin, B.A., Jacknowitz, A., and Raich, P.C. Cimetidine and the effect of warfarin. *Ann. Intern. Med.*, 90:993, 1979.

Willoughby, J.M.T. Cimetidine: Interaction with oral anticoagulants in man. *Lancet*, 2:317–319, 1979.

Free Communications—Session B

CHAIRS: *Hillary Lee, Ph.D.*
Food and Drug Administration
Rockville, Maryland

and *Thomas P. Laughren, M.D.*
Food and Drug Administration
Rockville, Maryland

Methylphenidate: Rate-Dependent Effects on Hyperactivity

Mark D. Rapport, Ph.D.,[1] and George J. DuPaul, Ph.D.[1]

Hyperactivity is currently viewed as an Attention Deficit Disorder (ADD) characterized by a short attention span, impulsivity, and excessive, nongoal directed activity which is pervasive over time and across settings (American Psychiatric Association, 1980). In recent years, there has been an increasing urgency in establishing effective treatment protocols for ADD children owing to the relatively high prevalence rate (i.e., 3% to 5% of school-age children) and protracted nature (Satterfield et al., 1982) of the disorder.

The most popular treatment for this disorder over the past decade (Rapport, 1983) involves the prescription of psychostimulant medication (e.g., methylphenidate, dextroamphetamine and, more recently, pemoline), which improves the performance of most ADD children on laboratory tests of sustained attention (Sykes et al., 1973), reflection-impulsivity (Brown & Sleator, 1979; Rapport et al., 1985a), and short-term memory (Rapport et al., 1985b; Sprague & Sleator, 1977), as well as their classroom on-task and academic completion rates (Rapport et al., 1980, 1982, 1985b). Despite the widespread use of psychostimulants with this population (Safer & Krager, 1983), there remains a dearth of information regarding the underlying mechanisms and/or specific overt variables which may contribute to their effectiveness.

Conversely, studies of central nervous system (CNS) stimulant effects in animal species have consistently shown that the drug effect often depends upon the rate of occurrence (the control rate) of a given behavior in a drug-free state, i.e., that the behavioral effect of the drug is rate-dependent (Dews, 1977; Dews & Wenger, 1977).

The results of laboratory investigations examining the existence of the rate-dependency phenomenon with human adults have been equivocal thus far (Dews & Morse, 1958; Stitzer & Domino, 1974). Recent investigations, however, have shown preliminary evidence of rate-dependent effects of methylphenidate and/or D-amphetamine upon the in-seat activity (Robbins & Sahakian, 1977) and operant key-pressing (Rapport et al., 1985) behaviors of ADD children. Unfortunately, examinations of rate-dependent effects of stimulant medication have been confined thus far to behaviors exhibited under contrived conditions and/or laboratory settings, thus limiting the applicability and external validity of the findings.

The present investigation sought to extend previous findings by examining the effects of several doses of methylphenidate upon a behavior which is integrally related to the measurement of an attention deficit (viz., the frequency of on-task behavior) in a setting which is especially problematic for most ADD children: The classroom. The purpose of the study was to determine the extent to which an overt behavioral variable (i.e., the rate of on-task behavior in the absence of medication) contributes to the medication effect upon the frequency of classroom on-task behavior or, stated differently, whether stimulant effects upon an exigent behavior in *esse situ* could be explained via a rate-dependency analysis.

---

[1] Children's Learning Clinic, Department of Psychology, University of Rhode Island, Kingston, RI 02881-0808.

The order in which authors are listed was randomly determined. Both authors contributed equally to the manuscript.

Materials and Methods

Children with chronic problems of inattention, impulsivity, and overactivity were referred to the Children's Learning Clinic (CLC) of the University of Rhode Island by local pediatricians and school system personnel. A total of 20 (18 males and 2 females) children (weight range = 18.9 to 38.25 kg; median = 24.3 kg) between the ages of 6 and 11 years (mean = 8.1 years) participated in the study after obtaining informed consent from their parents and meeting each of the following criteria: a) an independent diagnosis by the child's pediatrician and CLC's directing clinical psychologist using DSM-III (American Psychiatric Association, 1980) criteria for Attention Deficit Disorder with Hyperactivity (ADD-H); b) a maternal report of a developmental history consistent with hyperactivity (Barkley, 1981); c) a maternal rating of at least two standard deviations above the mean for the child's age on the Werry-Weiss-Peters Activity Scale (Routh et al., 1981); d) a teacher rating on the Abbreviated Conners Teacher Rating Scale (ACTRS) above 15, the designated cutoff score for hyperactivity (Werry et al., 1975); e) performance on the Matching Familiar Figures (MFF) Test (Kagan et al., 1964) characteristic of a "fast-inaccurate or impulsive" responder, i.e., faster than average responses and higher than average error rates for the child's age; and f) free from any gross neurological, sensory, or motor impairment and not presently taking medication.

All children were of average or above average intelligence (mean IQ = 105; SD = 10.8) as assessed by the Peabody Picture Vocabulary Test-Revised, Form L (Dunn & Dunn, 1981), from families of low to middle socioeconomic status (Hollingshead, 1975), and "favorable responders" to methylphenidate according to recently defined criteria (Rapport et al., 1985a,b).

A double-blind, placebo-controlled, within-subject (crossover) design was used in which all children received each of the four doses following baseline measures. Order of drug administration was determined by randomly assigning each child to one of 24 possible counterbalanced drug orders. Methylphenidate was prescribed by each child's respective pediatrician in the following doses: placebo, 5 mg (range = .13 to .26 mg/kg), 10 mg (range = .26 to .53 mg/kg), and 15 mg (range = .39 to .79 mg/kg). Fixed doses (vs. mg/kg) were prescribed to reflect normal pediatric practice in the United States (Physician's Desk Reference, 1985) and because optimal dose has been shown not to depend on a child's body weight (Kinsbourne & Swanson, 1979; Rapport et al., 1985a,b). The methylphenidate was packaged in colored gelatin capsules by the pharmacist to avoid detection of dose and taste. Capsules were placed in individually dated envelopes to insure accurate dose administration.

Children were seen weekly at the CLC for individual testing using a battery of cognitive, learning, impulsivity, attention, and motor tasks during an intensive 8-week study period, which is detailed elsewhere (Rapport et al., 1985a,b). Only the classroom measures will be described herein.

The classroom phase of the experiment involved 5 consecutive weeks of observation. Following baseline data collection (1st week), parents were given a week's worth of medication in pre-dated envelopes at one dose level (i.e., placebo, 5, 10, or 15 mg methylphenidate). This procedure continued until a child received each dose for 7 consecutive days. All weekly dosage changes (e.g., switching from 15 mg to 5 mg) occurred on Saturdays to control for potential rebound effects. Parents were instructed to give their children a medication capsule each morning, 1/2 hr prior to breakfast, and to tell them it was a vitamin supplement (i.e., to help control for expectancy (Rapport et al., 1982). Both used and unused envelopes were returned to control for medication compliance.

Children were observed in their regular classrooms for 20 min intervals, 3 days per week across the 5-week evaluation period. Classroom observations began 1 1/2 to 2 hrs after the children's morning medication in an effort to improve upon previous dose response studies (Sprague & Sleator, 1977) by controlling for time after medication. Children completed in-seat academic work assigned by the teacher during this time and were unobtrusively observed by trained undergraduate and graduate students for 60 continuous intervals during each observation period throughout the study. Each interval was divided into 15 sec of observation followed by 5 sec for recording. Classroom teachers and observers were blind to both when medication was administered and specific doses.

A child's behavior was categorized as either on-task or off-task in a manner identical to that used in earlier studies (Rapport et al., 1980, 1982, 1985b). A response was defined as a discrete 15-sec interval in which a child was observed to be on-task. Response rate was obtained for each child by calculating the mean number of responses per 20 min interval (maximum daily response rate = 60 per 20 min) over the 3-day observation period within each experimental condition. Interobserver reliability checks of child behavior were taken on 33% of the observation days for all children, and at least once during each experimental phase. Obtained reliability estimates (Hopkins & Hermann, 1977) were computed for occurrence (mean = .95), nonoccurrence (mean = .88), and overall agreement (mean = .95) (Bijou et al., 1968), with a mean Kappa value of .83 obtained for all observations.

Results

The mean on-task response rates (responses per 20 min) and standard deviations for baseline, placebo, and the three methylphenidate (5, 10, 15 mg) conditions are presented in the Table. A one-way analysis of variance with repeated measures across the five conditions was significant ($F = 24.92$; d.f. = 4,76; $p < .001$), with a follow-up Newman-Keuls test revealing significantly greater mean on-task response rates in all three methylphenidate conditions compared to baseline and placebo ($p < .01$). The mean on-task response rate in the 15 mg condition was significantly greater than those in 5 ($p < .01$) and 10 ($p < .05$) mg. No further significant differences were found.

TABLE

Mean On-Task Response Rates (Responses per 20 min) and Associated Standard Deviations (SD) for Baseline, Placebo, and Three Active Methylphenidate Conditions (5, 10, 15 mg) in a Sample ($N = 20$) of ADD Children

	On-Task Response Rate	
Condition	Mean	SD
Baseline	32.37	12.32
Placebo	32.40	15.68
5 mg	41.90	11.21
10 mg	46.18	11.26
15 mg	51.96	4.63

Note: The maximum daily on-task response rate = 60.00.

Rate-dependent effects of psychostimulants upon behavior have been classically analyzed by examining the relationship between the control response rate (response rate under placebo) and the output ratio (the ratio of response rate after medication to control response rate) (Dews & Wenger, 1977). In keeping with tradition, Figure 1 was drawn with log control rate plotted on the abscissa and log output ratio (drug rate/control rate × 100) on the ordinate with regression lines for each dose fitted by the method of least squares. Correlations between the two variables were −.96, −.98, and −.99 for 5, 10, and 15 mg, respectively, with all three significantly different from zero ($p < .001$). Thus, a negative linear relationship was found between control rate and output ratio at all three doses. A test for equality of slopes, with control rate as the covariate and each dose treated as a separate group, revealed that the 15 mg slope was significantly steeper than both the 5 and 10 mg slopes ($F = 11.28$; d.f. = 2,54; $p < .001$).

A final analysis was performed owing to the controversy regarding whether fixed-dose or milligram per kilogram (mg/kg) plots

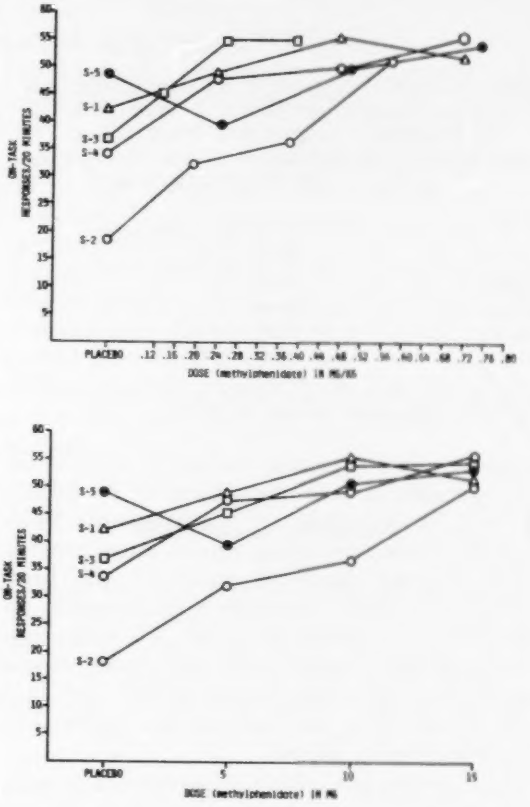


FIGURE 1. Log output ratio (drug rate/placebo control rate × 100) as a function of log placebo control rate for on-task response rate (responses per 20 min). Regression lines were fitted by the method of least squares for each dose. Individual scores across doses are represented by closed circles (5 mg), triangles (10 mg), and squares (15 mg).

should be used in evaluating dose effects in children receiving methylphenidate (Rapport et al., 1985a,b). Consequently, the on-task response rates of five children randomly selected from the participant group ($N = 20$) were plotted using both fixed-dose and mg/kg plots (*see* Figure 2). This procedure was used to facilitate graphical illustration and interpretation (i.e., drawn curves using all 20 children were too difficult to visually follow). A test of equality of the regression lines showed no signficant differences between the slopes of the dose-response curves obtained from the random subsample and the remaining 15 children, indicating that the former were representative of the total sample.

In examining the curves shown in Figure 2, it appears that children's on-task response rates show similar dose-related changes using both fixed-dose and mg/kg dose-response plots. Four of the five children (S-2, S-3, S-4, & S-5) performed optimally at the highest dose (compared with lower doses) regardless of whether fixed-dose or mg/kg plots were used; thus, corroborating the results of previous investigations showing individual responsivity to psychostimulant medication (Rapport et al., 1985a,b). Furthermore, weight calculated on a mg/kg basis does not appear to account for the obtained individual differences (e.g., note the differences in on-task behavior between S-2 and S-3 at .38 mg/kg).

Discussion

Our data have implications for both pediatric psychopharmacological research and the clinical practice of monitoring psychostimulants in ADD children. A review of the psychopharmacological research on ADD indicates that there have been no prospective empirical investigations which systematically assess whether a child's drug-free rate of behavior contributes to drug responsiveness (Reatig, 1984). The data presented herein establish this relationship by showing drug-induced proportional changes in ADD chil-

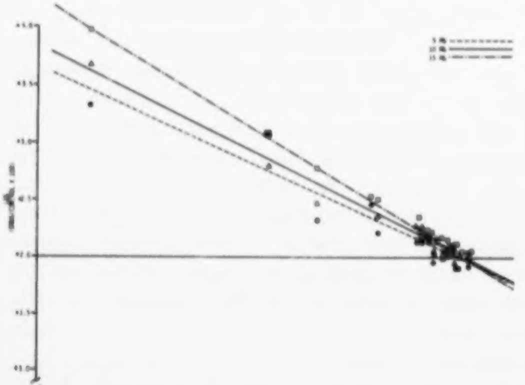


FIGURE 2. The mean on-task response rate per 20 min interval for five hyperactive children randomly chosen from the total group ($N = 20$) on placebo and three doses of methylphenidate. The top panel depicts dose-response curves in mg/kg. The lower panel shows dose-response curves in mg for comparison.

dren's attention which are consistent with the rate-dependency phenomenon found with lower species (Dews, 1977; Dews & Wenger, 1977). Thus, the rate of a child's overt behavior in a drug-free state clearly contributes to the effect of CNS stimulant on that behavior. The strength and shape of this relationship are affected by dose and the child's unique reaction to the drug, yet appear unrelated to body weight. Dosage should be directly manipulated in pediatric psychopharmacological studies and the cumbersome practice of using mg/kg dosage schedules may no longer be necessary (Rapport et al., 1985a).

The CNS stimulant methylphenidate is the most widely studied and prescribed medication for ADD children in the United States (Safer & Krager, 1983). Physicians typically use the titration method (Physician's Desk Reference, 1985) of increasing dosage until favorable reports are obtained by the parents and/or teacher. Both of these sources tend to base their judgments on the child's social behavior, which generally necessitates higher dosages for improvement than does cognitive performance (Sprague & Sleator, 1977). In order to assess the effects of methylphenidate on classroom performance, our data indicate that physicians need to obtain information regarding the child's rate of academic behavior both before and during clinical drug trials. School-based paraprofessionals may need to be recruited to provide this information to the pediatrician. The contribution of other variables (e.g., an individual's past history) and/or specific behaviors (academic completion and accuracy rates) to CNS stimulant effects in ADD children will need to be explicated in future studies.

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Washington, D.C.: Author, 1980.

Barkley, R.A. *Hyperactive Children: A Handbook for Diagnosis and Treatment*. New York: Guilford Press, 1981.

Bijou, S.W., Peterson, R.F., and Ault, M.H. A method to integrate descriptive and experimental field studies at the level of data and empirical concepts. *J. Appl. Behav. Anal.*, 1:175–191, 1968.

Brown, A.T., and Sleator, E.K. Methylphenidate in hyperkinetic children: Differences in dose effects on impulsive behavior. *Pediatrics*, 64:408–411, 1979.

Dews, P.B. Rate-dependency hypothesis. *Science*, 198:1182, 1977.

Dews, P.B., and Morse, W.H. Some observations on an operant in human subjects and its modification by dextroamphetamine. *J. Exp. Anal. Behav.*, 1:359–364, 1958.

Dews, P.B., and Wenger, G.A. Rate-dependency of the behavioral effects of amphetamine. In: Thompson, T., and Dews, P.B. (eds.), *Advances in Behavioral Pharmacology*, Vol. 1. New York: Academic Press, 1977.

Dunn, L.M., and Dunn, L.M. *Peabody Picture Vocabulary Test-Revised*. Circle Pines, Minn.: American Guidance Service, 1981.

Hollingshead, A.B. *Four Factor Index of Social Status*. New Haven: Yale University, 1975.

Hopkins, B.L., and Hermann, J.A. Evaluating interobserver reliability of interval data. *J. Appl. Behav. Anal.*, 10:121–126, 1977.

Kagan, J., Rosman, B.L., Day, D., et al. Information processing in the child: Significance of analytic and reflective attitudes. *Psychol. Monogr.*, 78, 1964.

Kinsbourne, M., and Swanson, J.M. Models of hyperactivity: Implications for diagnosis and treatment. In: Trites, R.L. (ed.), *Hyperactivity in Children: Etiology, Measurement and Treatment Implications*. Baltimore, Md.: University Park Press, 1979.

Physicians Desk Reference. Oradell, N.J.: Litton Industries, Inc., 1985.

Rapport, M.D. Attention deficit disorder with hyperactivity: Critical treatment parameters and their application in applied outcome research. In: Hersen, M., Eisler, R., and Miller, P. (eds.), *Progress in Behavior Modification*, Vol. 14. New York: Academic Press, 1983.

Rapport, M.D., DuPaul, G.J., and Smith, N.F. Rate-dependency and hyperactivity: Methylphenidate effects on operant responding. *Pharmacol. Biochem. Behav.*, 23:1–7, 1985.

Rapport, M.D., DuPaul, G.J., Stoner, G., et al. Attention deficit disorder with hyperactivity: The differential effects of methylphendiate on impulsivity. *Pediatrics*, 76:938–943, 1985a.

Rapport, M.D., Murphy, A., and Bailey, J.S. The effects of a response cost treatment tactic on hyperactive children. *J. School Psychol.*, 18:98–111, 1980.

Rapport, M.D., Murphy, A., and Bailey, J.S. Ritalin vs response cost in the control of hyperactive children: A within subject comparison. *J. Appl. Behav. Anal*, 15:205–215, 1982.

Rapport, M.D., Stoner, G., DuPaul, G.J., et al. Methylphenidate in hyperactive children: Differential effects of dose on academic, learning, and social behavior. *J. Abnorm. Child Psychol.*, 13:227–244, 1985b.

Reatig, N. Attention deficit disorder: A bibliography *Psychopharmacol Bull.*, 20(4):693–718, 1984.

Robbins, T.N., and Sahakian, B.J. "Paradoxical"effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behavioral pharmacology. *Neuropharmacology*, 18:931–950, 1979.

Routh, D.K., Schroeder, C.S., and O'Tauma, L. Development of activity level in children. *Dev. Psychol.*, 10:163–168, 1974.

Safer, D.J., and Krager, M.D. Trends in medication treatment of hyperactive school children. *Clin. Pediatr.*, 22:500–504, 1983.

Satterfield, J.H., Hoppe, C.M., and Schell, A.M. A prospective study of delinquency in 110 adolescent boys with attention deficit disorder and 88 normal boys. *Am. J. Psychiatry*, 139:795–798, 1982.

Sprague, R.L., and Sleator, E.K. Methylphenidate in hyperkinetic children: Differences in dose effects on learning and social behavior. *Science*, 198:1274–1276, 1977.

Stitzer, M., and Domino, E.F. Effects of d-amphetamine and secobarbital on key press rates in normal humans. *Arch. Int. Pharmacodyn. Ther.*, 207:288–297, 1974.

Sykes, D.H., Douglas, V.I., and Morgenstern, G. Sustained attention in hyperactive children. *J. Child Psychol. Psychiatry*, 14:213–220, 1973.

Werry, J., Sprague, R., and Cohen, M. Teacher rating scale for use in drug studies with children—An empirical study. *J. Abnorm. Child Psychol.*, 3:217–229, 1975.

The Therapeutic Effect of Clonidine in Attention Deficit Disorder With Hyperactivity: A Comparison With Placebo and Methylphenidate

Robert D. Hunt, M.D.,[1] Ruud B. Minderaa, M.D.,[2] and Donald J. Cohen, M.D.[1]

Introduction

Attention Deficit Disorder with Hyperactivity (ADD-H) has been estimated to affect approximately 250,000 children in the U.S.A. It is characterized by impulsivity, inattention, and hyperactivity (Hunt et al., 1982; Safer & Allen, 1976) which impairs academic learning, disrupts social and peer relations, and can greatly disturb functioning within the home and at school (Cantwell, 1975a; Halperin & Gittelman, 1982; Levy & Hobbes, 1981; Silver, 1981; Weiss & Hechtman, 1979). Recent evidence has established the persistence of this disorder into adolescence (Lerer & Lerer, 1977; Mendelson et al., 1971) and adulthood (Amado & Lustman, 1982; Weiss et al., 1979; Wood et al., 1976). ADD-H children may have an increased risk of developing anti-social behavior (Satterfield et al., 1982) and alcoholism and substance abuse (Eyre et al., 1982).

A genetic component to this disorder has been described (Cantwell, 1975b; Deutsch et al., 1982; Mendelson et al., 1971), which may suggest that it has a biological substrate. Altered noradrenergic functioning has been suggested by the low levels of urinary 3-methoxy 4-hydroxyphenylglycol (MHPG) (Shekim et al., 1979, 1982), and in increased human growth hormone (hGH) response to a clonidine challenge (Hunt et al., 1984).

Need for Alternative to Stimulant Medication

In spite of the excellent response of many children with ADD-H to stimulant medications such as methylphenidate and D-amphetamine, a substantial percent do not respond to or develop significant side effects from stimulants. Approximately 40% of well-diagnosed children have no response or exhibit a decrement in response on paired associate learning tasks following an acute dose of methyphenidate or cylert (Swanson & Kinsbourne, 1976). Their cognitive and social behavior may become exceedingly constricted and rigid. Although stimulant medication improves performance on selected cognitive laboratory tasks, the medication alone does not improve academic grades nor substantially alter other outcome measures (Gittelman-Klein, 1976, Quinn & Rapoport, 1974). Coupled with psychotherapy and special education, stimulants may improve academic adjustment and performance (Satterfield et al., 1979).

However, stimulant medications have multiple side effects and some specific contraindications for use. Transient side effects include anorexia, insomnia, stomach aches, afternoon withdrawal, and explosiveness (Cantwell, 1975a). Long-term side effects of stimulants may include growth suppression (Greenhill et al., 1980; Millichap, 1978), development of tics (Lowe et al., 1982), and hallucinosis (Young, 1981). Compliance with methylphenidate treatment is frequently low (Firestone, 1982; Sleator et al., 1982). There is a need for an alternative medication that would have the following characteristics: 1) fewer side effects and a more consistent duration of action; 2) therapeutic benefit for children whose ADD-H is associated with explosiveness, motor tics, personality rigidity; 3) safety in ADD-H adolescents who are at risk for substance abuse; 4) improvement in patient acceptance and compliance; and 5) more effective enhancement of academic performance.

---

[1] Yale Child Study Center, New Haven, CT 06510.

[2] Sophia Children's Hospital, Rotterdam, The Netherlands.

Clonidine

Clonidine is an alpha-adrenergic stimulating agent which acts preferentially on presynaptic alpha-2 neurons to inhibit noradrenergic activity (Aghajanian & Bunney, 1977; Cedarbaum & Aghajanian, 1977; Titeler & Seeman, 1980). It stimulates release of hGH (Gold et al., 1979; Hunt, 1984), and inhibits norepinephrine (NE) release which decreases the level of the NE metabolite MHPG in the urine (Charney, 1982; Hunt, in press). Clonidine is useful as an antihypertensive agent (Manheim et al., 1982), an inhibitor of opiate withdrawal (Gold et al., 1980), and it may have some short-term antianxiety effects (Redmond, 1979).

Many patients with Tourette's Syndrome (TS) frequently share with ADD-H children problems of impulsivity, inattention, and motor restlessness (Cohen et al., 1980). Children with TS demonstrate decreased tics and improved calmness and attention on clonidine (Cohen et al., 1980; Leckman et al., 1983).

Following good results with an open pilot study of 7 ADD-H boys treated with clonidine (4 ng/kg/day), we performed a double-blind placebo-crossover in 10 children.

Method

Subjects

Ten children, ages 11.6±0.54 (mean±SE) years, participated in 12 weeks of active treatment with clonidine.

All of the children had received special education; half were predominantly treated in this fashion. Four of the children had one or more first-degree relatives with a distinct history of ADD-H or learning disabilities. The families in this study were in the 3.2±0.4 socioeconomic status (Hollingshead, 1965).

Seven (70%) of those completing the study had previously been treated with stimulant medication for 3.2±.7 (mean±SE) years at a dose of 0.35±.12 mg/kg. Three of the parents reported that the stimulant medication had been beneficial; four had discontinued stimulants because of significant side effects.

Subject Selection

To be eligible for the study, a child had to meet DSM-III criteria for ADD-H and score at least 2.0 standard deviations (s.d.) above normal on the Hyperactivity Index (Barkley, 1981) of the Connors Behavior Rating Scale (C-BRS) as rated by either parent or teacher (Conners, 1969). All subjects had an IQ greater than 80 and had no symptom of psychosis or primary mood disturbance. All were medically healthy with no cardiac, endocrine, or neurological disorder.

An additional baseline assessment included two weekly ratings on the Parents' and Teachers' version of the Parents' Child Behavior Checklist (Achenbach, 1978), a standardized psychiatric interview using the Diagnostic Inventory for Children and Adolescents (DICA) by Herjanic and Weiner (1981), and a developmental and personal history (Personal Data Inventory developed by Shaywitz, 1982). Academic and behavioral records describing academic performance, behavior, and psychological and educational testing were obtained from their schools. Physical and neuromaturational exams, a complete blood count, thyroid indices, lead levels, ceruloplasm, electrolytes, blood urea nitrogen, and an electrocardiograph were also performed. The children were either drug-naive or were drug-free for 1 month prior to beginning clonidine. Informed consent from parents and assent from the children was obtained after they received a detailed description of the study.

Double-Blind Treatment Design and Implementation

Since the effects of clonidine require several weeks to stabilize, active clonidine was administered for 8 consecutive weeks. After 2 weeks of baseline assessment, subjects were randomly assigned to begin with either active clonidine or placebo for 2 weeks. The group initially treated with placebo ended their treatment with 2 additional weeks of placebo; the group initially treated with clonidine ended with 4 weeks of placebo. Subjects were randomly assigned to a treatment group by a research assistant, leaving clinicians blind to the treatment sequence. Parents were given coded tablets with computer-generated instructions specifying the tablet to be taken for each dose. Parents, teachers, children, and one clinician rater remained blind to the study design.

Medication Dose and Rate of Increase

The dose of clonidine was increased by 0.05 mg every other day until a dose of 4-5 µg/kg/d (about 0.05 four times a day) was achieved. Clonidine was tapered off gradually when children were returned to placebo in order to avoid a hypertensive reaction. Blood pressure and pulse were measured monthly at each clinic visit.

Evaluation of Therapeutic Response

Every 2 weeks parents and teachers completed the revised Conners Parents' Behavior Rating (48-item) and the Teachers' Behavior Rating (28-item) scales, respectively. *Every month* parents and children had a videotaped interview and repeated behavioral ratings. Two clinicians blind to the treatment condition rated the children using a scale which quantitatively scores the DSM-III specified symptoms for ADD-H; all raters also completed a global rating of improvement. A brief neuromaturational assessment battery was repeated monthly to monitor visual-motor coordination as evidenced by: sequential finger tap, the peghole test, the marble sorting, printing, and the Coding and Digit Symbol tasks from the Wechsler Intelligence Scale for Children—Revised (WISC-R). Auditory attention was assessed using Digit Span (forward and backwards). The Kagan Matching Familiar Figures Test provided an index of impulsivity, visual scanning, and frustration tolerance.

Data Analysis

Behavior and neuromaturational rating scores were compared at baseline, 1 month, 2 months, and during placebo withdrawal using a one-way analysis of variance with repeated measures. Comparisons between baseline and final week of clonidine (2 months) and clonidine and placebo were analyzed using a two-tailed *t* test.

Results

Clonidine's Effect On Conners' Behavior Ratings (*See* Table 1, Figures 1 and 2.)

Composite Ratings: Eight of the 10 children were rated as at least mildly (10 to 24%) improved by one observer. Seven children were rated as at least moderately (25 to 49%) improved by two observers; this rating was considered the minimal criteria for definite improvement. Six showed a substantial (50 to 74%) improvement as rated by at least one observer; 5 were rated as at least 50% improved in the classroom. Four subjects were reported to be substantially improved in two settings.

Teachers' Ratings

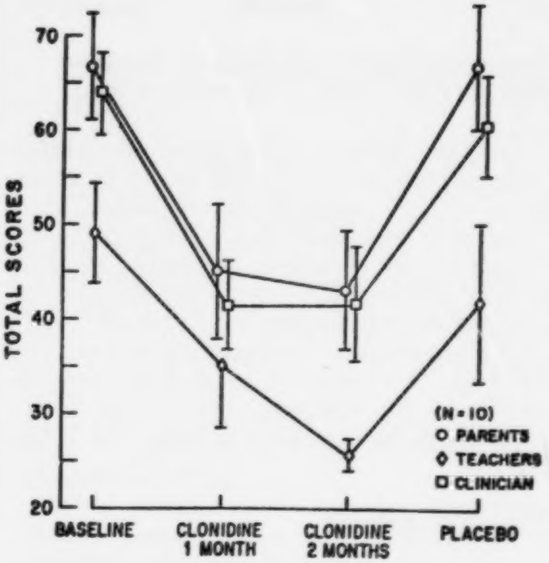
Before treatment with clonidine, teachers' total behavior rating on the Conners' 28-item scale for the group was 49.00±5.20 (mean±SE). After 8 weeks of treatment with clonidine the bi-weekly average of the teachers' behavior ratings demonstrated progressive improvement, with a final rating of 25.79 ±1.31 ($p = 0.001$). Similarly, the teachers' "Hyperactivity Index" (Barkley, 1981) dropped from pretreatment level of 1.99±0.16 to 1.12±0.06 at the end of active clonidine treatment ($p = 0.001$). Significant changes in conduct ($p = 0.4$) and inattention

TABLE 1

Overall Improvement for Individual Subjects During Treatment

	Rater		
Subject No.	Parent	Teacher	Clinician
1	1	2	1
2	2	3	1
3	4	3	3
4	2	2	2
5	2	3	3
6	2	0	1
7	3	2	3
8	0	NA	—
9	2	2	2
10	2	NA	2

Key: 0 = no significant change (less than 25% improvement or deterioration)
1 = mild improvement (10 to 24%)
2 = moderate improvement (25 to 49%)
3 = substantial improvement (50 to 74%)
4 = extreme improvement (more than 75%)
— = 25% overall deterioration
NA = not ascertained



p-VALUES	PARENTS	TEACHERS	CLINICIAN
BASELINE • CLON 2 mo	0.003	0.001	0.01
CLON 2 mo • PLACEBO	0.02	0.05	0.04

FIGURE 1. Total scores. Behavioral response to clonidine and placebo (crossover).

(*p* = 0.5) were also noticed by teachers. Five of the 8 children on whom ratings were completed demonstrated at least moderate (25%) improvement in overall behavior ratings; 5 were substantially (75%) improved. During the post-clonidine placebo period, the teachers observed at least a moderate (25 to 50%) deterioration in all but one child. Teachers' written comments indicated that children appeared "more relaxed," and had much more "on-task activity" during clonidine treatment and exerted more purposeful effort at school. They reported that children seemed less easily distracted or frustrated. Teachers described these children as being "better accepted by peers" and "less aggressive and explosive."

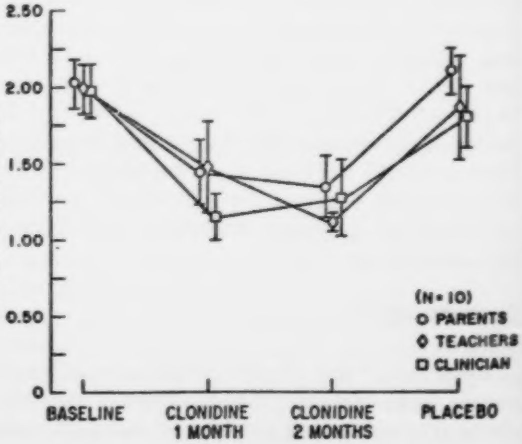
Parents' Ratings

Parents documented a similar response to clonidine treatment. Parents' overall behavior ratings (Conners' 48-item scale) for the group declined from a pretreatment level of 66.85±5.75 to 43.00±6.29 (*p* = 0.003) after 8 weeks of clonidine. Parents rated significant improvement in the following areas: "Hyperactivity Index" (2.03±0.16 to 1.34±0.21; *p* = 0.004); "Conduct Problems" (1.38±0.16 to 0.99±0.10; *p* = 0.01); and improvement in "Learning Problems" (2.36 ±0.17 to 1.53±0.28; *p* = 0.007); but no significant improvement occurred in factor scores for Anxiety or Psychosomatic problems.

During clonidine treatment, 3 children demonstrated a substantial decrease (50%), while 4 had a moderate (25%) decrease, in ADD-H symptoms. Three of the children, including both girls, showed no overall change according to their parents. Parents' ratings of children's overall behavior on subsequent *placebo* showed a substantial deterioration in 4 children, a moderate deterioration in an additional 2 children, and a mild deterioration in 2 more children; 1 child demonstrated slightly improved behavior. Ratings for "Hyperactivity" deteriorated to about the same degree during placebo.

Clinicians' Ratings

Based on direct clinical interviews and a review of the behavioral ratings, the clinicians reported a significant improvement in 8



p-VALUES	PARENTS	TEACHERS	CLINICIAN
BASELINE • CLON 2 mo	0.004	0.001	0.03
CLON 2 mo • PLACEBO	0.002	0.04	0.12

FIGURE 2. Hyperactivity index. Behavioral response to clonidine and placebo (crossover).

subjects in the primary DSM-III symptoms of ADD-H. Three children improved moderately and 5 improved mildly in overall symptoms of ADD-H.

On withdrawal from clonidine, clinicians also reported that 7 of 10 children developed more severe ADD-H symptoms, which were extreme in 4 subjects and moderate in 1. Ratings of "Hyperactivity" showed deterioration in 6 subjects; inattention and impulsivity worsened in 7 subjects on placebo. Clinicians' ratings of "Impulsivity" showed a similar response to placebo.

By direct clinicians' observation, these children were more cooperative during interviews while taking active clonidine. They performed the neuromaturational and cognitive tasks with less resistance and protest. Their mood appeared improved. They frequently described experiences of feeling more in control of anger and irritability, and having greater ability to solve problems. They expressed increased pride in their achievements and experienced less conflict and oppositionality at home and at school. They described an increase in their efforts to resolve conflicts and solve problems. They appeared more thoughtful, psychologically minded, and self-confident. This was most impressive in 3 children who otherwise had experienced minimal therapeutic benefit from their prior treatment with methylphenidate.

Placebo Withdrawal

When subjects returned to the placebo condition, their behavior rapidly deteriorated; symptoms usually returned within 2 to 4 days. Three of the children were unable to remain off medication for the full 4 weeks due to profound worsening of behavior that threatened to disturb classroom performance and placement. A significant deterioration in overall behavior for the group was noted by teachers ($p = 0.05$), parents ($p = 0.02$), and clinicians ($p = 0.04$).

Neuromaturational Testing

The scores for the neuromaturational tests showed that clonidine tended to improve performance in some tests beyond the effect of practice, but none of these changes reached significance. Clonidine's main effect on neuromaturational tasks was to diminish variability. This may indicate reduced distractibility and off-task behavior on clonidine. Clonidine did not impair subjects' performance of psychomotor tasks.

Side Effects

The main side effect was *sleepiness*, which occurred primarily for 30 to 60 minutes beginning about 1 hour after clonidine administration. In all but one child, this sleepiness subsided after 3 weeks and was dose dependent. For this child, sleepiness limited clonidine's usefulness. The mean *blood pressure* decreased 10% on clonidine; this produced no subjective symptoms other than occasional light-headedness immediately after standing or strenuous exertion. One child who had symptoms of mild *depression* prior to clonidine became more tearful and unhappy on clonidine. Children without prior symptoms of depressive disorder did not become depressed on clonidine.

Discussion

Clonidine significantly improved the overall behavior ratings of "Hyperactivity," "Impulsivity," and "Inattention" in children with ADD. Two children improved moderately (10 to 25%) on clonidine, while 5 improved substantially (25 to 50%). One subject showed no change or a slight deterioration on clonidine. The two girls were among the three poorest responders.

Clinical Impressions

Clonidine seemed to facilitate a maturational development characterized by increased reflectivity, heightened purposeful, goal-directed behavior, and less oppositional behavior. Clonidine enhanced children's frustration tolerance and enabled them to sustain effort toward age-appropriate objectives without feeling overwhelmed, inadequate, or incompetent.

Clinical Differentiation of Good and Poor Responders to Clonidine

The ADD-H children who responded best were those who had been overactive and lacked inhibition. Their capacity for social-relatedness and purposeful activity appeared intact but had been under-utilized due to their impulsivity. One child who did not benefit from clonidine met DSM-III criteria for both ADD-H and schizoid personality disorder. While this child was calmer on clonidine, he also became more disorganized, passive, and undirected. The poor response of two ADD-H girls may suggest a slightly different clinical or neurochemical process in these individuals.

Noradrenergic Mechanisms in ADD-H

The finding of therapeutic benefit from clonidine in ADD-H is of heuristic as well as practical significance, since it may advance our understanding of the role of noradrenergic mechanisms in this disorder.

Clonidine not only directly inhibits noradrenergic excitation, as evidenced by decreased firing of the locus coeruleus (Aghajanian & Bunney, 1977; Starke & Altman, 1973), and by diminished MHPG production (Cedarbaum & Aghajanian, 1976, 1977; Hunt et al., 1984; Leckman et al., 1980). Clonidine also has a modulating effect on the firing of dopaminergic neurons under conditions of stress (Antelman & Caggiula, 1977). Clonidine's effect in children with ADD-H may reflect both direct noradrenergic effects on cognition and anxiety—leading to improved frustration tolerance and performance—and secondary modulating effects on other monoamine systems. Chronic administration of a noradrenergic agent such as clonidine may alter the sensitivity of non-adrenergic receptors, such as dopamine, to their neurotransmitters (Cooper et al., 1978).

Norepinephrine (NE) mediates the expression of anxiety which may occur during phobic or panic states or during opiate withdrawal. NE activity of the locus coeruleus as measured by implanted electrodes in unanesthetized cats increased during arousal from sleep to wakening and in response to the introduction of a novel stimulus (Aston-Jones & Bloom, 1981; Foote & Bloom, 1979). This NE activation increased arousal and external vigilance of the animal. The symptoms of ADD-H may suggest a state of increased arousal that causes stimuli to seem excessively novel and engaging.

Biochemical factors may distinguish these children from normal, and may eventually contribute to predicting medication response. Clonidine may be preferentially useful in a biologically definable subgroup of noradrenergically over-responsive ADD-H children, who may be identified by levels of urinary MHPG or by response to a clonidine or yohimbine challenge.

Clonidine may be preferable to methylphenidate in children who have chronic tics, decreased appetite (anorexia), sleep disturbance (insomnia), excessive afternoon withdrawal, or growth retardation. It may also be beneficial to ADD-H children who are primarily impulsive, unreflective, and easily emotionally overwhelmed.

Further subtyping of ADD-H according to diagnosis of conduct disorder (Satterfield et al., 1982), aggression (Milich et al., 1982), degree of motor activity (Porrino et al., 1983), the presence of specific learning disabilities (Andrulonis et al., 1982; August and Stewart, 1982; Kupietz et al., 1982; O'Brien, 1982), and the extent of affective lability, explosiveness, or depression may clarify clinical or biological differences in ADD-H children.

We are performing an open-ended comparison of methylphenidate and clonidine on an additional 20 ADD-H children using similar behavioral and neuromaturational measures. Our clinical impressions support our earlier observations that clonidine treatment improves compliance, task orientation, and frustration tolerance, and reduces oppositional behavior. Parents especially appreciate the fact that clonidine can be given in the late afternoon or evening without interfering with the child's appetite or sleep. In some cases of extreme distractibility a combination of clonidine and low doses of methylphenidate appears safe and effective.

Further research is needed to compare clinical response of ADD-H children to clonidine and methylphenidate and to identify biochemical and clinical predictions of differential response.

References

Achenbach, T.M. The child behavior profile: I. Boys aged 6-11. *J. Consult. Clin. Psychol.*, 46:478–488, 1978.

Aghajanian, G.K., and Bunney, B.S. Dopamine "autoreceptors": Pharmacological characterization by microintophoretic single cell recording studies. *Arch. Pharmacol.*, 297:1–7, 1977.

Amado, H., and Lustman, P.J. Attention deficit disorders persisting in adulthood: A review. *Compr. Psychiatry*, 23:200–214, 1982.

Andrulonis, P.A., Glueck, B.C., Stroebel, C.F., et al. Borderline personality subcategories. *J. Nerv. Ment. Dis.*, 170:670–679, 1982.

Antelman, S.M., and Caggiula, A.R. Norepinephrine-dopamine interactions and behavior. *Science*, 194:646–653, 1977.

Aston-Jones, G., and Bloom, F.E. Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *J. Neurosci.*, 1:887–900, 1981.

August, G.J., and Stewart, M.A. Is there a syndrome of pure hyperactivity? *Br. J. Psychiatry*, 140:305–311, 1982.

Barkley, R.A. *Hyperactive Children: A Handbook for Diagnosis and Treatment.* New York: Guilford Press, 1981.

Cantwell, D.P. *The Hyperactive Child: Diagnosis, Management and Current Research.* New York: Spectrum Publications, 1975a.

Cantwell, D.P. Genetic studies of hyperactive children: Psychiatric illness in biological and adopting parents. In: Fieve, R., Rosenthal, D., and Brill, H. (eds.), *Genetic Research in Psychiatry*. Baltimore: Johns Hopkins University Press, 1975b, pp. 273–280.

Cedarbaum, J.M., and Aghajanian, G.K. Noradrenergic neurons of the locus coeruleus: Inhibition by epinephrine and activation by the alpha-antagonist piperoxane. *Brain Res.*, 112:412–419, 1976.

Cedarbaum, J.M., and Aghajanian, G.K. Catecholamine receptors on locus coeruleus neurons: Pharmacological characterization. *Eur. J. Pharmacol.*, 44:357–385, 1977.

Charney, D.S., Heninger, G.R., Sternberg, D.E., et al. Adrenergic receptor sensitivity in depression: Effects of clonidine in depressed patients and healthy subjects. *Arch. Gen. Psychiatry*, 39:290–294, 1982.

Cohen, D.J., Detlor, J., Young, J.G., et al. Clonidine ameliorates Gilles de la Tourette Syndrome. *Arch. Gen. Psychiatry*, 34:1350–1357, 1980.

Conners, C.K. A teacher rating scale for use in drug studies with children. *Am. J. Psychiatry*, 126:152–156, 1969.

Cooper, J.R., Bloom, F.E., and Roth, R.H., (eds.) Catecholamines II: CNS aspects. In: *The Biochemical Basis of Neuropharmacology*. New York: Oxford University Press, 1978, pp. 161–196.

Deutsch, C.K., Swanson, J.M., Cantwell, D.P., et al. Overrepresentation of adoptees in children with attention deficit disorder. *Behav. Genet.*, 12:231–238, 1982.

Eyre, S.L., Rounsaville, B.J., and Kleber, H.D. History of childhood hyperactivity in a clinic population of opiate addicts. *J. Nerv. Ment. Dis.*, 170:5229, 1982.

Firestone, P. Factors associated with children's adherence to stimulant medication. *Am. J. Orthopsychiatry*, 52:44757, 1982.

Foote, S., and Bloom, F.E. Activity of norepinephrine-containing locus coeruleus neurons in the unanesthetized squirrel monkey. In: Usdin, E., Kopin, I., and Barchas, J. (eds.), *Catecholamines: Basic and Clinical Frontiers*. New York: Pergamon Press, 1979, pp. 625–627.

Gittelman-Klein, R., and Klein, D.F. Methylphenidate effects in learning disabilities: Psychometric changes. *Arch. Gen. Psychiatry*, 33:655–664, 1976.

Gold, M.S., Redmond, D.E. Jr., and Kleber, H.D. Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Am. J. Psychiatry*, 136:100–102, 1979.

Gold, M.S., Pottash, A.L., Sweeney, D.R., et al. Clonidine decreases opiate withdrawal-related anxiety: Possible opiate noradrenergic interaction in anxiety and panic. *Substance Alcohol Actions Misuse*, 1:239–246, 1980.

Greenhill, L.L., Puig-Antich, J., Halperin, F., et al. Growth disturbances in hyperkinetic children. *Pediatrics*, 66:152–154, 1980.

Halperin, J.M., and Gittelman, R. Do hyperactive children and their siblings differ in IQ academic achievement? *Psychiatry Res.*, 6:253–258, 1982.

Herjanic, B., and Weiner, J. *Diagnostic Interview for Children and Adolescents.* Working document. Washington University Medical School, St. Louis, Mo., 1981.

Hollingshead, A.B. *Two-Factor Index of Social Position.* New Haven, Conn.: Yale Station, 1965.

Hunt, R.D., Cohen, D.J., Shaywitz, S.E., et al. Strategies for study of the neurochemistry of attention deficit disorder in children. *Schizophr. Bull.*, 8:236–251, 1982.

Hunt, R.D., Cohen, D.J., Anderson, G.M., and Clark, L. Possible change in noradrenergic receptor sensitivity with attention deficit disorder and hyperactivity: Response to chronic methylphenidate treatment. *Life Sci.*, 35:885-897, 1984.

Hunt, R.D., Cohen, D.J., Anderson, G.M., et al. Noradrenergic mechanisms in attention deficit disorder with hyperactivity. In: L. Bloomingdale (ed.), *Attention Deficit Disorder and Hyperactivity*, Vol. 3. New York: Spectrum Publications. (In press)

Kupietz, S.S., Winsberg, B.G., and Sverd, J. Learning ability and methylphenidate (ritalin) plasma concentration in hyperkinetic children: A preliminary investigation. *J. Am. Acad. Child Psychiatry*, 21(1):27–30, 1982.

Leckman, J.F., Detlor, J., Harcherik, D.F., et al. Acute and chronic clonidine treatment in Tourette's Syndrome: A preliminary report on clinical response and effect on plasma and urinary catecholamine metabolites, growth hormone, and blood pressure. *J. Am. Acad. Child Psychiatry*, 5:433–440, 1983.

Leckman, J.F., Maas, J.W., Redmond, D.E. Jr., et al. Effects of oral clonidine on plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) in man: Preliminary report. *Life Sci.*, 26:2179–2185, 1980.

Lerer, R.J., and Lerer, M.P. Response of adolescents with minimal brain dysfunction to methylphenidate. *J. Learn. Disabil.*, 10:223–228, 1977.

Levy, F., and Hobbes, G. The diagnosis of attention deficit disorder (hyperkinesis) in children. *J. Am. Acad. Child Psychiatry*, 20:376–384, 1981.

Lowe, T.L., Cohen, D.J., Detlor, J., et al. Stimulant medications precipitate Tourette's Syndrome. *JAMA*, 247:1729–1731, 1982.

Manheim, P., Paalzow, L., and Hökfelt, B. Plasma clonidine in relation to blood pressure, catecholamines, and renin activity during long-term treatment of hypertension. *Clin. Pharmacol. Ther.*, 31:445–451, 1982.

Mendelson, W., Johnson, N., and Stewart, M. Hyperactive children as teenagers: A follow-up study. *J. Nerv. Ment. Dis.*, 153:273–279, 1971.

Milich, R., Loney, J., and Landau, S. Independent dimensions of hyperactivity and aggression: A validation with playroom observation data. *J. Abnorm. Psychol.*, 91:183–198, 1982.

Millichap, J.G. Growth of hyperactive children treated with methylphenidate. *J. Learn. Disabil.*, 11:567–570, 1978.

O'Brien, J. School problems: School phobia and learning disabilities. *Psychiatr. Clin. No. Am.*, 5:297–307, 1982.

Porrino, L.J., Rapoport, J.L., Behar, D., et al. A naturalistic assessment of the motor activity of hyperactive boys. *Arch. Gen. Psychiatry*, 40:681–693, 1983.

Quinn, P.O., Rapoport, J.L., Bradbard, G., et al. Imipramine and methylphenidate treatments in hyperactive boys: A double-blind comparison. *Arch. Gen. Psychiatry*, 30:789–793, 1974.

Redmond, D.E. Jr. New and old evidence for the involvement of a brain norepinephrine system in anxiety. In: Fann, W.E., Pokorny, A., Karacan, I., et al. (eds.), *Phenomenology and Treatment of Anxiety*. New York: Spectrum, 1979, pp. 153–203.

Safer, D.J., and Allen, R.P. *Hyperactive Children: Diagnosis and Management*. Baltimore, Md.: University Park Press, 1976.

Satterfield, J.H., Cantwell, D.P., and Satterfield, B.T. Multimodality treatment: A one-year follow-up of 84 hyperactive boys. *Arch. Gen. Psychiatry*, 36:965–974, 1979.

Satterfield, J.H., Hoppe, C.M., and Schell, A.M. A prospective study of delinquency in 110 boys with attention deficit disorder and 88 normal adolescent boys. *Am. J. Psychiatry*, 139:795–798, 1982.

Shaywitz, S.E. The Yale Neuropsychoeducational Scales. *Schizophr. Bull.*, 8(2):360–424, 1982.

Shekim, W.O., Davis, L.G., Bylund, D.B., et al. Platelet MAO in children with attention deficit disorder and hyperactivity: A pilot study. *Am. J. Psychiatry*, 139:936–938, 1982.

Shekim, W.O., Dekirmenjian, H., and Chapel, J.L. Urinary catecholamine metabolites in hyperactive children treated with D-amphetamine. *Am. J. Psychiatry*, 134:1276–1279, 1979.

Silver, L.B. The relationship between learning disabilities hyperactivity, distractibility and behavioral problems: A clinical analysis. *J. Am. Acad. Child Psychiatry*, 20:385–391, 1981.

Sleator, E.K., Ullmann, R.K., and Von Neumann, A. How do hyperactive children feel about taking stimulants and will they tell the doctor? *Clin. Pediatr.*, 21:474–479, 1982.

Starke, K., and Altman, K.P. Inhibition of adrenergic neurotransmission by clonidine: An action on prejunctal α-receptors. *Neuropharmacology*, 12:339–349, 1973.

Swanson, J.M., Sandman, C.A., Deutsch, C., et al. Methylphenidate hydrochloride given with or before breakfast. I. Behavioral, cognitive, and electrophysiologic effects. *Pediatrics*, 72:49–55, 1983.

Swanson, J.M., and Kinsbourne, M. Stimulant related state-dependent learning in hyperactive children. *Science*, 192:1254–1256, 1976.

Titeler, M., and Seeman, P. Presynaptically acting catecholamines bind to alpha 2-adrenoreceptors labelled by 3H-clonidine. *Eur. J. Pharmacol.*, 67:187–92, 1980.

Weiss, G., and Hechtman, L. The hyperactive child syndrome. *Science*, 205:1348–1353, 1979.

Wood, D.R., Reimherr, F.W., Wender, P.H., et al. Diagnosis and treatment of minimal brain dysfunction in adults. *Arch. Gen. Psychiatry*, 33:1453–1460, 1976.

Young, J.G. Methylphenidate-induced hallucinosis: Case histories and possible mechanisms of action. *Dev. Behav. Pediatr.*, 2:35–37, 1981.

The Use of MK-801, a Novel Sympathomimetic, in Adults With Attention Deficit Disorder, Residual Type

Fred W. Reimherr, M.D.,[1] David R. Wood, M.D.,[1] and Paul H. Wender, M.D.[1]

Introduction

Attention Deficit Disorder (ADD) is one of the most frequently treated psychiatric disorders of childhood. However, of the diverse treatment approaches available, only the stimulant medications, particularly methylphenidate and dextroamphetamine, are generally accepted as effective. Unfortunately, treatment with stimulants presents several very significant problems.

One of the most serious is the risk of abuse. This is particularly true with adolescent or adult patients and makes physicians reluctant to consider clinical trials of stimulants if ADD is suspected. In the younger patient with ADD, parents may use the medication intended for their children. As a result, many patients who might be strongly responsive to medication are not treated with stimulant medication.

A second problem is the partial or complete unresponsiveness to stimulants of a significant percentage of patients with ADD. Although unexplained, this variability in response may reflect "artificial" factors such as misdiagnosis, poor compliance, or social conditions. Conversely, a significant percentage of these patients may represent "true" pharmacologic failures.

Finally, even when they are effective, the stimulants have a number of undesirable features. The requirement that they be taken two to four times per day promotes noncompliance. Pemoline, an alternative longer acting stimulant, is associated with liver problems, is a difficult medication to start, and has questionable long-term efficacy. Many patients or their families are not comfortable with regular use of stimulant medication. In children there is the possibility that all three medications will lead to diminished growth.

In the past it was felt that ADD disappeared with the onset of adolescence and did not occur in adulthood. Recent evidence suggests that it may continue through adolescence and into adulthood. The American Psychiatric Association has officially recognized this possibility by including ADD, Residual Type (ADD,RT) in the DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980). This development facilitates conducting clinical trials of experimental medications in ADD, since it allows one to avoid the special requirements attached to the use of experimental medications in children.

Collectively, these factors have led us to seek new pharmacologic approaches to the treatment of ADD. Preliminary work with a novel experimental compound developed by Merck Research Laboratories, MK-801, suggested that it merited testing in patients with ADD. Chemically, it is considered a dibenzocycloalkenimine, but it cannot be classified as a member of any accepted family of pharmacologic agents. In preliminary animal studies it is unique among chemical agents in possessing anticonvulsant, sympathomimetic, and anxiolytic actions. No other chemical is known to possess this cluster of properties.

In studies of radio-ligand binding, MK-801 does not compete with apomorphine, spiroperidol, serotonin, LSD, WB 4101 (measuring norepinephrine binding sites), quinuclidinyl benzilate (QNB) (measuring scopolamine binding sites), muscimol (measuring GABA binding sites), or 2-chloroadenosine. It does compete with diazepam binding acutely, but not chronically.

Central sympathomimetic activity has been assessed by measuring the induction of rota-

---

[1] Department of Psychiatry, University of Utah Medical Center, Salt Lake City, UT 84132.

The authors wish to thank David Tomb, M.D., of the University of Utah for his help in preparation of this report and Scott Reines, M.D., of Merck Research Laboratories for his support of this project.

tion in rats with unilateral nigrostriatal lesions produced by 6-hydroxydopamine (Clineschmidt, 1982b). MK-801 produced ipsilateral rotation which is usually produced by indirect dopamine agonist agents such as amphetamine, amfonelic acid, or methylphenidate. This effect was reduced by pretreatment with haloperidol, clozapine, prazosin (an alpha adreno-receptor antagonist), and alpha-methyl-paratyrosine. It was blocked completely by reserpine.

MK-801 also produced an increase in locomotor activity similar to that observed in animals treated with amphetamine, amfonelic acid, and methylphenidate (Clineschmidt, 1982b). Reserpine blocked this effect when it was produced by MK-801, methylphenidate, and amfonelic acid, but only partially inhibited the increase in activity produced by amphetamine. Alpha-methyl-para-tyrosine markedly reduced the increase in locomotor activity seen with amphetamine, but did not change the effect occurring with MK-801, methylphenidate, and amfonelic acid. All were blocked by haloperidol. Prazosin only blocked MK-801 and amphetamine.

Its anxiolytic properties have been examined in two different studies with rats (Clineschmidt, 1982c). Animals were taught to obtain food by pressing a lever; this response was then punished with electroshock. The rate of lever pressing following food deprivation was measured after treatment with diazepam, MK-801, and placebo. Both MK-801 and diazepam produced an increase in the rate of lever pressing. In a second study, fluid-deprived rats were given electrical shocks when they took sips of water. The number of sips of fluid was measured in rats treated with placebo, MK-801, and chlordiazepoxide. Both active agents produced an increase in the number of sips of water that the rats took. In a similar experiment done with squirrel monkeys, MK-801 produced no anxiolytic effect.

MK-801 has shown significant anticonvulsant activity in mice, preventing seizures induced by bicuculline and with electroshock (Clineschmidt, 1982a). This effect occurred at a dose of MK-801 that was lower than any of the comparison medications [clonazepam, phenobarbital, diazepam, phenytoin, (Y)-acetylenic GABA (gamma-aminobutyrate), sodium valproate, or trimethadione]. MK-801 also blocked seizures induced in rats with electroshock, pentylenetrazol (Metrazol), strychnine, or bicuculline. In this second set of studies with rats, MK-801 showed a spectrum of activity similar to phenytoin and unlike clonazepam. The anticonvulsant action of MK-801 was not affected by anticholinergics, antihistamine H1 receptor blockers, cimetidine, or antiserotonin agents (cyproheptadine, cinanserin, methylsergide, or methergoline). The action was antagonized by naloxone, theophylline, and haloperidol (most strongly). Its anticonvulsant action was completely reversed by HEAT and phenoxybenzamine, alpha-adrenoceptor blockers. Its anticonvulsant action was potentiated by propranolol.

Several small, open trials have been conducted in human subjects. In patients with seizure disorders, MK-801 appears to have anticonvulsant activity. Additional studies are being conducted. In 14 patients with anxiety disorders, a majority reported that it aggravated their symptoms and produced feelings of agitation. In a small number of patients with retarded depressions, one patient developed a confusional state and the others showed only modest improvement before termination of treatment.

Methods

This study was an open 6-week, outpatient trial limited to 10 patients. Treatment for more than 6 weeks with MK-801 was not available under any conditions. This project was approved by the Institutional Review Board of the University of Utah Medical Center.

Potential patients had to meet the following inclusion criteria:

1. ADD in childhood as defined by DSM-III;
2. Presence of attention difficulties as an adult;
3. Presence of hyperactivity as an adult; or
4. Two of the following:
   a. Quick or excessive temper,
   b. Poor organization or difficulty completing tasks,
   c. Over-reactivity to stress,

d. Excessive mood lability with dysphoric episodes, or

e. Impulsivity.

5. Females were required to be infertile;

6. Ages 21 to 65;

7. Five days drug-free; or

8. History of positive response to stimulant medication.

Potential patients were rejected if they met any of the following exclusion criteria:

1. Recent use of neuroleptics;

2. Major medical or neurological disease;

3. Recent history consistent with alcoholism, antisocial personality disorder, or drug abuse;

4. Significant abnormality on entry electrocardiogram (ECG), complete blood count (CBC), urine analysis (UA), blood chemistry, or physical examination;

5. History of allergic reaction to multiple drugs; or

6. Current or past history of major mood disorder, schizophrenia, psychotic symptoms, borderline personality, schizotypal personality, organic brain syndrome, or mental retardation.

Patients meeting these criteria were given a copy of the informed consent agreement containing a detailed description of the study. This document had been approved by the Institutional Review Board of the University of Utah Medical Center. Patients were instructed to review this document carefully and an appointment was made in 4 to 7 days to begin the study.

Patients initially received 7 days of placebo and then continued in the study if they still met the criteria for inclusion. Visits were at 1, 2, 3, 4, and 6 weeks. The following psychiatric rating instruments and medical measures were used:

1. Physician's global ratings of improvement (CGI) was obtained at each visit. This scale is a 7-point scale ranging from very much improved to very much worse.

2. Physician's global ratings of severity (CGS) was obtained at each visit. This is a 7-point scale ranging from no sign of illness to extremely symptomatic.

3. The Attention Deficit Disorder Scale (TADDS), a weighted scale of hyperactive behavior, was obtained at each visit. This scale assigns the following points for each area of symptoms:

12 points for inattention,
8 points for overactivity,
8 points for temper,
4 points for emotional reactivity, and
4 points for mood instability.

4. The Global Assessment Scale (GAS) at 0 and 6 weeks.

5. Vital signs at each visit.

6. Physical examination at 0 and 6 weeks.

7. ECG, UA, blood chemistry, and CBC at 0, 1, 2, 4, and 6 weeks.

The starting dose of MK-801 was .025 mg three times a day (t.i.d.). Maximum dose was .150 mg t.i.d. A flexible dosing schedule was followed.

Results

Ten adults, 6 males and 4 females, with ADD,RT were treated with MK-801. The average age of the subjects was 33. No patients were dropped during the placebo washout period and 8 completed the entire 6 weeks. Two dropped out at the third week because of an inadequate response to the medication.

We used TADDS, the CGI, and the CGS to classify patients as either responders or nonresponders. On the CGI, patients had to be rated as moderately or markedly improved to be considered treatment responders. On TADDS they had to show a 50% or greater improvement. On the CGS, they had to be rated no more than mildly ill. (We were unable to use the GAS to categorize the response of our patients.)

All three measures (TADDS, the CGI, and the CGS) produced similar results. For instance, on the CGI patients fell into two groups. Five of 10 patients were consistent responders. They improved and maintained their improvement for the full duration of the study. Five of the 10 patients were transient responders. These patients (including 2 who dropped out after 3 weeks of treatment) responded for 1 to 3 weeks in the beginning of the study, but did not maintain their improvement. The other two measures (TADDS and the CGS) produced the same groups, but the numbers of patients in each group changed by plus or minus 1 patient.

Three characteristics of the pattern of response are noteworthy. First, although our sample sizes are quite small, women responded better to MK-801. Three out of the 4 women (75%) in the study were rated as consistent responders. Conversely, only 2 out of the 6 men in the study (33%) were consistent responders.

Second, our patients showed a response within 1 to 2 weeks. This is similar to the effect observed with other stimulant medications which produce their response with no latency. The percent of symptoms on TADDS remaining each week is presented in Figure 1. The total score has been corrected to give equal weighting to each of the five factors on TADDS (concentration, hyperactivity, temper, mood, and emotional over-reactivity) because the raw score gives relatively greater weighting to concentration. Zero represents complete remission of all symptoms measured by TADDS. Within a week of treatment most patients had obtained a steady state of improvement.

Third, there seemed to be differences in the relative amount of improvement occurring in each of the symptoms measured by TADDS. Mood was most strongly affected. Concentration was least improved while hyperactivity, temper, and emotional reactivity fell in between. This is illustrated in Figure 2 which shows the average improvement at weeks 2, 3, 4, and 6. A 68% improvement occurred in mood. Hyperactivity, temper, and emotional reactivity averaged a 57% improvement. Concentration showed only a 43% improvement.

Medication side effects were minor. Six subjects maintained the same weight while two lost and two gained weight. There were no changes on the ECG or in pulse rate. Mean diastolic blood pressure dropped from 80 to 76. Mean systolic blood pressure dropped from 121.5 to 115.4. All side effects were mild to moderate in intensity. Additional side effects included dizziness (reported on four occasions), headache (reported on two occasions), diarrhea (reported on two occasions), increased appetite (reported on two occasions), insomnia (reported on two occasions), jitteriness (reported on two occasions), and confusion, memory loss, difficulty with ejaculation, fatigue, tinnitus, heart burn, and itching (all reported once). At the final visit, 5 patients reported side effects and 5 reported none. One patient had his dosage reduced to a relatively low level due to side effects. In this patient the trial was terminated at the third week due both to the presence of these side effects and the lack of a therapeutic response to MK-801.

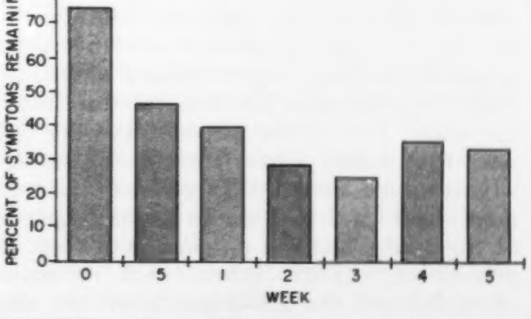


FIGURE 1. Percent of symptoms remaining at each visit as measured by the TADDS.

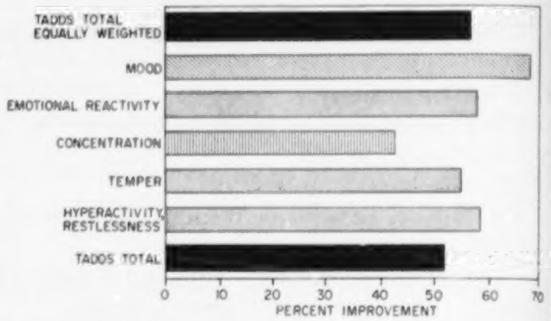


FIGURE 2. Percent improvement reported at weeks 2, 3, 4 and 6.

Although the dosing schedule was flexible, the majority of the patients were on .15 mg to .3 mg per day in three divided doses. Figure 3 contains a plot of the distribution of the total daily doses of MK-801 reported at weeks 2, 3, 4, and 6. The darker bars show the frequency of a particular dosage range in the patients classified as consistent responders with the CGI. The median dosage of the responders was .2 mg per day. The median dosage of the nonresponders was .225 mg per day. This plot shows that although most responders were in the .1 to .3 range, several responders were well above this range. A dosage plan that may be used in future studies will be discussed below.

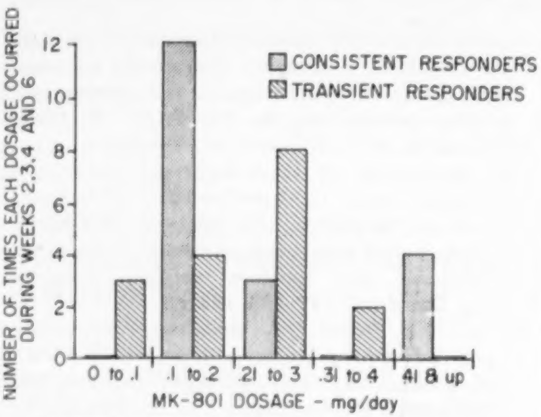


FIGURE 3. Dosage distribution of MK-801.

Conclusion

Several factors encourage optimism about the possible therapeutic value of MK-801, although the findings of this open, uncontrolled investigation must be interpreted with caution. First, there was no evidence that the patients abused or increased the dose of MK-801. Nor did they report any feelings of euphoria or increased energy.

Second, MK-801 appeared "different," not merely a less effective substitute for dextroamphetamine or methylphenidate. If one views ADD as having both a cognitive and an emotional component, MK-801 would appear to be more effective on the emotional component.

Third, several of our patients were outspoken in favor of MK-801. Even months later, several felt that they did better on MK-801: that with it they were more calm, in better control, and less reactive. As noted above, this was particularly true among our women patients. Two would not return to stimulants after being on MK-801.

Finally, in recent years we have conducted a number of open trials and controlled trials with small numbers of patients testing potential alternative medications for the treatment of ADD. These trials have focused on two classes of drugs: the monoamine oxidase inhibitors and metabolic precursors (Wender, 1983; Wood, 1985). This trial of MK-801 has been one of the most encouraging of these investigations.

The inclusion criteria that we adopted for this study present an important question concerning methodology in future drug studies of ADD. Should one select potential patients with ADD who are drug naive or should one select patients who have in the past been treated with stimulant medications? This question is more complex than it might appear initially. One would normally feel more confident about the diagnosis in a patient whom he had known for a significant period of time and had treated successfully in the past. Conversely, taking a patient off a medication which is producing a significant positive response is not easy. Research protocols usually require a drug-free interval of at least 1 week before starting the experimental treatment. However, it is difficult to know if this is an adequate period of time to allow a potential patient to recover from the lingering effects of past treatment with a psychoactive medication.

What dosage of MK-801 should be used in later studies? There appeared to be a bimodal dosage distribution among the consistent responders. One tenth of an mg per day in divided doses would be a reasonable starting dose. This should be raised very slowly to .25 mg per day over the next several weeks. If there has been no response after 3 weeks at this level, and if the patient can tolerate a higher dose, then a 1-week trial at a substantially higher dose such as .4 mg per day should be tried. This scheme would allow patients to be tried on both dosage levels which produced successful results in this study.

In light of a response rate of at least 50%, we feel additional studies with this agent in ADD,RT and normal childhood ADD are indicated. There might also be a role for this compound in other illnesses characterized by excessive temper, emotional reactivity, or impulsivity, such as borderline personality disorder or other personality disorders, particularly in women.

In summary, this was a short-term, open trial of MK-801. Half the patients were considered to be positive consistent responders to MK-801. The other half demonstrated a transient positive response to MK-801. Among the specific symptoms we monitored, mood showed the greatest relative improvement with MK-801. Temper, emotional reactivity, and over-activity all improved more than concentration. MK-801 appeared to be effective in the treatment of ADD,RT and its response appeared to be qualitatively different from that observed with the normal stimulant medications.

References

Clineschmidt, B.V., Martin, G.E., and Bunting, P.R. Anticonvulsant activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. *Drug. Dev. Res.*, 2:123–134, 1982a.

Clineschmidt, B.V., Martin, G.E., Bunting, P.R., et al. Central sympathomimetic activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. *Drug. Dev. Res.*, 2:135–145, 1982b.

Clineschmidt, B.V., Williams, M., Witoslawski, J.J., et al. Restoration of shock-suppressed behavior by treatment with (+)-5-methyl-10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5, 10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. *Drug. Dev. Res.*, 2:147–163, 1982c.

Wender, P.H., Wood, D.R., Reimherr, F.W., et al. An open trial of pargyline in the treatment of attention deficit disorder, residual type. *Psychiatry Res.*, 9:329–336, 1983.

Wood, D.R., Reimherr, F.W., and Wender, P.H. Amino acid precursors in the treatment of attention deficit disorder, residual type. *Psychopharmacol. Bull.*, 21(1):146–149, 1985.

The Prevalence of Tardive Dyskinesia in a Mentally Retarded Population[1]

Mary Ann Richardson, Ph.D.,[2] Gary Haugland, M.A.,[2] Raymond Pass, Ph.D.,[2] and Thomas J. Craig, M.D., M.P.H.[3]

Introduction

Mentally retarded (MR) patients comprise a nonpsychiatric population that has routinely been exposed to long-term neuroleptic treatment as a behavioral control measure. Rates of neuroleptic use among MR patients have been substantial in the past (25 to 60%) and, though in recent years there has been a trend to reduce dosage or discontinue treatment, these agents are still commonly used in these patients (Davis et al., 1982; Lipman et al., 1978). Unfortunately, there is a scarcity of data concerning the true prevalence of tardive dyskinesia (TD) and risk factors for its development across the full range of the MR. One study reported a 20.4% rate of the disorder among institutionalized MR children (ages 11 to 16) (Paulson et al., 1975). In that investigation the presence or absence of TD was not studied in relation to other patient characteristics. Another report, of parallel studies in two locations ($N=95$), reported a 33% prevalence of TD (Gualtieri et al., 1982). However, that study dealt with a patient population that was highly restricted since subjects were all referred by treating physicians who felt a trial neuroleptic withdrawal should be attempted, and further used inclusionary criteria such as an educational or workshop placement. A multiple regression analysis was performed on the data collected at one of the locations ($N=38$). The patients at that location were characterized by a mean age of 19.4 years, a mean treatment duration of 8.3 years, a mean IQ of 31.2 and a mean chlorpromazine (CPZ) equivalent dose of 239.9 mg. The analysis used moderate to severe TD as a dependent measure and isolated three significant independent variables: total lifetime exposure to neuroleptics, IQ, and the age at which neuroleptic treatment began. A review of TD studies in the MR including the report just described, with a total subject pool of 122, found rates for TD prevalences ranging from 29 to 36% (Kalachnik, 1983). The present study sought to add to this literature by a large-scale investigation in an institutionalized MR population. The investigation was also undertaken to study the presence or absence of TD in relation to risk variables that are peculiar to the MR and others that are shared with psychiatric patient populations. The facility studied provided a unique opportunity to evaluate the effect of drug discontinuation on TD prevalence because a policy had been instituted during the years prior to study initiation which encouraged the discontinuation of neuroleptics. The research team used criterion measures and methodology refined through several studies in psychiatric populations to help in the definition of commonalities and distinctions across these two neuroleptic-treated populations which might provide new information about the pathophysiology of the disorder itself.

Methods

A point prevalence study of TD was carried out among the residents of a state facility

---

[1] This study was supported in part by a grant from the Health Research Council of the New York State Health Planning Commission (HRC #13092). The authors wish to acknowledge the assistance of Frances Simpson and Ida Summers at the Nathan S. Kline Institute and the staff of the Staten Island Developmental Center.

[2] Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY 10962.

[3] State University of New York at Stony Brook, Stony Brook, NY 11794.

for the developmentally disabled with a total resident population of 721 individuals. All patients who had received a minimum of 1 year's neuroleptic treatment in the 5 years prior to study initiation (*N* = 299) were eligible to be included in the study, providing consent could be obtained. The TD evaluation was performed by using the Simpson Abbreviated Dyskinesia Scale (ADS) (Simpson et al., 1979) and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). The primary criterion measure of TD for the study was a dichotomy based on a global score derived from a subset of ADS items (lip chewing and lateral jaw movements, bon-bon sign, tongue protrusion, choreoathetoid movements of the tongue, cheek puffing and choreoathetoid movements of the finger/wrists and ankle/toes). This score, which has been described previously (Richardson & Craig, 1982), classified subjects as having TD if they demonstrated evidence of the disorder in the mild-severe range. Other dependent measures employed were a restricted dichotomous global score based on the same ADS subset as above, which classified subjects as having TD only if they achieved a moderate-severe score, a total TD score which was a summation of the scores for the items rated in the global score, and a criterion measure for TD (RD-TD) based on the AIMS scale which required the presence of at least moderate movements in one body area or mild movements in two body areas for a positive TD score (Schooler & Kane, 1983).

Additionally, three data collection instruments were specifically developed for studying this population. The first was a checklist of 66 conditions known to produce mental retardation (Brain, 1977; Robinson & Robinson, 1976) which was completed during the review of the patients' medical records prior to the TD rating. The second was a listing of 19 conditions known to cause retardation whose phenomenology includes neuromuscular symptoms. These conditions were also identified at the time of record review, and descriptions of their associated symptoms were used by the raters during the TD evaluation sessions to aid in differential diagnosis. The third was a checklist of 29 stereotyped movements (such as rocking) and mannerisms reported to be seen in the MR (Baumeister et al., 1980; Meir-Koll & Pohl, 1979; O'Gorman, 1979) for which the patient was rated during the course of the TD evaluation.

A computerized drug-ordering system in place at the facility for approximately 5 years prior to study initiation was used to extract the variables of total number of days on neuroleptics and days off neuroleptics immediately prior to rating day. The complete facility record was studied for each patient, and patient characteristics were extracted and studied as independent variables. These characteristics included: IQ; sex; age; length of time since first facility admission; abusive to self; abusive to others; nonverbal/speech problems; hyperactivity; epilepsy; and neurological problems other than epilepsy. Also included were the DSM-II MR etiological categories of: Infection and/or Intoxication; Trauma or Physical Agent; Disorders of Metabolism, Nutrition or Growth; Gross Brain Disease (postnatal); Unknown Prenatal Influence; Chromosomal Abnormality; Prematurity; Major Psychiatric Disorder; and Psychosocial Deprivation.

A reliability study on the Simpson ADS and the AIMS was performed between the first author and the primary rater (G.H.) among psychiatric inpatients (*N* = 25) with satisfactory results (Kappas .633–.744; Pearson *r*'s .788-.925). The first phase of the project consisted of a pilot study (*N* = 19) during which the first author rated concurrently with the primary rater. During this phase, it was determined that the validity of the ratings would be enhanced by observing the patients in their usual settings (i.e., dayroom, classroom) with an evaluation session of approximately 30 minutes. During the course of the study, 55% of the study population were rated twice; first, by the primary rater alone and then at a second session by both raters with the first author blind to the first rating, and with a consensual rating of both raters obtained at that second session.

Statistical methods used to analyze the data included chi-square analysis for categorical variables and the *t*-test statistic for continuous variables. Multivariate analyses were carried out using stepwise linear discriminant function analyses for the dichotomous dependent variables (Dixon et al., 1981; Nie et al., 1975) and a multiple linear regression was used for the continuous TD measure.

Results

Consents were obtained for 211 of the 299 eligible patients (70.6%). Chi-square analyses performed comparing the study population to the 88 clients for whom consents were not obtained on the variables of sex, age and DSM-II categories of retardation levels (mild, moderate, severe, or profound) revealed no significant differences. Of the 211 clients studied, 65.9% were male ($N = 139$) and 34.1% female ($N = 72$). The mean age of the subjects was 35.2 years with the mean length of time since first admission being 27.3 years. The mean IQ for the group was 15.5.

The prevalence of TD using the ADS mild-severe criterion measure was 29.9%. Using this measure, the TD positive group was characterized by a 92% rate of buccolingual-masticatory movements and an 80% rate of mild abnormal movements in at least two body areas or a moderate movement in at least one body area. The ADS moderate to severe criterion measure yielded a prevalence rate of 15.6% and the AIMS RD/TD, a rate of 48.8%. This latter criterion was highly correlated with the stereotypy, rocking (chi-square = 23.00, $p < .001$) which inflated the prevalence while the other two criterion measures were not affected by these movements (mild-severe, chi-square = 0.22, NS; moderate-severe, chi-square = 1.21, NS). The designation of TD-YES and TD-NO used for the remainder of this paper is based on the ADS mild-severe criterion measure.

The TD-YES group was significantly older than those without TD and significantly more likely to be female (*see* Tables 1 and 2). Residents with TD had experienced longer periods of institutionalization which was primarily an age-related phenomenon as the correlation between age and length of time since first admission was highly significant ($r = .63$, $p = .0001$).

Variables having to do with neuroleptic use on the day of TD evaluation were significantly associated with TD, while those having to do with neuroleptic history up to that day were not so associated. The rate of neuroleptic use at evaluation was significantly lower for the TD-YES group as was CPZ equivalent dose at evaluation (*see* Tables 1 and 2). These two drug-use variables were significantly correlated ($r = .47$, $p < .001$). However, the number of days receiving neuroleptics in the 5 years prior to evaluation, and the number of days continuously off neuroleptics prior to rating day for those not receiving medication at evaluation, were not significantly associated with the presence or absence of TD. The time interval off neuroleptics was also studied as a categorical variable with the following breakdown (months): 0-12, 12-24, 24-36, 36-60. There was no significant difference in TD status found for these breakouts (chi-square = 1.915, NS). Of the 84 residents not being treated with neuroleptics at evaluation, 57% had not received that class of drugs for 2 years or more.

The prevalence of TD varied according to DSM-II categories of retardation classified by etiology as shown in Table 1. Two of the categories showed a significant association with TD, one in a positive direction—Disorders of Metabolism, Nutrition, and Growth—and the other in a negative direction—Psychosocial Deprivation.

There was no association between the TD designation and epilepsy, and the category of other neurological problems.

The behavioral characteristics studied also showed no association with TD (abusive to self or others, nonverbal or having speech problems, hyperactivity, and the presence of the stereotyped movements rated).

The results of the stepwise discriminant function analysis carried out on the ADS mild-severe measure as shown in Table 3 indicated that the following variables were significant discriminators for TD (in order of entrance): Age (positive); Disorders of Metabolism, Nutrition, or Growth (positive); Psychosocial Deprivation (negative); and with a marginal association, Sex (female). Group membership was significantly predicted—$F(2.206) = 20.28$ $p < .01$, and the resulting canonical correlation was—$R = .53$. Table 3 also shows the classification matrix. This represents the accuracy (77.3%) in classifying each case into either TD-YES or TD-NO groups, compared to actual group membership when using the resultant classification function. A jackknifed procedure was used for internal cross-validity checking which produced an accuracy rate close to the original at 76.3%. Variables that did not reach significance as discriminators in this analysis, though they did show a significant association with TD in the bivariate comparisons were: neuroleptic use at evaluation, CPZ dose at evaluation, and length of time since first admission.

Discussion

The prevalence rate of 30% in this population, using the same phenomenological criteria applied in psychiatric patients, casts doubt on the assertion made by some investigators that TD is closely associated with the disease process of schizophrenia (Crow et al., 1983: Owens & Johnstone, 1982).

This study presents the first reported significant association of TD and age in an MR population. Age has been positively associated with TD in psychiatric inpatients by the current authors with the same criterion measure (Richardson et al., 1984) and by several other investigators in both psychiatric inpatients and outpatients (Kane & Smith, 1982). The commonality of this risk factor between these MR patients and psychiatric populations suggests a similar age factor in the TD vulnerability of both groups.

The status of the risk factor of female sex in this study presents still another similarity to the TD psychiatric literature in which female sex is an acknowledged risk factor but possibly secondary to age (Kane & Smith, 1982). While female sex was significantly associated with TD status in a bivariate comparison, sex entered only as a marginally significant variable in the multivariate analysis where age was highly significant. The sex designation, however, did add to the power of the linear combination to discriminate TD status, and for that reason was kept in the analysis despite its marginal association.

The two diagnostic categories that significantly contributed to the TD discrimination in the multivariate analysis deserve careful study. The category that was positively associ-

TABLE 1

Comparison of TD-YES* and TD-NO* Groups for Categorical Variables

Variables	Total Group	TD-YES		TD-NO		Test Statistics	
	N	N	%	N	%	Chi-Square	p-value
Sex							
Males	139	32	23.0	107	77.0	9.09	<.01
Females	72	31	43.1	41	56.9		
DSM-II Etiological Classification							
Infection & Intoxication	21	4	19.0	17	81.0	1.30	NS
Trauma or Physical Agent	42	12	28.6	30	71.4	0.04	NS
Disorders of Metabolism, Nutrition, or Growth	12	11	91.7	1	8.3	23.29	<.01
Gross Brain Disease	16	5	31.3	11	68.8	0.02	NS
Unknown Prenatal Influence	89	28	31.5	61	68.5	0.19	NS
Chromosomal Abnormality	15	5	33.3	10	66.7	0.09	NS
Prematurity	28	8	28.6	20	71.4	0.03	NS
Major Psychiatric Disorder	1	1	100.0	0	0.0	2.36	NS
Psychosocial Deprivation	16	0	0.0	16	100.0	7.37	<.01
Medical Conditions							
Epilepsy	83	23	27.7	60	72.3	0.30	NS
Other Neurological Problems	48	13	27.1	35	72.9	0.23	NS
Behavioral Problems							
Abusive to Self	118	33	28.0	85	72.0	0.48	NS
Abusive to Others	107	26	24.3	81	75.7	3.20	NS
Nonverbal/Speech Problems	133	36	27.1	97	72.9	1.95	NS
Hyperactivity	112	29	25.9	83	74.1	1.79	NS
Stereotypies (Observed)	161	48	29.8	113	70.2	0.00	NS
Score on Neuroleptics at Evaluation	127	31	24.4	96	75.6	4.52	<.05

*TD status determined using ADS mild-severe criterion measure.
NS - Not Significant.

TABLE 2

Comparison of TD-YES* and TD-NO* Groups for Continuous Variables

Variables	Total Group Mean	Total Group S.D.	TD-YES Mean	TD-YES S.D.	TD-NO Mean	TD-NO S.D.	Test Statistic *t*-Test	Test Statistic *p*-value
Age (years)	35.2	9.9	41.4	12.3	32.5	7.3	5.36	<.01
IQ	15.5	10.7	15.5	10.5	15.5	10.9	0.05	NS
No. Stereotypies	2.3	2.1	2.6	2.3	2.1	1.9	1.57	NS
Duration—Years Since 1st Admission	27.3	7.6	29.9	8.3	26.3	7.1	3.23	<.01
CPZ Equivalent Dose (mg)	192.0	306.5	127.0	218.1	220.0	334.0	2.38	<.05
Days on Neuroleptics in 5 Years Prior	1416.0	516.6	1339.0	526.4	1449.0	510.7	1.41	NS
Continuous Days Off Neuroleptics Prior to Rating Day**	784.0	464.7	822.0	448.1	761.0	477.5	0.58	NS

*TD status determined using ADS mild-severe criterion measure.

**Only patients *not* on neuroleptics on TD Rating Day are included in this variable ($N = 84$).

NS - Not significant.

ated with TD (Disorders of Metabolism, Nutrition, and Growth) ($N = 12$), was composed primarily of females (75%), had a mean age of 39.9, a mean IQ of 9.2, and a 50% rate of neuroleptic use at a 127.3 mg mean CPZ equivalent dose. The modal medical condition ($N = 7$) in this category was phenylketonuria (PKU). The TD prevalence among the PKU patients was 86% while the prevalence in the remainder of the study population was 27%. All of the 6 PKU patients given a positive TD rating displayed buccolingual/masticatory movements, such as tongue protrusion, choreoathetoid tongue movements, lip movements (pouting, puckering, or smacking), and chewing movements. These patients also displayed other abnormal motor behaviors which were not counted toward the TD designation. These included: rocking, fidgeting, trunk-twisting, self-biting, toe-walking, tension spasms, and surface stroking. Some of these behaviors have been described as part of the symptom picture of PKU (Knox, 1966; Walton, 1977). Despite the small sample size,

TABLE 3

Multivariate Analysis - Stepwise Discriminant Function

Variables Entered: DSM-II Category of Disorders of Metabolism, Nutrition and Growth
DSM-II Category of Psychosocial Deprivation
NL Use at Evaluation — No. of Days On NL in Prior 5 Years
CPZ Dose at Evaluation — No. of Days Off NL Prior to Evaluation
Age — Sex — Duration

Significant Discriminators

Variables in Order of Entrance		*F*-Statistic
Age (Positive)		36.182
Disorders of Metabolism, Nutrition, and Growth (Positive)		17.597
Psychosocial Deprivation (Negative)		5.830
Sex (Female)		3.575
Canonical Correlation:	$R = .53$	
Accuracy of Predicting Group Membership = 77.3% Overall		

Classification Matrix

Actual Group Membership	Classified Group Membership TD-NO	Classified Group Membership TD-YES
TD-NO	128 (86.5%)	20 (13.5%)
TD-YES	28 (44.4%)	35 (55.6%)

this particular vulnerability of PKU cases to develop TD is of interest since it is the first report of a single medical condition being associated with TD. This finding may have heuristic value in terms of the pathophysiology of TD and deserves further study.

The other diagnostic category related to TD, psychosocial deprivation, carried a significant negative association. None of the 16 patients in this category manifested symptoms of TD. The characteristics of this group differed markedly from the prior group (Disorders of Metabolism, Nutrition, or Growth) in that there was a lower rate of females (31%), a younger mean age (32.9), a higher mean IQ (19.3), and a higher rate of neuroleptic use (93.8%) at a higher mean CPZ dose (445.9 mg). Patients were most likely given this diagnosis in the absence of any physical cause for their retardation and in the presence of evidence of nurturance deprivation. This finding could be read as a weak organic risk factor for TD, as this was the category least likely to contain patients with structural brain deficits. The fact, however, that TD was not significantly associated with any of the diagnostic categories indicative of neurological trauma and/or neurological structural deficits such as infection or intoxication, trauma or physical agent, gross brain disease (postnatal), chromosomal abnormality, and prematurity, or medical conditions such as epilepsy or other neurological problems, argues against a strong association of TD and structural neurological impairments.

The lack of association between the primary TD designation (ADS mild-severe) and stereotypies was due to the highly specific phenomenological approach of the criterion measure, the simultaneous rating of well-specified stereotypical movements known to occur in untreated MR patients, and by the rigor of the rating session.

In summary, this study establishes a 30% prevalence of TD in a medically heterogeneous mentally retarded population. Risk-factor analyses demonstrated similarities to the TD psychiatric literature and provided information on the disorder not possible within psychiatric populations.

References

Baumeister, A.A., MacLean, W.E., Kelly, J., et al. Observational studies of retarded children with multiple stereotyped movements. *J. Abnorm. Child Psychol.*, 8(4):501–521, 1980.

Brain, W.R. *Brain's Diseases of the Nervous System*. 8th Ed. (Revised by J.N. Walton) Oxford: Oxford University Press, 1977.

Crow, T.J., Owens, D.G.C., Johnstone, E.C., et al. Does tardive dyskinesia exist? *Mod. Probl. Pharmacopsychiatry*, 21:206–219, 1983.

Davis, V.J., Cullari, S., and Breuning, S.E. Drug use in community foster group homes. In: Breuning, S.E., and Poling, A.D. (eds.), *Drugs and Mental Retardation*. Springfield, Ill: Charles C Thomas, 1982.

Dixon, W.J., Brown, M.B., Engelman, L., et al. (eds.), *BMDP Statistical Software, 1981*. Berkeley: University of California Press, 1981.

Gualtieri, C.T., Breuning, S.E., Schroeder, S.R., et al. Tardive dyskinesia in mentally retarded children, adolescents and young adults: North Carolina and Michigan studies. *Psychopharmacol. Bull.*, 18(1): 62–65, 1982.

Kalachnick, J. Tardive dyskinesia and the mentally retarded: a review. In: Breuning, S. (ed.), *Advances in Mental Retardation and Developmental Disabilities*, Vol. 2, New York: Raven Press, 1983.

Kane, J.M., and Smith, J.M. Tardive dyskinesia prevalence and risk factors, 1959 to 1979. *Arch. Gen. Psychiatry*, 39:473–481, 1982.

Knox, L.E. Phenylketonuria. In: Stanbury, J.B., Wyngaarden, J.B., and Fredrickson, D.S. (eds.), *The Metabolic Basis of Inherited Disease*. New York: McGraw-Hill Book Company, 1966, pp. 258–294.

Lipman, R.S., DiMascio, A., Reatig, N., et al. Psychotropic drugs and mentally retarded children. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978.

Meir-Koll, A., and Pohl, P. Chronobiological aspects of stereotyped motor behavior in mentally retarded children. *Int. J. Chronobiol.*, 6:191–209, 1979.

Nie, N.H., Hull, C.H., Jenkins, J.G., et al. *Statistical Package for the Social Sciences*, 2nd ed. New York: McGraw-Hill Book Co., 1975.

Owens, D.G.C., and Johnstone, E.C. Spontaneous involuntary disorders of momement. *Arch. Gen. Psychiatry*, 39:452–461, 1982.

Paulson, G.W., Rizvi, C.A., and Crane, G.E. Tardive dyskinesia as a possible sequel of long-term therapy with phenothiazines. *Clin. Pediatr.*, 14(10):953–955, 1975.

Richardson, M.A., and Craig, T.J. The coexistence of parkinson-like symptoms and tardive dyskinesia. *Am. J. Psychiatry*, 139(3):341–343, 1982.

Richardson, M.A., Pass, R., Craig, T.J., et al. Factors influencing the prevalence and severity of tardive dyskinesia. *Psychopharmacol. Bull.*, 20(1):33–38, 1984.

Robinson, N.M., and Robinson, H.B. *The Mentally Retarded Child, A Psychological Approach*, 2nd ed. New York: McGraw-Hill Book Company, 1976.

Walton, J.N. *Brain's Diseases of the Nervous System*, 8th Ed. (Revised by J.N. Walton) Oxford: Oxford University Press, 1977, pp. 832–833.

Neuroleptic-Induced Tardive Dyskinesia and Parkinsonism: Changes During Several Years of Continuing Treatment[1]

Daniel E. Casey, M.D.,[2,3] Uffe J. Povlsen, M.D.,[3] Birgit Meidahl, M.D.,[3] and Jes Gerlach, M.D.[3]

Tardive dyskinesia (TD), a syndrome of abnormal involuntary hyperkinetic movements, usually involves the mouth, tongue, and face, but may also cause choreoathetoid dyskinesias in the limbs and trunk. It occurs in predisposed individuals during or following the cessation of long-term neuroleptic treatment (Casey & Gerlach 1984). Since this disorder may occur in 15% of patients receiving extended neuroleptic therapy—and at even higher rates in the elderly—there is appropriate concern about the proper indications for using these highly effective antipsychotic drugs (Casey, 1985).

Difficult clinical choices must be made when managing patients with TD who benefit from neuroleptic drugs. Since these agents are the purported cause of TD, it is widely believed that they will also inevitably worsen TD if neuroleptic treatment is continued. However, there are few data either to corroborate or refute this commonly held belief. Reports about the natural history of TD noted several possible outcomes, including improvement, stabilization, or aggravation, either with or without continued treatment, but these evaluations tended to be of short duration (Pyke & Seeman, 1981; Schonecker, 1957; Smith et al., 1981; Urhbrand & Faurbye, 1960).

The long-term (5 years or more) outcome of TD has seldom been evaluated. In the few available studies, it was not always possible for the investigators to quantify or monitor the effects of adjustments in drug treatment, such as decreased, stable, or increased dose. Furthermore, changes in other neuroleptic-induced symptoms, such as parkinsonism, were not simultaneously assessed to account for the possible interaction of these two treatment-induced side effects. Therefore, this study evaluated long-term changes in TD and neuroleptic-induced parkinsonism in chronically ill psychiatric patients who required neuroleptic treatment for control of psychosis.

Methods

Patients

Thirty-three patients (6 females, 27 males) with chronic psychiatric illnesses and living in an institutionalized setting were assessed. The mean age was 65.6 years (range, 31 to 99 years).

Medications

The neuroleptic dose for each patient was recorded at the beginning of the evaluation and at 6-month intervals. Drug treatment was tailored to the individual patient's psychiatric needs. Neuroleptic doses were converted to chlorpromazine equivalents (CPZE) (Baldessarini, 1977). Mean daily dose at the end of the study period was 316 mg/day of CPZE (range, 0-1500 mg/day).

Design and Evaluation

Patients were evaluated at the time of entry into the study (baseline) and at one of 3-, 5-, 8-, 10-, or 11-year follow-up assessments in May 1984. A standardized examination for TD and parkinsonism was videotaped at the beginning and end of follow-up assessments. These tapes were randomly sequenced and scored by experienced raters who were blind to the year of assessment and drug treatment. TD was scored on the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) and parkinsonism was evaluated with the Sct. Hans Dyskinesia Scale (Gerlach, 1979). TD was defined by the recently proposed research criteria (Schooler & Kane, 1982). Data are presented as changes in group mean total scores.

---

[1] This study was supported in part by funds from the Veterans Administration Research and Merit Review Programs, and USPHS Grant MH-36657 from the National Institute of Mental Health. Marian Karr prepared the manuscript.

[2] Psychiatry Service, VA Medical Center, Departments of Psychiatry and Neurology, Oregon Health Sciences University, Portland, OR 97201.

[3] Departments AEH/H, Sct. Hans Mental Hospital, 4000 Roskilde, Denmark.

Reprint requests to: Daniel E. Casey, M.D., Psychiatry Service (116A), VA Medical Center, Portland, OR 97207.

Results

Over the follow-up period, a consistent pattern of outcome emerged. In the whole group of 33 patients, TD decreased 27% and parkinsonism increased 34% (*see* Table). There was a significant ($p<.05$) positive correlation between length of follow-up and TD improvement. Neuroleptic dosages increased modestly from 265 mg/day to 316 mg/day CPZE (*see* Table). Variable degrees of symptom changes were evident when the treatment was categorized by dosage changes of decreased, stable, and increased. In those patients whose neuroleptic decreased (from 646 mg/day to 230 mg/day) TD was unchanged and parkinsonism increased minimally by 9%. In patients receiving a stable neuroleptic dose (±100 mg/day CPZE average daily dose increased by 9% from 195 mg/day to 214 mg/day): TD decreased 24% and parkinsonism increased 31%. Increased dose (from 128 mg/day to 681 mg/day) was necessary to control psychotic symptoms in some patients. This group showed a 55% decrease in TD and a 21% increase in parkinsonism. In summary, TD remained stable or improved in most patients continuing neuroleptic treatment. No systematic or generalized increase in TD was observed. Furthermore, parkinsonism increased in about the same proportion as TD decreased.

Three of the 33 (9%) patients showed increased AIMS scores, but these were modest changes of +1 to +2 in the total AIMS assessments. These changes were unrelated to treatment status: medicines were discontinued in one patient, dosage was increased by 100 mg/day CPZE in another, and decreased by 75 mg/day in the third. None of these increased scores was of clinical significance and no patient had an increase in global ratings from mild or moderate categories.

Discussion

This study of the long-term outcome of TD indicates that this syndrome remains stable or gradually improves in the majority of patients receiving extended low to moderate neuroleptic dosage. These results are consistent with other studies which have evaluated changes in TD over periods of 5 years or more (Casey & Toenniessen 1983; Gardos et al. 1985; Yagi & Itoh 1984). Furthermore, the few patients who experience increases in TD show only modest changes in symptoms.

The lack of TD aggravating effect by neuroleptics is seen in all the treatment groups. The decreased dose group would be most likely to show an increase in TD, as reduced neuroleptic dose would further unmask existing symptoms and lead to the appearance that TD increased. This was not the case. However, the lack of substantive change in TD at the study end point may be accounted for by offsetting effects of unmasking which would tend to increase symptoms and gradual improvement which would have the effect of decreasing symptoms. The stable dose group provides the best opportunity to evaluate the effects of continuing neuroleptic therapy because the masking or unmasking effects are minimized. The decrement in AIMS scores refutes the proposal that continued neuroleptic treatment will inevitably aggravate TD. Finally, the increased dose group might be expected to show more TD in later years after the initial masking or suppressive effect of neuroleptics was subsequently unmasked by "breakthrough" phenomena. However, this again was not the case.

Some caveats must be emphasized. Most importantly, these conclusions cannot be extended to groups of patients which are substantively different from this study cohort. It is not possible to predict the outcome of a similar study if much higher neuroleptic doses were employed. Similarly, different age groups may have different outcomes. Though increasing age is generally correlat-

TABLE

Changes in Drug Dose, AIMS, and Parkinsonism

Dose Group	No Pts	CPZE[a] BL[d]-5/84[e]	AIMS[b] BL[d]-5/84[e]	PARK[c] BL[d]-5/84[e]	Percent Change CPZE[a]	Percent Change AIMS[b]	Percent Change PARK[c]
All	33	265–316	6.7–4.9	6.8–9.0	↑20	↓27	↑34
Decrease	6	646–230	6.0–5.9	8.4–9.1	↓64	↓1	↑9
Stable	20	195–214	6.9–5.2	6.3–8.3	↑9	↓24	↑31
Increase	7	128–681	6.8–3.0	5.2–6.3	↑432	↓55	↑21

[a] Chlorpromazine equivalent;
[b] Abnormal Involuntary Movement Scale;
[c] Parkinsonism;
[d] Baseline;
[e] May, 1984.

ed with decreasing improvement in TD (Casey & Toenniessen, 1983: Smith & Baldessarini, 1980), this group of patients, averaging 65.6 years of age, still showed considerable symptom amelioration over many years. Thus, irreversible TD may not be as pervasive as is widely believed. This time course suggests that combining the concepts of gradually resolving and persisting TD are worthwhile, as TD improvement correlated with length of follow-up.

The role of drug-induced parkinsonism in TD requires further discussion. Other long-term TD investigations have not concomitantly evaluated these syndromes, so opportunities for comparing and contrasting these findings are not yet available. The large majority of patients in this study had coexisting TD and drug-induced parkinsonism, though this point is seldom discussed (Richardson & Craig 1982). The hypothesis that dopaminergic function occurs along a unidimensional continuum of a relative deficit (parkinsonism) to relative excess (TD) is insufficient to explain these coexisting syndromes. However, the inverse changes of TD decrease and parkinsonian increase do support the proposal that these disorders share, at least in part, some reciprocally functioning or dysfunctioning mechanisms. Perhaps the decreased TD is due to a masking bradykinetic effect of parkinsonism.

Increasing age may be an important contributor to the decreasing TD and increasing parkinsonism, as idiopathic parkinsonism occurs with increasing age. Though it is not possible to distinguish whether patients had idiopathic or drug-induced parkinsonism, it must be assumed that patients had at least the drug-induced syndrome because they were receiving neuroleptics. Some of these patients might currently have or eventually go on to develop idiopathic parkinsonism. Furthermore, it may be that the addition of neuroleptics is sufficient to increase subclinical parkinsonism to the level of clinically obvious symptoms, which would subsequently revert to subclinical phenomena if drugs were discontinued.

In summary, TD remains stable or gradually improves in patients receiving long-term, low to moderate dose neuroleptics. TD seldom increases—and then only moderately in this treatment setting. Neuroleptic therapy as an "aggravating agent" of existing TD is unproven. These drugs, at least in conservative doses, are not contraindicated in TD patients with psychosis that is responsive to neuroleptic therapy. TD and parkinsonism change reciprocally, though slowly, over several years. Further study of these coexisting and covarying syndromes is required.

References

Baldessarini, R.J. *Chemotherapy in Psychiatry.* Cambridge: Harvard University Press, 1977, pp. 12–56.

Casey, D.E. Spontaneous and tardive dyskinesia: clinical and laboratory studies. *J. Clin. Psychiatry,* 46 (4, Sec. 2):42-47, 1985.

Casey, D.E., and Gerlach, J. Tardive dyskinesia: management and new treatment. In: Stancer, H.C., Garfinkel, P.E., and Rakoff, V.M. (eds.), *Guidelines for the Use of Psychotropic Drugs.* New York: Spectrum Publications, 1984, pp. 183–203.

Casey, D.E., and Toenniessen, L.M. Neuroleptic treatment in tardive dyskinesia: can it be developed into a clinical strategy for long-term treatment? In: Ban, T.A., Pichot, P., and Poldinger, L.W. (eds.), *Modern Problems of Pharmacopsychiatry,* Vol. 21. Basel: S. Karger, 1983, pp. 65–79.

Gardos, G., Cole, J.O., Perenyi, A., et al. Five-year follow-up study of tardive dyskinesia. In: Kemali, D., and Racagni, G. (eds.), *Chronic Treatments in Neuropsychiatry.* New York: Raven Press, 1985, pp. 37–42.

Gerlach, J. Tardive dyskinesia. *Dan. Med. Bull.*, 26:209-245, 1979.

Guy, W. *ECDEU Assessment Manual for Psychopharmacology.* Washington, D.C.: U.S. Government Printing Office, 1976, pp. 534–537.

Pyke, J., and Seeman, M.V. Neuroleptic-free intervals in the treatment of schizophrenia. *Am. J. Psychiatry,* 138:1620–1621, 1981.

Richardson, M.A., and Craig, T.J. The coexistence of parkinsonism-like symptoms and tardive dyskinesia. *Am. J. Psychiatry,* 139:341-343, 1982.

Schonecker, M. Ein eigentumliches Syndrom im oralen Bereich bei Megaphenapplikation. *Nervenarzt,* 28:35, 1957.

Schooler, N.R., and Kane, J.M. Research diagnoses for tardive dyskinesia. *Arch. Gen. Psychiatry,* 39:486-487, 1982.

Smith, J.M., and Baldessarini, R.J. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. *Arch. Gen. Psychiatry,* 37:1368–1373, 1980.

Smith, J.M., Burke, M.P., and Moon, C.O. Long-term changes in AIMS ratings and their relation to medication history. *Psychopharmacol. Bull.*, 17(1):120–121, 1981.

Uhrbrand, L., and Faurbye, A. Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine, and electroconvulsive therapy. *Psychopharmacologia,* 1:408-418, 1960.

Yagi, G., and Itoh, H. A ten-year follow-up study on tardive dyskinesia, with special reference to the influence of neuroleptic administration on the long-term prognosis. Proceedings of the Collegium Internationale Neuro-Psychopharmacologicum, 1984.

Integrating Incidence and Prevalence of Tardive Dyskinesia[1]

John M. Kane, M.D.,[2] Margaret Woerner, Ph.D.,[2] Michael Borenstein, Ph.D.,[2] James Wegner, Ph.D.,[2] and Jeffrey Lieberman, M.D.[2]

Introduction

Epidemiologic studies of tardive dyskinesia (TD) are important in clarifying the scope of the problem and identifying potential risk factors with the ultimate aim of prevention, i.e., reducing the incidence of the condition.

Considerable difficulty remains, however, in integrating available information. We have previously reviewed the wide range of prevalence estimates in the literature and suggested possible explanations for the degree of variation (Kane & Smith, 1982). Prevalence estimates appear to vary enormously from population to population, and most explanations for this have focused on putative risk factors for the development of the condition. In addition, however, it is also important to consider risk factors contributing to the persistence of the condition once it has developed, since variations between populations in the course of TD will also have an important impact on point prevalence.

In this report we will discuss our current findings with regard to incidence and prevalence in the same population and present some findings with regard to risk factors which might influence the incidence and/or persistence of TD.

Incidence of TD

We have previously reported preliminary findings from an ongoing prospective study of TD development (Kane et al., 1982, 1984). This report presents more recent data analyses for the first 616 neuroleptic-treated patients from the main sample in this study, and for 52 patients entered into the study specifically because they had shown severe extrapyramidal side effects (EPS) to neuroleptic drugs upon examination by the research team.

The Table presents the demographic characteristics of the two groups. The most important feature is that these patients are relatively young and have been followed from early in their treatment course (the median exposure to neuroleptics at study entry is 12 months for the main sample, 5 months for the EPS sample).

Figure 1 displays the results of life-table analyses which present the incidence of TD as a function of time on neuroleptics for the main sample. Three survival curves are plotted on this figure. The first shows the incidence of any TD; the second shows the incidence of TD which persisted for 3 months or more; the third shows the incidence of cases which persisted for 6 months or more.

TABLE

Prospective Study of Tardive Dyskinesia Characteristics of the Neuroleptic-Treated Samples at Study Entry

		Regular Sample ($N = 616$)	EPS Sample ($N = 52$)
Sex:	Male	57%	65%
	Female	43%	35%
Age:	Mean	28	27
	S.D.	10	11
	Range	14-72	16-76
Diagnosis:	Affective Disorder	19%	25%
(Hospital)	Schizoaffective	11%	10%
	Schizophrenia	58%	56%
	Other	12%	9%
Total Months Exposure to Neuroleptics:			
	Mean	22	15
	S.D.	26	20
	Range	0-143	0.25-72
	Median	12	5
Age at First Neuroleptic Treatment:	Mean	24	23
	S.D.	9	8
	Range	7-71	15-64

---

[1] This work was supported by USPHS Grant MH-32369 and Contract 278-81-0032 from the National Institute of Mental Health.

[2] Hillside Hospital, a Division of Long Island Jewish Medical Center, Glen Oaks, NY 11004.

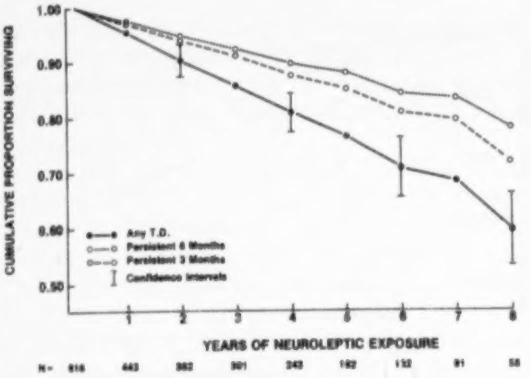


FIGURE 1. Tardive dyskinesia over eight years of neuroleptic exposure.

The overall TD incidence (and 95% confidence intervals) is 18.5% (±4.5%) following 4 years of cumulative exposure to neuroleptics, and 40% (±7%) following 8 years of exposure. The incidence of TD which persists for at least 3 months is 13% (±3%) at 4 years and 29% (±7%) at 8 years. The incidence of TD which persists for at least 6 months is 11% (±3%) at 4 years and 22% (±6%) at 8 years.

The incidence figures presented here are somewhat higher than those we have presented in the past. This is primarily because these figures include data from patients who had TD the first time they were seen (Baseline TD). In the past we had eliminated these cases on the grounds that they had not been followed prospectively, and the point at which they had actually developed TD was not known. However, if we include cases that have *no* TD at baseline and exclude those that do, we will invariably underestimate the incidence. For this reason we have elected to include the Baseline TD cases in the current analyses, and have used their neuroleptic exposure prior to baseline as an estimate of the exposure prior to TD. This does include some error, making the curve higher than it should be. However, we estimate that the amount of this error is small since the Baseline TD cases make up only a third of the TD cases and therefore have a small impact on the total curve.

It is important to note that the hazard rates for any-TD and for persistent-TD appear to be proportional to each other; i.e., there is no evidence that the cases which develop after short exposure are all nonpersistent, while the cases which develop after long exposure are persistent.

Risk Factors for TD

We have conducted a number of analyses with the goal of identifying factors related to the incidence of TD. Except as noted, all analyses were conducted with the 616 patients who either had TD at baseline or were at risk (treated with neuroleptics) while under observation in the prospective study. These analyses are preliminary in nature: in particular, some of the relationships presented here could be due to confounds with other variables which may emerge as the data base increases.

Age. For any given level of exposure to neuroleptics the incidence of TD is higher among older than among younger patients (chi-square = 12.86, $df = 1$, $p = .0003$ by the Wald test). The relationship between age and TD is curvilinear: the risk of TD appears to remain fairly stable through ages 20 to 40, but then rises dramatically with increases in age (chi-square for curvilinear component = 3.72, $df = 1$, $p = .05$). Following 2 years of exposure, the likelihood of TD is about 10% for a 20-year-old and 18% for a 50-year-old patient. Following 4 years of exposure, these figures are 18% for a 20-year-old and 30% for a 50-year-old patient. The value of age as a predictor of TD remains significant when we control for sex (chi-square = 10.13, $df = 1$, $p = .0015$).

Sex. The hazard rate is slightly (but not significantly) higher for women than it is for men (chi-square = 2.20, $df = 1$, $p = .14$). The interaction of sex by age is not significant.

Diagnosis. The incidence of TD was significantly higher among patients diagnosed as affective disorders than it was among either schizoaffectives, paranoid schizophrenics, or other schizophrenics (DSM-II, hospital diagnosis). The most significant distinction was between the pure affective disorders versus the paranoid/other schizophrenics combined. The increased risk associated with the affective disorders in this case remained significant even when we controlled for sex, history of treatment with lithium, electroconvulsive therapy, and age (chi-square = 9.77, *df* = 1, *p* = .002).

Lithium. Within diagnostic category (affective disorder vs. any schizophrenic), prognosis was better for patients who had taken lithium at some point than for those with no history of lithium treatment (chi-square = 5.89, *df* = 1, *p* = .02). Note that lithium use was more common among the affective disorders (43% with history of lithium vs. 9% for schizophrenics), and the affective disorder patients in general appear to have a poor prognosis. Therefore, when we look at lithium without taking diagnosis into account, we find no relationship to incidence (chi-square = 0.61, *df* = 1, *p* = .43).

EPS. The 52 patients who had been entered specifically because of their severe EPS ratings on examination by the research team were compared with the 369 "at-risk" patients who had no history of EPS in their charts (Baseline TD cases were excluded). The TD incidence for the EPS patients is markedly higher than that of the comparison group. Overall the hazard rate for the EPS patients is 2.32 times that of the others (chi-square = 6.64, *df* = 1, *p* = .01), and there is some evidence that the risk ratio could be even higher (3.60) during the first 2 years of exposure. Following 4 years of exposure, the rate of TD is 15% in the comparison group and 37% in the EPS group (Figure 2).

Outcome of TD

Preliminary analyses on the course of TD have been conducted employing data from 96 patients who developed TD during the prospective study.

On the basis of the entire follow-up course, each patient was classified as either remitted, masked, or persistent. A patient was classified as remitted if his global TD ratings were less than 2 (mild TD) for at least two consecutive ratings encompassing at least a 3-month period. A patient could be classified as remitted if these criteria were met, even if the TD later re-emerged. The patient was classified as a "persistent remission" if these criteria were met and the patient never subsequently met criteria for TD. Patients were classified as masked if they met the criteria for remission only following an increase in medication dosage and were classified as persistent if they never met the criteria. In the analyses presented here, the masked cases were treated as persistent.

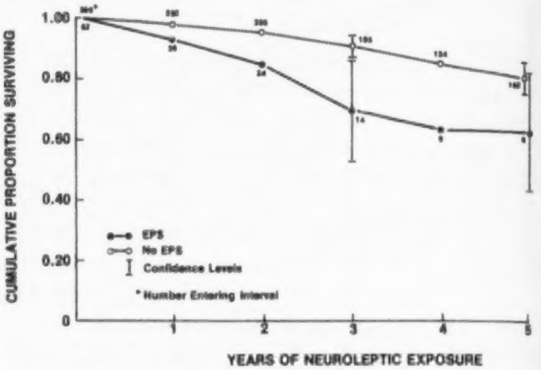


FIGURE 2. EPS as a risk factor for T.D.

Figure 3 presents TD outcome over 2 years of follow-up. When we look at any remissions (ignoring the possibility of a later re-emergence) a total of 32% (95% confidence interval ± 10%) of the patients remit over the first year, and a total of 47% (± 12%) remit over the first 2 years. When we look at persistent remissions only, these figures are 23% (± 10%) for the first year and 33% (± 14%) over the first 2 years.

Exploration of factors related to TD outcome indicate that, as reported based upon earlier analyses (Kane et al., 1984), prognosis is better for patients who develop TD following short-term exposure to neuroleptics than for those who developed TD following long-

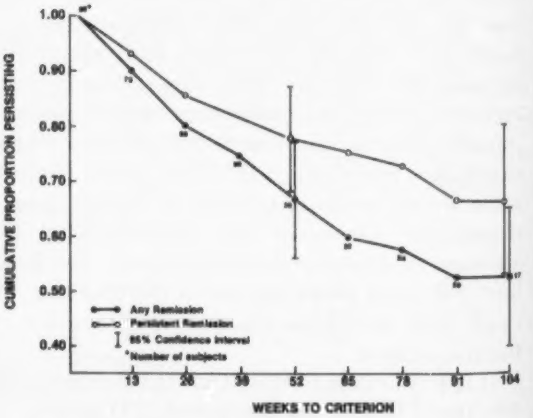


FIGURE 3. Tardive dyskinesia outcome.

er exposure ($p = .05$). There is a suggestion that the importance of prior exposure is greater for women than for men, but gender by itself is not significantly related to TD outcome.

Two measures of treatment after the development of TD have been found to predict outcome: prognosis is better for patients treated with neuroleptics for a smaller proportion of the follow-up period ($p = .05$), and for those treated with lower modal doses during follow-up ($p = .009$). These predictors of outcome are confounded with each other, and with the current sample size it is difficult to identify the unique contribution of each. Thus far, our analyses suggest that modal dose during follow-up is a critical variable with an impact over and above the effect of prior medication history. Proportion of time on medication during follow-up may be more critical for older than younger people; the former appear to have little chance of remitting if maintained on medication after TD develops.

Prevalence of TD

We have recently completed a large-scale survey of the prevalence of TD involving more than 2,000 subjects from two geriatric and three psychiatric populations, including Hillside Hospital. The methodology and some preliminary results were presented previously (Kane et al., 1985; Lieberman et al., 1984a,b). In this report we are focusing on the Hillside sample since the incidence figures discussed above are derived from this population.

Preliminary exploration of variables related to the presence of TD indicated that within each of the psychiatric samples the TD rate increases with increasing age. Further analyses revealed that the impact of age on TD prevalence varies as a function of sex, and of length of exposure to neuroleptics. Figure 4 illustrates the interaction of age and sex in relation to TD prevalence for the Hillside sample. Among women, TD is more prevalent among older than younger people ($r = .42$, $p = .001$). For men, there is a trend in the same direction ($r = .11$, $p = .12$). The fact that this correlation is smaller than the correlation for the women appears to reflect a real fact of risk; that it fails to reach significance for the men reflects in part the relatively narrow age range in the Hillside sample.

The other side of this coin is that sex is more important as a risk factor in older people than it is in younger people. Whether or not sex will prove significant as a risk factor depends upon the age range of the sample; in the Hillside sample it is significant. The following p values were obtained using multiple regression analysis: main effect for sex, $p = .036$; main effect for age, $p = .001$; interaction, $p = .012$.

Figure 5 graphs TD prevalence as a function of the interaction of age and length of neuroleptic exposure in the Hillside sample. It is evident that for the younger people (age<30) there is only a small increase in the probability of getting TD with longer expo-

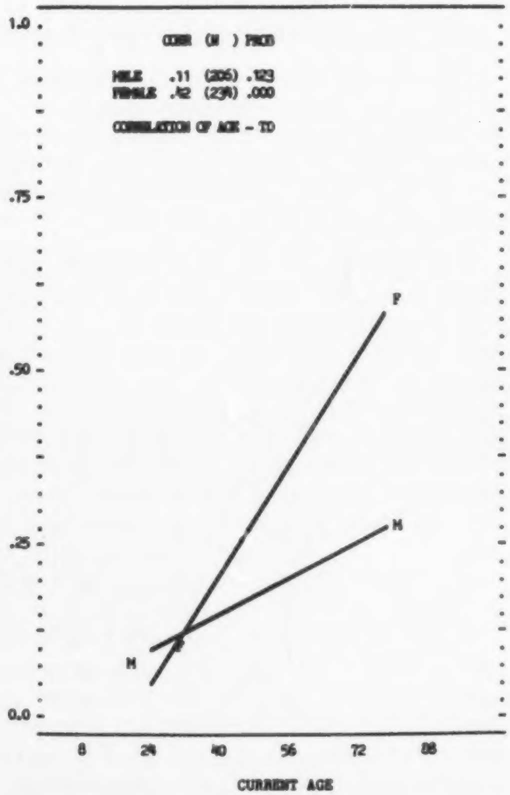


FIGURE 4. Hillside: TD as a function of age and sex.

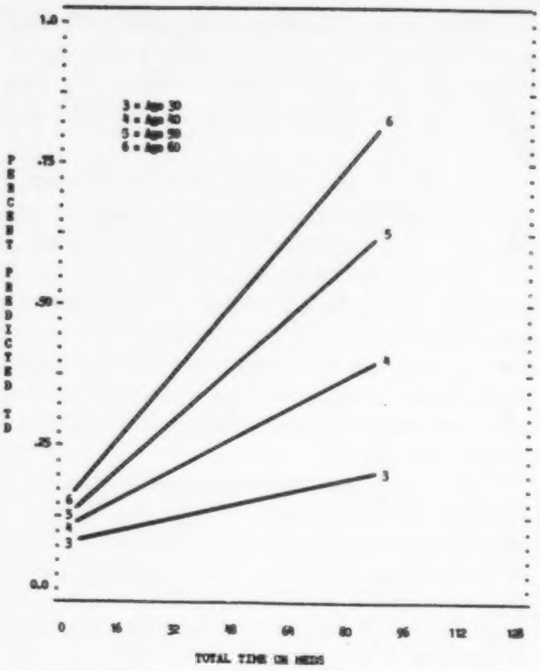


FIGURE 5. **TD as a function of duration and age.**

sure to neuroleptics, while for the older people TD prevalence increases sharply with increased exposure. The regression analysis yielded the following *p* values: main effect for age = .001; main effect for exposure = .019; interaction = .016.

It seems likely that the interaction reflects, in part, the fact that duration of exposure is truly a more important factor in TD development among older, than among younger people. However, this interaction could also partly reflect the findings presented above, from our study of outcome of TD among patients in the incidence study. Since the data under discussion stem from a prevalence survey, we do not know how long the individuals have had TD; i.e., how old they actually were when TD developed, and what length of drug exposure preceded it. However, it is clear that the duration of exposure employed in the analyses includes not only neuroleptic treatment *prior* to TD, but also some treatment *following* TD development. Our preliminary findings with regard to TD outcome suggest that treatment with neuroleptics following TD development is a more critical factor in TD persistence among older, than younger people. Thus, we would expect that even if the impact of neuroleptic exposure on the *development* of TD were equal across all ages, the TD would be less likely to remit, and *prevalence* would therefore be higher, among the older people.

Discussion

Our data suggest that the integration of incidence and prevalence requires knowledge about risk factors for the development of TD and risk factors for the persistence of TD once it develops. Certain findings are of particular clinical importance. Older individuals are not only more vulnerable to developing TD but also more likely to have it persist if neuroleptic medication is continued. Prognosis of TD is better for those patients treated for a smaller proportion of time during the follow-up period and for those treated with lower modal doses during follow-up.

By developing strategies to reduce the risk of TD in vulnerable individuals, and to increase the likelihood of a favorable outcome in those who have developed TD, we may be able to make meaningful progress in reducing the extent of this problem.

References

Kane, J.M., and Smith, J. Tardive dyskinesia: Prevalence and risk factors 1959-1979. *Arch. Gen. Psychiatry*, 39:473–481, 1982.

Kane, J.M., Woerner, M., Weinhold, P., et al. A prospective study of tardive dyskinesia development: Preliminary results. *J. Clin. Psychopharmacol.* 2:345–349, 1982.

Kane, J.M., Woerner, M., Weinhold, P., et al., Incidence of tardive dyskinesia: Five-year data from a prospective study. *Psychopharmacol. Bull.*, 20 (3):387–389, 1984.

Kane, J.M., Woerner, M., Lieberman, J.A., et al. The prevalence of tardive dyskinesia. *Psychopharmacol. Bull.*, 21(1):136–139, 1985.

Lieberman, J., Kane., J.M., Woerner, M., et al. Prevalence of tardive dyskinesia in elderly samples. *Psychopharmacol. Bull.*, 20(3):382-386, 1984a.

Lieberman, J., Kane, J.M., Woerner, M., et al. Prevalence of tardive dyskinesia in elderly patients. *Psychopharmacol. Bull.* 20(1):22–26, 1984b.

A Five-Year Follow-up Study of Tardive Dyskinesia

Guy Chouinard, M.D., M.Sc.(Pharmacol), F.R.C.P.(C), F.A.P.A.,[1,2,3] Lawrence Annable, B.Sc., Dip.Stat.,[1,2] Pierre Mercier, Ph.D.,[1,2] and Andree Ross-Chouinard, M.D.[1,2]

Introduction

Prevalence studies of tardive dyskinesia (TD) in neuroleptic-treated patients have investigated factors associated with the presence of the disorder. The most reliable finding is that TD is more prevalent in older patients. In 1975, we carried out a cross-sectional study of TD in all 256 schizophrenic patients receiving neuroleptic maintenance treatment in the outpatient clinic of the Allan Memorial Institute (Chouinard et. al, 1979b). At that time, we reported the prevalence of TD in the clinic to be 31% (in fact, 23% met the recently proposed Schooler and Kane research diagnostic criteria for TD) (1982). Stepwise multiple logistic regression analysis suggested the following risk factors for TD (in order of statistical significance): advanced age, long records of hospitalization, poor therapeutic response to neuroleptics, and fluphenazine medication [oral or intramuscular (i.m.)]. There was also an inverse relationship between parkinsonism and TD, patients tending to have one or the other disorder but usually not both.

We now report a 5-year follow-up of these patients, focusing in particular on an investigation of factors related to the subsequent development of TD in a cohort of 131 patients who did not present the disorder in 1975.

Method

In 1975 TD and parkinsonism were assessed by a neurologist (A.R.-C.) in all 256 schizophrenic outpatients receiving maintenance antipsychotic medication in the Special Follow-Up Clinic of the Allan Memorial Institute. The scale used was the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard and Ross-Chouinard (Chouinard et al., 1979a, 1980), and the presence of TD was determined according to the Schooler and Kane Research Criteria (1982) which require at least moderate dyskinetic movements in one body area or mild dyskinetic movements in two body areas. The presence of parkinsonism was also determined on a similar basis. Psychopathology was assessed by one of the authors (G.C.) who conducted a psychiatric interview. The schizophrenic illness of patients was classified as good or poor prognosis using the World Health Organization (WHO) scale for prognosis. Data were collected on demographic characteristics, treatment history, neuroleptic type and dosage converted to chlorpromazine equivalents (Davis, 1980), and antiparkinsonian drugs. Patients with a history of meningitis, brain trauma, neurosyphilis, or an abnormality on neurological examination associated with a neurological disease were classified by the neurologist as having brain damage.

In 1980, 169 of the original cohort of 256 patients (65%) were reassessed by the same neurologist and psychiatrist after 5 years of further neuroleptic treatment, using the same rating scales and criteria as before. At this time it was confirmed that all patients met the DSM-III criteria for schizophrenia. Eighty-seven of the original 256 patients (35%) were lost to follow-up because of either failure to return to the clinic, transfer elsewhere, or death. Table 1 compares the characteristics of patients lost to follow-up with those of patients who were reassessed in

---

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute, Royal Victoria Hospital, Montreal, Quebec, Canada.
[2] Department of Psychiatry, McGill University, Montreal, Quebec, Canada.
[3] Research Department, Hôpital Louis-H. Lafontaine, Montreal, Quebec, Canada.

TABLE 1

Patient Characteristics (1975): Differences Between Follow-up Cohort of Patients and Those Lost to Follow-up

	Follow-up Cohort ($N = 169$)	Lost to Follow-up ($N = 87$)	Statistical Significance of Difference[a] p
Men/Women	83/86	54/33	0.07
Age	42 (23-67)[b]	39 (19-63)[b]	0.06
Treatment duration (yrs)	10.5 (0.1-22)[b]	8.0 (0.1-21)[b]	0.001
Dosage (CPZ equivalents)	487 (15-4000)[b]	506 (0-5000)[b]	0.82
Brain damage	25%	14%	0.05
Neuroleptic type			
p.o. only	61%	52%	0.20
i.m. only	18%	18%	0.96
p.o. and i.m.	20%	24%	0.48
Antiparkinsonian medication	55%	67%	0.10
Tardive dyskinesia (research criteria)[c]	22%	24%	0.89
Parkinsonism[d]	33%	44%	0.13

[a] Chi-square test with Yates' correction for percentages, t test for means (two-sided).
[b] Mean (minimum-maximum).
[c] Schooler and Kane (1982).
[d] At least two items with scores ≥2 or one item with score ≥3.

1980. Patients lost to follow-up were more likely to be male ($p = 0.07$), younger (mean difference = 3 years, $p = 0.06$), treated for a shorter period of time (mean difference = 2.5 years, $p = 0.001$), less likely to have brain damage ($p = 0.05$), and more likely to be receiving antiparkinsonian medication ($p = 0.10$). There were no significant differences between the two groups, however, with respect to prevalence of TD or parkinsonism in 1975.

TABLE 2

Patient Characteristics: Cohort of 131 Patients With No TD in 1975

	1975		1980
Men/Women		61/70	
Age	40 (23-67)[a]		45 (27-72)[a]
Duration of treatment (yrs)	9.5 (0.1-22)[a]		14 (4.4-26)[a]
Dosage (mg/day CPZ equivalents)	300 (15-4000)[a]		338 (6-4200)[a]
Poor schizophrenic prognosis		72%	
Brain damage		24%	
Neuroleptic type			
p.o. only	66%		36%
i.m. only	18%		60%
p.o. and i.m.	16%		5%
Antiparkinsonian medication	53%		68%

[a] Median (minimum - maximum).

The characteristics of the cohort of 131 patients who did not present TD in 1975 and who were reassessed in 1980 are shown in Table 2. During this period the policy in the clinic was to switch patients from daily oral (p.o.) neuroleptics to long-acting i.m. neuroleptics (mostly fluphenazine enanthate or decanoate) if feasible. Antiparkinsonian medication was prescribed only if necessary and not prophylactically. Polypharmacy was avoided as far as possible. The principal changes in treatment may be summarized as follows: 1) there was a switch from p.o. to i.m. medication in 45% of patients; 2) a reduction in neuroleptic dosage (chlorpromazine equivalents) (Davis, 1980) in 48% of patients;

TABLE 3

Prevalence of TD and Parkinsonism in 1975 and 1980: Cohort of 169 Patients Assessed in 1975 and 1980

		1975 (Percent)	1980 (Percent)
Tardive dyskinesia	(research criteria)[a]	22	44
Men	($N = 83$)	27	43
Women	($N = 86$)	19	45
Parkinsonism[b]		33	72
Men	($N = 83$)	39	76
Women	($N = 86$)	28	69

[a] Schooler and Kane (1982).
[b] At least two items with scores ≥2 or one item with score ≥3.

and 3) an increase in antiparkinsonian dosage in 45% of patients.

Results

Prevalence of TD in all reassessed patients ($N = 169$). Table 3 shows the prevalence of TD (Schooler & Kane, 1982) and parkinsonism in the 169 patients assessed in both 1975 and 1980. The prevalence of TD increased from 22% to 44% ($p<0.001$, McNemar's test) and that of parkinsonism from 33% to 72% ($p<0.001$, McNemar's test). There was no significant ($p<0.05$) difference between the sexes with respect to the prevalence of either TD or parkinsonism on either occasion. There was, however, a tendency ($p<.10$, $\chi^2 = 3.65$) for more parkinsonism in men than women in 1975, but not in 1980.

Development of TD in reassessed patients ($N = 131$). In the cohort of 131 patients who did not present TD in 1975, 46 patients (35%) developed TD, while the prevalence of parkinsonism increased from 32% to 71%. Stepwise multiple logistic regression analysis (Kleinbaum et al., 1982) was used to predict the development of TD (coded 0,1) during the period 1975 to 1980. The exploratory variables included for selection were of two types: those thought to be of possible etiological significance in the development of TD, and those known or suspected to uncover covert TD. The etiological variables included were: sex, age, duration of neuroleptic treatment (dichotomized and coded as follows: 0 = <5 yrs, 1 = ≥5 yrs), schizophrenic prognosis (0 = good, 1 = poor), brain damage (0 = none, 1 = present), and parkinsonism score (1975); the uncovering or confounding variables were: reduction in neuroleptic dosage, switch from daily p.o. to long-acting i.m. neuroleptic (the uncovering mechanism may be through a decline in blood level at the end of the injection interval when all patients were assessed), and an increase in antiparkinsonian dosage.

The model building strategy used was to start with all main effects in the model and then carry out forward selection to add any significant second-order product (i.e., interaction) terms (Kleinbaum et al., 1982). Second-order product terms were considered because we were unable to obtain a good fit with main effects only. An alpha level of 5% was used throughout. Because there were nine main effects and 36 second-order interaction terms as candidates for selection, this analysis should be regarded as exploratory, particularly where variables of marginal statistical significance were selected.

The results of the stepwise logistic regression analysis are shown in Table 4. Three main effects were significant at the 5% level: parkinsonism score (1975), poor schizophrenic prognosis, and treatment duration (>5 years). Also, two variables were significant at the 10% level: a switch from p.o. to i.m. medication and a neuroleptic dosage reduction. In addition to these main effects two interac-

TABLE 4

Variables Related to Development of TD (1975–1980): Results of Stepwise Logistic Regression Analysis ($N = 131$)

Variable	Coefficient	S.E.	χ^2	p
Intercept	−5.07	1.43	12.58	0.0004
Parkinsonism score (1975)	0.13	0.06	4.68	0.03
Poor schizophrenic prognosis	1.09	0.53	4.31	0.04
Treatment duration	1.42	0.73	3.75	0.05
p.o. to i.m. switch	1.12	0.61	3.37	0.07
Neuroleptic dosage reduction	0.80	0.45	3.18	0.07
Age	0.03	0.02	1.33	0.25
Antiparkinsonian dosage increase	−0.57	0.54	1.11	0.29
Sex	0.15	0.46	0.11	0.74
Brain damage	−0.01	0.66	0.00	0.98
p.o. to i.m. switch x parkinsonism score	−0.23[a]	0.09	7.08	0.008
Antipark. increase x brain damage	2.20	1.04	4.51	0.03

[a] Negative coefficient indicates that effect of presence of both risk factors is less than sum of each main effect (lack of additivity).

TABLE 5

Predictive Ability of Multiple Logistic Regression Model

		Predicted (1980)		
		No TD	TD	Total
True (1980)	No TD	75	10	85
	TD	23	23	46
	Total	98	33	131

Sensitivity (true positives) = 50%
Specificity (true negatives) = 88%

tion terms were added to the model: 1) that between the medication switch and parkinsonism score with a negative coefficient ($p = 0.008$), indicating that the risk of TD with both factors present is less than the sum of their separate risks and, more specifically, that the patients most at risk for developing TD were those with high parkinsonism scores in 1975 who remained on the same medication type (either p.o. only or i.m.) in 1980; and 2) that between an antiparkinsonian dosage increase and brain damage with a positive coefficient ($p<0.05$), indicating that brain-damaged patients were more vulnerable to the effect of antiparkinsonian increase. The effects of age and sex were not significant ($p>0.10$), although it is worth noting that age and duration of treatment were correlated somewhat ($r = 0.44$, $p<0.001$). We examined the goodness-of-fit of this model by comparing the predicted cases ($p>0.5$) with the true cases of TD (Table 5): sensitivity (true positives) was 50% which is fair, and specificity (true negatives) was 88%, which is good.

Because the 1975 parkinsonism score appeared to be the best predictor of subsequent TD development, we repeated the stepwise logistic regression analysis including the change in parkinsonism score (1975 to 1980) as an additional variable. The results of this analysis were that the new variable, change in parkinsonism score, became the best predictor of TD development ($p = 0.001$) with 1975 parkinsonism score second. The new model increased the sensitivity of prediction to 54% while the specificity remained at 88%.

Annual incidence rate of TD. The 5-year cumulative incidence rate of TD in the cohort of 131 patients who did not present TD at the 1975 assessment was 35% (46/131). This is equivalent to a mean annual incidence rate of 8.4% (Kleinbaum et al., 1982). However, this does not consider remissions (or misclassifications) among patients who presented TD in 1975 but not in 1980 of which there were 9/38 cases representing a 5-year cumulative remission rate of 24% or a mean annual remission rate of 5.5%. Thus the mean annual incidence rate of TD corrected for remissions was 2.9%.

Discussion

These results suggest that three etiologic factors may be important in the development of TD. The presence of severe parkinsonism which cannot be suppressed by antiparkinsonian medication appeared to be a precursor of TD development. There was also evidence that worsening of parkinsonism was associated with TD development. Whereas in 1975 we observed an inverse relationship between parkinsonism and TD, in 1980 both disorders were commonly present simultaneously. During this interval the patients had both grown older and been exposed to more neuroleptic treatment, so that a more advanced stage of extrapyramidal movement disorder had probably been reached. One contribution to the changed relationship may have been the decrease in dopamine synthesis with aging, especially in male patients, as found in PET scan studies.

The second risk factor for TD was poor schizophrenic prognosis, which tends to confirm our earlier finding (Chouinard et al., 1979b) of an association between poor therapeutic response to neuroleptics and TD. Duration of neuroleptic treatment also appeared to be a risk factor with 5 to 10 years of exposure being a critical period. This finding has intuitive appeal but has not generally been substantiated in prevalence surveys. The correlation between treatment duration and age in the present population probably explains why we failed to find age an important predictor here, although it was the first variable selected in our 1975 prevalence survey (Chouinard et al., 1979b). Another factor to be considered is that these patients may constitute a special subgroup inasmuch as they were those patients in the clinic who did not present TD in 1975, despite presence of risk factors in some cases.

Three variables that may perhaps be characterized as uncovering or, in statistical terminology, confounding factors rather than etiologic factors were also identified as associated with the manifestation of TD: a switch from p.o. to i.m. medication in those without parkinsonism, a neuroleptic dosage reduction, and an increase in antiparkinsonian medication in brain-damaged patients. The explanation for the appearance of the medication switch as a risk factor may be that blood levels tend to decline toward the end of the injection interval (when all these patients were assessed), and a decline in dopamine receptor blockade at this point would tend to uncover any covert dyskinesia. This may be the explanation for our previous finding of an association between fluphenazine treatment and TD (Chouinard et al., 1979b) as many patients were receiving i.m. fluphenazine. A study in two patients using neuroleptic radioreceptor assay measurements of neuroleptic blood levels at different points during the injection period supports this view (Chouinard et al., 1982). The uncovering effect on TD of neuroleptic dosage reduction is well-known; that of anticholinergic antiparkinsonian dosage increase has also been documented (for example, Chouinard et al., 1979c), but the finding of increased vulnerability of brain-damaged patients in this respect is new. In our earlier prevalence study of TD (Chouinard et al., 1979b) in this population, we found that brain-damaged patients tended to have more severe forms of TD than those without brain damage. Thus, there seems to be some evidence to suspect that brain-damaged patients are at greater risk for the disorder.

The estimated 2.9% annual incidence rate of TD corrected for remissions is similar to that reported by Kane et al. (1982) from a prospective study of TD development, although the latter study is of a younger and heterogeneous population of patients with schizophrenia or manic-depressive disorder.

We believe that a large-scale prospective study of TD development in a homogeneous population of newly-treated schizophrenic patients would clarify further the risk factors.

References

Chouinard, G., Annable, L., Ross-Chouinard, A., et al. Ethopropazine and benztropine in neuroleptic-induced parkinsonism. *J. Clin. Psychiatry*, 40:73–81, 1979a.

Chouinard, G., Annable, L., Ross-Chouinard, A., et al. Factors related to tardive dyskinesia. *Am. J. Psychiatry*, 136:79–83, 1979b.

Chouinard, G., de Montigny, C., and Annable, L. Tardive dyskinesia and antiparkinsonian medication. *Am. J. Psychiatry*, 136:228–229, 1979c.

Chouinard, G., Ross-Chouinard, A., Annable, L., et al. Extrapyramidal Symptom Rating Scale. *Can. J. Neurol. Sci.*, 7:233, 1980.

Chouinard, G., Creese, I., Boisvert, D., et al. High neuroleptic plasma levels in patients manifesting supersensitivity psychosis. *Biol. Psychiatry*, 17:849–852, 1982.

Davis, J.M. Antipsychotic drugs. In: Kaplan, H.I., Freedman, A.M., and Sadock B.J. (eds.) *Comprehensive Textbook of Psychiatry*, Vol. 3, 3rd ed., Baltimore, Md.: Williams & Wilkins, 1980, pp. 2257–2289.

Kane, J.M.. Woerner, M, Weinhold, P., et al. A prospective study of tardive dyskinesia development: preliminary results. *J. Clin. Psychopharmacol.*, 2:345–349, 1982.

Kleinbaum, D.G., Kupper, L.L., and Morgenstern, H. *Epidemiologic Research*. Belmont, Calif.: Lifetime Learning Publications, 1982.

Plasma Fluphenazine Levels in Patients Receiving Two Doses of Fluphenazine Decanoate[1]

Stephen R. Marder, M.D.,[2] John W. Hubbard, Ph.D.,[3] Theodore Van Putten, M.D.,[2] Edward M. Hawes, Ph.D.,[3] Gordon McKay, Ph.D.,[3] Jim Mintz, Ph.D.,[2] Philip R.A. May, M.D.,[2] and Kamal K. Midha, Ph.D.[3]

Plasma level monitoring has the potential for being particularly useful in maintenance treatment. One of the serious problems in selecting a maintenance dose is that there are few guidelines available for deciding when a particular dose is adequate for a particular patient. This differs from the treatment of acute schizophrenia in that the clinician may not be able to titrate dose against active signs and symptoms. In this regard, anything which would help make dose selection in maintenance therapy less of a trial-and-error proposition would be welcome.

We explored the usefulness of plasma fluphenazine levels in the context of a double-blind comparison of what we defined as a very low (5 mg) and a conventional dose (25 mg) of fluphenazine decanoate (FD) administered every 14 days over a 1-year period (Marder et al., 1984).

Method

The subjects were 45 men referred to an outpatient research clinic at a large urban V.A. hospital. All were diagnosed as suffering from a Schizophrenic Disorder using DSM-III. The design of this study is described in detail in a prior publication (Marder et al., 1984).

After giving written informed consent, subjects were managed on a stable dose of FD for 2 or more months. Individuals who could not be stabilized on 25 mg or less every 14 days were dropped from the study. Following stabilization, all neuroleptics were stopped for 4 weeks. (This actually entailed missing one injection of FD.) At this point, all subjects were given a test dose of 5 mg of FD. Blood for plasma level measurement was drawn before and 24 hours after the injection. Two weeks after the test dose, patients were randomized to a double-blind trial of 5 or 25 mg of FD administered every 14 days. For the 5 mg group, FD was prepared in miglyoil: for the 25 mg group, in sesame seed oil. Further blood samples were drawn at 1, 2, 3, 6, 9, and 12 months following entry. Samples were drawn 2 weeks following the previous injection or just before the next injection was administered.

Plasma levels of fluphenazine were measured using a radioimmunoassay (RIA) (Midha et al., 1980) which was validated for specificity using gas chromatography with mass spectrophotometry (Dudley et al., 1983).

When patients demonstrated a worsening of 3 or more points on Brief Psychiatric Rating Scale (BPRS) cluster scores for thought disturbance or paranoia, they were considered to have a psychotic relapse. Most were rather mild and easily managed by adjusting the drug dose. (Relapses in this report were designated exacerbations in a prior publication.)

Results

The Figure describes the mean fluphenazine concentrations for patients treated with the two doses. Patients were dropped from this analysis when their dosage was adjusted as a result of relapse. Thus, the *N*'s reflect a diminishing sample due to dropout and relapse. However, results based only on com-

---

[1] This study was supported by the Veterans Administration Medical Research Service and the UCLA Mental Health Clinical Research Center for the Study of Schizophrenia (National Institute of Mental Health), R.P. Liberman, M.D., Director.

[2] West Los Angeles Veterans Administration Medical Center, Brentwood Division and the UCLA School of Medicine, Los Angeles, CA 90073.

[3] College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

Reprint requests to Dr. Stephen R. Marder, West L.A. V.A. Medical Center, 11301 Wilshire Blvd., Los Angeles, CA 90073.

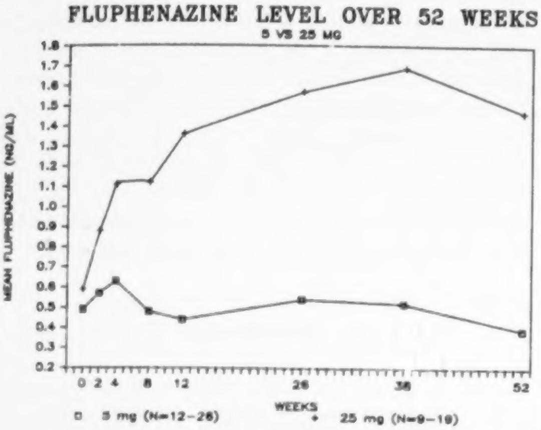


FIGURE. Mean plasma fluphenazine levels for patients treated with 5 or 25 ng of FD every 14 days. Differences between the two dosage groups are statistically significant at 8 weeks and thereafter.

plete cases through 52 weeks looked virtually identical. Although the values were similar at baseline and 2 weeks, by 8 weeks fluphenazine levels were significantly higher for patients treated with 25 mg—and remained significantly higher for the remainder of the year. For clarity, the standard deviations were left off this Figure. They were very large—often larger than the means. Levels for the 5 mg group remained reasonably stable over the year whereas the 25 mg group required 3 to 6 months to reach a stable level. Even though the high dose patients received fivefold the dose of low dose patients, there was some overlap.

We also examined the relationship between steady-state fluphenazine concentrations and vulnerability to psychotic relapse. We used the concentrations at 6 months since this was the amount of time it took plasma concentrations to reach steady state. We compared these levels with psychotic relapses during the next 18 months. The mean fluphenazine level was 0.57 ng/ml for relapsers and 1.01 ng/ml for nonrelapsers. This difference, however, was not statistically significant. Although 5 of the 10 patients who eventually relapsed had plasma levels below 0.5 ng/ml, 7 of the 19 patients who did not relapse were also in this range. None of the patients with plasma levels of greater than 1.5 ng/ml relapsed.

We also studied the relationships between fluphenazine levels at 3 months and side effects. Plasma concentrations correlated with the score for Akinesia ($r = .52$, $p = .002$), the BPRS cluster score for Retardation ($r = .52$, $p = .002$), and Total BPRS ($r = .39$, $p = .02$).

The relationship between side effects and plasma level was also examined in a pooled within-subject analysis of the ratings of side effects and fluphenazine levels over all rating occasions. For this analysis, "dummy" variables were forced into a hierarchical analysis of the side effect ratings to remove between-subject effects. We then computed the amount of variance which was explained by the addition of information about either fluphenazine (FLU) or log (FLU+1). For the log-transformed FLU, the relationship approached statistical significance at the $p = .097$ level for akinesia and reached significance at the $p = .016$ level for akathisia.

Discussion

We found that patients who received 25 mg of FD every 14 days required from 3 to 6 months to reach a stable steady state. This finding indicates that a dose of FD which may be appropriate during the first weeks of treatment may be excessive a few months later. It suggests that when a higher dose is given for maintenance, a reasonable practice might be to gradually decrease the dose or increase the interinjection interval during the first 6 months of treatment.

Although plasma fluphenazine concentrations were lower in patients who eventually relapsed, this difference did not reach statistical significance. Finding relationships between plasma concentration and clinical response probably requires a larger sample size when studying maintenance treatment as opposed to acute treatment. This is because of the greater variance related to such factors as the lengthy period of time during which patients may be exposed to environmental stressors and the unpredictable relationship between the time a dose is altered and the time to relapse. Our findings, however, do suggest that patients who have plasma levels of greater than 1.5 ng/ml are less likely to relapse than those with much lower plasma levels. The correlations between plasma levels and side effects suggest that this added protection may be at the cost of more personal discomfort. This finding is consistent with a previous report on the same population in which patients treated with 25 mg had higher side effect ratings than those treated with 5 mg—even though both groups were treated aggressively with antiparkinson medications (Marder et al., 1984). This suggests that finding the best maintenance dose may require a complex risk-benefit analysis in which the amount of protection given to the patient should be weighed against the amount of side effect-induced discomfort that the person can tolerate.

In conclusion, our data do not indicate that the measurement of fluphenazine level alone will be helpful in determining whether a patient is more vulnerable to relapse. Finding a reasonable threshold plasma level may require the measurement of parent fluphenazine as well as its psychoactive metabolites or the development of an even more sensitive analytical method. We did find, however, that plasma level measurement may be useful in determining when a patient is receiving too much drug. The correlations between fluphenazine levels and side effects indicate that patients with high plasma levels may benefit from having their drug dose reduced.

References

Dudley, J., Rauw, G., Hawes, E.M., et al. Correlation of fluphenazine plasma levels versus clinical response in patients: A pilot study. *Prog Neuro-Psychopharmacol. Biol. Psychiatry*, 7:791–795, 1983.

Marder, S.R., Van Putten, T., Mintz, J., et al. Costs and benefits of two doses of fluphenazine. *Arch. Gen. Psychiatry*, 41:1025–1029, 1984.

Midha, K.K., Cooper, J.K., and Hubbard, J.W. Radioimmunoassay for fluphenazine in human plasma. *Commun. Psychopharmacol.*, 4:107–114, 1980.

An Early Phase II Clinical Trial of Remoxipride in Schizophrenia With Measurement of Plasma Neuroleptic Activity

Guy Chouinard, M.D., M.Sc. (Pharmacol), F.R.C.P.(C),[1,2] and L. Turnier, M.D.[2]

A wide variety of chemical classes of drugs such as phenothiazines, thioxanthenes, butyrophenones, diphenylbutylpiperidines, and benzamides have been found to have antischizophrenic effects. Relative in vitro affinities for D_1 and D_2 dopamine receptors differentiate classical antipsychotics such as fluphenazine (relatively equivalent in blocking D_1 and D_2 receptors) from butyrophenones and diphenylbutylpiperidines. Haloperidol and pimozide, for example, have respectively 200 and 900 times more affinity for D_2 than D_1 receptors (Christensen et al., 1984). It is interesting to note that remoxipride, a new substituted benzamide, has no known affinity for D_1 receptors, and thus appears to be a selective D_2 receptor-blocking agent (Ogren et al., 1983). In addition, remoxipride was found to have a preferential effect in mesolimbic and extrastriatal dopamine containing neurons (Ogren et al., 1983). Remoxipride is an S(-)-3-bromo-N-[1-ethyl-2-pyrrolidinyl) methyl]-2,6-dimethoxy-benzamide monohydrate. We report an early Phase-II clinical trial of remoxipride in the treatment of chronic schizophrenia with and without acute exacerbation.

Method

Twenty patients satisfying the study criteria given below were selected for inclusion in the trial and transferred to our research ward of Hôpital Louis-H. Lafontaine. The selection criteria required that: 1) the patients be aged between 18 and 65 years: 2) a primary hospital diagnosis of schizophrenia be confirmed by the research psychiatrist on the basis of the DSM-III (American Psychiatric Association, 1980): and 3) patients with physical illness, childhood schizophrenia, organic brain syndrome, mental retardation, alcoholism, epilepsy, or drug addiction and women of childbearing potential be excluded from the study.

The study population consisted of 13 men and 7 women aged between 27 and 62 years (median: 48 years), who had been hospitalized on 1 to 18 occasions (median: 6), for a total duration of 2 to 30 years (median: 10.6 years). The schizophrenic disorder was classified by DSM-III criteria as paranoid in 13 patients, undifferentiated in 3 patients, and disorganized in 4 patients, of which 14 cases were chronic without acute exacerbation and 6 chronic with acute exacerbation.

Before entering the trial, all patients were receiving haloperidol (6 to 80 mg/day, median: 30) and a central anticholinergic antiparkinsonian, procyclidine (7.5–40 mg/day, median: 22.5). No other psychotropic drugs were taken by the patients before entering the trial. Haloperidol was abruptly discontinued and patients underwent a 4-day placebo single-blind washout period during which procyclidine was gradually decreased and discontinued.

Patients were then treated for 6 weeks with remoxipride at dosages determined according to therapeutic effect and side effects. The medication was given in the form of tablets prepared in a dosage strength of 50 mg and was administered in a twice-daily regimen. The initial dose varied between 50 mg and 100 mg/day. Thereafter, the dosage was adjusted according to therapeutic effect with the condition that individual dose increments did not exceed 100 mg/day and did not occur at intervals of less than 3 days.

Assessment of symptoms was based on

---

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute, Royal Victoria Hospital, Montreal, Quebec, Canada, and Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

[2] Research Department, Hôpital Louis-H. Lafontaine, Montreal, Quebec, Canada.

clinical interviews conducted by a single clinical investigator (G.C.). Mental status was scored on admission (while on haloperidol), at the end of washout (day 0) and weekly on the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) and a 7-point Clinical Global Impression (CGI) severity of illness. Factor scores were formed from the items of the BPRS (Overall & Klett, 1972). Extrapyramidal symptoms were recorded weekly on the Extrapyramidal Symptom Rating Scale of Chouinard and Ross-Chouinard (Chouinard et al., 1980, 1984); biochemistry, urinalysis, hematology, EEG, and ECG were done at regular intervals. Blood samples were taken in a fasting state before and 1 hour after ingestion of the morning dose of medication for measurement of plasma remoxipride concentrations and neuroleptic levels. Plasma neuroleptic activity was determined using a radioreceptor technique developed by Creese and Snyder (1977), Lader (1980), and Cohen et al. (1980), and remoxipride blood concentrations by a high performance-liquid chromatography method.

Results

Drug Dosages

Dosages of remoxipride were increased gradually from 50 mg/day to a maximum of 500 mg/day (the maximum daily dose permitted was 600 mg). At week 6 the doses varied between 75 mg/day and 500 mg/day (median: 225 mg/day). Eleven of the 20 patients were administered minimal doses of clonazepam, as needed, for agitation ($n = 8$), insomnia ($n = 2$), anxiety ($n = 1$), and aggressiveness ($n = 1$) that was not well-controlled by the study medication; the mean daily dosages of clonazepam in these patients ranged from .05 to .57 mg (median: .09 mg). Upon admission to the trial, all patients were receiving procyclidine to control parkinsonian symptoms (mean: 23.1 mg/day) while at the end of the treatment period with remoxipride 15 patients (75%) required procyclidine administration (mean: 17.4 mg/day). Comparison of week 6 and pre-washout doses of procyclidine shows a trend to a decline (paired t test, $t = 1.8$, $p < .10$, two-tailed) in patients' need for antiparkinsonian medication. No other psychotropic drugs were given during the trial.

Therapeutic Effect

All patients completed 42 days of active treatment. The Table shows the mean admission, baseline and weekly scores for all patients on the BPRS and CGI. There was a statistically significant deterioration (paired t test, $p < .001$) at the end of placebo washout in the BPRS total score and statistically significant improvement occurred at the end of the treatment period in the CGI (paired t: 2.8, $p = .01$, two-tailed) and the BPRS total score ($t = 2.3$, $p = .03$). The response of each patient was classified on a 7-point scale ranging from very much worse to very much im-

TABLE

Mean Admission, Baseline, and Weekly Scores for the BPRS, CGI, and Parkinsonism and Tardive Dyskinesia on the Extrapyramidal Symptom Rating Scale (ESRS)

	BPRS		CGI		ESRS			
					Parkinsonism		Tardive Dyskinesia	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Admission	20.8	4.5	4.20	0.52	8.8	4.8	3.3	2.8
End of Washout	31.8**	11.4	4.60	0.75	8.5	4.7	3.5	3.1
Week 1	26.3	8.1	4.65	0.59	9.9	5.1	3.3	2.9
Week 2	25.9	11.2	4.45	0.95	11.3	5.6	3.4	3.3
Week 3	21.1	9.6	4.00	0.80	9.2	5.9	4.4	3.3
Week 4	23.4	12.8	4.10	0.91	9.5	5.5	4.4	3.9
Week 5	20.8	10.9	3.85	0.88	7.5	5.5	5.2	3.2
Week 6	24.5*	11.8	3.95*	0.89	7.3	4.1	4.3	3.6

*$p < .05$, paired t test, compared to End of Washout

**$p < .001$, paired t test, compared to Admission.

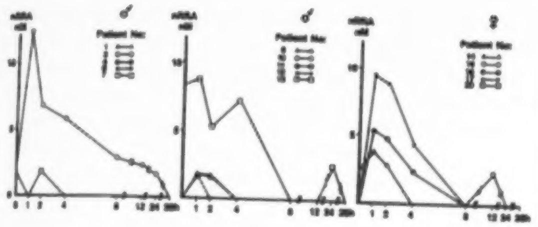


FIGURE 1

proved: 16 patients were considered to be improved (10 much improved, 6 minimally improved), and 4 patients minimally worse.

Extrapyramidal Symptoms and Adverse Effects

The admission, baseline, and weekly mean scores for parkinsonism and tardive dyskinesia (TD) on the Extrapyramidal Symptom Rating Scale are also shown in the Table. There was a decline in parkinsonism at Week 6 compared to admission while patients were on haloperidol treatment. Comparison of Week 6 with baseline scores shows a significant decline (paired *t* test: 2.65, $p = .02$, two-tailed) in hyperkinetic parkinsonian symptoms (factor formed by adding scores for tremors and akathisia) during remoxipride treatment. There was a tendency for an increase of overt TD in the total score for dyskinetic movements at baseline when patients had been withdrawn from neuroleptics compared to admission (when patients were on haloperidol); thus, after 6 weeks of drug administration remoxipride appeared to have little masking effect on TD.

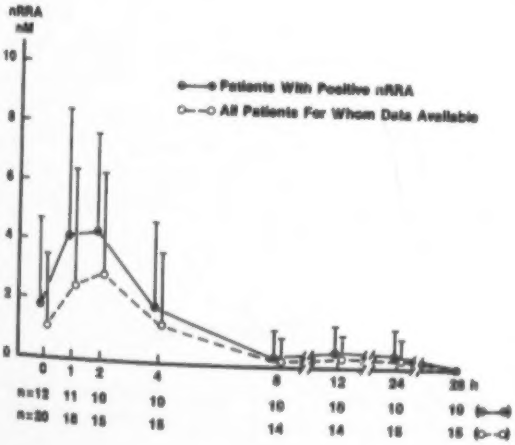


FIGURE 2

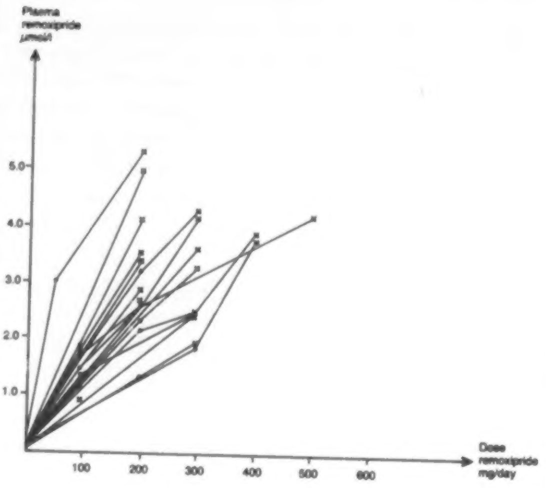


FIGURE 3

The following adverse experiences (of moderate intensity) were judged to be related to the study drug (number of cases in parentheses): akathisia (9), fatigue (7), insomnia (7). Remoxipride produced a statistically significant ($p<.05$, paired *t* test) lowering of the supine systolic blood pressure at the end of the clinical trial (mean admission—120.3 mm Hg, Day 42—111.8 mm Hg). There was a statistically significant ($p<.001$, paired *t* test) but small decrease in the mean body weight at the end of the trial (from 67.1 kg at admission to 65.1 kg at the end of the trial). Eight patients (40%) at the beginning of the clinical trial had mild EEG abnormalities, probably related to their prior neuroleptic intake. Of

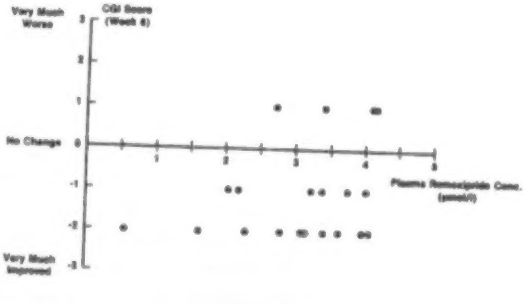


FIGURE 4

these patients, 2 had an improvement and 2 no changes, while in the 4 other patients there was some evidence of remoxipride producing EEG effects: mild irregular bitemporal theta activity, paroxystic activity induced by photic stimulation and increases in slow activity. On the ECG remoxipride produced nonspecific ST-T wave changes in 6 patients. Transient changes in white blood cell count (inversion of the proportion of neutrophiles upon lymphocytes) were noticed in 2 patients and transient vacuoles in lymphocytes (<1%) were observed in 3 patients.

Plasma Radioreceptor Activity

Baseline and day 42 blood samples were analyzed for neuroleptic activity using calf caudate homogenate and [^{3}H]spiperone as ligand. Activity was detected in the plasma of 5 patients at baseline (end of washout), whereas little or no activity could be demonstrated in the samples obtained on day 42. Indeed, analysis of serial blood samples drawn at 1, 2, 4, 8, 12, 24, and 28 hours after the last morning dose on day 42 showed 12 patients with maximum concentrations ranging from 1.7 to 12.3 nmol/l (median: 3) and 8 patients with no activity. Blood samples were analyzed in quadruplicate and the limit of the assay was 6 nmol/l haloperidol units. Results presented are the means of the four measurements (Figures 1 and 2).

Plasma Concentrations of Remoxipride

Serial plasma remoxipride concentrations in individual patients were measured following the last dose of remoxipride (Day 42). Maximum concentrations occurred within 2 hours after drug intake and ranged between 1.8 µmol/l (50 mg dose) and 10.8 µmol/l (250 mg dose). The mean elimination half-life was 5.9 hours (range: 4.1-10.7 hours). When individual patient steady-state plasma remoxipride concentrations were plotted against dose, steady-state concentration and dose were linearly related (Figure 3). There was no evidence of correlation between plasma remoxipride concentrations or drug dosage and therapeutic effect (Figures 4 and 5).

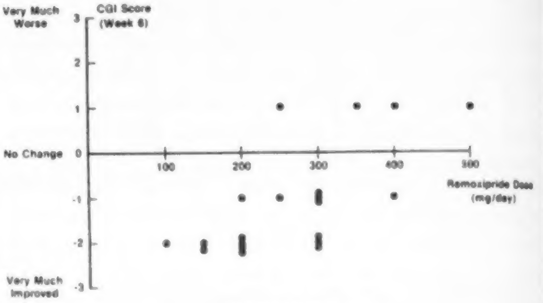


FIGURE 5

Discussion

The marked improvement seen in half of these schizophrenic patients suggests that remoxipride has an anti-schizophrenic effect. The decline in parkinsonism is consistent with the hypothesis that remoxipride has less effect on the nigrostriatal system (Ogren et al., 1983). Remoxipride was found to have little masking effect on TD. By the same token, this might suggest that remoxipride would have correspondingly less potential to induce TD in newly treated patients, but this would need to be investigated. The lack of serum neuroleptic activity in the majority of blood samples shows that the drug has low affinity for [^{3}H]spiperone binding which makes this method less useful for neuroleptic activity measurements, due to its low sensitivity versus remoxipride, when using calf caudate. Remoxipride can act with a configuration of the receptor other than the one labelled with spiroperidol, thus ligands such as [^{3}H]n-propylnorapomorphine could be used for D_2 receptors in human studies of remoxipride. These results underline the importance of a drug's D_2-dopamine receptor-blocking properties in achieving an anti-schizophrenic effect.

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III), 3rd ed., Washington, D.C., 1980.

Chouinard, G., Ross-Chouinard, A., Annable, L., et al.

Extrapyramidal symptom rating scale. *Can. J. Neurol. Sci.*, 7:233, 1980.

Chouinard, G., Ross-Chouinard, A., Gauthier, S., et al. An extrapyramidal rating scale for idiopathic and neuroleptic-induced parkinsonism and dyskinesia. 14th C.I.N.P. Congress. Abst. F-13, 1984.

Christensen, J., Arnt, J., Hyttel, J., et al. Pharmacological effects of a specific dopamine D-1 antagonist SCH 23390 in comparison with neuroleptics. *Life Sci.*, 34:1529–1540, 1984.

Cohen, B.M., Herschel, M., Miller, E., et al. Radioreceptor assay of haloperidol tissue levels in the rat. *Neuropharmacology*, 19:663–668, 1980.

Creese, I., and Snyder, S.H. A simple and sensitive radioreceptor assay for antischizophrenic drugs in blood. *Nature*, 270:180–182, 1977.

Lader, S.R. A radioreceptor assay for neuroleptic drugs in plasma. *J. Immunoassay*, 1:57–75, 1980.

Ogren, S.O., Hall, H., Kohler, C., et al. Remoxipride, a new potential antipsychotic compound with selective anti-dopaminergic actions in the rat brain. *Eur. J. Pharmacol.*, 102:459–474, 1983.

Overall, J.E., and Gorham, D.R. The brief psychiatric rating scale. *Psychol. Rep.*, 10:799–812, 1962.

Overall, J.E., and Klett, C.J. *Applied Multivariate Analysis.* New York: McGraw-Hill Book Co., 1972.

Measuring Adverse Drug Reactions in a Postmarketing Surveillance System[1]

Seymour Fisher, Ph.D.,[2] Stephen G. Bryant, Pharm. D.,[2] and Ronica M. Kluge, M.D.[3]

We have recently initiated a large-scale study aimed at developing new methods for collecting postmarketing surveillance data on prescription drug experiences in an ambulatory population. These new monitoring methods are designed to complement rather than replace existing physician-initiated voluntary reporting of adverse drug reactions (ADRs). The current study, while primarily oriented toward validating a patient-initiated monitoring system, actually compares two different approaches to ADR surveillance. One is based upon patient-initiated reports via toll-free telephone to a cadre of interviewers who have been trained to record in a standardized way the relevant information obtained from the patient. The second method utilizes computer-directed similar telephone interviews initiated by the interviewing staff.

Since many practitioners and researchers use some form of clinical interview to elicit potential ADRs, it is important to examine the validity of such interview information. These interviews may range from a casual inquiry about how the patient has been feeling since starting the drug to a detailed review of organ systems (e.g., Maclay et al., 1984; Mellinger, 1984; Rauch, 1979). The purpose of this paper is to show that, while spontaneously reported symptoms are uniformly reliable in detecting ADRs, symptoms elicited by system review may lead to gross overestimation of true ADRs.

Method

The study is based upon a cohort of patients receiving a new prescription for certain targeted drugs. The target drugs were selected from two classes of therapeutic agents with markedly disparate, well-documented ADR profiles (tricyclic antidepressants and antibiotics).

Study Design

At the time a targeted prescription is being dispensed at our outpatient pharmacies, cooperation is randomly solicited from half of the patients (Experimentals) via a printed notice attached to the outside of their medication bag: this patient package "outsert" provides a brief, concise statement of what the patient is being requested to do, the reason for the request, and a removable sticker (to be placed on the bathroom mirror or elsewhere) that gives our toll-free number along with a summary of details about how to report "*any* new or unusual symptoms" during the next 2 weeks. The other half of the patients (Controls) do not receive any outsert, but are interviewed approximately 2 weeks later by telephone. These Control interviews are computer-directed so that the questions and various response options appearing on the interviewer's video screen are almost completely determined by the patient's prior responses.

The Standardized Interview

If the ultimate goal is to be able to reliably detect the occurrence of postmarketing ADRs, then—as noted by Lasagna (1971) and Wardell et al. (1979)—the first step must be the development of a standardized method of collecting accurate reports of new or unusual "adverse clinical events" (ACEs) during or following a drug's use. An ACE

---

[1] This study is supported in part by USPHS Grant MH-39661 from the National Institute of Mental Health.

[2] Department of Psychiatry and Behavioral Sciences, The University of Texas Medical Branch, Galveston, TX 77550.

[3] Department of Internal Medicine, The University of Texas Medical Branch, Galveston, TX 77550.

may or may not turn out to be an ADR, depending upon additional information that permits inferences about potential causality; but all ADRs must first be valid ACEs.

When a call from an Experimental patient is received, or when we initiate a call to a Control patient, the ensuing interview tries to obtain complete information about all ACEs being reported. The standardized interview used to identify, describe, and quantify ACEs was developed from modifications of SAFTEE, the National Institute of Mental Health's "Systematic Assessment For Treatment Emergent Events" (Levine & Schooler, 1984). The modified telephone interview has four sections: a general inquiry for spontaneously reported ACEs, a systematic ACE inquiry, a post-spontaneous inquiry, and a medication inquiry.

The opening questions center only on spontaneously reported ACEs. With patient-initiated calls from Experimentals, the interviewer records verbatim the symptom(s) that prompted the patient to call. In staff-initiated Control interviews, the key initial question is simply "Have you noticed any new or unusual symptoms during the past 10 days or so?" For each symptom spontaneously mentioned by the patient, the interviewer records details about its onset, duration, frequency, pattern, and severity.

The general inquiry is followed by a systematic inquiry covering each of the specific organ systems or areas relevant to the two target drug classes. Special emphasis is again placed on eliciting only recent unusual changes: e.g., "Have you noticed any changes in your skin during the past 10 days or so?"; "Have you had any unusual problems with your mouth or tongue?" When a "No" response is elicited to any of these system-review questions, the interviewer does not pursue the area any further for fear of encouraging over-reporting through suggestion (i.e., unlike the original SAFTEE interview, we avoid asking leading questions like "Has your mouth been dry?" or "Have you had any rashes?").

At the end of the systematic inquiry the patient is offered one more opportunity to recall any other unusual changes. The final part of the interview then determines when the patient most recently started the target medicine; whether it is still being taken and with any significant dosage changes; whether and when it had been used previously; what other medicines were being taken regularly; and—if one or more ACEs were reported—whether starting the drug unequivocally preceded each ACE onset, and whether the patient attributed the new symptoms to any of the medications.

Data Analyses

The data presented here are based on 231 staff-initiated, computer-directed interviews with Control patients who a) were over 18 years old, b) did not receive an outsert or any other indication at the pharmacy of study participation, and c) when interviewed approximately 2 weeks later, reported having started the target drug and were not taking any drug from the other target class. The sample had a mean age of 45.0 years (s.d. = 15.6); 81.8% were female; 53.6% were Caucasian (38.9% were Black, 6.9% were Hispanic).

As noted previously, all ADRs must first be valid ACEs. A valid ACE is defined as any untoward reaction that began only after the patient started the target drug and within the specific allowable 14-day reporting period. A patient could have reported one or more valid ACEs during the general inquiry, the systematic inquiry, or the post-spontaneous inquiry; these ACEs are referred to as Spontaneous, Systematic, and Post-Spontaneous ACEs, respectively. In addition, because there is general agreement on a core set of expected side effects for the antibiotics and tricyclic antidepressants constituting our target drugs, we can single out those valid ACEs matching one of our assumed "true adverse drug reactions." Table 1 lists the symptoms defined as antibiotic and tricyclic ADRs prior to the study and reported by our Control patients in the three interview sections. Any one of the nine antibiotic ADRs reported by an antibiotic patient was recorded as an ACE+; similarly, any of the 12 tricyclic ADRs reported by a tricyclic patient was also recorded as ACE+. Conversely, any of the antibiotic ADRs reported by a tricyclic patient, or any of the tricyclic ADRs reported

TABLE 1

Pre-defined Adverse Drug Reactions[a]

Antibiotics[b]	Tricyclic Antidepressants[b]
Sore mouth	Dry mouth
Sore tongue	Daytime drowsiness or excessive sleeping
Itching	Light-headedness or dizziness
Rash	Fainting
Hives	Rapid or irregular heartbeat
Stomach ache or pain	Blurred vision
Nausea or vomiting	Headache or head pain
Cramps	Shakiness or tremor
Diarrhea	Constipation
	Delay in starting urination
	Decreased force of urine stream
	Numbness or tingling (extremity)

[a] These common adverse drug reactions were selected from Long (1977), USP (1983), and the approved labeling.

[b] Antibiotics: ampicillin, doxycycline, penicillin, tetracycline; tricyclics: amitriptyline, doxepin, imipramine.

by an antibiotic patient, are shown as ACE−'s.

Obviously, these pre-defined ADRs are not unique to the two target drug classes. However, since their ADR profiles have little overlap, and since patients could not be taking drugs from both classes concomitantly, in effect we have reduced the likelihood that our tricyclic patients would experience an antibiotic ADR or our antibiotic patients would experience a tricyclic ADR. It follows then that a) most of the true ADRs will be a subset of reported ACE+'s; b) true ADRs should be found where there are a minimum of ACE−'s, and c) therefore we can create an indicator of ADR sensitivity by comparing the presence of ACE+'s relative to ACE−'s within any defined group of patients:

$$\text{ADR Index} = \frac{(\text{ACE}+) - (\text{ACE}-)}{(\text{ACE}+) + (\text{ACE}-)}$$

This index can range from 1.00 (reflecting maximum sensitivity of a system in detecting the pre-defined ADRs) through 0.00 to −1.00 (indicating the extent to which ACE−'s are obscuring ADR detection).

In order to be able to conclude with a high level of confidence that a particular ACE was caused by a particular drug and is therefore a true ADR, it is first necessary to rule out attribution of the ACE to any one of the alternative causes listed in Table 2. Note that since the only condition under which no ACE−'s would be expected is when all six competing categories of potential causes can be ruled out (e.g., via statistical adjustment in a randomized controlled study), the primary validity tests are limited to whether a mean ADR Index is significantly positive or whether one mean is significantly larger (i.e., more sensitive) than another.

Results

Table 3 gives the frequency and rate per hundred of the 151 patients who had one or more valid ACEs. Each patient was classified as having either no valid ACEs or at least one valid ACE. Within each drug class ADR incidence estimates are first based upon ACEs reported anywhere in the interview, and are then shown cumulatively beginning with spontaneously reported ACE+'s during the general inquiry, and proceeding through the systematically elicited ACE+'s to the post-spontaneously reported ACE+'s.

Looking at the total group we see that almost two-thirds (65.4%) of all patients at some point in the interview reported at least one new or unusual symptom that appeared within 2 weeks after starting their target medication. When we limit the analysis to only ACE+'s (representing matches with a true ADR), we find that 30 to 40% of the patients are reporting symptoms that could indeed be true ADRs. Table 3 then shows in which sec-

TABLE 2

Competing Hypotheses to Account for an Adverse Clinical Event (ACE)

1. Natural course of the primary illness for which the target drug was prescribed.
2. Natural complications of the primary illness.
3. Onset of a new illness.
4. Independent environmental factors capable of producing the ACE.
5. Placebo effects associated with starting the target drug.
6. Other medications, foods, or substances taken concomitantly with the target drug.

TABLE 3

Frequency of Patients With One or More Valid ACEs

	Antibiotics		Tricyclics		Total	
	N	Rate[a]	*N*	Rate[a]	*N*	Rate[a]
Total Interviews	132		99		231	
Any ACE	89	67.4	62	62.6	151	65.4
Any ACE+	43	32.6	39	39.4	82	35.5
Spontaneous ACE+	23	17.4	11	11.1	34	14.7
Systematic ACE+	19	14.4	25	25.3	44	19.0
(cumulative)	42	31.8	36	36.4	78	33.8
Post-Spontaneous ACE+	1	0.8	3	3.0	4	1.7
(cumulative)	43	32.6	39	39.4	82	35.5

[a] Per 100 patients

tions of the interview these ACE+'s were elicited.

Spontaneous ACE+s reported during the general inquiry yielded only about a 15% incidence overall. However, when ACE+'s subsequently elicited during the systematic inquiry are added to the incidence rates obtained from the general inquiry alone, the overall rate is markedly increased: almost doubled for the antibiotics, and tripled for the tricyclics.

The final post-spontaneous inquiry augments the estimated incidence rates only slightly. Fewer than 2% of the total sample reported an ACE+ here when they had not already done so in either the general or systematic inquiry.

Thus, depending upon whether you focus on all ACEs, or only upon ACE+'s, and depending upon whether you base your estimates on the total interview or just the initial general inquiry, ADR incidences for these target drugs could range from a high of 67% to a low of less than 15%. To determine whether ACE+'s reported anywhere in the interview are equally valid, it is necessary to examine how ACE−'s are being reported along with ACE+'s. Table 4 presents these data for each of the three interview sections. During the general inquiry there were more patients in both drug classes with at least one spontaneous ACE+ than there were patients with one or more spontaneous ACE−'s. Although there were disproportionately more ACE− patients in the antibiotic group, the ADR Index means of .19 and .38 (not significantly different) indicate that both antibiotic and tricyclic groups were accurately discriminating true ADRs: the pooled mean ADR Index of .25 is significantly different from zero at the .03 level.

When we turn to the systematic inquiry, however, something is strikingly awry. The mean ADR Index for the total group is .00, stemming from very different results in the antibiotic and tricyclic samples. While tricyclic patients continued to discriminate as well as previously, an extraordinarily large number (32) of the antibiotic patients who had not spontaneously reported an ACE+ are now reporting ACE−'s, overwhelming the 19 patients now reporting one or more ACE+'s. The mean ADR Index for the antibiotics is negative and significantly different from the mean ADR Index of .42 for the tricyclics. Obviously, many of the pre-defined ADRs from the tricyclic target drug profile were being elicited from antibiotic patients throughout the systematic inquiry, even when they were reporting few new true antibiotic ADRs. Since there were three more pre-defined tricyclic ADRs than antibiotic ADRs, one has to consider the possibility that

TABLE 4

ADR Index for Different Interview Sections

	Antibiotics	Tricyclics	Total
Spontaneous ACEs			
Patients with at least 1 ACE+ or 1 ACE−	30	16	46
At least 1 ACE+	23	11	34
At least 1 ACE−	16	5	21
Mean ADR Index[a]	.19	.38	.25
t(*df* = 44)		<1 (*p* = N.S.)	
Systematic ACEs			
At least 1 ACE+ or 1 ACE−	40	30	70
At least 1 ACE+	19	25	44
At least 1 ACE−	32	12	44
Mean ADR Index	−.31	.42	.00
t(*df* = 68)		3.75 (*p* < .001)	
Post-Spontaneous ACEs			
At least 1 ACE+ or 1 ACE−	2	4	6
At least 1 ACE+	1	3	4
At least 1 ACE−	1	2	3
Mean ADR Index	.00	.25	.17
t(*df* = 4)		<1 (*p* = N.S.)	

[a] For each patient who had at least one ACE+ or one ACE−, an individual ADR Index is calculated based upon the total number of ACE+s and ACE−s reported by that patient. A different ADR Index, calculated by subtracting the frequency of patients with at least one ACE− from the frequency of patients with at least one ACE+ and dividing by the combined frequencies, yields almost identical results.
N.S. = Not Significant

antibiotic patients had more opportunity by chance to report an ACE that matched one of the tricyclic ADRs. However, that same opportunity was present for spontaneous ACEs during the general inquiry.

Table 4 further shows that during the final post-spontaneous inquiry only 6 patients mentioned an ACE+ or an ACE− for the first time. Despite the extremely small numbers, the data yield a tricyclic positive ADR Index consistent with accurate ADR detection while the two antibiotic patients, after having completed the systematic inquiry, yield an ADR Index of zero.

Discussion

We are not aware of any other postmarketing surveillance study that has so closely and systematically examined the incidence of *all* new symptoms during a 10- to 14-day period following the start of a drug. One of the clearest findings emerging from this study is that almost two-thirds of our patients did report a new ACE, and even when limiting the analysis to known ADRs, we find between 30% and 40% of our patients reported at least one "true" ADR (ACE+) at some point in the interview. The fundamental issue here centers on two interrelated questions: whether ACEs reported anywhere in the interview are equally likely to be ADRs, and whether the true ADR incidence for these target drugs is therefore really as high as is estimated by the total interview.

Our results clearly indicate that ADRs can be accurately detected for antibiotics and tricyclics using spontaneously reported ACEs, with incidence estimates of 17.4% and 11.1%, respectively. ACEs elicited by systematic inquiry increase the incidence estimates substantially, but totally destroy the discrimination of true antibiotic ADRs. On the other hand, tricyclic ADRs were effectively detected in all segments of the interview, and while the total estimate of 39.4% is within the range estimated by Klein et al. (1980), these authors qualify their figures by noting "that the data on (antidepressant) side effects are often confusing and show great variation from study to study."

Although it can be argued that only a comprehensive interview can detect possible ADRs, a systematic review of organ systems may be highly prone to eliciting ACEs consisting of more noise than signal. Huskisson & Wojtulewski (1974) have shown that inflated incidence estimates can occur and true side effects can be obscured when specific checklist questions are asked. But even without a checklist litany, a likely mechanism by which spurious ACEs may get unwittingly introduced is found in the realization that simply asking repeated "non-leading" questions focusing on possible side effects can exert subtle demands to reply positively—not so much by remembering distinctive symptoms that the patient forgot to report spontaneously, but by calling up perceptions associated with the illness or other drug-irrelevant causes. In the present study, out of 21 antibiotic patients reporting "decreased appetite," 19 were elicited during the systematic inquiry!

While our results do not unequivocally imply that incidence estimates based upon a systematic inquiry will necessarily overestimate the true incidence, the finding that inclusion of these ACEs drastically impaired the accurate detection of true antibiotic ADRs should dictate extreme caution for the investigator who is attempting either to detect new ADRs or to estimate true ADR incidences. Spontaneously reported ACEs appear to be the most reliable source for uncovering ADRs, although the actual population incidences may sometimes thereby be underestimated.

References

Huskisson, E.C., and Wojtulewski, J.A. Measurement of side effects of drugs. *Br. Med. J.*, 2:698–699, 1974.

Klein, D.F., Gittelman, R., Quitkin, F., and Rifkin, A. (eds.). *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*. Baltimore, Md.: Williams & Wilkins, 1980.

Lasagna, L. Decision processes in establishing the efficacy and safety of psychotropic agents. In: Levine, J., Schiele, B.C., and Bouthilet, L. (eds.), *Principles and Problems in Establishing the Efficacy of Psychotropic Agents*. Washington, D.C.: U.S. Government Printing Office, 1971, pp. 29–50.

Levine, J., and Schooler, N. SAFTEE (Systematic Assessment for Treatment Emergent Events): A new technique for detecting side effects in clinical trials. *Clin. Neuropharmacol.*, 7(Suppl.):856–857, 1984.

Long, J.W. *The Essential Guide to Prescription Drugs.* New York: Harper & Row, 1977.

Maclay, W.P., Cronder, D., Spiro, S., and Turner, P. Postmarketing surveillance: Practical experience with ketotifen. *Br. Med. J.*, 288:911–914, 1984.

Mellinger, G.D. Community survey methods for postmarketing drug monitoring. Presented at annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 1984.

Rauch, E.F. Data entry experience with the Flexeril surveillance program. *Drug. Inform. J.*, July-Sept.:75–83, 1979.

USP. USPDI: II. Advice for the patient. Rockville, Md.: U.S. Pharmacopeial Convention, 1983.

Wardell, W.M., Tsianco, M.C., Anavekar, S.N., and Davis, H.T. Postmarketing surveillance of new drugs: I. Review of objectives and methodology. *J. Clin. Pharm.*, 19:85, 1979.

Estazolam in the Treatment of Insomnia

Roberto A. Dominguez, M.D.,[1] Burton J. Goldstein, M.D.,[1] Alan F. Jacobson, Ph.D.,[1] and Richard M. Steinbook, M.D.[1]

In many cases of insomnia no overt medical, pharmacologic, or psychiatric cause can be found to explain this symptom. A poor sleep pattern often interferes with daytime activities. When non-pharmacologic treatments have been ineffective or insufficient, the judicious intermittent use of hypnotics is indicated. Hypnotics are most helpful when the disturbed sleep pattern is transient, as in acute situational reactions, hospitalization, jet lag, or after changes in work schedule. Because of their higher therapeutic index, lesser potential for abuse, and superior effectiveness, the benzodiazepines have replaced the barbiturates as the modern hypnotics. Three are currently marketed in the United States, and they differ in their pharmacokinetic profile and metabolism.

Estazolam is the generic name of a new triazolobenzodiazepine marketed in Japan since 1975 and presently under development as a hypnotic in the United States (*see* Figure). After single 2.0 mg oral doses, estazolam appears in the plasma within 30 minutes, and its mean peak plasma level occurs after 2.6 hours. Its mean elimination half-life is about 15 hours (Allen et al., 1983). It produces no long-acting metabolites or hepatic microsomal enzyme induction. After multiple doses, its accumulation is complete within 3 days. Placebo-controlled polysomnographic studies have demonstrated the hypnotic efficacy of estazolam in doses of 2 mg (Roehrs et al., 1983). Other clinical studies have confirmed its short-term efficacy in various doses against placebo (Walsh et al., 1984). This trial had as its objective the systematic assessment of estazolam's hypnotic efficacy and side-effect profile in comparison to flurazepam (Dalmane®) and placebo.

This was a double-blind, randomized study, using balanced parallel placebo and active control groups. Patients were assigned to receive either estazolam 2.0 mg, flurazepam 30 mg, or placebo and instructed to take the medication 30 minutes prior to bedtime for 7 consecutive nights. The trial was conducted in outpatient symptomatic volunteers (Brauzer & Goldstein, 1973). The demographics and presenting complaints of symptomatic volunteers are similar to those patients who are prescribed most hypnotics by their family physician. Subjects had to be in good health, had to be free from emotional or substance abuse disorders, and had to abstain from sedatives for at least 2 weeks. The inclusive age range was 21 to 65 years.

All patients suffered from at least a 3-month history of subjective complaints of insomnia. Those eligible for the study reported a history of daytime distress associated with insomnia plus an estimated total sleep time of 6 hours or less. Additionally, all patients complained of at least one of the following symptoms: a) difficulty in falling asleep of 60 minutes or more; or b) at least three nocturnal awakenings, or at least 1 hour of wakefulness during the night. A detailed written in-

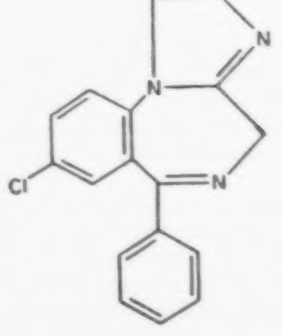


FIGURE. Chemical structure of estazolam.

---

[1] Department of Psychiatry, School of Medicine, University of Miami, Miami, FL 33136.

TABLE 1

Global Evaluation of Efficacy Results

	Treatment Comparison P-values		
	E vs. P	F vs. P	F vs. E
Sleep latency	0.008(E)^{a}	0.006(F)^{a}	0.966(NS)
Sleep duration	<0.001(E)^{b}	<0.001(F)^{b}	0.930(NS)
Nocturnal awakenings	<0.001(E)^{b}	<0.001(F)^{b}	0.425(NS)
Depth of sleep	<0.001(E)^{b}	<0.001(F)^{b}	0.587(NS)
Quality of sleep	<0.001(E)^{b}	0.083(F)^{c}	0.004(E)^{a}
Overall improvement	<0.001(E)^{b}	<0.001(F)^{b}	0.289(NS)

^{a,b,c}indicate a significant difference at the 0.10, 0.01, 0.001 levels, respectively. The significant better treatment is indicated in parentheses.

Abbreviations: E = Estazolam, F = Flurazepam, P = placebo

formed consent was signed by each patient during the screening interview. Pre-study evaluations for eligibility were performed within 4 days prior to drug administration. Medications that could influence sleep were prohibited. Alcohol, caffeinated beverages, and napping were discouraged. Physical examinations and laboratory tests were performed at the screening visit and within 3 days of the last study dose. Also a comprehensive drug screen was obtained at baseline. Two questionnaires were completed by each patient each morning of the study, beginning on the morning after the first dose. During the final visit the investigator reviewed the study questionnaires with each patient and a global evaluation was made of efficacy and side effects. Drug compliance was confirmed by history, completed questionnaires, and a pill count during the final visit.

Seventy-four patients were screened and started the double-blind study. Four did not return for the final visit. Another 5 patients (2 on estazolam, 1 on flurazepam, and 2 on placebo) had a positive urine drug screen at baseline and their efficacy results were excluded from the analysis. Thus, data from 65 patients (20 on estazolam, 24 on flurazepam, 21 on placebo) were used for the efficacy analysis. Many patients deviated from the instructions given them relating to bedtime habits and ingestion of caffeinated and alcoholic beverages. Approximately 60% of the patients did not take their medication 30 minutes prior to bedtime or deviated from their stated usual bedtime by 1 hour at least one night during the study. Additionally some patients took caffeinated beverages (51%), or alcohol (54%), or napped (61%) at least once during the study. Data from these patients were included in the efficacy analysis on the basis that they closely resemble the general hypnotic-taking population, and the occurrence of these deviations was balanced among treatment groups. Statistical analysis showed the three treatments groups to be comparable with respect to all major demographic variables. All groups were also comparable at baseline regarding estimated sleep variables.

Global evaluations completed by the investigators demonstrated that both active treatments were significantly superior to placebo in all measurements used to assess quantity of sleep ($p<.01$). There were no significant differences between the active treatment groups (Table 1). A global rating of "quality of sleep" reflected how rested and refreshed patients reported they felt upon arising. Estazolam proved superior to placebo ($p<.001$) but improvement in the flurazepam group failed to reach significance ($p=.083$). In this measure estazolam was preferred over flurazepam ($p=.004$).

Results from the patient's daily sleep questionnaires paralleled those of the global assessments. Collective mean scores from the 7 treatment nights showed that both estazolam and flurazepam significantly reduced the number of nocturnal awakenings ($p<.01$), improved the total length of sleep, plus the depth and quality of sleep (all p's$<.001$). There were no significant differences among the active treatments. Patients reported that their length of time to fall asleep did not improve as much as other measures. Overall improvement in estimated sleep latency only showed a trend in favor of estazolam

TABLE 2

Global Evaluations of All Side Effects

	Estazolam (E) ($N=20$)	Flurazepam (F) ($N=24$)	Placebo (P) ($N=21$)
Mean	1.6^{a}	2.0	1.3
STD	0.8	0.8	0.6

Summary of statistical comparisons:
E vs. F = NS
E vs. P = NS
F vs. P = $p<.01$
1 = None, 2 = Mild, 3 = Moderate, 4 = Severe

TABLE 3

Total Number of Treatment-Emergent Symptoms (TES) Reported

	Estazolam	Flurazepam	Placebo
Residual daytime effects (% of total TES reported) (drowsy, fatigued lethargic, drugged, exhausted, sleepy, decreased concentration, etc.)	15(71%)	30(73%)	0
Stomach discomfort/nausea	2	2	2
Headaches	1	1	1
Bitter taste	0	3	0
Irritability	0	2	0
Others	3	3	2
Total	21	41	5

(*p* = .088) and flurazepam (*p* = .093) over placebo.

More patients reported adverse effects with flurazepam (83%) than with estazolam (50%). Residual daytime drowsiness and fatigue accounted for approximately 70% of all side effects reported for both active treatment groups. A significantly greater ratio of patients on estazolam (*p*<.005) and flurazepam (*p*<.0001) reported side effects than on placebo. Also, a significantly greater ratio of patients reported side effects on flurazepam than on estazolam (*p* = .017). Perhaps the most important measurement of side effects was a global assessment by the investigators of their severity (Table 2). There was no statistically significant difference in the global evaluations of side effects between estazolam and placebo treated patients, or between both active treatments. However, there was a significant difference (*p* = .0018) between flurazepam- and placebo-treated patients. Comparison of baseline and final vital signs and laboratory studies did not show any clinical or statistical significance.

As discussed, patients on both active treatment groups reported that their length of time to fall asleep did not improve as much as other measures. In interpreting this finding, it is important to note that most patients enrolled in this study (73%) complained of sleep maintenance problems, rather than a sleep latency disturbance. Therefore, given this population, it is not surprising that neither estazolam nor flurazepam treatment resulted in a statistical improvement in sleep latency. This interpretation is consistent with that of another published report (Roehrs et al., 1983) which concluded that the lack of statistical improvement of complaints of sleep latency with estazolam when compared to placebo was not surprising in a patient population in which 47% did not have an objective disturbance in sleep latency.

Not only does this study strongly confirm the hypnotic efficacy of estazolam, but it also shows that the new drug is better tolerated than flurazepam. In the literature, residual daytime effects have been more frequently reported with flurazepam than with other intermediate half-life benzodiazepines (Bliwise et al., 1984; Fillingim, 1982; Wesnes & Warburton, 1984). In the assessment used to measure how refreshed and rested each subject felt upon arising, estazolam was favored over flurazepam. Treatment-related side effects were less frequent with estazolam (Table 3). Also, the overall severity of these reactions favored the new drug. Additionally, significantly fewer patients complained of any side effects with estazolam than with flurazepam.

References

Allen, M.D., Greenblatt, D.J., and Arnold, J.D. Single- and multiple-dose kinetics of estazolam, a triazolobenzodiazepine. *Psychopharmacology,* 66:267–274, 1983.

Bliwise, D., Seidel, W.F., Greenblatt, D.J., et al. Nighttime and daytime efficacy of flurazepam and oxazepam in chronic insomnia. *Am. J. Psychiatry,* 141:191–195, 1984.

Brauzer, B., and Goldstein, B.J. Symptomatic volunteers: Another patient dimension for clinical trials. *J. Clin. Pharmacol.*, 13:89–98, 1973.

Fillingim, J.M. Double-blind evaluation of temazepam, flurazepam, and placebo in geriatric insomniacs. *Clin. Ther.*, 4:369–380, 1982.

Roehrs, T., Zorick, F., Lord, N., et al. Dose-related effects of estazolam on sleep of patients with insomnia. *J. Clin. Psychopharmacol.*, 3:152–156, 1983.

Walsh, J.K., Targum, S.D., Pegram, V., et al. A multicenter clinical investigation of estazolam: Short-term efficacy. *Curr. Ther. Res.*, 36:866–874, 1984.

Wesnes, K., and Warburton, D.M. A comparison of temazepam and flurazepam in terms of sleep quality and residual changes in performance. *Neuropsychobiology,* 11:225–229, 1984.

NCDEU Workshop/Microcomputer Interest Group

CHAIR: *Joanne B. Severe, M.S.*
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Microcomputer Database Management Systems Concepts

David Robert Gastfriend, M.D.[1]

In the years since 1977, when microcomputers first became commercially available, the database management system (DBMS) has proven to be an efficient, cost-effective tool for clinical research. Microcomputer DBMS software programs are widely available commercially, offer a variety of powerful functions, and provide a range of ease of operation to suit any researcher, from the technophobe to the hacker. The selection of a particular DBMS for clinical research depends upon several factors, such as what kind of data will be stored, how much data will be stored, how the data storage will be organized, what kinds of analyses will be performed on the data, and whether more than one user will need to use the database at the same time.

What Is a Database? (Wiederhold, 1981)

At its simplest, a database is *a filing system*. Like a file card box for article references, or a Rolodex device for phone numbers, it is a tool for storing any data worth retrieving later. These examples have limited usefulness, however, because they use a physical structure to organize data.

Consider the situation in which one has each patient's name, address, and identification number listed vertically in that order on a Rolodex card, and the Rolodex deck is organized in alphabetical order by patient's last name. If it also became necessary to be able to look up patients just by identification numbers, one solution would be to photocopy each card, cut out the identification number line, paste it in at the top of a new card, then place the cards in the second Rolodex holder in numerical sequence. This example points out the limitations of a system that uses a physical layout to organize data. A computerized database would do this electronically and would allow both types of Rolodex card to be printed once the basic data are entered.

A computerized DBMS stores data in files, or lists, with a minimum of duplication. Each list can be used for a variety of purposes, because the program can reorganize it with relative independence of any physical layout. The *location* of any individual piece of data is indicated internally as a symbolic reference point rather than a physical reference point. This makes it possible a) to rearrange data to create a variety of useful reports with it; b) to perform complex searches called *queries*; and c) to add new types of data elements subsequently within existing records.

---

[1] Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114.

What Is "Data"?

The design of a computerized database begins by *listing what data are needed* for storage and analysis. The current range of microcomputer DBMS software makes it possible to store various kinds of data. Most DBMS programs are adept at managing numbers, formulae, and alphabetical characters, while a few have special qualities that treat words, sentences, paragraphs, and pictures (such as digitized drawings, x-rays, and scans) as discrete data elements.

How Are Data Represented in the Computer?

Data are represented by a set of microscopic switches which can exist in either a high or low voltage state (on or off). If a switch is off, this corresponds to 0; if it is left on, it stands for 1. Each switch is the electronic equivalent of a base two, or binary, digit. In computerese, a *binary digit* is called a *bit*.

Since real data elements are not adequately represented by only a 0 or 1, several bits are needed to represent the whole range of characters in use. There are about 100 distinct keys on the typewriter, including the digits from 0 to 9, all the characters in the alphabet, and punctuation symbols.

How many bits are required in order to represent all of these characters of real data? If we allot two bits per character, this allows us to represent four distinct characters: 0, 1, 2, and 3 (by the binary codes 00, 01, 10, and 11, respectively). Therefore, a set of 7 bits is needed in order to represent 100 distinct characters, and another bit is used as a marker for accuracy—altogether 8 bits. This set of 8 bits is the smallest number of switches that will represent all the decimal system characters, the alphabet, and punctuation symbols. Each *set of 8 bits* is called a *byte*. The coding system for all these characters is standardized throughout all microcomputers, and is called ASCII (pronounced "AS-key," for American Standard Code for Information Interchange).

Calculation of Data Storage Needs for a Study

Just as file cabinets vary in size, number of drawers, capacity, etc., DBMS programs vary in how much data can be stored. It is necessary to understand how data elements are stored and to calculate the total data storage needs a study will require, prospectively. For example, consider the design of a database for a study of the dose response to lithium. In order to represent a single lithium level, a value which can range from 0.0 to 9.9, the computer will need to allocate one byte for each digit, or two bytes per level to be stored. (The decimal point will be handled differently than a digit and need not be counted here.)

Each patient gets varying doses of lithium, and each week, for 10 weeks, each patient has lithium levels drawn and several rating scales recorded. The file containing all the study data will contain a record for each patient, and at the conclusion of the study each record will contain 10 different lithium levels, 1 for each week of the study. Since each lithium level will take up 2 bytes, this data field alone will use 20 bytes per patient. If 100 patients will participate in the study, we will be storing 2,000 bytes, or 2 kilobytes (K) of data just for this one variable. The variable, lithium dose, ranges from 0 to approximately 3,000 mg/day, for a total of 4 bytes (or characters) times 10 recordings times 100 patients. For this variable, then, we'll be storing another 4K of data. If we add a few scales on each patient, we must be careful in planning ahead of time how much data we will want to be storing. Here is a sample calculation:

$$5\ \frac{\text{scales}}{\text{subject}} \times 15\ \frac{\text{questions}}{\text{scale}} \times 2\ \frac{\text{characters}}{\text{question}}$$

$$\times 10\ \text{weeks} \times 100\ \frac{\text{subjects}}{\text{week}}$$

$$= 150{,}000\ \text{characters}$$

$$= 150\text{K bytes}$$

Steps in Using Database Management

All database management systems operate using the same basic steps of 1) data and file definition, 2) data entry, and 3) data retrieval (Figure 1). Once one understands these in operation on one DBMS program, it becomes relatively easy to learn another program.

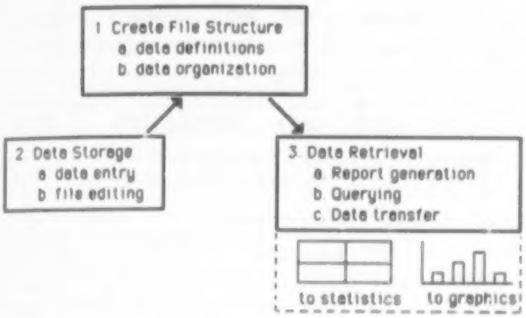


FIGURE 1. **Steps in using database management.**

The first and most important step in using a DBMS package is data and file definition. This consists of analyzing what data a study will gather, and defining and restricting which data items will be stored in order to construct what is known as a *data dictionary*. The data dictionary is a list of the data elements that will be stored, the *form* of data elements (e.g., "00/00/00" for dates), as well as the *content* of each element (so that a date of 11/35/85 should be excluded if the data dictionary is complete in its description of form and content of a date element).

Once the data dictionary is complete, data items can be organized into a database structure. To create a Rolodex file like the one above, each item must be stored in a set place whose location has to be defined (analogous to row and column of the Rolodex card). Every program has limits as to how many different data elements can be stored in a patient's record, how many records in a file. Therefore, in addition to the initial calculation of total data storage needs (shown above), it is necessary to map out whether one file will be sufficient to hold all data elements, or whether it will better to break up the data into several files—demographic data, medication data, lab data, scales, etc. The limitations of different DBMS programs in accommodating different file structures will be discussed below.

With a structure established for the database and definitions set for acceptable data elements, the process of data entry can begin. This is one area in which the computer's abilities enhance studies by promoting the capture of accurate data. As the user enters each value, the microprocessor can compare it with its respective data definition in form and content. In the event of an inconsistency, the computer prompts the user to correct the mistake. Only then will it store the new value in the patient's record.

An important feature of many DBMS programs is the ability to accept and store data from other programs (e.g., computer-administered psychometric tests), biofeedback instruments, and other computers. To do this, a DBMS program needs a function which accepts a stream of data in the same format as the output of the initial program. The standardized ASCII code is the most common format for sending a stream of data from one computer to another or one program to another within the same computer.

Data retrieval is the *raison d'etre* for database management systems. At its simplest, retrieval can be used to print a copy of each patient's record. Since DBMSs can reorganize data with relative independence from any physical layout, it is possible to do a more complex and very useful function called *searching*. Searching can be used to gather just the improvement scores from all patients' records, or to compile the data into a particular format for statistical analysis. Once initial data have been entered, searching can be used to review an entire file of records for missing data, prompting the user to complete the data entry process, and to allow editing of stored data which, although consistent in form and content, are still incorrect.

The ability to electronically rearrange or *sort* the order of data can also save considerable labor and time. In the example study 100 subjects are treated with lithium for 10 weeks and data are gathered from the history, mental status, lab tests, vital signs, and rating scales. Each data element is coded numerically and entered each week as it is obtained. At the conclusion of the trial we rearrange the order of the data set from the simple chronologic form in which it was gathered to the order needed for the analysis. In this final form, the patients are listed according to who entered the study first, then second, etc. After each subject is listed, then their baseline data is listed, then week 1 data, then week 2, etc. When subject 1's data are fully listed, then subject 2's follows. Sorting can be performed in different ways upon any data element in a record, such as chronologically by age of subject or date of visit, alphabetically by name of subject or clinician, or ordinally by lowest dose to highest.

Querying is a retrieval function which produces a more specialized search of the data, linking values from different data elements. An example of a query would be: "list all subjects with lithium levels greater than 1.2 who had global improvement scores of>3 for 2 or more consecutive weeks." Another important function of retrieval is the ability to extract data from the database to perform statistics or to graph. Few DBMSs are programmed to perform a full range of statistical tests, so additional software is usually required to do this (Crouch, 1985). However, if a database can report its retrieved data in the same data transfer format as that accepted by the statistical package, time can be greatly reduced and errors can be eliminated by making an electronic transfer of the data.

Forms of File Organization (King et al., 1983)

The simplest microcomputer programs for constructing a database are called *file management systems.* These have a structure like a vertical list, making these programs easiest to learn for the new user. The variables of the list can be sorted in different ways to create different reports, but each list is separate. It is often useful or necessary (because of the finite capacities of a DBMS program) to use more than one file to store different types of data—demographic data might go into the "Patient" file, while treatment data might go into a "Visits" file. Figure 2 depicts a file management system with two different files (here in the format of tables), with no relation between the data in the patient file and the visit file. Each of these is just a two-dimensional file structure. Being able to store these data but not to be able to keep the two sets of files linked, is a ridiculous limitation. A better file organization is needed, necessitating a more flexible program that allows us to symbolically relate each patient in the first list to their respective visits and medications in the second list, and so on. This type of program is called a *relational database management system* (Figure 3).

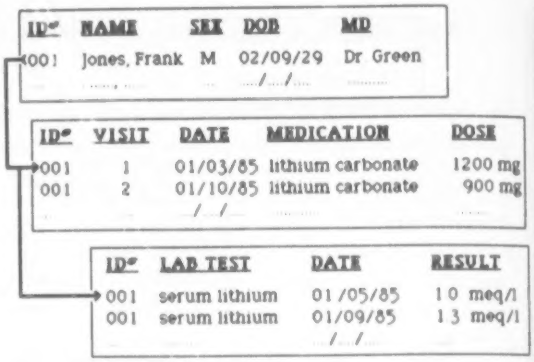
PATIENT FILE

ID*	NAME	SEX	DOB	MD
001	Jones, Frank	M	02/09/29	Dr. Green
009	Brown, Lynn	F	11/30/54	Dr. Gold
378	Doe, Donald	M	09/18/44	Dr. Dow
...	..., ...	...	.../.../...	....

VISIT FILE

ID	VISIT	DATE	MEDICATION	DOSE
001	1	01/03/85	lithium carbonate	1200 mg
001	2	01/10/85	lithium carbonate	900 mg
009	9	01/10/85	amitryptyline	150 mg
...	...	.../.../...	....	....

FIGURE 2. A file management system. Data from one file cannot be linked with that in another.



ID*	NAME	SEX	DOB	MD
001	Jones, Frank	M	02/09/29	Dr Green
...	..., ...	...	.../.../...	....

ID*	VISIT	DATE	MEDICATION	DOSE
001	1	01/03/85	lithium carbonate	1200 mg
001	2	01/10/85	lithium carbonate	900 mg
...	...	.../.../...	....	......

ID*	LAB TEST	DATE	RESULT
001	serum lithium	01/05/85	1.0 meq/l
001	serum lithium	01/09/85	1.3 meq/l
...	......	.../.../...	...

FIGURE 3. Relational database. The arrows indicate that relations can be drawn between data fields in different files, creating a three-dimensional file structure.

The relational database program is able to create relationships between data fields in different files, either right from the beginning or long after the initial format was laid out and even after much data has been stored in the system. A relational database management system allows users to create relations between data organized in different lists, e.g., as represented by the arrows. So while a file management system is like a two-dimensional list, a relational database is three-dimensional or more.

There is another form of organization that is multi-dimensional, and allows different files to relate to one another: the *hierarchical DBMS.* In hierarchical files, data elements are organized in several levels, structured one below another, like an inverted tree (Figure 4). This structure is set out from the beginning, however, and can't be changed once data are entered—the structure is fixed. This might seem a limitation, but is really an advantage for clinical researchers. The database for any given study should usually be laid out from the outset anyway, and a hierachical structure is easier to set up and to comprehend later. It also makes the data easier to search later. Finally, for clinical data, it is usually important that *one particular relationship be fixed: time*. Since we treat our patients over time, and they respond over time, any particular lab test or therapeutic intervention should always be forced to relate to time first, and to anything else second. DBMSs that fix certain relationships are called *hierarchical DBMSs*. When a hierarchical DBMS is designed to *fix the relationship of all items with respect to time*, it is called a *time-oriented DBMS*. A time-oriented DBMS is essential for building a clinical database.

Actual Use of Database Management Systems on Microcomputers

Some DBMSs let you select a task from a list of the possible alternatives, or *menu*; others require one to remember or look up a set of command codes. For the nonexpert user, *menu-driven* programs are much easier, because there is no need to memorize the options and less likelihood of forgetting how the program operates. The most popular DBMS in the world, dBase II, is only command-driven, but most of the newer programs offer a choice. DBase III, MetaFile, R:base 5000, and File Manager, allow the user to work from either menus or commands (Gresehover, 1984).

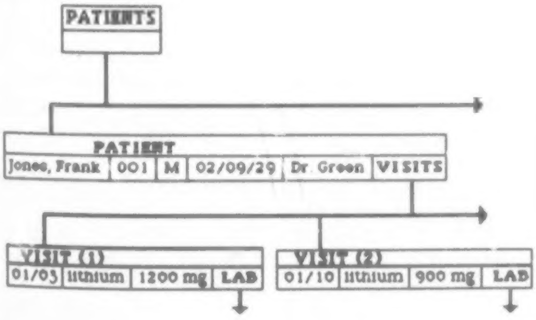


FIGURE 4. Heirarchical database, an inverted tree structure. Although fixed, the file structure can be time-oriented and is well suited to the data organization of clinical trials.

Some DBMSs have extensive statistical and graphics functions built in. These are called integrated DBMSs and their retrieval facilities include the transfer of data from the database subprogram to the statistical or graphics subprogram. Integrated DBMSs are time-saving because one doesn't have to rekey data from the database program to the statistical or graphics package. On the other hand, in the commercial software market, many integrated programs operate like a Swiss army knife—jack of all trades, master of none. While Lotus 1-2-3 might not meet the database needs of a research study, others such as Medlog (Layard, 1983) and Clinical Research System II (Crouch, 1985) are specifically designed for clinical trials.

In trials where more than one user will need to access records at one time, a multiuser DBMS is required. There are a growing number of general purpose microcomputer multi-user DBMSs on the market as well as some specifically developed for managing medical information, such as COSTAR (Barnett, 1984) and VA File Manager (Houser, 1984). These programs include additional features to protect information in the database from the vicissitudes of having multiple and simultaneous users. Two of these features are file lockout and security identification codes.

The following example demonstrates the need for *file lockout*: If a patient's chart folder is removed from the file drawer and then a lab slip is absent-mindedly dropped into the proper location, the slip falls to the bottom of the file drawer, forever misplaced. This mechanism of data loss can be prevented in a computerized database with file lockout. If a research assistant accesses a subject's file to enter a serum level while the researcher tries to update his assessment of the same subject, the system first updates the serum level, momentarily "locking" the file and holding the investigator's assessment entry. Once the level has been electronically updated, the investigator's entry is then recorded.

Security identification codes can be assigned for different levels of users, in the form of passwords. A secretary's password may gain access to demographic and schedule data (but not clinical), a clinician's may gain access to his own patients' clinical data (but hides placebo/drug status fields), and the principal investigator's password yields access to the aggregate.

Finally, the Veterans Administration File Manager program is worthy of special mention because it is a multi-user, hierarchical database (time oriented) and is designed to be a "programmerless system," allowing the user to set up his own complex flexible clinical database without extensive technical knowledge or time investment (Gastfriend et al., 1984).

Summary

With their increasing power and decreasing costs, microcomputers are proving a valuable tool for clinical research data management. A wide variety of database management systems is commercially available, offering differing levels of ease of use and capabilities (Bond, 1984). In selecting the best software program, the researcher must consider what types of data elements will be stored and must make an approximate calculation of total data storage needs. The three basic forms of file organization are: 1) file management systems; 2) relational DBMSs; and 3) hierarchical DBMSs. File management systems are easiest to learn but are too limited for most studies. Relational DBMSs allow free rearrangement of complex relations between different files, but these relations can become very abstract and learning to use them can be as difficult as learning a new programming language. Hierarchical DBMSs are more powerful than file management systems and are more understandable than relational DBMSs. For novice or casual users, menu-driven programs are more easily learned and used, but those accessing computerized files on a daily basis will appreciate newer programs that allow switching from menu mode to command mode of operation. Finally, options such as data transfer into the database or out of it, integration of statistical or graphics functions designed for clinical research, and multi-user operation are becoming available in microcomputer DMBS software and enhanced productivity as well as accuracy.

References

Barnett, G.O. The application of computer-based medical record systems in ambulatory practice. *N. Engl. J. Med.*, 319(25):1643–1650, 1984.

Bond, G. A database catalog. *Byte*, 9(11):227–238, 1984.

Crouch, M. PC clinical testing. *PC Mag.*, 19:263–264, 1985.

Gastfriend, D.R., Bauer, L., Bhatty, A., and Rosenbaum, J.F. Software considerations in the development of an integrated clinical-research database in psychopharmacology. *Comput. Psychiatry/Psychol.*, 6(2):19–22, 1984.

Gresehover, R.S. Metafile: One of the new breed of database management systems. *M.D. Computing*, 1(5):24–41, 1984.

Houser, W.R. End user software engineering: The experience of the Veterans Administration decentralized hospital computer program. *MUG Q.*, 13(3):3–11, 1984.

King, C., Manire, L., and Strong, R.M. Comparing data management systems in clinical research: 1983 survey. In: Dayhoff, R.E. (ed.), Proceedings of the Seventh Annual Symposium on Computer Applications in Medical Care. Silver Spring, Md.: IEEE Computer Society, 1983, pp. 715–719.

Layard, M.W. Medlog: A microcomputer-based clinical data management system. In: Lindberg, D.A.B., Van Brunt, E.E., and Jenkin, M.A. (eds.), AAMSI Congress 83, Proceedings of the Congress on Medical Informatics. Bethesda, Md.: American Association for Medical Systems and Informatics, 1983, pp. 464–468.

Wiederhold, G. *Databases for Health Care*. New York: Springer-Verlag, 1981.

SAFTEE: Data System for Side Effect Assessment Scale

Dean J. Clyde, Ph.D.[1]

The National Institute of Mental Health (NIMH) has developed a method for assessing side effects of drugs. The assessments are recorded on case report forms called Systematic Assessment for Treatment-Emergent Events (SAFTEE) (Levine & Schooler, 1984).

Clyde Computing Service[1] received a grant from the NIMH under the Public Health Service Small Business Innovation Research Program to develop software for handling SAFTEE data on microcomputers. Because of the variable length records resulting from data collection via the SAFTEE form, a specialized data entry system was required.

Most data collection instruments or case report forms used in clinical trials have a fixed number of questions generating the same fixed number of variables for each patient. For this type of data, software for the data entry (and verification) into microcomputers is widely available. The Clyde Statistical Analysis System (Clyde, 1984) for IBM Personal Computers is one available software system. However, SAFTEE forms permit a varying number of questions and answers for each patient. A number of specific adverse health events are printed on the forms and the clinician may also write in additional events that the patient reports. This results in data records of variable lengths.

The SAFTEE system software is written for use on the IBM Personal Computer. The program allows for data entry and data summarization as well as transfer to other software systems or database management packages. Use of other database software is the most efficient way to handle the statistical analysis of these data.

The microcomputer package R:base 5000 (Microrim, 1985) was selected from approximately 75 such available packages because of its power and capacity to accept variable length records. In order to save disk space on the microcomputer, the data generated by SAFTEE are compressed into one bit per data item before being transfered into R:base 5000 (which tries to store data in 32 bits per item).

Investigators who collect SAFTEE data in clinical trials can either obtain the programs from Clyde Computing Service and do their own data entry or make arrangements to send the forms to the Clyde Computing Service for entry and analyses.

References

Clyde, D.J. *Clyde Statistical Analysis System*. Fort Lauderdale, Fla.: Clyde Computing Service, 1984.

Levine, J., and Schooler, N.R. SAFTEE (Systematic Assessment for Treatment Emergent Events): A new technique for detecting side effects in clinical trials. *Clin. Neuropharmacol.*, 7(Suppl.):856–857, 1984.

Microrim, Inc. R:base 5000. Bellevue, Wash.: Microrim, Inc., 1985.

---

[1] Clyde Computing Service, P.O. Box 030398, Fort Lauderdale, FL 33303.

best copy available

Microprocessor-Based Assessment of Attention Deficit Disorders (ADD)

Michael Gordon, Ph.D.[1]

Dissatisfaction with formulating a diagnosis of ADD with hyperactivity (ADD-H) based almost entirely upon clinical judgment or the perception of raters has spawned the development of behavior-based assessment procedures. These efforts typically involve administration of the Continuous Performance Test (Rosvold et al., 1956) or related measures of attention and self-control (Davenport, 1972; Doyle et al., 1976; Hiscock et al., 1979; Margolis, 1972). Although bulky and expensive electromechanical devices had previously been required, researchers are now programming microcomputers to administer these laboratory tasks to children (Conners, 1980; Klee & Garfinkel, 1983).

Use of the microcomputer has certain advantages, including flexibility of administration, the ability to store multiple data points, and, if a microcomputer is already available, cost-effectiveness. This approach, however, does have drawbacks for the researcher and, in particular, the clinician. The size of even portable microcomputers can make testing in multiple sites cumbersome. It is perhaps for this reason that standardization samples for software-driven programs tend to be, at best, limited in number and breadth. The transport of disk drives, monitors, keyboards, and the computer itself from location to location often discourages use of the procedure in other than a single research or clinic setting.

Another potential limitation of microcomputer-based testing stems from concerns surrounding the reliability of administration. Computer monitors vary in the size, shape, intensity, and color of displayed characters. Each brand of computer presents to the child a different keyboard, and accepts different types of peripherals, such as "joysticks," which are often used as manipulanda. Without control over such critical factors as the amount of pressure necessary to actuate a switch, or the accuracy of timed sequences, repeatable administration across multiple microcomputers cannot be assured.

Finally, ADD-H children, despite a reputation for academic underachievement, routinely display a fine facility for disassembling delicate equipment. Unless the examiner is immediately present, the highly impulsive child will inevitably stick a finger in disk drives, unplug cables, adjust monitors, or in some other fashion interrupt standard administration of the task. Efforts to secure the microcomputer are often unsatisfactory because they usually involve additional hardware, cabling, and expense.

An alternative approach to testing attention and self-control has been developed by the author (Gordon & McClure, 1983, 1984). The goal of this project has been to establish a practical, reliable, and well-standardized procedure available to both researchers and clinicians. The Gordon Diagnostic System (GDS) is a microprocessor-based, portable unit which, without an external microcomputer, allows for the administration of multiple tasks. The Delay Task, based upon a DRL operant schedule, requires the child to inhibit responding in order to gain a reward. Specifically, the child is instructed to press a button, wait, and then press the button again. If she or he refrains from responding for at least 6 seconds, a light flashes and a reward counter increments. If the child responds before the interval elapses, then the timer resets and no reward points are recorded. The GDS Delay Task generates three major scores: the number of responses (button presses), the number of correct responses (i.e., Correct), and the Efficiency Ratio, which represents the percentage of correct responses.

The GDS also contains the Vigilance Task, which is a version of the Continuous Performance Test (Rosvold et al., 1956). The child is presented with a series of digits on the front display and is told to press the button every time a "9" appears that had been preceded by a "1." The GDS records the number of correct presses, the number of times the child fails to press the button when the "1/9" combination appears (i.e., errors of omission), and the number of extraneous button presses (i.e., errors of commission). For the testing of younger children, the GDS contains a "1" mode, which requires the subject to press the button every time a "1" appears. The same performance measures are recorded.

---

[1] SUNY-Upstate Medical Center, Syracuse, NY 13210.

Although normative data were gathered using standard settings for task parameters, the design allows the user to select a wide range of parameters. This feature enabled the modification of parameters for the testing of adults as well as very young children.

Because the GDS is controlled by a programmable microprocessor, additional tasks can be explored. One such enhancement being studied is a version of the Vigilance Task which assesses the impact of distraction on a child's ability to sustain attention. This Distractibility Task is identical to the standard Vigilance Task except that random digits flash at random intervals on the outer positions of the LED display. The subject is still required to press the blue button when a "9" comes right after a "1." The only difference is that numbers flash on either side of the center (i.e., relevant) digit. Other enhancements under development are designed to evaluate attention across sensory modalities.

Even though the GDS administers tasks independently of a microcomputer, it can communicate with external hardware via an RS232C communications port. Software is available which allows for the direct transmission of GDS data to a microcomputer where it can be tabulated, graphed, stored, and compared to normative data. Connection of the GDS to a microcomputer enables collection of some ancillary data which cannot be extracted from the stand-alone unit.

The portability and ease-of-operation of the GDS has allowed for large-scale data collection. The standardization sample is composed of 1,100 boys and girls from 3 to 16 years of age (Gordon & Mettelman, 1985). An additional 1,100 hyperactive and nonhyperactive protocols from various subject populations, including the deaf, blind, Spanish-speaking, emotionally disturbed, and learning disabled, have also been gathered.

A series of validational studies has shown that these game-like tasks differentiated accurately between hyperactive and nonhyperactive children from both outpatient and day treatment settings (Gordon, 1979; McClure & Gordon, 1984). In a sample of school-referred children, the GDS distinguished children with ADD from those classified as reading disabled, overanxious, and normal (Gordon & McClure, 1983). Over 20 university and medical center research sites are currently conducting investigations involving the GDS. Most studies concern the effectiveness of the GDS for determining drug responsivity and for evaluating the success of pharmacotherapy (Atkinson, 1985; Barkley, 1985; Rapport, 1985). Others are investigating the use of the GDS for evaluating children with known brain damage, preschoolers considered "at-risk" for impulsive behavior, and the relationship between GDS scores and observational measures of classroom behavior. The GDS is also being used by school systems and pediatric practices across the country for the clinical evaluation of ADD-H.

Comments and Conclusions

A chronic impediment in the field of ADD-H has been the paucity of universal criteria and procedures for subject selection and treatment monitoring. Even in the realm of behavioral assessment, where truly creative approaches to testing children have been developed, procedures have generally not been sufficiently practical or well-standardized to allow for acceptance by the majority of professionals (Loney, 1981). As such, most continue to rely on rating scales or tests, such as the Wechsler Intelligence Scale for Children (WISC-R) (Wechsler, 1974), which have been shown to be of limited usefulness in differentiating between groups (Douglas, 1972). Furthermore, comparison of studies across research programs has often been hampered by idiosyncratic measures or sets of criteria.

The GDS represents an effort to establish a standard procedure for evaluating certain aspects of attention and self-control. While it is more costly and, in certain respects, less flexible than software-driven approaches, its portability, ruggedness, and extensive base of normative data offer the user greater assurance of reliable administration and valid interpretation. The growing acceptance of the GDS within the professional community also permits greater comparison of data across studies.

It must be emphasized, however, that the GDS was never intended as a divining rod for ADD-H. This is a complex disorder which represents an array of subgroups and interactive diagnostic dimensions. The GDS is seen as an important tool to be used only in conjunction with other selection criteria and clinical judgment.

References

Atkinson, A.W., Cohen, P.C., and Kelly, P.C. Attention deficit disorder: The effects of ritalin on self-esteem—A comparison of ACTeRS teacher scale, Conners' parent scale, and Gordon Diagnostic System in diagnosis and management. Paper presented at the American Academy of Pediatrics Meeting, Atlanta, Georgia, April 1985.

Barkley, R.A. Assessment of stimulant drug responding in ADD-H children. Paper presented at the 93rd Annual Convention of the American Psychological Association, Los Angeles, California, August 1985.

Conners, C.K. *Continuous Performance Test* [Computer program]. Kensington, Maryland: Behavioral Medicine, Inc., 1980.

Davenport, W. Vigilance and arousal: Effects of different types of background stimulation. *J. Psychol.*, 82:339–346, 1972.

Douglas, V.I. Stop, look and listen: The problem of sustained attention and impulse control in hyperactive and normal children. *Can. J. Behav. Sci.*, 4:259–282, 1972.

Doyle, R.B., Anderson, R.P., and Halcomb, C.G. Attention deficits and the effects of visual distraction. *J. Learn. Disab.*, 9:59–65, 1976.

Gordon, M. The assessment of impulsivity and mediating behaviors in hyperactive and nonhyperactive children. *J. Abnorm. Psychol.*, 7:317–326, 1979.

Gordon, M., and McClure, F.D. The objective assessment of attention deficit disorder. Paper presented at the 91st Annual Convention of the American Psychological Association, Anaheim, California, 1983.

Gordon, M., and McClure, F.D. Assessment of attention deficit disorders using the Gordon Diagnostic System. Paper presented at the 92nd Annual Convention of the American Psychological Association, Toronto, Canada, 1984.

Gordon, M., and Mettelman, B.B. *Threshold Tables for the Gordon Diagnostic System.* (Available from Clinical Diagnostics, Inc., 300 E. Mineral Avenue, Suite 6, Littleton, Colorado 80122), 1985.

Hiscock, M., Kinsbourne, M., Caplan, B., and Swanson, J.M. Auditory attention in hyperactive children: Effect of stimulant medication on dichotic listening performance. *J. Abnorm. Psychol.*, 88:27–32, 1979.

Loney, J. Evaluating treatments for childhood hyperactivity: Some methodological considerations. In: Gadow, K.D., and Loney, J. (eds.), *Psychosocial Aspects of Drug Treatment for Hyperactivity.* Boulder, Colo.: Westview Press, 1981, pp. 77–103.

Klee, S.H., and Garfinkel, B.D. The computerized continuous performance task: A new measure of inattention. *J. Abnorm. Child Psychol.*, 11(4):489–496, 1983.

Margolis, J.S. *Academic Correlates of Sustained Attention.* (Unpublished thesis, University of California, Los Angeles, 1972.)

McClure, F.D., and Gordon, M. The performance of disturbed hyperactive and nonhyperactive children on an objective measure of hyperactivity. *J. Abnorm. Child Psychol.*, 12(4):561–572, 1984.

Rapport, M.D. Comparing classroom and clinic measures of ADD: Dose response effects. Paper presented at the 93rd Annual Convention of the American Psychological Association, Los Angeles, California, August 1985.

Rosvold, H.E., Mirsky, A.F., Sarason, I., et al. A continuous performance of brain damage. *J. Consult. Psychol.*, 20:343–350, 1956.

Weschsler, D. *Weschsler Intelligence Scale for Children-Revised*. New York: Psychological Corporation, 1974.

A Microcomputer-Based Psychophysiology Data Acquisition and Analysis System

C. Keith Conners, Ph.D.,[1,2] Roy Clymer, Ph.D.,[1] and Robert S. Sherrick, Ph.D.[1]

The recording of autonomic and electrophysiologic signals from patients under different conditions of drug treatment, cognitive tasks, or emotional states can provide an important source of information in clinical research settings. However, the considerable costs of the laboratory equipment, the degree of technical expertise required, and the labor-intensive requirements of analysis and display of information are all factors which have limited the application of psychophysiologic techniques to a relatively few dedicated laboratories. The advent of the microcomputer, however, promises to make these methods more widely available to psychopharmacologists and clinician-researchers.

In this article we describe a comprehensive, general purpose Apple computer-based psychophysiologic data analysis and acquisition system which was developed in the course of drug and nutrition studies with children. The software system is flexibly designed to allow for creation of a variety of testing paradigms which might require the simultaneous acquisition of data from several physiologic channels during active subject problem-solving and performance testing. The system allows for a comprehensive assessment of behavioral, cognitive, electrocortical, and autonomic variables, which has proven to be valuable in drug studies where it is desirable to examine the impact of a drug upon multiple response systems at different dosages and over different time periods. The system is menu-driven and easily learned by nontechnically oriented users.

Hardware

The most expensive part of a psychophysiologic system is the human operator, who, in addition to the time spent actually acquiring data, must usually spend many hours in the scoring and reduction of the vast quantities of data obtained during test sessions. The Apple II+ or Apple IIe, because of its remarkably low cost and flexibility, is a powerful tool for addressing this aspect of the psychophysiology problem.

After the operator, the most significant costs are usually associated with the equipment required to detect and transduce the physiologic signals into electrical energy which can be analyzed for its frequency and amplitude characteristics in relation to experimental parameters. Many companies now manufacture suitable and relatively inexpensive modular components for signal acquisition and transduction which obviates the need for expensive polygraphic equipment.* These components are designed for different physiologic signal characteristics and typically will amplify, shape, filter, integrate, or compare the analog physiologic signals which can then be used for further analysis.

Once acquired, such signals must be converted from their continuous (analog) voltage form into a numeric (digital) form suitable for further analysis. Analog-to-digital (A/D) conversion of input signals is greatly facilitated by an interface which utilizes pre-defined machine language routines which require only a simple BASIC-like higher-order interpretive computer language. This general re-

---

[1] Laboratory of Behavioral Medicine, Children's Hospital National Medical Center, Washington, D.C. 20010.
[2] Department of Psychiatry, George Washington University School of Medicine, Washington, D.C. 20016.

Address reprint requests to: C.K. Conners, Ph.D., Laboratory of Behavioral Medicine, Children's Hospital National Medical Center, 111 Michigan Avenue, N.W., Washington, DC, 20010.

*A high-quality, inexpensive source for modular signal processing equipment which we have used is Med Associates, Box 47, East Fairfield, VT 05448.

quirement can best be met by dedicated hardware which flexibly acquires many channels of information simultaneously, including binary (off-on) information such as button pushes or movement events: and which provides the timing and display requirements ordinarily available only on expensive polygraphs. We have used the Cyborg ISAAC Model 91a* for this purpose. The ISAAC® system (Integrated System for Automated Acquisition and Control) includes 16 input channels for A/D conversion, and 16 binary input channels. It also contains computer-controllable binary and analog outputs which can be used to control an experiment, including four D/A and 16 binary outputs. The system also has four Schmitt Trigger inputs, a counter, and on-board 32-bit clock. All of these functions may be easily controlled by a high-level BASIC-like language, LABSOFT® which consists of simple statements which can be added to Applesoft programs. Analog signals are processed as IRIG signals (1.4 volts full scale), a format compatible with most popular polygraphs, and FM tape recorders. Digital signals use standard 5-volt TTL logic.

Although the LABSOFT program is simple and fairly powerful, it has two important limitations which restrict its utility: 1) It does not allow easily for multiple functions to be performed in real time at once (e.g., taking A/D samples while monitoring for subject button presses). The LABSOFT program is fast when doing only a single task. For example, it can take A/D samples at 1,000 samples per second. When faced with performing multiple tasks simultaneously, however, it is considerably slower. A typical psychophysiological application might require measuring several channels of electroencephalograph (EEG), electrocardiograph (ECG) R-wave timing, subject button-press responses, activity level, and subject respirations all at the same time. Multiple functions can only be performed at a great sacrifice in speed. 2) LABSOFT is large, and allows only 4K bytes of computer memory for data storage in a 64K Apple if both high-resolution graphics pages of the Apple are being used for data display of incoming analog information.

Software

In order to circumvent the speed and memory size problems, a machine language software package called ISIINT was developed that requires only 2K of memory and can perform up to 14 functions simultaneously. ISIINT is like LABSOFT in that it consists of utility routines that can be called from Applesoft Basic programs. Applesoft integer arrays are used for passing parameters and data between the Applesoft Basic program and the ISIINT utilities. ISIINT uses one of the ISAAC timing elements to generate a real time clock that can be started and stopped under program control. Clock interrupts or "tics" can be set in software to occur as often as 1 per millisecond (msec) or as seldom as once every 65 seconds.

Through the use of the ISIINT utilities, any type of input or output that the ISAAC hardware is capable of performing can be scheduled to occur at a specified clock interrupt. For example, an A/D operation can be scheduled to occur at the 500th clock tic via a call to the ISIINT utilities. With another call to ISIINT, the clock can be started with a clock tic spacing of 10 msec. The A/D operation will then occur exactly 5 seconds after the clock is started without further interven-

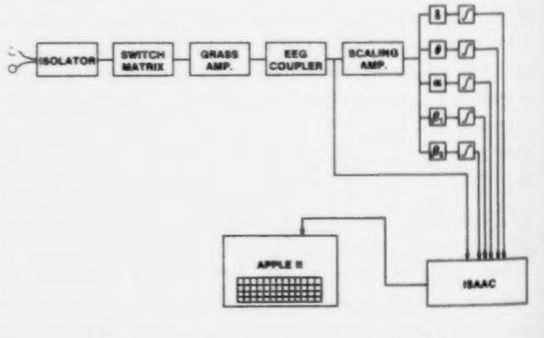


FIGURE 1. EEG/Evoked potential data collection system. Data from the subject electrodes passes through an optical isolator (required for subject protection), to a Grass EEG amplifier. The analog signal is then digitized by ISAAC and stored in an Apple array for EP measurement. The same signal is passed through sharp Butterworth bandpass filters for measurement of relative power in each of 5 frequency bands.

---

*ISAAC and LABSOFT are trademarks of the Cyborg Corporation, 55 Chapel Street, Newton, MA 02158.

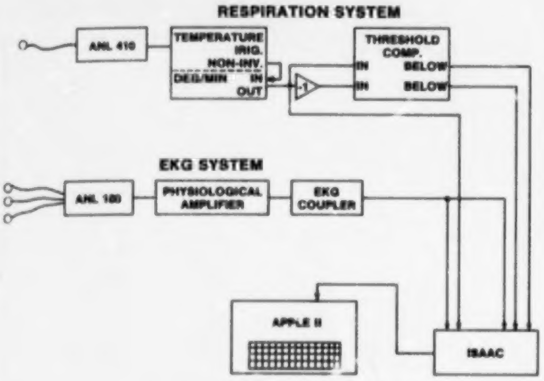


FIGURE 2. Respiration and heart rate data collection system. A thermistor attached to the nostril provides a temperature signal which changes with inspiration/expiration. The thermistor signal is amplified and transduced by a Med Associates ANL 410 module and converted to a value representing inspiration or expiration by a threshold comparator. The R-wave of the ECG (collected from the Med Associates ANL 100 module) is amplified and converted to a binary pulse used to activate an ISAAC Schmitt Trigger. The ISAAC and ISIINT routines are used to calculate interbeat intervals. The Apple-II+ can display the analog information in real time on the high-resolution screen during data collection.

tion by the Applesoft program. All ISIINT input/output operations occur in the "background" while an Applesoft Basic program is running in the "foreground." When many background input/output operations are scheduled, the foreground Basic program runs more slowly than normal, but it is not otherwise affected. When data become available via background input operations, they are placed into Basic integer arrays.

In addition to allowing all possible ISAAC input/output operations and real-time clock control, ISIINT also allows the user to schedule PEEK and POKE operations, read the clock, read background operation status information, and perform several useful functions not associated with the real time clock, such as adding two Basic integer arrays in a fraction of the time required by a similar routine in Applesoft Basic (this latter capability permits immediate display of averaged EEG-evoked potential data). Since all utility functions are accessed via Applesoft Basic "Call" operations, ISIINT is simple to use and does not require a knowledge of assembly language or a detailed understanding of the ISAAC hardware. Parameters and data are passed via integer arrays. Upon receiving a call, ISIINT may either perform a function immediately (such as clearing the counter, starting or stopping the clock), schedule a function, stop an already scheduled function, or enter a value (such as the time). The action taken by ISIINT depends upon the values passed to it in the parameter array.

Sample Application

A description of a study recently conducted using the Apple/ISAAC/ISIINT system may serve to demonstrate its capabilities. An experiment was conducted to ascertain the behavioral and physiological effects of a drug and a placebo given in two dosage regimens. In the single-dose condition a large dose of the investigational drug was given in the beginning of the experiment. In the distributed-dose condition the same quantity of drug was given, but in four equal doses 1 hour apart. In order to make the experiment double-blind, all dosages were matched for volume. Thus, in the distributed-dose condition the volume of the first drink, although containing one quarter of the drug, was equal to the first drink in the single-dose condition due to the addition of an appropriate quantity of placebo. Similarly, three placebo doses were given in the single-dose condition to match the quarter-doses given in the distributed dose condition. Subjects were 8- to 12-year-old normal children. It was desired to collect information on attentional set through the cardiac deceleration to a warned reaction-time task; on cortical alertness through quantitative EEG and visual evoked response; on behavioral attentiveness through a continuous performance task (CPT); on respiration rate associated with attention deployment; and on general activity obtained from counters attached to a stabilimiter in the subject's chair.

The primary performance measure was a "letter-form" version of the CPT. In this task the subject is required to press a response key whenever two letters appear in sequence from a series which includes both letters and letter-like forms matched for area (and consequently for brightness). This task, although an interesting measure of attending in itself,

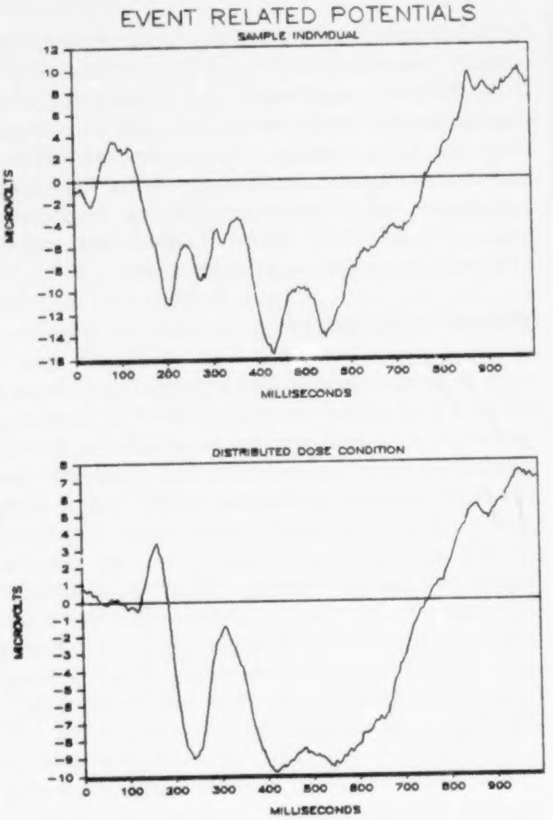


FIGURE 3. Individual and group-evoked potentials collected with ISIINT.

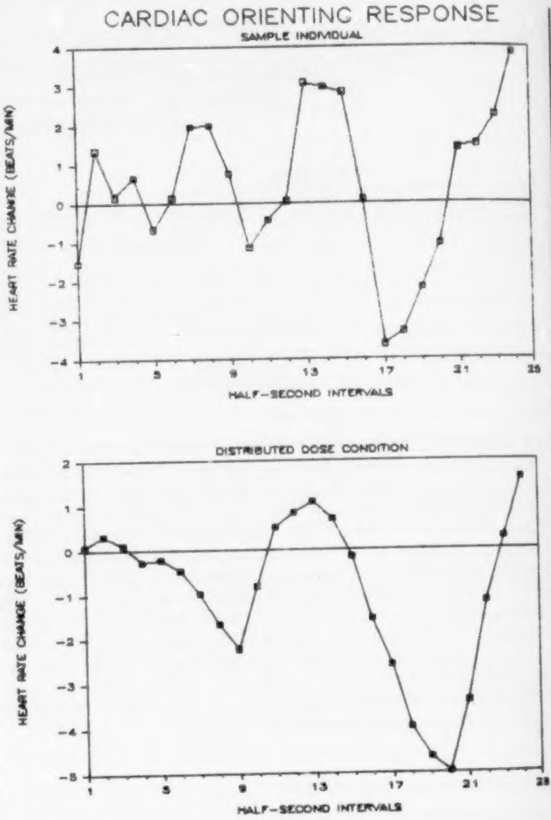


FIGURE 4. Individual and group cardiac changes during a 6-second warned reaction-time task.

has the added advantage of allowing the simultaneous gathering of averaged visual evoked potentials generated from both letter and form-stimuli, making it possible to ask interesting questions regarding hemisphere-specific processing. Figure 1 is a diagram of the hardware system used to gather EEG data.

A single input electrode (Cz referred to linked mastoids) was used to gather both ERP data and frequency band data. During the CPT task the Apple/ISAAC/ISIINT system was used to gather and average the EEG waveforms for 1,000 msecs following each visual stimulus presented on the monitor. The ISIINT program provided two averaged waveforms, one for the correct rejections and one for hits.

The CPT task also provided four performance measures: number of hits, number of correct rejections (targets which did not require and did not elicit a response by S), number of errors of commission (key presses to stimuli which were not the target), and the average reaction time to press the key after a target. Thus, a single task allowed monitoring of a variety of behavioral and psychophysiological variables.

A second task which also sampled two measurement levels was a warned reaction time task (Simons et al., 1979). The R-wave from a standard Lead II ECG activated one of the Schmitt trigger inputs of the ISSAC. The interbeat interval was recorded and converted to a rate per 1/2 second interval (Gatchel & Lang, 1973). A series of 20 reaction time trials was presented, with sampling beginning 3 seconds prior to the onset of a 6-second warning tone. The subject pressed a response

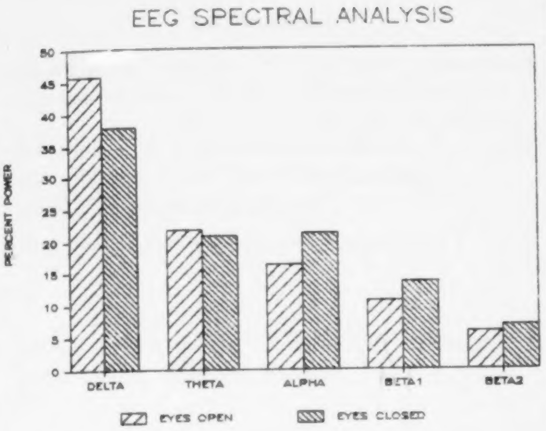


FIGURE 5. Changes in relative EEG power with eyes open and eyes closed.

key when a circle appeared on the monitor at the end of the warning tone. The heart rate was expressed as a deviation from the prestimulus average heart rate and an averaged evoked cardiac response was obtained by averaging across the 20 trials (Simons et al., 1979). In addition, the cardiac-orienting task yielded measures of misses, errors of commission, and warned reaction time. An automatic detection and correction routine removed artifacts created by movement.

Sixty-second samples of three additional psychophysiological measures were obtained periodically throughout the experiment. Respiration rate was obtained from a nasal thermistor taped near the nostril and peak change in temperature was used to identify respiratory influxes. Heart rate was obtained from the same Lead II ECG used in the warned reaction time task. Finally, the EEG from the Cz electrode was fed to a series of filters and integrators from the modular input equipment which provided on-line measurements of the relative proportion of power in each of the five EEG frequency bands (theta, delta, alpha, beta1, and beta2). Note that this "hardware" function could be easily obtained by software programmed to achieve the same goal. Each of these measures was sampled for 30 seconds with S's eyes open and then 30 seconds with their eyes closed. Figure 2 is a block diagram of the components used to obtain these measures.

Results

Since the purpose of this article is a description of the Apple/ISAAC/ISIINT system, the results of this experiment will be discussed only insofar as they are illustrative of the data gathering capabilities of the system.

Figure 3 displays some of the averaged evoked response data. The top panel is the ERP of a single subject, averaged across 88 correct hits. The bottom panel shows the evoked response to hits averaged across 20 subjects in the single-dose condition. The individual peak amplitudes and latencies were hand scored by a program which displays the EPs on the Apple high-resolution screen and allows the use of an adjustable cursor which reads out the time and amplitude of the wave wherever it is positioned. Subsequent statistical analyses may then be performed upon appropriate peaks.

Typical evoked cardiac response data are shown in Figure 4. Again the upper panel shows the data from a representative subject, while the lower panel shows the data averaged across all subjects. The data show the expected tri-phasic response (Gatchel & Lang, 1973).

In Figure 5 some of the EEG frequency band data is presented. The EEG was taken for 30 seconds with eyes open, then the eyes were closed and a minute later 30 seconds of EEG with eyes closed was taken. The data show the increase in alpha and expected shift to lower frequencies with eyes closed. (Not shown here are the sequential activity counts which were collected throughout the subject-day, or the respiration data.)

Conclusion

Most laboratories interested in psychophysiological recording will have access to the appropriate signal collection input modules, but the most difficult and expensive task is the computer storage, analysis, and display of the data. Typically, this has required mini-computers which are both expensive and difficult for the non-programmer to use. The system described here allows a comprehensive and sophisticated behavioral, electrophysiologic, and psychophysiologic experiment that is flexible and easy to use. Data are immediately displayed and graphed without long delay between the experiment and subsequent data reduction. The cost of this system compared to others may recommend it as a valuable experimental tool.

References

Gatchel, R.J., and Lang, P.J. Accuracy of psychophysical judgments and physiological response amplitude. *J. Exper. Psychol.*, 98:175–183, 1973.

Simons, R., Ohman, A., and Lang, P.J. Anticipation and response set and cortical, cardiac and electrodermal correlates. *Psychophysiology*, 16:222–233, 1979.

A Brain Function Diagnostic and Study Unit for Psychotropic Drug Development and Psychopharmacology Research

Turan M. Itil, M.D.,[1,3] Donald M. Shapiro,[2] Emin Eralp,[3] Ahmet Akman,[3] and Kurt Z. Itil[3]

Quantified electroencephalogram (EEG), evoked potential (EP), and neuropsychological tests have been proven to be reliable objective tests to study the effects of drugs on human brain function. In particular, when analyzed by digital computer, EEG can provide information about the minimum effective dose of a drug on the central nervous system (CNS), the onset and duration of CNS effects, and the mode of action of psychotropic drugs (Dolce & Kunkel, 1974; Fink, 1969; Itil, 1974). Recent investigations indicate that computer-analyzed EEG (CEEG™) can determine the type of psychotropic properties of the compound, its potency, and therapeutic window (Fink, 1974; Herrman, 1982; Itil et al., 1979). CEEG has also been applied successfully to determine the bioavailability and bioequivalency of psychotropic drugs and predicted therapeutic outcome in individual patients (Fink, 1974; Itil, 1974, 1977; Itil & Krynicki, 1983).

This paper summarizes a new system called the Brain Function Diagnostic Unit (BFDU™) (Itil et al., 1985) which provides information on brain function and its changes due to drug effects based on Quantitative Neurophysiological Testing results (EEG, EP, sleep), Interactive Neuropsychological and Psychometric tests, and integrative medical and neuropsychiatric summary data.

Quantitative Neurophysiological Testing

Computer EEG data collection and analysis system: The electrical phenomena of the brain, collected through a newly developed electrode helmet, are amplified via standard EEG machine amplifiers. The activity is recorded on a standard EEG strip chart by a conventional EEG writing system. (In the case of research, where the standard EEG strip chart may not be required, sensitive preamplifiers and laser printers may be used instead of the standard EEG machines.)

The same bioelectrical phenomena recorded on the strip chart are also first sent to the special 8-channel filter unit, then 8-channel analog-to-digital converter and, finally, to the microcomputer (IBM-PC/XT,AT or compatible). In addition to the EEG equipment and a microcomputer, some special peripheral hardware is required to conduct the EEG analysis with brain mapping:

a. Math Coprocessor
b. High Resolution Color Board
c. High Resolution Analog RGB Color Monitor
d. High-Speed Near Letter-Quality Printer

An extensive software package to conduct the following operations for these EEG data is also part of the BFDU:

1. A Clinical-Diagnostic EEG Program.

Provides quantitative outputs for each individual EEG lead, the frequency distribution of the mean of eight leads, and instant EEG reports with interpretation (unconfirmed). Simultaneously, colored hard copy topographic Dynamic Brain Map® are provided to help in the discrimination of abnormal or borderline records from normals.

2. Research EEG Programs.

For 8 to 16 channel power spectrum based on 6 to 22 variables and 8 to 16 channel period analysis (interval or zero-cross analysis) with 6 to 22 measurements.

---

[1] Division of Biological Psychiatry, New York Medical College, Tarrytown, NY 10691.
[2] Computer Center, New York Medical College, Tarrytown, NY 10691.
[3] HZI Research Center, Tarrytown, NY 10691.

3 Statistical Packages Which Yield:

Drug-induced changes (pre- minus post-drug) based on univariate statistics.

Drug versus placebo discrimination based on univariate and multivariate statistics.

Individual and group CEEG drug profiles based on *t* profiles.

Drug classification based on HZI's CEEG database using correlation statistics.

Time- and dose-related CNS effects for group and individual subjects based on regression analysis.

Classification of individual subjects' response with the HZI database to determine psychotropic potency of a drug and to predict the therapeutic outcome.

Graphic packages of the statistical outputs and database classifications (hard copy).

Serial comparisons (predrug minus post-drug) by statistical means and by topographic colored brain maps.

Evoked Potential Data Collection and Analysis System

The major part of hardware for EP data collection analysis such as EEG machine, microcomputer (IBM-PC/XT or AT) and electrode headset are the same as used for the EEG data collection and analysis. The only additional hardware required are different types of stimulators (acoustic, visual, and tactile), built specially for our EP system.

Software specific to EP data includes, for example, standard (conventional) 8- to 16-channel analyses with hard copy; an instant clinical report (unconfirmed); colored dynamic topographic brain maps based on different types of EP; and an automatic artifacting system.

There are also some unconventional features, including: high signal-noise ratio; separate analysis of EP based on different EEG frequency patterns; selective averaging, etc.

Interactive Neuropsychological Test System

For the interactive neuropsychological and cognitive test batteries, in addition to the IBM-PC/XT or AT, a psychological test station is required. This station includes another microprocessor (Z-80), a specially developed monitor, light pen, and control panel.

New programs were developed in collaboration with the computer center of the Austrian Road Safety Board to conduct the following tests:

Non-verbal intelligence test, concentration test, simple choice reaction time test, long-term memory test, speed-distance estimation test, optical memory test, sensor-motor coordination test (tracking test), tapping test, and a list of questions on current physical and mental state.

The results of these tests are provided in three different formats:

1. A graphic format, which includes the summary of raw data and the comparison of the data with age-related norms.

2. Interpretation of each individual test result (unconfirmed).

3. A summary report on neuropsychological test results as required by the clinician (unconfirmed interpretation).

Integrative Clinical Report

A series of medical, neuropsychiatric questions are asked about the past history and present symptomatology of the patient. The answers suspected to be related to brain dysfunction of the patient will be integrated into a clinical-practical acceptable format. For the questions, either a rating scale is used, or the patient is given a lap computer which has an interactive approach. The lap computer is a Radio Shack Model 100 with 24K memory, built in RS-232 port, and modem. The integrative summary is provided in a clinically useful format.

Conclusions

BFDU has the following major advantages:

1. The BFDU has been developed on a building-block principle. One can start with a computer EEG system which includes a standard EEG machine (any 8- to 16-channel with IRIG output), an IBM personal microcomputer (XT or AT), and some peripheral hardware (printer, monitor, sine wave generator). If one requires the EP system, one needs to purchase only a stimulator and additional

software. For neuropsychological tests, one needs to purchase a neuropsychological test station and additional programs. With a simple lap computer and additional software, one completes the BFDU system.

2. All three major tests, EEG, EP, and Neuropsychological Tests, are done by standard equipment and the output are also standard. Software provides much additional information to the standards, including quantitative data, statistical results, and color topographic Dynamic Brain Maps which are useful both for psychopharmacology and clinical research.

3. The system is self-monitored by software for technical problems and/or artifacts so that no special manpower for the computer or other test is required.

4. BFDU provides instant clinical-diagnostic EEG reports to determine whether psychiatric patients or subjects included in psychopharmacology trials exhibit any abnormal brain functions; thus computer EEG can be used to screen subjects with "organicity" to exclude from the psychopharmacology studies.

5. BFDU can be used in every phase of psychotropic drug studies, but most significantly during Phase I trials (Itil et al., 1972, 1977, 1979, 1984). Using CEEG, the following important CNS *efficacy* information of a new compound is obtained during Phase I *safety* trials:

- To determine the *CNS effectiveness* of a compound based on CEEG changes between pre- and postdrug administration. All marketed psychotropic drugs produce statistically significant CEEG changes.
- To establish the "*bioavailability*" of a compound on the CNS based on pharmacodynamic changes. In addition to the typical pharmacokinetic measurements (e.g., t_{max}, c_{max}, and AUPDC), CEEG parameters can also be used for time and dose response curves.
- To classify the quality of the CNS effects of a compound, thus to *predict* the type of the *psychotropic properties* using HZI's CEEG database. It was established that drugs with similar CEEG profiles produce equivalent therapeutic effects. Based on CEEG profiles of four major psychotropic drug groups (CNS depressants–neuroleptics; mood elevators–antidepressants; anxiety relievers–anxiolytics–hypnotics; cognitive activators–psychostimulants) and CEEG "prints" of 840 subclasses of 139 CNS effective drugs, the computer can classify the type of psychotropic properties of a new compound.
- To predict the *therapeutic window* of a new compound. The doses of which CNS effects can statistically be discriminated from placebo and also can be classified by the computer database as psychotropic are also therapeutically effective.
- To *predict the potency* of the psychotropic properties of a new compound. According to the studies, the more potent a compound the more patients show "typical" CEEG effects (CEEG profiles) within 1 to 3 hours after a single dose oral administration. The more typical CNS effects are, the better classified is a compound by the computer database to a psychotropic drug group. Among the 139 CNS effective drugs, Valium[R], Elavil[R], and dextroamphetamine are the most homogeneous CNS effective compounds. If a new compound is administered to 12 healthy subjects and more than 75% of the subjects are classified with a typical response, this indicates that the studied compound shall have homogeneous effects on the CNS; thus it will be a potent psychotropic.
- Last, but not least, CEEG can be useful to demonstrate the CNS effects of drugs in individual subjects or a group of subjects after single or multiple doses. Thus, CEEG can be used to monitor CNS effects of psychotropic drugs. If there is no significant change in EEG also, no therapeutic effects can be expected in psychiatric patient populations.

References

Dolce, G., and Kunkel, H. (eds.). *Computerized EEG Analysis*. Stuttgart: Gustav Fischer Verlag, 1974.

Fink, M. EEG and human psychopharmacology. *Ann. Rev. Pharmacol.*, 9:241–258, 1969.

Fink, M. EEG application in psychopharmacology. In: *Psychopharmacological Agents*, Vol. III. New York: Academic Press, 1974, pp. 159–174.

Fink, M. In: Itil, T. (ed.), *Psychotropic Drugs and the Human EEG* (Series: *Modern Problems of Psychopharmacology*). Basel: S. Karger, 1974, p. 76.

Herrman, W.M. *Electroencephalography in Drug Research*. Stuttgart/New York: Gustav Fischer Verlag, 1982.

Itil, T.M. (ed.) *Psychotropic Drugs and the Human EEG* (*Series: Modern Problems of Psychopharmacology*). Basel/New York: S. Karger AG, 1974.

Itil, T.M. Bioavailability and bioequivalence of psychotropic drugs based on computerized EEG measurements. *Drugs Exptl. Clin. Res.*, 1(1–2):251–257, 1977.

Itil, T.M., and Krynicki, V.E. Quantitative pharmaco-EEG in determining bioavailability and bioequivalency of psychotropic drugs. In: Garrett, E.R., and Hirtz, J.L. (eds.), *Drug Fate and Metabolism Methods and Technique*, Vol. 4, Chapt. 6. New York: Marcel Dekker, Inc., 1983.

Itil, T.M., Bhattachy, A., Polvan, N., et al. Fluvoxamine (DU-23,000), a new antidepressant. Quantitative pharmaco-electroencephalography and pilot clinical trials. In: Radouco-Thomas, C. (ed.), *Progress in Neuro-Psychopharmacology*, Vol. 1, Oxford/New York: Pergamon Press, 1977, pp. 309–322.

Itil, T.M., Polvan, N., and Hsu, W. Clinical and EEG effects of GB-94, a "Tetracyclic" and antidepressant effects of double-blind controlled trial. *Curr. Ther. Res.*, 14(7):395–413, 1972.

Itil, T.M., Soldatos, C., Bozak, M., et al. CNS effects of ISF-2522, a new nootropic (APhase) safety and CNS efficacy study with quantitative pharmaco-EEG and pharmaco-psychology. *Curr. Ther. Res.*, 26(5):525–538, 1979.

Itil, T.M., Michael, S.T., Baccari, S., et al. Antidepressant effects of flutracen, a long-acting patent thymoleptic (a double-blind controlled trial). *Curr. Ther. Res.*, 35(6):1014–1032, 1984.

Itil, T.M., Shapiro, D.M., Eralp, E., et al. A new brain function diagnostic unit, including the dynamic brain mapping of computer-analyzed EEG, evoked potential, and sleep (a new hardware/software system and its application to psychiatry and psychopharmacology). *New Trends in Exptl. Clin. Psychiatry*, C.I.C. Edizioni Internationali S.R.L., 21(2): Oct.–Dec., 1985.

BMDPC: BMDP Statistical Software for Microcomputers

MaryAnn Hill, Ph.D.[1]

In the fall of 1984, BMDP began distributing statistical software for IBM personal computers—the XT and AT, and compatibles such as the COMPAQ+. Since the BMDPC programs are the same as the BMDP mainframe programs, this development gives users the full power of a major, well-tested statistical package on a personal computer. The minimum requirements for a system to support BMDPC are a hard disk, an 8087 floating-point processor, 640 kilobytes of memory, and the capacity for double-sided, double-density floppy diskettes.

BMDPC is described in the following three sections: what is BMDP and how does it work, how does BMDPC differ from BMDP on the mainframe, and what is coming soon for BMDPC?

What Is BMDP and How Does It Work?

BMDP is a library of programs. Each program addresses a specific task or analysis: one program prints frequency tables and fits log linear models, another estimates a multiple linear regression equation, etc. BMDP provides a broad range of data description features and statistical analyses including *t* tests, analysis of variance (ANOVA) and covariance (ANCOVA) (repeated measures, multivariate ANOVA, mixed models), multiple regression (forward and backward stepping, all subsets, regression diagnostics), discriminant analysis, nonlinear regression, logistic regression, log linear models, cluster analysis, factor analysis, time series, and survival analysis including the Cox proportional hazards regression model. Most importantly, many procedures provide supports for the data analyst—graphical displays, diagnostics, and alternative tests that help the analyst estimate the degree to which assumptions (necessary for the analysis) are violated.

Each program uses the same basic set of instructions to describe the input data, name the variables, specify acceptable range limits and flags for missing data, select cases (old females from Clinic B in Boston), re-express data (change = baseline—week 4), and identify groups (male smokers, ... , female nonsmokers).

BMDP instructions are written in English sentences and are grouped into paragraphs. The most "basic set" of BMDP instructions (describing a data set containing pre- and post-exercise pulse measures) is shown in Figure 1. For many analyses, this basic set is all you need. For example, if these instructions were submitted to the factor analysis program, the output would contain a univariate data summary, a correlation matrix, eigenvalues associated with each factor, factor scores and Mahalanobis' distances for each case to the centroid of all cases, factor loadings with and without an orthogonal rotation, plots of loadings, and plots of factor scores. To limit the number of factors, or change the rotation type, the user adds instructions to the basic set.

Some programs require that paragraphs be added to the basic set. In Figure 2, a PLOT paragraph is added, requesting that the post-exercise pulse values be plotted against age in a bivariate scatterplot. The output, in addition to the scatterplot, includes the equation

```
/  INPUT          VARIABLES ARE 6.
                  FORMAT IS FREE.

/  VARIABLES      NAMES ARE ID, SEX, SMOKE,
                     AGE, PULSE_1, PULSE_2.

/  END
```

FIGURE 1. Basic BMDP instructions for data where each subject has an I.D., a code for sex and for smoking status, age, and pre and post exercise pulse values.

---

[1] Department of Psychiatry, UCLA School of Medicine, West Los Angeles VA Medical Center (Brentwood Division) and BMDP Statistical Software, Inc., Los Angeles, CA 90025.

```
/  INPUT           VARIABLES ARE 6.
                   FORMAT IS FREE.

/  VARIABLE        NAMES ARE ID, SEX, SMOKE,
                      AGE, PULSE_1, PULSE_2.

/  PLOT            YVAR IS PULSE_2.
                   XVAR IS AGE.

/  END
```

FIGURE 2. A PLOT paragraph is added to the basic set requesting a bivariate scatterplot of pulse versus age.

of the line of best fit (the location of this line is marked on the plot frame), the correlation (with tail probability), the residual mean square, and the means and standard deviations of pulse and age.

If, instead of a plot, the researcher wants a two-way table to test if the proportion of smokers is the same for males and females, the PLOT paragraph in Figure 2 is replaced by the TABLE paragraph in Figure 3.

A TRANSFORM paragraph, available in all programs, is useful for re-expressing data. All the usual arithmetic operators (multiplication, division, exponentiation) and functions (logs, square root, trigonometric) are available. Recently, for ease of data manipulation, more than 24 new transformation functions were added to the package. These functions produce results across variables on a record (e.g., SUM totals, say, 15 items on a record): other functions provide the mean, the minimum, the maximum, and the slope. Functions are also available to convert day-month-year dates to Julian form or to the number of days since January 1, 1960 (and vice versa).

How Does BMDPC Differ From BMDP on the Mainframe?

Researchers do not have to give up familiar mainframe options and features. Each BMDPC program (e.g., stepwise regression) has the *same* options, instructions, and documentation as its mainframe counterpart. But is the researcher handicapped with respect to size of problem and computational time? Yes, to problem size, if the analysis is on census data; no, for many of the studies in psychiatry, for which I am involved. Most BMDP programs do not require the data to be kept in memory—so problem size may be limited by the number of data items that can be stored on the hard disk. In Appendix B.2 of the *BMDP Statistical Software Manual, 1985 Reprinting*, formulas are given for the capacity of each particular analysis. For the standard mainframe installation, the maximum number "M" in these formulas is 15,000 (M is usually a function of the number of variables, number of groups, or number of cells in an ANOVA design). For BMDPC, the maximum value of "M" is 16,000. For example, if three megabytes are set aside on the hard disk for the data file, Program 1D could compute descriptive statistics for ten variables and 75,000 cases. More than 100 variables may be included in a stepwise regression run.

In sizable studies, millions of numbers may be collected when, say, for 200 subjects, many rating forms are administered repeatedly over time. Computing tasks for these studies may be distributed between the PC and the mainframe. For example, the data for each instrument could be cleaned separately on the micro at the center where they are collected, and later shipped or networked to a mainframe for merging with data from other centers. It should be pointed out that this distribution of computing also applies to the debugging of the BMDP instructions for analysis. The fine tuning of the instructions can be carried out on the micro for a subsample of the data and the instructions can then be shipped as text to the mainframe for final analysis of the complete file.

Of course, computation on the micro is slower than on the mainframe. However, the researcher is the only user on the micro, so the person sitting at a micro may not feel handicapped. On an IBM PC/XT, the time to execute the All Possible Subsets Regression searching algorithm for 23 variables is 45 seconds (by wrist watch). A factor analysis

```
/  TABLE           ROW IS SEX.
                   COLUMN IS SMOKE.
```

FIGURE 3. When a TABLE paragraph is added to the basic set of instructions the output contains a two-way frequency table plus the chi-square test of independence.

with 24 variables, including an orthogonal rotation, computation of factor scores, and other supplementary displays and supporting information, takes two minutes. Using the new BMDP Data Manager (described below), it took roughly 11 minutes by wrist watch to

- —do *complex transformations* on each of 1,205 records in File A containing weekly clinic visits for 225 patients. For each record, transformation functions were used to check the number of missing values, sum 20 items, compare the total with another value, etc.
- —use *aggregate functions* to generate 225, records with summary measures (i.e., one new record per patient summarizing his experience across weekly clinic visits).
- —*join* this summary file *side-by-side* with File B, a 225-record demographic file, using the patient ID as a merge key.

In addition to the standard mainframe programs, BMDPC includes a line editor that allows the user to access both data and/or instruction files without leaving the program. With the new editor, the user loads the program once and makes a series of runs, inserting additional instructions or making corrections after each run, thus avoiding the delay of reloading the program after each error. The editor allows the user to get files from the system and to return modified files back to the system.

One difference between BMDPC and the mini and mainframe BMDP is the license procedure. Mainframe and mini-computer users lease the complete BMDP package for an annual fee—they have an annually renewable license. BMDPC users select a group or subset of the programs and pay a one-time-only fee—a perpetual license. Discounts are available for multiple copies of BMDPC leased to universities and research facilities.

What Is Coming Soon for BMDPC?

Each new release of BMDP includes modifications and enhancements. This year BMDP plans to introduce a new system: for managing data. This past year, BMDP began distributing the structural equations modeling program, EQS.

The Data Manager. An exciting new product to be released in 1985 is the data manager system that merges files, extracts summary information from sets of records that vary in number, and performs other file restructuring operations. In Figure 4, the procedures for merging files are illustrated. In Figure 4a, the subject ID is used as a key to merge records side-by-side from three files containing history, laboratory, and questionnaire data. In 4b, records from file B are

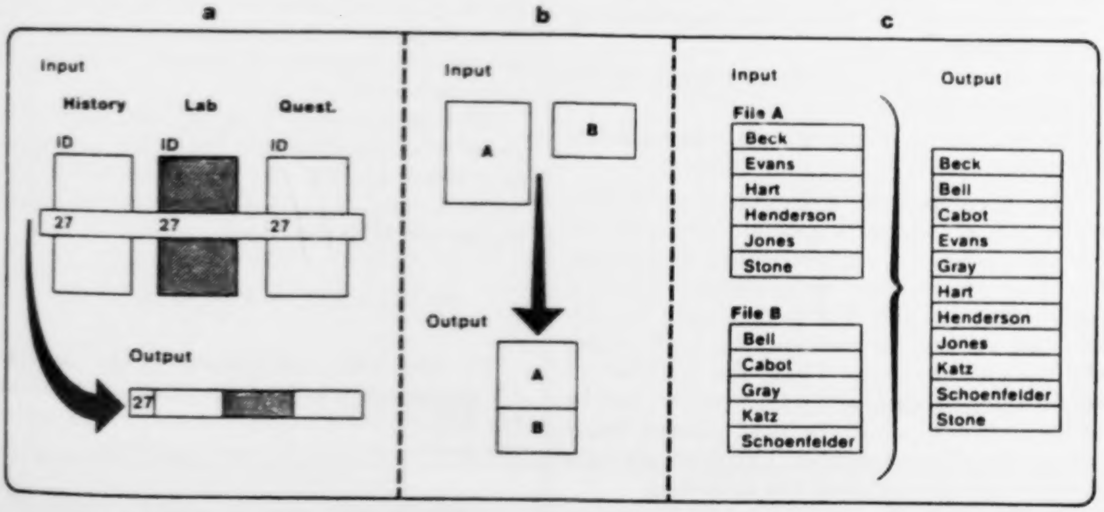
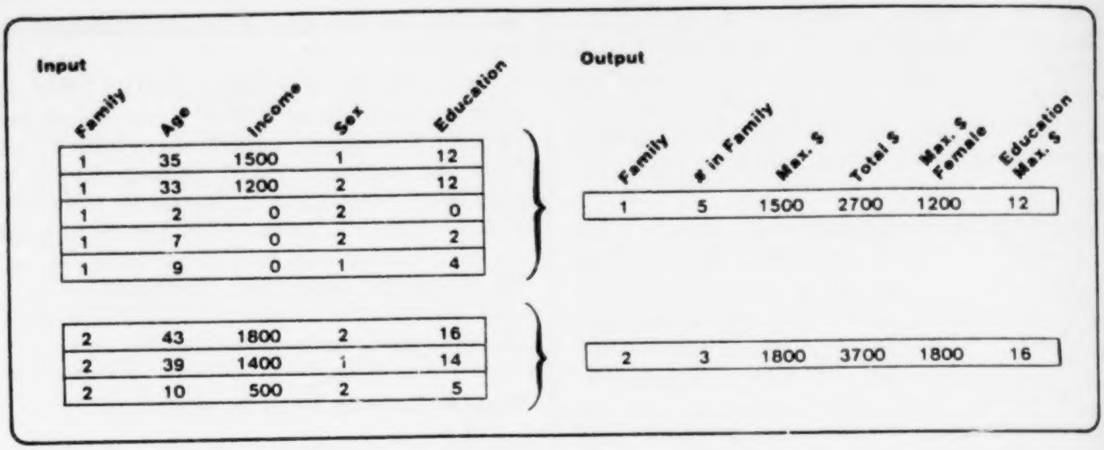


FIGURE 4. **Merging files (a) side-by-side, (b) end-to-end, and (c) interleaving records.**



Input

Family	Age	Income	Sex	Education
1	35	1500	1	12
1	33	1200	2	12
1	2	0	2	0
1	7	0	2	2
1	9	0	1	4
2	43	1800	2	16
2	39	1400	1	14
2	10	500	2	5

Output

Family	# in Family	Max. $	Total $	Max. $ Female	Education Max. $
1	5	1500	2700	1200	12
2	3	1800	3700	1800	16

FIGURE 5. Generating summary records.

added to the end of file A. In 4c, the subject's name is used to interleave records alphabetically from two input files. Output from more than two dozen summary functions can be 1) added to each input record, 2) used to generate summary records, or 3) added to records higher up in the hierarchy. For example, if a file contains records for individual family members with age, sex, education, monthly income, etc. (*see* Figure 5), you can use the summary functions to extract, for each family,

—the number of family members

—the total family income

—the maximum income for one member, the maximum for the males, the maximum for the females

—the education level of the member with the maximum income

—the sex of the member with maximum income

The development of measures to characterize social supports (social networks) of mental patients is an interesting illustration of how to extract information from a nonrectangular file. For each patient we collect one record for each person with whom the patient interacts. Thus, the number of records per patient varies. One patient has 18 in his network, while the next patient interacts with only two people. Variables on each member's record include the following:

—age, sex, frequency of contact, relationship to patient (relative, friend), etc.

—information about roles—the patient's interaction with each member (does he borrow money from the member, spend free time with him, etc.).

—a tally of the interaction with every member in the network (yes, Bill interacts with Jose: no, Bill does not interact with Sue, etc.).

The goal is to generate one record for each patient that summarizes the characteristics of his network: network size (the number of members), number of members interacting in at least one role, total number of roles experienced by the patient, the maximum number of interactions with one member, the member (e.g., mom) about whom the patient feels most negative and the contact score with this person, the number of "others" available for free-time activities, etc.

The generation of these summary measures is straightforward using the aggregate functions. To find the most negative feeling score among a patient's network members, we use the MIN function

MOST_NEG = MIN (FEELING).

To find who this person is, we use the FVAL function to find the value of the variable RELATION in the first record for which the feeling score was most negative.

WHO_NEG = FVAL (RELATION,
FEELING EQ MOST_NEG).

The ability to incorporate conditions in the summary functions also allows us to generate some measures using only the family records, other measures to summarize the nonfamily members. We did this for the number of family members and the number of others used in free time activities. Results were saved and plotted using the 9D miniplot options (*see* Figure 6). We grouped the patients by severity of illness (illness code 1 is severe, 4 is well) and ethnicity. The average number of friends is plotted on the vertical axis. A quick look at the plots provides a description of the results. Use of family members (F) for free time does not appear to be associated with severity of illness. However, use of "others" (O) does decrease markedly with illness, and the decrease is more dramatic for Anglos. The difference between family and "others" is smaller for the Hispanics—they appear to use more family members (probably because their families are larger).

Other data management supports are available to help produce the desired output file. You may *sort records* numerically and alphabetically; *select cases interactively*, e.g., male blue collar workers over 50 years of age who worked in an asbestos factory, *re-express data* using more than 30 functions and operators (LOG_WT = LOG (WEIGHT)), *convert dates* in day, month, and year form to Julian dates or days since January 1, 1960, report *univariate statistics* (n, $\bar{x}$, s, min, and max) for values of variables on input records or records created through file operations *print data* in user-specified fields or preassigned fields, etc. When limitations on computer funds make on-line data editing prohibitive, a batch edit capability is available also. Another feature the system provides is a *record map*—a

```
SYMBOLS -- F=FAMILY  O=OTHERS

         ...+....+....+....+....         ...+....+....+....+....
         -                     -         -                     -
         -                 O   -         -                     -
      3  +                     +      3  +                     +
V        -                     -         -                     -
A        -                     -         -                 O   -
R        -                     -         -                     -
I        -                     -         -                     -
A     2  +                     +      2  +                     +
B        -            O        -         -                     -
L        -                     -         -            O        -
E        -       O             -         -                     -
S        -                     -         -       O             -
      1  +                     +      1  +                     +
         -                     -         -  *    F         F   -
         -       F         F   -         -            F        -
         -  *         F        -         -                     -
         ...+....+....+....+....         ...+....+....+....+....
            1         3                     1         3
                 2         4                     2         4
                ILLNESS                         ILLNESS

            ETHNICTY= ANGLO                 ETHNICTY= HISPANIC
```

FIGURE 6. Number of family members (F) and others (O) available for free time activities (by illness and ethnicity).

graphical display in which each character represents the presence of a record.

The system was designed to handle the great majority of tasks encountered in research projects, while remaining reasonably easy to use. You should *not* require a programmer who is an expert in file structures in order to use it effectively. A data analyst can use the various data manipulation procedures interactively to learn both about the *structure of the records* (e.g., in a clinical trial, how many visits are missed for each patient? What is the pattern of return visits?) and the actual *data values* from cells defined by one or more grouping variables. For example, at 3 months, what is the change from baseline in clinical outcome scores for drug 1 completers (i.e., those subjects who remained on study 1 year), drug 1 dropouts, drug 2 completers, and so on.

Structural Equations Modeling Program. In 1985, BMDP began distribution of EQS (pronounced like the letter X), the structural equations modeling program developed by Professor Peter Bentler at UCLA. EQS permits distribution-free multivariate analyses, including multivariate regression, path analysis, simultaneous equation models, confirmatory factor analysis, latent variable models, etc. Structural equation models allow theory testing with nonexperimental data and for that reason are often called causal modeling methods. EQS is designed so that it requires no knowledge of matrix algebra. Models are specified using an equation language in the form

$$V1 = .5 * V2 + .8 * V3 + E1,$$

where variable V1 is regressed on variables V2 and V3, with error E1. The numbers preceding the asterisks are initial parameter estimates. In addition to parameter estimation using least squares, generalized least squares and maximum likelihood methods (based on elliptical theory) are available for nonnormal data. EQS is currently running on IBM and VAX computers as well as the IBM PC/XT and AT. Versions for other hardware will follow. Professor Bentler is widely published in the area of statistical methodology and is a past president of the Psychometric Society (1982–83).

Projects Under Development. As part of an NIMH research project at UCLA, a test program has been completed for repeated measures analysis of variance with incomplete data. W.J. Dixon is the principal investigator, and R. Jennrich and M. Schluchter are involved in design and programming for the project. In addition to handling incomplete data, the program allows a user-specified structure for the covariance parameters. This approach allows the data analyst to examine several different structures, each having important subject-matter interpretations.

Another program in design stage will allow the analysis of repeated measures categorical data, and at our office in Cork, Ireland, a program for correspondence analysis is under development.

How does BMDP decide what to include in the software? Suggestions come from several sources, including letters submitted by users. A panel of outside advisors meets twice a month to evaluate the suggestions. The panel includes members from the academic community and members actively involved in consulting in a variety of real world applications.

References

Dixon, W.J., Brown, M.B., Engelman, L., et al. (eds.). *BMDP Statistical Software, 1985 Reprinting*. Berkeley: University of California Press, 1985.

Hill, M.A. *BMDP User's Digest, 3rd Edition*. BMDP Statistical Software, Inc., Los Angeles, 1984.

Communications: Microcomputer/ Mainframe Interfacing

Pierre Mercier, Ph.D.[1]

There are a number of practical and technical aspects related to the use of microcomputers in communication with mainframes. In a typical session such as exemplified below, the user logs-on to a mainframe computer using an asynchronous terminal emulator program and issues the necessary commands to transfer to data file to the microcomputer's storage device.

The basic technical aspects involved in performing this task include the essential hardware components, ASCII coding, serial interfacing (RS–232C), and modulation-demodulation. Trapping and correction of transmission errors must also be performed.

A Sample Application

In order to establish communications between a microcomputer and some remote machine, the user must first load a Terminal Emulator Program and set the necessary parameters. The data communication parameters will be explained in detail later; let us assume that default values are appropriate for now. Turning on the communications line, a TERMINAL READY message appears at the top of the screen. The IDENTIFICATION and PASSWORD statements are then required to access the mainframe. The exact order and syntax of these steps may vary from installation to installation but they are typical of the process.

The user is now on-line and can issue any command that the mainframe understands, or use any program that runs on it, with the associated processing power. On the other hand, it may be desirable to take the content of a data file which resides on the mainframe storage device, list its content on the screen, and record it on the microcomputer's disk drive at the same time. Within the restrictions imposed by the size of the destination device (typically in the range 120–320 Kilobytes for floppy drives or 5–20 Megabytes for hard disks on microcomputers versus 100–317 Megabytes for a mainframe disk pack), these data are then available for processing by the micro (e.g., using a statistical analysis program), thus saving on-line costs and generally offering a more interactive environment.

To execute the transfer, the data destination is first identified by creating a new file on the microcomputer's disk directory. Next, the terminal is put in RECORD mode and a DISPLAY command is sent to the remote. At this point, a listing of the file is obtained which is then automatically saved on the local disk. It is now possible to terminate the session (OFF), and replace the terminal emulator program with the application program needed to process the newly acquired data (e.g., statistical analysis).

The Communication Process

The communication circuit used in the preceding example comprises a number of distinct elements. The circuit starts at one end with the mainframe computer or, more technically, the Data Terminal Equipment (DTE—a computer or machine which provides data in the form of digital signals at its output), continues with the front-end processor which acts as an interface between the Central Processing Unit (CPU) and the various input-output units, to the MODulator-DEModulator (MODEM—a type of Data Communication Equipment (DCE) that converts digital data to an analog signal for transmission on telephone circuits), to the telephone lines or any suitable transmission channel such as microwaves or radio waves, to another MODEM, to another interface (often such as the RS–232C serial interface), and finally to the microcomputer.

---

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada H3A 1A1

Along the communications circuit, the data (letters, numbers, and other symbols) are represented according to certain coding schemes. A scheme very widely used for computers to communicate with peripherals is the American Standard Code for Information Interchange or ASCII (Mackenzie, 1980). This code effectively uses 7 bits to represent 128 different symbols. These include the usual alphanumerical symbols found on a typewriter. For instance, upper case 'A' is represented as 100 0001 binary, corresponding to decimal value 65, whereas lower case 'a' is 110 0001, equivalent to decimal value 97, and so on. Some control characters are also available (decimal values 0–31), so called because they are acted upon by the computer rather than merely displayed. The most commonly used are probably 'carriage return' (mnemonic: CR, decimal value = 13) and 'line feed' (LF, 12 decimal), which respectively bring the cursor or printhead to the leftmost position on a line and move to a new line. Other characters such as 'bell' (BEL, 7 decimal), 'backspace' (BS, 8 decimal) and 'form feed' (LF, 12 decimal) are fairly self-explanatory, but others are not so obvious.

In the case of a file transferred from a mainframe, each data line begins on a new line (LF) and terminates with a carriage return (CR). In addition, a device control character such as DC3 (19 decimal) might be inserted at the end of each line. It means 'reader-off,' i.e., the sender is not finished transmitting, more data is coming, and the sender will not accept input. The very last character, DC1 (17 decimal) means 'reader-on,' i.e., transmission has ended for now, input will be accepted. The communication protocol determines which control characters are used and how they are acted upon. It may vary from one system to another and it will be necessary to obtain that information from the system managers before establishing communications.

As mentioned before, ASCII is a widespread code for communications. Inside the computer at each end, the coding might be different. An IBM mainframe will use the Extended Binary Coded Decimal Interchange Code (EBCDIC) where 8 bits represent each symbol. Many microcomputers will use an 8 bit extended ASCII internally (the standard ASCII does not use the most significant bit which always has value 0). The necessary translation for communications will generally be done by the computer, in a manner transparent to the user.

There is another more important difference between internal data manipulation and external communications. The computer will generally move data around in a parallel manner. Each piece of information will typically be manipulated 8, 16, or 32 bits at a time, depending on the CPU word size. The electrical signals forming the bits each travel along a line or wire, but telephone lines and other channels do not have so many wires so the data need to be transmitted serially, one bit at a time. This conversion process is accomplished by a serial interface. There are more than one type of serial interface but the RS–232C is the most widely used on microcomputers. Simplifying to the extreme, this interface has a data register capable of parallel input (all bits of one character simultaneously) and serial output (all bits of one character one after the other) and vice-versa, with appropriate timing.

The telephone line not only forces serial transmission but it also requires that the digital pulses of the computer (e.g., 0 volts = 0, +5 volts = 1) be transformed or modulated using waves (e.g., 1070 Hz = 0, 1270 Hz = 1). This is accomplished by the modem. To obtain an orderly exchange of data, the modem needs to be controlled by the computer, via the serial interface and a wire cable allowing the use of up to 25 different signals.

Depending on the system you communicate with, transmission will take place in the either duplex or half-duplex. In duplex, the hardware allows sending and receiving of data at the same time (using different frequency bands) whereas in half-duplex, transmission occurs in one direction at a time. IBM mainframes use half-duplex communications.

In programming a serial interface or simply setting the parameters of a terminal emulator program, it is necessary to specify the speed at which the data will be transmitted along the channel. The RS–232C is designed to offer a range of 'Baud rates' between 50 and 19200. The Baud rate is the number of signaling elements per second. It can be understood as the number of bits per second (Bps) for the purpose of the current discussion, although the two are not always equivalent: techniques exist to transmit more than one bit per Baud.

A number of problems can arise during communication which can alter the nature of the signals and distort or destroy data. Noise on the telephone line, for instance, could interfere with the frequency of the signal and make a 0 appear as a 1 on arrival. The most reliable strategy would consist in sending the received message back to the sender and compare this copy with the original; but that would at least double transmission time, not to mention all the processing required to compare the messages.

Various methods exist to check for possible errors while maintaining a lower overhead (Lin & Costello, 1983). One is PARITY checking. Recall that the standard ASCII code uses only 7 bits while most microcomputers have a word length of at least 8 bits. During communications the eighth bit can be set or reset according to how many of the 7 character bits are set. For instance, enabling even parity would consist in setting the eighth bit when and only when there is an odd number of 1's in the remaining 7 bits such that overall there would always be an even number of 1's. This parity testing is usually carried out by the interface which will flag any problem.

Another method uses HAMMING CODES. This method associates a parity bit with bits 1, 3, 5, and 7, another parity bit with bits 2, 3, 6, and 7, and a third parity bit with bits 4, 5, 6, and 7. Upon character reception, these extra parity bits are computed from the received data and compared with those sent with the data. Depending on the pattern of change obtained, it can be determined which of the 7 character bits is faulty and correct it. For instance:

1) Data to be sent:
x1 x2x3 x4x5x6x7 = 1 00 0100
2) Transmitted data:
P1x1P2x2x3P3x4x5x6x7 = 0100010100
3) Data groups P1x1 x3 x5 x7 = 01 0 1 0
with even parity: P2x2x3 x6x7 = 000 00
P3x4x5x6x7 = 10100
4) Received data with error in bit x6:
0100010110
5) P's computed from received data:
P3 = 0 P2 = 1 P1 = 0
6) P's received with the data:
P3 = 1 P2 = 0 P1 = 0
7) Change in P's: C3 = 1 C2 = 1 C1 = 0
8) Decimal equivalent of C3C2C1 binary code: (110) = 6
9) Therefore bit 6 is incorrect:
received 1, change to 0
Data Code transmitted should be:
1 00 0100

The ability to isolate which bit was denatured during transmission costs two extra bits per character relative to simple parity checking. This overhead could become unacceptable: at low speed (e.g., 300 Bps), eight more minutes would be required to transfer an 80K characters file (80,000 char X 8 bits/300 Bps/60 seconds = 36 minutes, versus 44 minutes with 10 bits).

Data integrity is the crucial aspect of communications, particularly where file transfers are concerned. A number of protocols have been devised to achieve reliable communications. Here is a brief overview of the strategy used by KERMIT, a protocol developed at Columbia University (Da Cruz & Catchings, 1984):

- Communication takes place in half-duplex over ordinary transmission lines.
- ASCII characters are transmitted in packets of variable length (0–96) in alternate directions and a reply (positive or negative acknowledgment) is required for each packet.
- Only printable characters are used for transmission; non-printable characters (0 to 31) are prefixed with a special character (#) and converted for transmission by adding 32 to their decimal value.
- Each packet begins with a mark, normally SOH (ASCII 01 or CTRL-A), followed by a length field.
- The length is the number of ASCII characters in the packet following this field, including control characters (maximum = 94).
- The next character is the packet sequence number (0–63, wrapping around after a group of 64).
- Then comes a packet type identifier indicating whether the packet contains data, an acknowledgment, a command to be executed immediately, etc.

- Following is the actual contents of the packet, i.e., the data if any.
- The packet terminates with the block-check sequence.
- The system must react within a specified time interval: otherwise a time out occurs and the packet is retransmitted.

The standard error detection provided in the final block-check is an arithmetic checksum, which is the addition of the ASCII values of all the characters in the packet, excluding the mark and the check itself. The result can approach 12,000 (ASCII 127 × 94). The binary representation of this number is 14 bits long (10111011100000) thus two characters would be necessary to represent it fully. This represents a much lower overhead than the addition of 3 extra bits per character as in the Hamming code. The checksum method will leave some errors undetected since with up to 94 characters per sum, there are many combinations that can produce the same sum. According to the protocol designers, the probability of an undetected error is 1/4096 for a two-character checksum.

Another method of error detection allowed in the protocol is a 16 bit Cyclic Redundancy Check (CRC). Essentially, the CRC passes the characters through a shift register with feedback loops such that each bit of the transmitted message affects the block check character more than once. This method will detect all error bursts of 16 bits or less in length and 99.99% of longer ones (MacNamara, 1977).

With such a protocol, what would be the consequences of transmission errors?

- If the SOH is garbled, all characters become ignored until the next mark.
- If any other character in the packet is distorted into SOH, the rest of this packet is taken as a new one but its spurious nature will be caught at the length, sequence, or block-check level.
- If the length field is garbled into a larger value, the checksum will be absent or in any case wrong, leading to a retransmission. If the distortion causes a value smaller than the real length to arrive, then the system will hang, waiting for missing extra characters, until a preset time out is reached.
- If the sequence number, the type field, one or more data characters, or the checksum are distorted, the checksum should be wrong, causing retransmission of that packet.

Conclusion

Having a terminal emulator program at your disposal is certainly a cost efficient strategy since it allows your microcomputer to double up as a terminal.* This is fine if one simply needs access to a mainframe to execute sizable tasks. If the objective is to transfer data files between the two computers in order to use them on either machine, the program must provide reliability checks.

This text attempted to overview some of the basic technical aspects involved in terminal emulation. From the user's point of view at least, other aspects may be very significant such as full-screen editing capabilities (IBM 3270 emulation). These depend on such considerations as what the mainframe system supports and how extensively terminal-mode is used. Although not covered here, they would remain important aspects to consider in selecting or writing a program.

References

Da Cruz, F., and Catchings, B. KERMIT: A file transfer protocol for universities, Part 1: Design considerations and specifications. *Byte*, 9(6):255–278, 1984.

Lin, S., and Costello, D.J., Jr. *Error Control Coding: Fundamentals and Applications*. Englewood Cliffs, N.J.: Prentice-Hall, 1983.

Mackenzie, C.E. *Coded Character Sets, History and Development*. Reading Mass.: Addison-Wesley, 1980.

MacNamara, J.E. *Technical Aspects of Data Communications*. Maynard, Mass.: Digital Press, 1977.

---

*A documented listing of a minimal terminal emulator program is available from the author. This program is written in BASIC for a Hewlett-Packard 9816. It uses some machine-dependent features and performs error detection but not correction. It can be used to learn and build from.

Expert Systems in Psychiatry

Michael Feinberg, M.D., Ph.D.,[1] and
Robert K. Lindsay, Ph.D.[1]

There is a documented shortage of psychiatrists in the United States (GMENAC, 1980), and the estimates of the prevalence of psychiatric illness used to develop this report were lower than the figures in recent population surveys (Myers et al., 1984). Further, most prescriptions for antidepressants are written by non-psychiatrists (Johnson, 1974; Ketai, 1978; Kline, 1974), and the great majority of depressed patients seen by a sample of primary care physicians were treated inappropriately (Weissman et al., 1981). These data highlight the need for improving the treatment provided to the majority of mentally ill patients. We believe that computers can act as consultants to non-psychiatrist clinicians, resulting in improved patient care.

The appropriate computer technology is a form of applied artificial intelligence called *expert systems*. Expert systems are computer programs that encode some of the knowledge used by experts in a particular field and apply an inference-making procedure to this knowledge. There are now several hundred expert systems in various stages of development, covering a broad range of disciplines, a few of which are in active application. Examples of the more mature systems include those used for molecular structure elucidation in organic chemistry (Lindsay et al., 1980), configuration of computer systems (McDermott, 1982), mineral exploration (Campbell et al., 1982), and analysis of pulmonary function tests (Aikins et al., 1982); *see* also Duda and Shortliffe (1983), and Buchanan and Shortliffe (1983).

Expert systems can make accurate diagnoses in internal medicine, even when the patient has several diagnoses. The performance of the program Caduceus (nee Internist) was tested on a group of CPC's (clinical-pathological conferences) from the *New England Journal of Medicine*. The program was correct as often as were the referring physicians, but less often than the expert consultants who discussed the cases (Miller et al., 1982). This record should be considered in light of the fact that the human experts were particularly knowledgeable in a delimited area of internal medicine, while the program's performance was tested on a wide range of cases. Other expert systems can do as well as the best human consultant, but in a narrower domain. These include the Casnet program for the diagnosis of glaucoma (Kulikowski & Weiss, 1982) and programs for acid-base/electrolyte disorders (Patil et al., 1982).

Some expert systems can explain the reasons for asking a question, making a diagnosis, or recommending a therapeutic regimen, although the explanations have tended to be superficial rather than phrased in terms of basic principles. Caduceus, for example, works well but offers no amenities to the user; in the current jargon, it is not user-friendly. In particular, it cannot explain why it reached a diagnosis other than by displaying its initial probability data and its calculations. The program as written has no concept of time, and cannot make use of the order in which symptoms occurred, or of such concepts as episodes of illness or the rate of onset of a symptom. Fagan and his associates (Horvitz et al., 1984) have used a similar, Bayesian method in an expert system for the differential diagnosis of lymphomas using data gathered from inspection of a slide. In this situation, there are no temporal relationships to account for.

Shortliffe (1976; Buchanan & Shortliffe, 1984) wrote perhaps the best known medical expert system, MYCIN, which can diagnose and make treatment recommendations for meningitis and septicemia. The group at Stanford went on to separate the control structure of MYCIN from its knowledge about infectious diseases. The resulting program, called EMYCIN (Essential MYCIN), can "reason" in any domain and thus forms the basis of a wide variety of expert systems (van Melle, 1981, 1984). Each new expert system can be written by constructing a new knowledge base in the form of if-then (production) rules with a minimum of "program-

---

[1] Mental Health Research Institute, Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109-0010.

ming" required. The principles involved have shaped the design of expert systems and are central to the work we are doing.

As we have noted, it is extremely important that an expert system be able to explain its behavior to the client. This is so for two reasons. First, it is necessary for client acceptance. Second, it is necessary if the client and program are to work together in a manner that makes use of their complementary abilities. MYCIN, and EMYCIN-based systems in general, have a primitive explanation facility derived from the rule-based style of programming itself. Since rules are a more-or-less transparent and modular form of knowledge representation, informing the client that decisions were reached via such-and-such a rule is readily possible. Insofar as the rules succeed in encapsulating meaningful knowledge, these "explanations" are valuable.

The example below shows a rule from an expert system for the Hamilton Rating Scale and the explanation based on the rule:

```
RULE 003

[This rule is tried in order to find out
whether retardation is severe or worse.]
  If: 1) Retardation is moderate or worse,
         and
      2) A: Interview is prolonged by slowed
            speech,
         B: Gait is slow-with-decreased-associ-
            ated-movements, or
         C: Time to complete self-ratings is
            abnormally long
  Then: It is definite (1.0) that retardation
is severe or worse.
      9) Does slowed speech prolong the in-
         terview to a marked degree?
      ** WHY
[i.e., WHY is it important to determine
whether interview is prolonged by slowed
speech?]
[3.0] This will aid in determining wheth-
      er retardation is severe or worse. It
      has already been established that
      [3.1] retardation is moderate or
            worse
      Therefore, if
      [3.2] 1) Interview is prolonged by
               slowed speech,
            2) Gait is slow-with-decreased-
               associated-movements, or
            3) Time to complete self-rat-
               ings is abnormally long
  then
   it is definite (1.0) that retardation is
  severe or worse.
  [RULE 003]
```

However, some rules are necessary simply to control certain record keeping functions in the program, and when these are offered as part of explanation the result is often puzzling (e.g., "I asked for that datum because that is one of the things I need to know."). Furthermore, the rule set does not contain the reasons for its own construction, and so a more global explanation cannot be obtained from it.

Swartout (1981, 1983) has developed a more sophisticated explanation facility for an expert system. He constructed an expert system that explains its questions and actions in terms of underlying knowledge, such as basic physiology and pharmacology, by having the expert system incorporate that information and literally build its own higher level knowledge on the foundation of the underlying concepts. The examples below show two explanations of the reason for asking about serum potassium before prescribing digoxin. The first is from a rule-based system; the second, from Swartout's explanation system.

1) What is the level of serum potassium?
   Enter numerical value = = = > why?
   My top goal is to begin therapy. One step in doing that is to check sensitivities. I am now trying to check sensitivity due to potassium.
2) Please enter the value of serum-k:why?
   The system is anticipating digitalis toxicity. Decreased serum-k causes increased automaticity, which may cause a change to ventricular fibrillation. Increased digitalis also causes increased automaticity. Thus, if the system observes decreased serum-k, it reduces the dose of digitalis due to deceased serum-k.
   Please enter the value of serum-k:3.7.

There have been a few recent attempts to apply expert systems methods to psychiatry, and interest in these applications has been growing. Heiser and Brooks (1978; Brooks & Heiser, 1980) began a project, called HEADMED, in the late 1970's. Their program used EMYCIN (van Melle, 1981) and was designed to work backward from available medications, attempting to select the one that was indicated by rules that related drugs to symptoms. This system was never fully implemented.

A small system applying knowledge engineering methods was constructed in 1983 by two medical externs at Stanford University Medical School. That program, called BLUEBOX (Mulsant & Servan-Schreiber, 1984), contained about 175 rules written in EMYCIN. We studied and ran this program and discussed it with its authors at length prior to beginning our own efforts. Neither HEADMED nor BLUEBOX was ever subjected to validation tests.

Erdman (1983) developed two computer-based diagnostic models for depression, based on the advice and expertise of a psychiatrist. One model was represented as a "flowchart" of questions and answers; the second "decision theoretic" model was based on statistical relations of symptoms and illness. These models were applied to a limited sample of (eight) actual cases that were also analyzed by a group of psychiatrists and a group physicians (non-psychiatrists). Neither model correlated well with the average of the psychiatrists' recommendations; the flow chart model doing no better than a random selection, the probabilistic model doing slightly better (kappa = .44). However, Erdman found a positive effect of these models on the confidence of non-psychiatric users.

We employed three programming tools for expert systems in the pilot studies. Two of these, EMYCIN (van Melle, 1981) and AGE (Nii & Aiello, 1979), were made available to us on the SUMEX national computer resource for artificial intelligence in medicine, located at Stanford University and accessed over computer network (Tymnet). The third is a commercial programming system for expert systems, KEE, developed by Intellicorp of Palo Alto, and used on a Xerox 1108 and a Symbolics 3600 scientific workstation. We first used EMYCIN to develop a system to consult in the use of the Hamilton Rating Scale, a standard tool for evaluation of depression (Hamilton, 1960, 1967). This expert system taught us several important lessons about constructing expert systems in general and about using EMYCIN to do so. We also developed a pilot version of a rule-based inference system for the diagnosis of depression, derived from observation of clinical interviews by an expert diagnostician (Feinberg). This system was initially developed on SUMEX using the AGE system. The AGE software is not maintained as a production tool by the SUMEX staff, and access over the network is slow and limited to standard keyboad/CRT interactions. Our experiences in using EMYCIN and AGE on SUMEX via Tymnet also convinced us that we would make more rapid progress using local machines, once past the pilot stages. SUMEX served us very well for pilot work, but will not be adequate for more intensive work with a larger knowledge base.

We sought a more efficient alternative, and one of us (RKL) was able to obtain an academic grant from Intellicorp allowing us to use the KEE system. This is a commercial product which runs on sophisticated workstations such as the Xerox 1108. Intellicorp provides documentation, maintenance (including bug reporting by electronic mail), and training. We have been using KEE to develop an expert system on the somatic treatment of depression.

An Expert System for the Diagnosis of Depression

There has been a growing emphasis in American psychiatry on careful diagnosis using clearly defined clinical criteria (APA, 1980; Feighner et al., 1972; Feinberg & Carroll, 1982, 1983; Spitzer et al., 1975). These efforts have led to several lists of criteria for the diagnosis of psychiatric disorders. The "St. Louis" criteria (Feighner et al., 1972) were succeeded by the Research Diagnostic Criteria (RDC), formulated by researchers from St. Louis and New York (Spitzer et al., 1975). The RDC led directly to the criteria that are now quasi-official in American psychiatry, DSM-III (APA, 1980). All of these lists of criteria were based on a combination of clinical opinion and literature review.

These diagnostic systems have been shown to be acceptably reliable, but their validity has not been as well demonstrated.

The criterion lists mentioned above have emphasized the diagnosis of affective disorders (e.g., depression), reflecting earlier evidence that American psychiatrists tended to overdiagnose schizophrenia in preference to affective disorders (Cooper et al., 1972). Several groups in England and the United States have used multivariate statistics to differentiate subtypes of depression. Roth and his colleagues (Carney et al., 1965) published a discriminant index (the Newcastle Diagnostic Index) for distinguishing "endogenous" from "neurotic" depressed patients. Kiloh et al. (1972) confirmed their results in a separate population. We have done similar work, deriving two discriminant indices for separating endogenous depressed (ED) patients (unipolar or bipolar) from those with nonendogenous ("neurotic") depression (ND). We cross-validated these indices in separate groups of patients, and also validated them against an external standard, the dexamethasone suppression test (Feinberg & Carroll, 1982, 1983). The Newcastle and Michigan Indices tend to contain the same symptoms, and both tend to differ from the criterion lists based on "clinical wisdom."

We have continued our work on the differential diagnosis of depression using an expert system written by Fagan and co-workers at Stanford (Horvitz et al., 1984). This program, Pathfinder, is being developed to distinguish among lymphomas on the basis of data gathered from inspection of a slide, using modified Bayesian statistics and logic similar to that of Internist-1 (Miller et al., 1982). We have applied Pathfinder to the task of distinguishing endogenous and nonendogenous depression. The knowledge base we provided includes marginal probabilities computed on data from the patients studied by Feinberg and Carroll (1982), specifically, the probability that a particular symptom will be present at a certain intensity in each diagnostic group and the probability that a patient with a given level of a symptom will belong to each diagnostic group. We used the Pathfinder program to assign diagnoses to a separate group of patients, with the results shown in the table. The program computes the probability of the patient's belonging to each diagnostic group, and we have assigned the patient to a group if the probability of his membership is above 0.66 (i.e., 2:1 odds or better). As expected, the results are almost exactly those obtained using the Michigan Discriminant Index for separating unipolar ED from ND patients (Feinberg & Carroll, 1982).

Pathfinder Diagnosis

		ED	?	ND	Total
Clinical	ED	17	5	4	26
Diagnosis	ND	6	4	15	25
					51

Forty-two of the 51 patients in this group were classified by the program (82%). Of these, 32 of 42 (76%) were classified correctly. This is far better than chance but we are trying to improve this by adding clinical features not included in the discriminant index.

The Pathfinder program can be run in two modes. The first, used to produce the results above, calculates the probability of each diagnosis from the (complete) data for each patient, based on the marginal probabilities in the knowledge base. In the second mode, more consistent with what one usually expects from an expert system, the program sequentially asks for the additional information that will be most useful in reaching a diagnosis until it can assign a sufficiently high probability to the patient's belonging to one diagnostic group. An example of computer-clinician dialogue for each mode is available from the authors. Our work to date has shown that the program can reach acceptably accurate diagnoses, but we will not have an accurate picture of its suitability for our particular problem until we have added more diagnoses and more clinical features to the knowledge base.

References

Aikins, J.S., Kunz, J.C., Shortliffe, E.H., and Fallat, R.J. PUFF: An expert system for interpretation of pulmonary function data. *Comput. Biomed. Res.*, 16:199–208, 1983. (Reprinted in Clancey, W.J., and Shortliffe, E.H., 1984.)

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Health Disorders*, 3rd ed. Washington, D.C.: American Psychiatric Association, 1980.

Brooks, R.E., and Heiser, J.F. Some experiences with transferring the MYCIN system to a new domain. Correspondence. *IEEE Trans. Pattern Analysis Machine Intelligence PAMI*, 2:477–479, 1980.

Buchanan, B.G., and Shortliffe, E.H. (eds.). *Rule-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project*. Reading, Mass.: Addison-Wesley, 1984.

Campbell, A.N., Hollister, V.F., Duda, R.O., and Hart, P.E. Recognition of hidden mineral deposits by artificial intelligence programs. *Science*, 217:927–932, 1982.

Carney, M.W.P., Roth, M., and Garside, R.F. The diagnosis of depressive syndromes and the prediction of ECT response. *Br. J. Psychiatry*, 111:659–674, 1965.

Cooper, J.E., Kendell, R.E., Gurland, B.J., et al. *Psychiatric Diagnosis in New York and London*. London: Oxford University Press, 1972.

Duda, R.O., and Shortliffe, E.H. Expert systems research. *Science*, 220:261–268, 1983.

Erdman, H.P. A comparison of computer consultation programs for primary care physicians: Impact of decision-making model and explanation capability. Doctoral dissertation, University of Wisconsin-Madison, 1983.

Feighner, J.P., Robins, E., Guze, S.B., et al. Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiatry*, 26:57–63, 1972.

Feinberg, M., and Carroll, B.J. Separation of subtypes of depression using discriminant analysis: I. Separation of unipolar endogenous depression from nonendogenous depression. *Br. J. Psychiatry*, 140:384–391, 1982.

Feinberg, M., and Carroll, B.J. Separation of subtypes of depression using discriminant analysis. II. Separation of bipolar endogenous depression from nonendogenous ("neurotic") depression. *J. Affective Disord.*, 5:129–139, 1983.

GMENAC: Graduate Medical Education National Advisory Committee Summary Report to the Secretary of Health and Human Services. Washington, D.C.: U.S. Government Printing Office, 1980.

Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry*, 23:56–62, 1960.

Hamilton, M. Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychol.*, 6:278–296, 1967.

Heiser, J.F., and Brooks, R.E. Design considerations for a clinical psychopharmacology advisor. Proceedings, Second Annual Symposium on Computer Applications in Medical Care. New York: IEEE, 1978, pp. 278–285.

Horvitz, E.J., Heckerman, D.E., Nathwani, B.N., and Fagan, L.M. Diagnostic strategies in the hypothesis-directed PATHFINDER system. *Proceedings of the first conference on artificial intelligence applications*, 1984, pp. 630–636.

Johnson, D.A.W. A study of the use of antidepressant medication in general practice. *Br. J. Psychiatry*, 125:186–192, 1974.

Ketai, R. Family practitioners' knowledge about treatment of depressive illness. *JAMA*, 235:2600–2603, 1978.

Kiloh, L.G., Andrews, G., and Neilson, M. The relationship of the syndromes called endogenous and neurotic depression. *Br. J. Psychiatry*, 121:183–196, 1972.

Kline, N.S. Antidepressant medication: A more effective use by general practitioners, family physicians, internists, and others. *JAMA*, 227:1158–1160, 1974.

Kulikowski, C.A., and Weiss, S.M. Representation of expert knowledge for consultation: The CASNET and EXPERT projects. In: Szolovits, P. (ed.), *Artificial Intelligence in Medicine*. Boulder, Colo.: Westview Press, 1982, pp. 21–55.

Lindsay, R.K., Buchanan, B.G., Feigenbaum, E.A., and Lederberg, J. *Applications of Artificial Intelligence for Organic Chemistry: The DENDRAL Project*. New York: McGraw Hill Book Co., 1980.

McDermott, J. R1: A rule-based configurer of computer systems. *Artif. Intell.*, 19:39–88, 1982.

Miller, R.A., Pople, H.E., and Myers, J.D. INTERNIST-1, An experimental computer-based diagnostic consultant for general internal medicine. *New Engl. J. Med.*, 307:468–476, 1982. Reprinted in Clancey, W.J., and Shortliffe, E.H., (eds.), *Readings in Medical Artificial Intelligence*. Reading, Mass.: Addison-Wesley, 1984, pp. 190–209.

Mulsant, B., and Servan-Schreiber, D. Knowledge engineering: A daily activity on a hospital ward. *Comput. Biomed. Res.*, 17:71–91, 1984.

Myers, J.K., Weissman, M.M., Tischler, G.L., et al. Six-month prevalence of psychiatric disorders in three communities. *Arch. Gen. Psychiatry*, 41:959, 1984.

Nii, H.P., and Aiello, N. AGE (Attempt to Generalize): A knowledge-based program for building knowledge-based programs. *Proc. Int. Joint Conf. Artif. Intell.*, 6:645–655, 1979.

Patil, R.S., Szolovits, P., and Schwartz, W.B. Modeling knowledge of the patient in acid-base and electrolyte disorders. In: Szolovits, P. (ed.), *Artificial Intelligence in Medicine*. Boulder, Colo.: Westview Press, 1982, pp. 191–226.

Shortliffe, E.H. *A Computer-Based Medical Consultant: MYCIN*. Amsterdam: Elsevier, 1976.

Spitzer, R.L., Endicott, J., and Robins, E. *Research Diagnostic Criteria*, 2nd ed. New York State Department of Mental Hygiene, New York Psychiatric Institute, Biometric Research Divison, 1975.

Swartout, W.R. Explaining and justifying expert consulting programs. *Proc. of Seventh Inter. Joint Conf. on*

Artif. Intell., 2:815–823. Los Altos, Calif.: William Kaufmann, 1981.

Swartout, W.R. XPLAIN: A system for creating and explaining expert consulting programs. Marina del Rey, Calif.: Information Sciences Institute, ISI Reprint Series ISI/RS-83-4, 1983.

van Melle, W. The EMYCIN Manual. Stanford University: Heuristic Programming Project Report HPP-81-16, 1981.

van Melle, W. The structure of the MYCIN system. In: Buchanan, B.G., and Shortliffe, E.H. (eds.), *Rule-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project*. Reading, Mass.: Addison-Wesley, 1984, pp. 67–77.

Weissman, M.M., Myers, J.K., and Thompson, D. Depression and its treatment in a U.S. urban community: 1975–1976. *Arch. Gen. Psychiatry*, 38:417–421, 1981.

CUMULATIVE INDEX

Psychopharmacology Bulletin

A. Contents Index

Vol. 21, No. 1, 1985

1 **Annual NCDEU Meeting (1984)—Abridged Proceedings—Consensus Conferencing—**

2 Notes on the Consensus Development Process — *David J. Kupfer and Margaret C. McDonald*

7 An NIMH View of Consensus Conferencing — *Harold Alan Pincus*

Carbamazepine in Psychiatric Disorders —

10 Carbamazepine in Bipolar Illness — *Robert M. Post and Thomas W. Uhde*

18 Carbamazepine and Lithium: Different Profiles in Affective Disorder? — *Bernard Lerer, Norman Moore, Elaine Meyendorff, Sung-Ran Cho, and Samuel Gershon*

Medical Compliance —

23 Compliance in the Long-Term Treatment of Schizophrenia — *John M. Kane and Michael Borenstein*

28 Adherence to Methylphenidate Therapy in a Pediatric Population: A Preliminary Investigation — *Ronald T. Brown, Kathi A. Borden, and Stephen R. Clingerman*

37 Implications of Noncompliance on Research in Affective Disorders — *Ellen Frank, Robert F. Prien, David J. Kupfer, and Lisa Alberts*

Receptor Modulation as a Treatment Strategy —

43 Serotonin Agonists and Beta-Adrenergic Agonists as a Treatment for Depressive Disorder: A Direct Clinical Application — *Stephen M. Stahl*

Blood Levels of Haloperidol and Clinical Response —

48 Haloperidol Plasma Levels and Clinical Response: Basic Concepts and Clinical Data — *John M. Davis, Stephen E. Ericksen, Stephen Hurt, Sidney S. Chang, Javaid I. Javaid, Haroutune Dekirmenjian, and Regina Casper*

52 Haloperidol and Thioridazine Drug Levels and Clinical Response in Schizophrenia: Comparison of Gas-Liquid Chromatography and Radioreceptor Drug Level Assays — *Robert C. Smith, Richard Baumgartner, Alla Burd, G.K. Ravichandran, and Mary Maudlin*

59 Does a Therapeutic Window for Plasma Haloperidol Exist?: Preliminary Chinese Data — *Steven G. Potkin, Yucun Shen, Dongfeng Zhou, Herbert Pardes, Liang Shu, Bruce Phelps, and Russell Poland*

62 Plasma Haloperidol Levels and Clinical Response: Confounding Variables — *Michael L. Mavroidis, David L. Garver, Donald R. Kanter, and Jack Hirschowitz*

66 Absence of Relationship of Serum Haloperidol Concentration and Clinical Response in Chronic Schizophrenia: A Fixed-Dose Study — *Llewellyn B. Bigelow, Darrell G. Kirch, Tammy Braum, Esa R. Korpi, Richard L. Wagner, Steven Zalcman, and Richard Jed Wyatt*

69 Plasma Levels of Haloperidol and Clinical Response — *Theodore Van Putten, Stephen R. Marder, Philip R.A. May, Russell E. Poland, and Ronald P. O'Brien*

Free Communications—Session A —

73 An Early Phase II Clinical Trial with Follow-up of Tomoxetine (LY139603) in the Treatment of Newly Admitted Depressed Patients — *G. Chouinard, L. Annable, J. Bradwejn, A. Labonte, B. Jones, P. Mercier, and M.-C. Belanger*

77 The Dexamethasone Suppression and TRH Stimulation Tests in the Initial Phase of Depression Treatment — *Javier I. Escobar, Angelos Halaris, Lewis Baxter, Glenn Schwarcz, Mark Thompson, Margo Lea Hurwicz, MaryAnn Hill, Melinda Young, Kathleen Daugherty, and April Clemens*

81 A Prospective Study of Lithium-Induced Nephropathy: Preliminary Results — *Jay D. Amsterdam, Diane Jorkasky, Larry Potter, and Malcolm Cox*

85 A Controlled Study of the Effects of Antidepressants on Sexual Function — *Wilma M. Harrison, Jonathan Stewart, Anke A. Ehrhardt, Judith Rabkin, Patrick McGrath, Michael Liebowitz, and Frederic M. Quitkin*

89 Effects of Naloxone on Cognitive Deficits Following Electroconvulsive Therapy — *Henry A. Nasrallah, Nils Varney, Jeffrey A. Coffman, John Bayless, and Suzanne Chapman*

91 Efficacy and Withdrawal of Two Potent Benzodiazepines: Bromazepam and Lorazepam — *R. Fontaine, L. Annable, P. Beaudry, P. Mercier, and G. Chouinard*

93 Psychomotor Performance Following the Long-Term Use of Benzodiazepines — *Irwin Lucki, Karl Rickels, and Andrew M. Geller*

97 Brotizolam in the Treatment of Insomnia — *Roberto A. Dominguez, Burton J. Goldstein, Alan F. Jacobson, and Richard M. Steinbook*

101 A Clinical Rating Scale for Symptoms of Psychosis in Alzheimer's Disease — *Barry Reisberg and Steven H. Ferris*

Free Communications—Session B —

105 FDA's Monitoring of Clinical Trials — *Walter Sloboda and Carolanne Currier*

107 Attrition and its Consequence in a Clinical Trial of Placebo, Imipramine, and Phenelzine — *Jeffrey S. Markowitz, Judith G. Rabkin, Patrick J. McGrath, Jonathan Stewart, and Frederic M. Quitkin*

110 Psychopharmacologic Treatment and Informed Consent: Empirical Research — *Barbara Stanley, Michael Stanley, Judith Stein, Lisa Guido, and Roxanna-Pentland Transit*

114 A Trial of Adjunctive Imipramine in Post-psychotic Depression — *Samuel G. Siris, Arthur Rifkin, Gerard T. Reardon, Seshagiri R. Dotti, Patricia Foster, and Elaine Casey*

117 Experience with a Drug-Free Month in Schizophrenic Outpatients — *Douglas W. Heinrichs and William T. Carpenter, Jr.*

120 A Comparison of the Clinical Effects of Bromperidol, a New Butyrophenone Derivative, and Haloperidol on Schizophrenia Using a Double-Blind Technique — *Hitoshi Itoh*

123 Methylphenidate Challenge Tests and Course of Schizophrenia — *Jeffrey A. Lieberman, John M. Kane, Dominick Gadaletta, Jorge Ramos-Lorenzi, Kenneth Bergmann, James Wegner,and Hana Novacenko*

130 Tardive Dyskinesia and Depressive Symptoms in Schizophrenics — *Mary Ann Richardson, Raymond Pass, Zachary Bregman, and Thomas J. Craig*

136 The Prevalence of Tardive Dyskinesia — *John M. Kane, Margaret Woerner, Jeffrey Lieberman, Paul Weinhold, William Florio, Morton Rubinstein, John Rotrosen, Janos Kurucz, Sukdeb Mukherjee, Kenneth Bergmann, and Nina R. Schooler*

140 Neuroleptic-Related Dyskinesias in Autistic Children: A Prospective Study — *Richard Perry, Magda Campbell, Wayne H. Green, Arthur M. Small, Maria L. Die Trill, Karen Meiselas, Robert R. Golden, and Stephen I. Deutsch*

144 Desipramine in the Treatment of Attention Deficit Disorder in Adolescents — *David R. Gastfriend, Joseph Biederman, and Michael S. Jellinek*

146 Amino Acid Precursors for the Treatment of Attention Deficit Disorder, Residual Type — *David R. Wood, Frederick W. Reimherr, and Paul H. Wender*

150 A Controlled Trial of Clomipramine in Childhood Obsessive-Compulsive Disorder — *Martine F. Flament, Judith L. Rapoport, Carol J. Berg, and Clinton Kilts*

153 **Cumulative Index—Psychopharmacology Bulletin—1984—**

Contents Index

Authors Index

B-1 **Psychopharmacology—A Recurring Bibliography—**

Vol. 21, No. 2, 1985

167 **Introduction**—*Natalie Reatig*

Pharmacotherapy for ADD-H Adolescents Workshop —

169 Follow-up Studies on Outcome of Hyperactive Children — *Gabrielle Weiss*

178 Adolescent Outcome of Hyperactive Children Treated with Stimulants in Childhood: A Review — *Lily Hechtman*

192 Pharmacotherapy in ADD Adolescents with Special Attention to Multimodality Treatments — *Ronald T. Brown, Kathi A. Borden, and Stephen R. Clingerman*

212 Prevalence of Medication Treatment for Hyperactive Adolescents — *Daniel J. Safer and John M. Krager*

216 A Review of Studies of Drug Treatment Efficacy with Attention Deficit Disorder with Hyperactivity in Adolescents — *Christopher K. Varley*

222 Pharmacological Treatment of Attention Deficit Disorder, Residual Type (ADDRT, "Minimal Brain Dysfunction," "Hyperactivity" in Adults) — *Paul H. Wender, David R. Wood, and Fred W. Reimherr*

232 New Drug Trials in Attention Deficit Disorder — *Judith L. Rapoport, Alan Zametkin, Maureen Donnelly, and Deborah Ismond*

237 Diagnosing ADD-H in Adolescents — *Rachel Gittelman and Salvatore Mannuzza*

243 Issues in the Study of Adolescent ADD-Hyperactivity — *C. Keith Conners*

A Summary of the Workshop Proceedings

251 Pharmacotherapy of ADD in Adolescents: What Do We Know, Where Should We Go, How Should We Do It? — *Dennis P. Cantwell*

Pharmacotherapy and Mental Retardation Workshop —

258 Emotional Problems in the Mentally Retarded: The Need for Assessment and Treatment — *Johnny L. Matson*

262 Issues in Pharmacology with the Mentally Retarded — *Susan Mouchka*

268 Psychoactive Drug Use in Public and Community Residential Facilities for Mentally Retarded Persons — *James Intagliata and Chris Rinck*

279 A National Study of Prescribed Drugs in Institutions and Community Residential Facilities for Mentally Retarded People — *Bradley K. Hill, Elizabeth A. Balow, and Robert H. Bruininks*

285 Establishing Socially Validated Drug Research in Community Settings — *Martin Agran and James E. Martin*

291 Prevalence and Efficacy of Stimulant Drug Use with Mentally Retarded Children and Youth — *Kenneth D. Gadow*

304 Psychopharmacology in the Mentally Retarded and a Few Related Issues — *C. Thomas Gualtieri and J.M. Keppel*

310 Behavioral Interactions Induced by Chronic Neuroleptic Therapy in Persons with Mental Retardation — *Stephen R. Schroeder and C. Thomas Gualtieri*

316 Diagnosis and Pharmacotherapy of Schizophrenia in the Retarded — *Frank J. Menolascino, Stephen L. Ruedrich, Charles J. Golden, Ph.D., and James E. Wilson, Pharm.D.*

Workshop Summary —

323 Issues and Future Research Directions of Pharmacotherapy in Mental Retardation — *Stephen R. Schroeder*

Brief Report —

327 An Applied Tardive Dyskinesia Monitoring System (ATDMS) — *John E. Kalachnik*

329 Pharmacotherapy and Mental Retardation/Developmental Disability: A Bibliography — *Natalie Reatig*

Adverse Drug Reaction —

334 "Time-less" Risks (A Hazard of Risk Assessment: The Example of Seizure and Antidepressants — *Paul Leber*

Articles —

339 ACTeRS Useful in Screening Learning Disables from Attention Deficit Disordered (ADD-H) Children — *Rina K. Ullmann*

345 Carbamazepine in Tardive Dyskinesia — *András Perényi and Dániel Sztaniszláv*

347 Biochemistry of Alzheimer's Disease — *Ira R. Berry and Lionel Borkan*

B-1 **Psychopharmacology— A Recurring Bibliography—**

357 **In the Pipeline—***Barry Blackwell*

23rd Meeting of the ACNP—1984— Abridged Proceedings —

New Approaches to the Genetics of Psychiatric Disorders —

361 Additional Cerebrospinal Fluid Proteins Found in Schizophrenia and Creutzfeldt-Jakob Disease — *Michael G. Harrington and Carl R. Merril*

365 Cerebral Ventricular Enlargement as a Possible Genetic Marker for Schizophrenia — *Lynn E. DeLisi, Lynn R. Goldin, Joel R. Hamovit, M. Elizabeth Maxwell, David Kurtz, John I. Nurnberger, and Elliot S. Gershon*

Bright Light, Melatonin, and Biological Rhythms: Implications for the Affective Disorders —

368 Treating Phase Typed Chronobiologic Sleep and Mood Disorders Using Appropriately Timed Bright Artificial Light — *Alfred J. Lewy, Robert L. Sack, and Clifford M. Singer*

New Strategies in the Therapy of Affective Disorders —

373 The Serotonin/Norepinephrine-Linked Beta-Adrenoceptor System and the Mode of Action of Antidepressant — *Elaine Sanders-Bush, P. Jeffrey Conn, and Fridolin Sulser*

379 Serotonergic Modulation of Cortical Rat Noradrenergic System in the Mechanism of Action of Antidepressant Drugs — *N. Brunello, I. Mocchetti, A. Volterra, V. Cuomo, and G. Racagni*

385 The GABA Hypothesis of Depression and Antidepressant Drug Action — *G. Bartholini, K.G. Lloyd, B. Scatton, B. Zivkovic, and P.L. Morselli*

Do We Need CSF Studies in Clinical Pharmacology? —

389 CSF, Plasma, and Urine: What Do Concomitant Measurements of Norepinephrine and Its Metabolites Mean? — *Markku Linnoila, Elizabeth A. Lane, Sally Guthrie, Ioanis Parashos, Matthew Rudorfer, and William Z. Potter*

396 Can CSF Measures Distinguish Among Schizophrenia, Depression, Movement Disorders, and Dementia? — *Stephen M. Stahl*

400 Clinical Implications of Neurochemical Mechanisms of Appetite Regulation—Neuropeptidergic Regulation of Feeding — *John E. Morley, Blake A. Gosnell, Dean D. Krahn, James E. Mitchell, and Allen S. Levine*

406 Peptide-Catecholamine Interaction: Feeding and Satiety — *Robert D. Myers*

412 Brain Neurotransmitters and Appetite Regulation — *Sarah F. Leibowitz*

419 Disturbances of Norepinephrine Metabolism and α-2 Adrenergic Receptor Activity in Anorexia Nervosa: Relationship to Nutritional State — *Walter H. Kaye, Harry E. Gwirtsman, C. Raymond Lake, Larry J. Siever, David C. Jimerson, Michael H. Ebert, and Dennis L. Murphy*

Pharmacologic Model of Anxiety in Man —

424 Isoproterenol-Induced Anxiety States — *Robert Pohl, John Rainey, Aurelio Ortiz, Richard Balon, Heminder Singh, and Richard Berchou*

428 The Lactate Infusion Model — *Jack M. Gorman, Donald Dillon, Abby J. Fyer, Michael R. Liebowitz, and Donald F. Klein*

434 Panic Anxiety and Lactate Metabolism — *John M. Rainey, Jr., Charles E. Frohman, Ken Warner, Stewart Bates, Robert B. Pohl, and Vikram Yeragani*

Biological and Behavioral Reactions to Stress —

438 Regulation of Adrenocorticotropin Release From the Anterior Pituitary — *Terry Reisine*

443 Melancholia in Rodents: Neurobiology and Pharmacology — *Fritz A. Henn, Joel Johnson, Emmeline Edwards, and David Anderson*

447 Neurochemical Basis of Stress-Induced Depression — *Jay M. Weiss and Prudence Goodman Simson*

458 Serotonin-Behavior Interactions in Vervet Monkeys — *Michael T. McGuire and Michael J. Raleigh*

Enkephalin-Endorphins: Emotional Stress, Depression, and the Immune System —

464 Selectivity of Opioid Agonists and Antagonists for the Various Opioid Receptor Types — *A.E. Takemori and P.S. Portoghese*

466 Opioid Peptides in the Adrenal Pituitary Axis — *Christopher J. Evans, Elizabeth Erdelyi, and Jack D. Barchas*

472 The Alpha MSH-Specific and Arcuate Pro-Opiomelanocortin Neuronal Systems of the Hypothalamus: Observations on Their Connectivity and Response to Colchicine Treatment — *Karl M. Knigge, Diane T. Piekut, and Shirley A. Joseph*

476 Depression, Hypothalamic-Pituitary-Adrenocortical Activity, and Lymphocyte Function — *Ziad Kronfol and J. Daniel House*

479 Involvement of Opioid Peptides in the Analgesic, Immunosuppresive, and Tumor-Enhancing Effects of Stress — *James W. Lewis, Yehuda Shavit, Gregory W. Terman, Linda R. Nelson, Fredricka C. Martin, Robert Peter Gale, and John C. Liebeskind*

485 Endorphins, Immune Function, and Cancer — *John E. Morley, Neil Kay, John Allen, Timothy Moon, and Charles J. Billington*

489 The Ying-Yang Hypothesis of Opioid Peptide Immunomodulation — *Nicholas P. Plotnikoff*

Psychobiological Markers for Schizophrenia: State of the Art and Future Perspectives —

490 Introduction and Summary — *Joseph Zubin*

497 Are There State-Dependent Markers in Schizophrenia? — *Daniel P. van Kammen, Jules P. Rosen, Jeffrey Peters, Robert Fields, and Welmoet B. van Kammen*

503 Vulnerability to Schizophrenia: Childhood Indicators Predict Adult Outcome — *Ernest Hartmann, Walter Mitchell, Patricia Brune, and Daniel Greenwald*

509 Distractibility as a Marker of Vulnerability to Schizophrenia — *Bonnie Spring*

513 Neurophysiological Aspects of Information Processing in Schizophrenia — *Stuart R. Steinhauer*

518 Sensory and Perceptual Behavioral Markers of Schizophrenia — *Mitchell L. Kietzman*

Neuropeptides Modulating Dopaminergic Function: New Horizons for the Dopamine Hypothesis of Schizophrenia —

523 Cholecystokinin Potentiates Dopamine-Mediated Behaviors in the Nucleus Accumbens, a Site of CCK-DA Co-Existence — *Jacqueline N. Crawley*

Toxic Effects of Psychomotor Stimulants —

528 Persistent Effects of Amphetamine, *p*-Chloroamphetamine, and Related Compounds on Central Dopamine and Serotonin Neurons in Rodents — *Ray W. Fuller*

Alternate Treatment Strategies in Schizophrenia: Focus on the Deficit State —

533 High-Dose Versus Low-Dose Strategies in the Treatment of Schizophrenia — *John M. Kane, Arthur Rifkin, Margaret Woerner, Gerald Reardon, Dolores Kreisman, Richard Blumenthal, and Michael Borenstein*

Panic Disorder and Major Depression: Epidemiology, Family Studies, Biologic, and Treatment Response Similarities —

538 The Epidemiology of Anxiety Disorders: A Highlight of Recent Evidence — *Myrna M. Weissman, Philip J. Leaf, Charles E. Holzer III, and Kathleen R. Merikangas*

543 Major Depression and Panic Disorder: A Family Study Perspective — *James F. Leckman, Myrna M. Weissman, Kathleen R. Merikangas, David L. Pauls, Brigitte A. Prusoff, and Kenneth K. Kidd*

546 Neuroendocrine Abnormalities in Panic Disorder — *Peter P. Roy-Byrne, Thomas W. Uhde, Philip W. Gold, David R. Rubinow, and Robert M. Post*

551 Panic Disorder and Major Depression: Biological Relationships — *Peter P. Roy-Byrne and Thomas W. Uhde*

555 Lactate Infusion in Patients With Depression and Anxiety — *Patrick J. McGrath, Jonathan W. Stewart, Wilma Harrison, Frederic M. Quitkin and Judith Rabkin*

558 Effect of Panic Attacks on the Treatment of Atypical Depressives — *Michael R. Liebowitz, Frederic M. Quitkin, Jonathan W. Stewart, Patrick J. McGrath, Wilma Harrison, Judith Rabkin, Elaine Tricamo, Jeffrey S. Markowitz, and Donald F. Klein*

562 Panic Attacks in Outpatients With Depression: Response to Antidepressant Treatment — *Donald S. Robinson, Allen Kayser, John Corcella, Desmonde Laux, Kevin Yingling, and Diantha Howard*

Hormones and Depression—An Update —

568 Hormones and Depression—Conceptual Transitions — *Uriel Halbriech*

Peripheral Models for the Study of Neurotransmitter Receptors in Man —

573 Yohimbine and Clonidine Recognize Different States of Adrenergic Receptors on Human Platelets: Reconsideration of Studies on Platelet Alpha-2 Receptors in Depressive Illness — *John E. Piletz and Angelos Halaris*

579 Nocturnal Serum Melatonin in Major Depressive Disorder Before and After Desmethylimipramine Treatment — *Richard P. Brown, Stanley Caroff, James J. Kocsis, Jay Amsterdam, Andrew Winokur, Peter Stokes, and Alan Frazer*

Patterns of Cognitive Effects of Somatic Therapies —

582 Effect of Neuroleptic Treatments on Attention, Information Processing, and Thought Disorder — *Herbert E. Spohn, Lolafaye Coyne, Fred Mittleman, Jan Larson, Mary Johnston, Judy Spray, and Kenneth Hayes*

Brain Imaging in Psychiatry: New Developments —

588 Magnetic Resonance Imaging Studies of Schizophrenia — *Robert C. Smith, Richard Baumgartner, Marcos Calderon, Awatif Affas, G.K. Ravichandran, and I. Donald Peters*

595 Dopamine Receptor Binding of C-11-3-N-Methylspiperone in the Caudate in Schizophrenia and Bipolar Disorder: A Preliminary Report — *Dean F. Wong, Henry N. Wagner, Jr., Godfrey Pearlson, Robert F. Dannals, Jonathan M. Links, Hayden Ravert, Alan Wilson, Sudhir Suneja, Eythor Bjorvvinssen, Michael J. Kuhar, and Larry Tune*

Studies of Peripheral Monoamine Receptors in Affective Illness —

599 Platelet Alpha-Adrenergic Receptor Function in Affective Disorders and Schizophrenia — *Marian S. Kafka, Larry J. Siever, John I. Nurnberger, Thomas W. Uhde, Steven Targum, Dermot M.J. Cooper, Daniel P. van Kammen, and Nancy S. Tokola*

603 Studies of Beta-Adrenergic Receptors in Leukocytes of Patients With Affective Illness and Effects of Antidepressant Drugs — *Ghanshyam N. Pandey, Philip Janicak, and John M. Davis*

Social Phobias: Diagnosis, Pathophysiology, and Treatment —

610 Psychopharmacological Treatment of Social Phobia — *Michael R. Liebowitz, Jack Gorman, Abby Fyer, Raphael Campeas, Andrew Levin, Sharon Davies, and Donald F. Klein*

615 Behavioral Treatment of Social Phobia — *Isaac Marks*

Improvement With Antidepressants: Timing and Relationship to Biochemical Events —

619 Delayed Biochemical Changes Following Antidepressant Treatment — *Michael F. Sugrue*

Pharmacogenetics: A Preclinical and Clinical Perspective —

623 Molecular Basis of Drug-Resistance Mutations in C. Elegans — *James B. Rand and Richard L. Russell*

631 Biophysical Alterations in Cell Membranes Associated With Psychotherapeutic Drug Exposure, Psychopathology, and Aging — *George S. Zubenko and Bruce M. Cohen*

641 Relevance of Genetic Variability to Clinical Psychopharmacology — *Bruce M. Cohen and George S. Zubenko*

Noradrenergic Mechanisms and the Drug Withdrawal Syndrome —

651 Adrenergic Agonist Therapy in Alcohol Withdrawal States in Man — *Paul Cushman, Jr., William Lerner, and Michael Cramer*

Targeting the Central Nervous System: New Drug Delivery Technologies for Psychotropic Agents —

657 Chemical Approaches to Drug Delivery to the Central Nervous System — *Colin R. Gardner*

663 Peripheral Models for the Study of Neurotransmitter Receptors in Man — *Stephen M. Stahl*

672 Implantable Narcotic Antagonists: A Possible New Treatment for Narcotic Addiction — *C. Nora Chiang, Akira Kishimoto, Gene Barnett, and Leo E. Hollister*

Pharmacologic Challenge Strategies in Alzheimer's Disease: Basic and Clinical Issues —

676 Cognitive and Behavioral Sensitivity to Scopolamine in Alzheimer Patients and Controls — *Trey Sunderland, Pierre Tariot, Edward A. Mueller, Dennis L. Murphy, Herbert Weingartner, and Robert M. Cohen*

680 Low- and High-Dose Naloxone in Dementia of the Alzheimer Type — *Pierre N. Tariot, Trey Sunderland, Herbert Weingartner, Dennis L. Murphy, Martin R. Cohen, and Robert M. Cohen*

Poster Session —Editor's Choice

683 The Window of Vulnerability in the Ontogeny of the Dopamine Receptor — *Jeanette C. Miller and Arnold J. Friedhoff*

686 Depression in Adults With a History of Prenatal DES Exposure — *Heino F.L. Meyer-Bahlburg, Anke A. Ehrhardt, Jean Endicott, Norma P. Veridiano, E. Douglas Whitehead, and Felix H. Vann*

690 Cortisol and Prolactin Responses to Dexamethasone in Major Depression, Chronic Pain, and Chronic Pain With Major Depression — *Joseph H. Atkinson, Jr., Edwin F. Kremer, S. Craig Risch, and David S. Janowsky*

694 Evidence for a Daily Rhythm of Plasma HVA in Normal Controls But Not in Schizophrenic Patients — *Allen R. Doran, David Pickar, Rodrigo Labarca, Patrice Douillet, Owen M. Wolkowitz, John W. Thomas, Alex. Roy, and Steven M. Paul*

698 Imipramine for Treatment of Chronic Depression — *James H. Kocsis, Allen Frances, J. John Mann, John Sweeney, Carlyle Voss, Barbara Mason, and Richard P. Brown*

701 A New Postsynaptic Serotonin Receptor Agonist Suitable for Studies in Humans — *Edward A. Mueller, Dennis L. Murphy, Trey Sunderland, and Julia Jones*

705 Addition of Estrogen to Imipramine in Female-Resistant Depressives — *Joseph Zohar, Baruch Shapira, Gerald Oppenheim, Frank J. Ayd, and Robert H. Belmaker*

707 Lidocaine Kindling is Accompanied by an Increase in Apomorphine Stereotype and Mesolimbic Dopamine D Receptor Density — *John G. Csernansky, Cynthia A. Csernasky, Seth A. Glick, and Leo E. Hollister*

Vol. 21, No. 4, 1985

RATING SCALES AND ASSESSMENT INSTRUMENTS FOR USE IN PEDIATRIC PSYCHOPHARMACOLOGY RESEARCH

713 **From the Editor's Desk —**

714 **Introduction to This Issue —** ***Judith L. Rapoport and C. Keith Conners***

Demographic Data and Family History —

719 ***Documentation of Demographic Data and Family History of Psychiatric Illness — *Magda Campbell and Michael Palij***

722 Demographic Template — *Magda Campbell*

728 ROS (Research Obstetrical Scale) — *Arnold J. Sameroff, R. Seifer, and M. Zax*

731 **Prior Medication Record — *NIMH***

Psychiatric Interviews —

737 ***Psychiatric Interviews Suitable for Use in Research With Children and Adolescents — *Helen Orvaschel***

747 CGAS (A Children's Global Assessment Scale) — *David Shaffer, Madelyn S. Gould, James Brasic, Paul Ambrosini, Prudence Fisher, Hector Bird, and Satwant Aluwahlia*

749 Rutter-Graham Psychiatric Interview for Children — *Michael Rutter and Philip Graham*

753 Children's Psychiatric Rating Scale (Scoring) — *Barbara Fish*

765 Children's Psychiatric Rating Scale — *NIMH*

Neurological Examinations —

773 Revised Physical and Neurological Examination for Subtle Signs — *Martha Bridge Denckla*

780 Scoring for Revised Physical and Neurological Examination for Subtle Signs — *Martha Bridge Denckla*

793 PANESS (Physical and Neurological Examination for Soft Signs) — *NIMH*

Diagnosis —

803 *DSM-III-R Pediatric Psychopharmacology — *Judity L. Rapoport*

Rating Scales and Checklists for Psychopharmacologic Trials —

809 ***Rating Scales and Checklists for Child Psychopharmacology — *C. Keith Conners and Russell A. Barkley***

816 Parent Symptom Questionnaire — *C. Keith Conners*

823 Teacher Questionnaire — *C. Keith Conners*

828 Teacher Questionnaire (Follow-up School Report) — *C. Keith Conners*

832 IGRS (Inpatient Global Rating Scale) — *C. Keith Conners*

835 Child Behavior Rating Form — *Craig Edelbrock*

839 CGI (Clinical Global Impression) Scale — *NIMH*

845 The Aberrant Behavior Checklist — *Michael G. Aman, Nirbhay N. Singh, Alistair W. Stewart, and Carolyn J. Field*

851 GSS (General Scoring Sheet)—Basic — *NIMH*

Measures of Social Skills —

855 ***Development of a Rating Scale to Measure Social Skills in Children: The Matson Evaluation of Social Skills With Youngsters (MESSY) — *Johnny L. Matson, Anthony F. Rotatori, and William J. Helsel***

861 Matson Evaluation of Social Skills With Youngsters (MESSY): (Teacher Rating Form) — *Johnny L. Matson and Karen Esveldt-Dawson*

865 Matson Evaluation of Social Skills With Youngsters (MESSY): (Self-Rating Form) — *Johnny L. Matson and Karen Esveldt-Dawson*

869 Social Interaction Observation Code — *Howard Abikoff, Diane Martin, and Rachel Gittelman*

Performance Measures —

****PLEASE NOTE:** All references in this paper are presented in a single reference section to be found on pages 1111-1124.*

877 ***Assessing Drug Effects on Academic Performance — _Kenneth D. Gadow and H. Lee Swanson_**

887 ***Measures of Cognitive Functioning Appropriate for Use in Pediatric Psychopharmacology Research Studies — _James M. Swanson_**

891 ***The Computerized Continuous Performance Test — _C. Keith Conners_**

893 ***Measuring Activity Level in Children — _C. Keith Conners_**

898 Hillside Behavior Rating Scale (Behavior During Testing) — *Rachel Gittelman and Donald Klein*

901 Classroom Observation Code: A Modification of the Stony Brook Code — *Howard Abikoff and Rachell Gittelman*

Ratings for Attention Deficit Disorders —

913 ***Some Thoughts on the Diagnosis of ADD-H in Adolescents — _Rafael Klorman_**

915 **Introduction to the Use of ACTeRS — _Rina K. Ullmann, Esther K. Sleator, and Robert L. Sprague_**

917 ACTeRS (ADD-H Comprehensive Teacher's Rating Scale) —

921 ADD-H Adolescent Self-Report Scale — *C. Keith Conners and Karen C. Wells*

923 Parent Questionnaire of Teenage Behavior (Modified Conners) — *Rachel Gittelman*

925 Self-Evaluation (Teenager's) Self-Report — *Rachel Gittelman*

927 AQCC (Adult Questionnaire-Childhood Characteristics) Scale — *Paul H. Wender*

929 **Bibliography on Rating and Assessment Instruments for Attention Deficit Disorder (ADD) — _Natalie Reatig_**

Ratings for Anxiety Disorders —

933 Ratings for Anxiety Disorders — *Rachel Gittelman*

934 Children's Manifest Anxiety Scale: Parent Ratings — *Rachel Gittelman*

936 Children's Manifest Anxiety Scale: Child Ratings — *Rachel Gittelman*

939 Parent's Questionnaire (Modified Conners): Anxiety and Mood Items Added — *Rachel Gittelman*

945 Teacher Rating Scale ((Modified Conners): Anxiety and Mood Items Added — *Rachel Gittelman*

Ratings for Childhood Depression —

951 ***Scales of Potential Use in the Psychopharmacologic Treatment of Depressed Children and Adolescents — _Theodore A. Petti_**

957 DMS-III Symptom Checklist for Major Depressive Disorders — *Javad Kashani, Donald McKnew, and Leon Cytryn*

959 BID (The Bellevue Index of Depression) — *Theodore A. Petti*

969 PNID (Peer Nomination Index of Depression — *M. M. Lefkowitz and E. Tesing*

972 SADLI (School Age Depression Listed Inventory) — *Theodore A. Petti*

976 Interview for the SADLI — *Theodore A. Petti*

979 Children's Depression Rating Scale-Revised — *Elva O. Poznanski*

991 ISC (The Interview Schedule for Children) — *Maria Kovacs*

995 CDI (The Children's Depression Inventory) — *Maria Kovacs*

Ratings for Eating Disorders —

1001 ***Rating Scales in the Eating Disorders — _Katherine A. Halmi_**

****PLEASE NOTE:* All references in this paper are presented in a single reference section to be found on pages 1111-1124.*

1004 Anorexic Behavior Scale — *Peter D. Slade*

1005 Anorectic Attitude Questionnaire — *Solomon C. Goldberg, Katherine A. Halmi, and Elke D. Eckert*

1008 Eating Attitudes Test — *David M. Garner and Paul E. Garfinkel*

1009 Eating Disorder Inventory — *David M. Garner, M. P. Olmsted, and J. Polivy*

1011 Binge Scale Questionnaire — *Raymond C. Hawkins and Pamelia F. Clement*

1013 Binge-Eating Questionnaire — *Katherine A. Halmi, James R. Falk, and Estelle Schwartz*

1017 Bulimia Interview Form — *Timothy Walsh and Madeline Gladis*

1025 Eating Disorders Questionnaire — *James E. Mitchell*

Ratings for Autism —

1047 ***Behavioral and Cognitive Measures Used in Psychopharmacological Studies of Infantile Autism — *Magda Campbell and Michael Paliz***

1053 CARS (Childhood Autism Rating Scale) — *E. Schopler, R. J. Reichler, and B. R. Renner*

Ratings for Obsessive-Compulsive Disorders —

1057 The Leyton Obsessional Inventory-Child Version — *Carol J. Berg, Judith L. Rapoport, and Martine Flament*

Rating for Adverse Effects —

1063 ***Measurement of Side Effects Including Tardive Dyskinesia — *Magda Campbell***

1067 DOTES (Dosage Record and Treatment Emergent Symptom Scale) — *NIMH*

1069 TESS (Treatment Emergent Symptoms Scale—Write-In) — *NIMH*

1073 STESS (Subjective Treatment Emergent Symptoms Scale) — *NIMH*

1077 AIMS (Abnormal Involuntary Movement Scale) — *NIMH*

1081 Protocol for Rating Drug-Related AIMS, Stereotypies, and CPRS Assessments — *Magda Campbell*

1082 Timed Stereotypies Rating Scale — *Magda Campbell*

1085 **Laboratory Tests for Drug Studies — *Judith L. Rapoport***

Measures of Medication Compliance —

1089 *Measurement of Compliance — *Esther K. Sleator*

Grant Support and Ethical Issues —

1097 The Grant Support Program of the Pharmacologic and Somatic Treatment Research Branch — *Natalie Reatig*

1100 DHHS Internal Policies for Reviewing Protections to Human Subjects in Research — *Natalie Reatig*

1105 Ethical Issues in Research With Children: A Bibliography — *Natalie Reatig*

1111 **References for All Starred * Papers —**

***PLEASE NOTE:** *All references in this paper are presented in a single reference section to be found on pages 1111-1125.*

B. Author Index

Abikoff, Howard
  Vol. 21, No. 4, 1985, pp. 869, 901
Affas, Awatif
  Vol. 21, No. 3, 1985, p. 588
Agran, Martin
  Vol. 21, No. 2, 1985, p. 285
Alberts, Lisa
  Vol. 21, No. 1, 1985, p. 37
Allen, John
  Vol. 21, No. 3, 1985, p. 485
Aluwahlia, Satwant
  Vol. 21, No. 4, 1985, pp. 747
Aman, Michael G.
  Vol. 21, No. 4, 1985, pp. 845
Ambrosini, Paul
  Vol. 21, No. 4, 1985, pp. 747
Amsterdam, Jay D.
  Vol. 21, No. 1, 1985, p. 81
  Vol. 21, No. 3, 1985, p. 579
Anderson, David
  Vol. 21, No. 3, 1985, p. 443
Annable, L.
  Vol. 21, No. 1, 1985, pp. 73, 91
Atkinson, Joseph H., Jr.
  Vol. 21, No. 3, 1985, p. 690
Ayd, Frank J.
  Vol. 21, No. 3, 1985, p. 705

Balon, Richard
  Vol. 21, No. 3, 1985, p. 424
Balow, Elizabeth A.
  Vol. 21, No. 2, 1985, p. 279
Barchas, Jack D.
  Vol. 21, No. 3, 1985, p. 466
Barkley, Russell A.
  Vol. 21, No. 4, 1985, pp. 809
Barnett, Gene
  Vol. 21, No. 3, 1985, p. 672
Bartholini, G.
  Vol. 21, No. 3, 1985, p. 385
Baumgartner, Richard
  Vol. 21, No. 1, 1985, p. 52
  Vol. 21, No. 3, 1985, p. 588
Baxter, Lewis
  Vol. 21, No. 1, 1985, p. 77
Bayless, John
  Vol. 21, No. 1, 1985, p. 89
Beaudry, P.
  Vol. 21, No. 1, 1985, p. 91
Belanger, M-C
  Vol. 21, No. 1, 1985, p. 73
Belmaker, Robert H.
  Vol. 21, No. 3, 1985, p. 705
Berchou, Richard
  Vol. 21, No. 3, 1985, p. 424
Berg, Carol J.
  Vol. 21, No. 1, 1985, p. 150
  Vol. 21, No. 4, 1985, pp. 1057
Bergmann, Kenneth
  Vol. 21, No. 1, 1985, pp. 123, 136
Berry, Ira R.
  Vol. 21, No. 2, 1985, p. 347
Biederman, Joseph
  Vol. 21, No. 1, 1985, p. 144
Bigelow, Llewellyn B.
  Vol. 21, No. 1, 1985, p. 66
Billington, Charles J.
  Vol. 21, No. 3, 1985, p. 485
Bird, Hector
  Vol. 21, No. 4, 1985, pp. 747
Bjorvvinssen, Eythor
  Vol. 21, No. 3, 1985, p. 595
Blackwell, Barry
  Vol. 21, No. 3, 1985, p. 357
Blumenthal, Richard
  Vol. 21, No. 3, 1985, p. 533
Borden, Kathi A.
  Vol. 21, No. 1, 1985, p. 28
  Vol. 21, No. 2, 1985, p. 192
Borenstein, Michael
  Vol. 21, No. 1, 1985, p. 23
  Vol. 21, No. 3, 1985, p. 533
Borkan, Lionel
  Vol. 21, No. 2, 1985, p. 347
Bradwejn, J.
  Vol. 21, No. 1, 1985, p. 73
Brasic, James
  Vol. 21, No. 4, 1985, pp. 747
Braun, Tammy
  Vol. 21, No. 1, 1985, p. 66
Bregman, Zachary
  Vol. 21, No. 1, 1985, p. 130
Brown, Richard P.
  Vol. 21, No. 3, 1985, pp. 698, 579
Brown, Ronald T.
  Vol. 21, No. 1, 1985, p. 28
  Vol. 21, No. 2, 1985, p. 192
Bruininks, Robert H.
  Vol. 21, No. 2, 1985, p. 279

Brune, Patricia
  Vol. 21, No. 3, 1985, p. 503
Brunello, N.
  Vol. 21, No. 3, 1985, p. 379
Burd, Alla
  Vol. 21, No. 1, 1985, p. 52

Campbell, Magda
  Vol. 21, No. 1, 1985, p. 140
  Vol. 21, No. 4, 1985, pp. 719, 722,1047, 1063, 1081–1082
Campeas, Raphael
  Vol. 21, No. 3, 1985, p. 610
Cantwell, Dennis P.
  Vol. 21, No. 2, 1985, p. 251
Caroff, Stanley
  Vol. 21, No. 3, 1985, p. 579
Carpenter, William T., Jr.
  Vol. 21, No. 1, 1985, p. 117
Casey, Elaine
  Vol. 21, No. 1, 1985, p. 114
Casper, Regina
  Vol. 21, No. 1, 1985, p. 48
Chang, Sidney S.
  Vol. 21, No. 1, 1985, p. 48
Chapman, Suzanne
  Vol. 21, No. 1, 1985, p 89
Chiang, C. Nora
  Vol. 21, No. 3, 1985, p. 672
Cho, Sung-Ran
  Vol. 21, No. 1, 1985, p. 18
Chouinard, G.
  Vol. 21, No. 1, 1985, pp. 73-91
Clemens, April
  Vol. 21, No. 1, 1985, p. 77
Clement, Pamelia F.
  Vol. 21, No. 4, 1985, pp. 1011
Clingerman, Stephen R.
  Vol. 21, No. 1, 1985, p. 28
  Vol. 21, No. 2, 1985, p. 192
Coffman, Jeffrey A.
  Vol. 21, No. 1, 1985, p. 89
Cohen, Bruce M.
  Vol. 21, No. 3, 1985, pp. 631, 641
Cohen, Robert M.
  Vol. 21, No. 3, 1985, p. 680
Conn, P. Jeffrey
  Vol. 21, No. 3, 1985, p. 373
Conners, C. Keith
  Vol. 21, No. 2, 1985, p. 243
  Vol. 21, No. 4, 1985, pp. 714, 809–832, 891, 893, 921
Cooper, Dermot M.J.
  Vol. 21, No. 3, 1985, p. 599
Corcella, John
  Vol. 21, No. 3, 1985, p. 562
Cox, Malcolm
  Vol. 21, No. 1, 1985, p. 81
Coyne, Lolafaye
  Vol. 21, No. 3, 1985, p. 582
Craig, Thomas J.
  Vol. 21, No. 1, 1985, p. 130
Cramer, Michael
  Vol. 21, No. 3, 1985, p. 651
Crawley, Jacqueline N.
  Vol. 21, No. 3, 1985, p. 523
Csernansky, Cynthia A.
  Vol. 21, No. 3, 1985, p. 707
Csernansky, John G.
  Vol. 21, No. 3, 1985, p. 707
Cuomo, V.
  Vol. 21, No. 3, 1985, p. 379
Currier, Carol Anne
  Vol. 21, No. 1, 1985, p. 105
Cushman, Paul
  Vol. 21, No. 3, 1985, p. 651
Cytryn, Leon
  Vol. 21, No. 4, 1985, p. 957

Dannals, Robert F.
  Vol. 21, No. 3, 1985, p. 595
Daugherty, Kathleen
  Vol. 21, No. 1, 1985, p. 77
Davies, Sharon
  Vol. 21, No. 3, 1985, p. 610
Davis, John M.
  Vol. 21, No. 1, 1985, p. 48
  Vol. 21, No. 3, 1985, p. 603
Dekirmenjian, Haroutine
  Vol. 21, No. 1, 1985, p. 48
DeLisi, Lynn E.
  Vol. 21, No. 3, 1985, p. 365
Denckla, Martha Bridge
  Vol. 21, No. 4, 1985, pp. 773, 780
Deutsch, Stephen I.
  Vol. 21, No. 1, 1985, p. 140
Die Trill, Maria L.
  Vol. 21, No. 1, 1985, p. 140
Dillon, Donald
  Vol. 21, No. 3, 1985, p. 428
Doddi, Seshagiri R.
  Vol. 21, No. 1, 1985, p. 114
Dominguez, Roberto A.
  Vol. 21, No. 1, 1985, p. 97

Donnelly, Maureen
  Vol. 21, No. 2, 1985, p. 232
Douillet, Patrice
  Vol. 21, No. 3, 1985, p. 694
Dovan, Allen R.
  Vol. 21, No. 3, 1985, p. 694

Ebert, Michael H.
  Vol. 21, No. 3, 1985, p. 419
Eckert, Elke D.
  Vol. 21, No. 4, 1985, pp. 1005, 1025
Edelbrock, Craig
  Vol. 21, No. 4, 1985, p. 835
Edwards, Emmeline
  Vol. 21, No. 3, 1985, p. 443
Ehrhardt, Anke A.
  Vol. 21, No. 1, 1985, p. 85
  Vol. 21, No. 3, 1985, p. 686
Endicott, Jean
  Vol. 21, No. 3, 1985, p. 686
Erdelyi, Elizabeth
  Vol. 21, No. 3, 1985, p. 466
Ericksen, Stephen E.
  Vol. 21, No. 1, 1985, p. 48
Escobar, Javier I.
  Vol. 21, No. 1, 1985, p. 77
Esveldt-Dawson, Karen
  Vol. 21, No. 4, 1985, pp. 855–865
Evans, Christopher J.
  Vol. 21, No. 3, 1985, p. 466

Falk, James R.
  Vol. 21, No. 4, 1985, pp. 1013
Ferris, Steven H.
  Vol. 21, No. 1, 1985, p. 101
Field, Carolyn J.
  Vol. 21, No. 4, 1985, pp. 845
Fields, Robert
  Vol. 21, No. 3, 1985, p. 497
Fish, Barbara
  Vol. 21, No. 4, 1985, p. 753
Fisher, Prudence
  Vol. 21, No. 4, 1985, pp. 747
Flament, Martine F.
  Vol. 21, No. 1, 1985, p. 150
  Vol. 21, No. 4, 1985, pp. 1057
Florio, William
  Vol. 21, No. 1, 1985, p. 136
Fontaine, R.
  Vol. 21, No. 1, 1985, p. 91
Foster, Patricia
  Vol. 21, No. 1, 1985, p. 114
Frances, Allen
  Vol. 21, No. 3, 1985, p. 698
Frank, Ellen
  Vol. 21, No. 1, 1985, p. 37
Frazer, Alan
  Vol. 21, No. 3, 1985, p. 579
Freeman, Linda N.
  Vol. 21, No. 4, 1985, p. 979
Friedhoff, Arnold J.
  Vol. 21, No. 3, 1985, p. 683
Frohman, Charles E.
  Vol. 21, No. 3, 1985, p. 434
Fuller, Ray W.
  Vol. 21, No. 3, 1985, p. 528
Fryer, Abby J.
  Vol. 21, No. 3, 1985, pp. 428, 610

Gadaletta, Dominick
  Vol. 21, No. 1, 1985, p. 123
Gadow, Kenneth D.
  Vol. 21, No. 2, 1985, p. 291
  Vol. 21, No. 4, 1985, pp. 877
Gale, Robert Peter
  Vol. 21, No. 3, 1985, p. 479
Gardner, Colin R.
  Vol. 21, No. 3, 1985, p. 657
Garfinkel, Paul E.
  Vol. 21, No. 4, 1985, pp. 1008
Garner, David M.
  Vol. 21, No. 4, 1985, pp. 1008, 1009
Garver, David L.
  Vol. 21, No. 1, 1985, p. 62
Gastfriend, David R.
  Vol. 21, No. 1, 1985, p. 144
Geller, Andrew M.
  Vol. 21, No. 1, 1985, p. 93
Gerard T. Reardon
  Vol. 21, No. 1, 1985, p. 114
Gershon, Elliot S.
  Vol. 21, No. 3, 1985, p. 365
Gershon, Samuel
  Vol. 21, No. 1, 1985, p. 18
Gittelman, Rachel
  Vol. 21, No. 2, 1985, p. 237
  Vol. 21, No. 4, 1985, pp. 869, 898, 901, 923–925,
933–945
Gladis, Madeline
  Vol. 21, No. 4, 1985, pp. 1017
Glick, Seth A.
  Vol. 21, No. 3, 1985, p. 707

Gold, Philip W.
  Vol. 21, No. 3, 1985, p. 546
Goldberg, Solomon C.
  Vol. 21, No. 4, 1985, pp. 1005
Golden, Charles J.
  Vol. 21, No. 2, 1985, p. 316
Golden, Robert R.
  Vol. 21, No. 1, 1985, p. 140
Goldin, Lynn R.
  Vol. 21, No. 3, 1985, p. 365
Goldstein, Burton J.
  Vol. 21, No. 1, 1985, p. 97
Gorman, Jack M.
  Vol. 21, No. 3, 1985, pp. 428, 610
Gosnell, Blake A.
  Vol. 21, No. 3, 1985, p. 400
Gould, Madelyn S.
  Vol. 21, No. 4, 1985, pp. 747
Graham, Philip
  Vol. 21, No. 4, 1985, p. 749
Green, Wayne H.
  Vol. 21, No. 1, 1985, p. 140
Greenwald, Daniel
  Vol. 21, No. 3, 1985, p. 503
Gualtieri, C. Thomas
  Vol. 21, No. 2, 1985, pp. 304, 310
Guido, Lisa
  Vol. 21, No. 1, 1985, p. 110
Guthrie, Sally
  Vol. 21, No. 3, 1985, p. 389
Gwirtsman, Harry E.
  Vol. 21, No. 3, 1985, p. 419

Halaris, Angelos
  Vol. 21, No. 1, 1985, p. 77
  Vol. 21, No. 3, 1985, p. 573
Halbreich, Uriel
  Vol. 21, No. 3, 1985, p. 568
Halmi, Katherine A.
  Vol. 21, No. 4, 1985, pp. 1001, 1005, 1013
Hamovit, Joel R.
  Vol. 21, No. 3, 1985, p. 365
Harrington, Michael G.
  Vol. 21, No. 3, 1985, p. 361
Harrison, Wilma M.
  Vol. 21, No. 1, 1985, p. 85
  Vol. 21, No. 3, 1985, pp. 555, 558
Hartmann, Ernest
  Vol. 21, No. 3, 1985, p. 503
Hatsukami, Dorothy
  Vol. 21, No. 4, 1985, p. 1025
Hawkins, Raymond C.
  Vol. 21, No. 4, 1985, pp. 1011
Hayes, Kenneth
  Vol. 21, No. 3, 1985, p. 582
Hechtman, Lily
  Vol. 21, No. 2, 1985, p. 178
Heinrichs, Douglas W.
  Vol. 21, No. 1, 1985, p. 117
Helsel, William J.
  Vol. 21, No. 4, 1985, pp. 855
Henn, Fritz A.
  Vol. 21, No. 3, 1985, p. 443
Hill, Bradley K.
  Vol. 21, No. 2, 1985, p. 279
Hill, Maryann
  Vol. 21, No. 1, 1985, p. 77
Hirschowitz, Jack
  Vol. 21, No. 1, 1985, p. 62
Hollister, Leo E.
  Vol. 21, No. 3, 1985, pp. 672, 707
Holzer, Charles E., III
  Vol. 21, No. 3, 1985, p. 538
House, J. Daniel
  Vol. 21, No. 3, 1985, p. 476
Howard, Diantha
  Vol. 21, No. 3, 1985, p. 562
Hurt, Stephen
  Vol. 21, No. 1, 1985, p. 48
Hurwicz, Margo Lea
  Vol. 21, No. 1, 1985, p. 77

Intagliata, James
  Vol. 21, No. 2, 1985, p. 268
Ismond, Deborah
  Vol. 21, No. 2, 1985, p. 232
Itob, Hitoshi
  Vol. 21, No. 1, 1985, p. 120

Jacobson, Alan F.
  Vol. 21, No. 1, 1985, p. 97
Janicek, Philip
  Vol. 21, No. 3, 1985, p. 603
Janowsky, David S.
  Vol. 21, No. 3, 1985, p. 690
Javaid, Javaid I.
  Vol. 21, No. 1, 1985, p. 48
Jellinek, Michael S.
  Vol. 21, No. 1, 1985, p. 144
Jimerson, David C.
  Vol. 21, No. 3, 1985, p. 419

Johnson, Joel
Vol. 21, No. 3, 1985, p. 443
Johnston, Mary
Vol. 21, No. 3, 1985, p. 582
Jones, B.
Vol. 21, No. 1, 1985, p. 73
Jones, Julia
Vol. 21, No. 3, 1985, p. 701
Jorkasky, Diane
Vol. 21, No. 1, 1985, p. 81
Joseph, Shirley A.
Vol. 21, No. 3, 1985, p. 472

Kafka, Marian S.
Vol. 21, No. 3, 1985, p. 599
Kalachnik, John E.
Vol. 21, No. 2, 1985, p. 327
Kane, John M.
Vol. 21, No. 1, 1985, pp. 23, 123, 136
Vol. 21, No. 3, 1985, p. 533
Kanter, Donald R.
Vol. 21, No. 1, 1985, p. 62
Kashani, Javad
Vol. 21, No. 4, 1985, p. 957
Kay, Neil
Vol. 21, No. 3, 1985, p. 485
Kaye, Walter H.
Vol. 21, No. 3, 1985, p. 419
Kayser, Allen
Vol. 21, No. 3, 1985, p. 562
Keppell, J.M.
Vol. 21, No. 2, 1985, p. 304
Kidd, Kenneth K.
Vol. 21, No. 3, 1985, p. 543
Kietzman, Mitchell L.
Vol. 21, No. 3, 1985, p. 518
Kilts, Clinton
Vol. 21, No. 1, 1985, p. 150
Kirch, Darrell G.
Vol. 21, No. 1, 1985, p. 66
Kishimoto, Akira
Vol. 21, No. 3, 1985, p. 672
Klein, Donald F.
Vol. 21, No. 3, 1985, pp. 428, 558, 610
Vol. 21, No. 4, 1985, pp. 898
Klorman, Rafael
Vol. 21, No. 4, 1985, pp. 913
Knigge, Karl M.
Vol. 21, No. 3, 1985, p. 472
Kocsis, James H.
Vol. 21, No. 3, 1985, pp. 579, 698
Korpi, Esa R.
Vol. 21, No. 1, 1985, p. 66
Kovacs, Maria
Vol. 21, No. 4, 1985, pp. 995
Krager, John M.
Vol. 21, No. 2, 1985, p. 212
Krahn, Dean D.
Vol. 21, No. 3, 1985, p. 400
Kreisman, Dolores
Vol. 21, No. 3, 1985, p. 533
Kremer, Edwin F.
Vol. 21, No. 3, 1985, p. 690
Kronfol, Ziad
Vol. 21, No. 3, 1985, p. 476
Kuhar, Michael J.
Vol. 21, No. 3, 1985, p. 595
Kupfer, David J.
Vol. 21, No. 1, 1985, pp. 3, 37
Kurtz, David
Vol. 21, No. 3, 1985, p. 365
Kurucz, Janos
Vol. 21, No. 1, 1985, p. 136

Labarca, Rodrigo
Vol. 21, No. 3, 1985, p. 694
Labonte, A.
Vol. 21, No. 1, 1985, p. 73
Lake, C. Raymond
Vol. 21, No. 3, 1985, p. 419
Lane, Elizabeth A.
Vol. 21, No. 3, 1985, p. 389
Larson, Jan
Vol. 21, No. 3, 1985, p. 582
Laux, Desmond
Vol. 21, No. 3, 1985, p. 562
Leaf, Philip J.
Vol. 21, No. 3, 1985, p. 538
Leber, Paul
Vol. 21, No. 2, 1985, p. 334
Leckman, James F.
Vol. 21, No. 3, 1985, p. 543
Lefkowitz, M.M.
Vol. 21, No. 4, 1985, p. 969
Leibowitz, Sarah F.
Vol. 21, No. 3, 1985, p. 412
Lerer, Bernard
Vol. 21, No. 1, 1985, p. 18
Lerner, William
Vol. 21, No. 3, 1985, p. 651
Levine, Allen S.
Vol. 21, No. 3, 1985, p. 400

Levine, Andrew
  Vol. 21, No. 3, 1985, p. 610
Lewis, John W.
  Vol. 21, No. 3, 1985, p. 479
Lewy, Alfred J.
  Vol. 21, No. 3, 1985, p. 368
Lieberman, Jeffrey A.
  Vol. 21, No. 1, 1985, pp. 123, 136
Liebeskind, John C.
  Vol. 21, No. 3, 1985, p. 479
Liebowitz, Michael R.
  Vol. 21, No. 1, 1985, p. 85
  Vol. 21, No. 3, 1985, pp. 428, 558, 610
Links, Jonathan M.
  Vol. 21, No. 3, 1985, p. 595
Linnoila, Markku
  Vol. 21, No. 3, 1985, p. 389
Lloyd, K. C.
  Vol. 21, No. 3, 1985, p. 385
Lucki, Irwin
  Vol. 21, No. 1, 1985, p. 93

Mann, J. John
  Vol. 21, No. 3, 1985, p. 698
Mannuzza, Salvatore
  Vol. 21, No. 2, 1985, p. 237
Marder, Stephen R.
  Vol. 21, No. 1, 1985, p. 69
Markowitz, Jeffrey S.
  Vol. 21, No. 1, 1985, p. 107
  Vol. 21, No. 3, 1985, p. 558
Marks, Isaac
  Vol. 21, No. 3, 1985, p. 615
Martin, Diane
  Vol. 21, No. 4, 1985, pp. 869
Martin, Fredricka C.
  Vol. 21, No. 3, 1985, p. 479
Martin, James F.
  Vol. 21, No. 2, 1985, p. 285
Mason, Barbara
  Vol. 21, No. 3, 1985, p. 698
Matson, Johnny L.
  Vol. 21, No. 2, 1985, p. 258
  Vol. 21, No. 4, 1985, pp. 855–865
Maudlin, Mary
  Vol. 21, No. 1, 1985, p. 52
Mauroidis, Michael L.
  Vol. 21, No. 1, 1985, p. 62
Maxwell, M. Elizabeth
  Vol. 21, No. 3, 1985, p. 365
May, Philip R.A.
  Vol. 21, No. 1, 1985, p. 69
McDonald, Margaret C.
  Vol. 21, No. 1, 1985, p. 3
McGrath, Patrick J.
  Vol. 21, No. 1, 1985, pp. 85, 107
  Vol. 21, No. 3, 1985, pp. 555, 558
McGuire, Michael T.
  Vol. 21, No. 3, 1985, p. 458
McKnew, Donald
  Vol. 21, No. 4, 1985, p. 957
Meiselas, Karen
  Vol. 21, No. 1, 1985, p. 140
Menolascino, Frank J.
  Vol. 21, No. 2, 1985, p. 316
Mercier, P.
  Vol. 21, No. 1, 1985, pp. 73, 91
Merikangas, Kathleen R.
  Vol. 21, No. 3, 1985, pp. 538, 543
Merrill, Carl R.
  Vol. 21, No. 3, 1985, p. 361
Meyendorff, Elaine
  Vol. 21, No. 1, 1985, p. 18
Meyer-Bahlburg, Heino F.L.
  Vol. 21, No.3, 1985, p. 686
Miller, Jeanette C.
  Vol. 21, No. 3, 1985, p. 683
Mitchell, James E.
  Vol. 21, No. 3, 1985, p. 400
  Vol. 21, No. 4, 1985, pp. 1025
Mitchell, Walter
  Vol. 21, No. 3, 1985, p. 503
Mittleman, Fred
  Vol. 21, No. 3, 1985, p. 582
Mocchetti, J.
  Vol. 21, No. 3, 1985, p. 379
Mokros, Harmut B.
  Vol. 21, No. 4, 1985, p. 979
Moon, Timothy
  Vol. 21, No. 3, 1985, p. 485
Moore, Norman
  Vol. 21, No. 1, 1985, p. 18
Morley, John E.
  Vol. 21, No. 3, 1985, pp. 400, 485
Morselli, P. L.
  Vol. 21, No. 3, 1985, p. 385
Mouchka, Susan
  Vol. 21, No. 2, 1985, p. 262
Mueller, Edward A.
  Vol. 21, No. 3, 1985, p. 701
Mukherjee, Sukdeb
  Vol. 21, No. 1, 1985, p. 136
Murphy, Dennis L.
  Vol. 21, No. 3, 1985, pp. 419, 701

Myers, Robert D.
  Vol. 21, No. 3, 1985, p. 406

Nasrallah, Henry A.
  Vol. 21, No. 1, 1985, p. 89
Nelson, Linda R.
  Vol. 21, No. 3, 1985, p. 479
Novacenko, Hana
  Vol. 21, No. 1, 1985, p. 123
Nurnberger, John I.
  Vol. 21, No. 3, 1985, pp. 365, 599

O'Brien, Ronald P.
  Vol. 21, No. 1, 1985, p. 69
Olmsted, M.P.
  Vol. 21, No. 4, 1985, pp. 1009
Oppenheim, Gerald
  Vol. 21, No. 3, 1985, p. 705
Ortiz, Aurelio
  Vol. 21, No. 3, 1985, p. 424
Orvaschel, Helen
  Vol. 21, No. 4, 1985, pp. 737

Palij, Michael
  Vol. 21, No. 4, 1985, pp. 719, 1047, 1063
Pandey, Ghanshyam N.
  Vol. 21, No. 3, 1985, p. 603
Parashos, Ioanis
  Vol. 21, No. 3, 1985, p. 389
Pardes, Herbert
  Vol. 21, No. 1, 1985, p. 59
Pass, Raymond
  Vol. 21, No. 1, 1985, p. 130
Paul, Steven M.
  Vol. 21, No. 3, 1985, p. 694
Pauls, David L.
  Vol. 21, No. 3, 1985, p. 543
Pearlson, Godfrey
  Vol. 21, No. 3, 1985, p. 595
Perenyi, Andras
  Vol. 21, No. 2, 1985, p. 345
Perry, Richard
  Vol. 21, No. 1, 1985, p. 140
Peters, I. Donald
  Vol. 21, No. 3, 1985, p. 588
Peters, Jeffrey
  Vol. 21, No. 3, 1985, p. 497
Petti, Theodore A.
  Vol. 21, No. 4, 1985, pp. 951, 959, 972-976
Phelps, Bruce
  Vol. 21, No. 1, 1985, p. 59
Pickar, David
  Vol. 21, No. 3, 1985, p. 694
Piekut, Diane T.
  Vol. 21, No. 3, 1985, p. 472
Piletz, John E.
  Vol. 21, No. 3, 1985, p. 573
Pincus, Harold Alan
  Vol. 21, No. 1, 1985, p. 7
Plotnikoff, Nicholas P.
  Vol. 21, No. 3, 1985, p. 489
Pohl, Robert B.
  Vol. 21, No. 3, 1985, pp. 424, 434
Poland, Russell
  Vol. 21, No. 1, 1985, pp. 59, 69
Polivy, J.
  Vol. 21, No. 4, 1985, pp. 1009
Portoghese, P. S.
  Vol. 21, No. 3, 1985, p. 464
Post, Robert M.
  Vol. 21, No. 1, 1985, p. 10
Potkin, Steven G.
  Vol. 21, No. 1, 1985, p. 59
Potter, Larry
  Vol. 21, No. 1, 1985, p. 81
Potter, William Z.
  Vol. 21, No. 3, 1985, p. 389
Poznanski, Elva O.
  Vol. 21, No. 4, 1985, pp. 979
Prien, Robert
  Vol. 21, No. 1, 1985, p. 37
Prusoff, Brigitte A.
  Vol. 21, No. 3, 1985, p. 543
Pyle, Richard
  Vol. 21, No. 4, 1985, p. 1025

Quitkin, Frederic M.
  Vol. 21, No. 1, 1985, pp. 85, 107
  Vol. 21, No. 3, 1985, pp. 555, 558

Rabkin, Judith
  Vol. 21, No. 1, 1985, pp. 85, 107
  Vol. 21, No. 3, 1985, pp. 555, 558
Racagni, G.
  Vol. 21, No. 3, 1985, p. 379
Rainey, John M., Jr.
  Vol. 21, No. 3, 1985, pp. 424, 434
Raleigh, Michael J.
  Vol. 21, No. 3, 1985, p. 458

Ramos-Lorenzi, Jorge
  Vol. 21, No. 1, 1985, p. 123
Rand, James B.
  Vol. 21, No. 3, 1985, p. 623
Rapoport, Judith L.
  Vol. 21, No. 1, 1985, p. 150
  Vol. 21, No. 2, 1985, p. 232
  Vol. 21, No. 4, 1985, pp. 714, 803, 1057, 1085
Ravert, Hayden T.
  Vol. 21, No. 3, 1985, p. 595
Ravichandran, G.K.
  Vol. 21, No. 1, 1985, p. 52
  Vol. 21, No. 3, 1985, p. 588
Reardon, Gerald
  Vol. 21, No. 3, 1985, p. 533
Reatig, Natalie
  Vol. 21, No. 4, 1985, pp. 929, 1097–1105
Reichler, R. J.
  Vol. 21, No. 4, 1985, pp. 1053
Reimherr, Frederick W.
  Vol. 21, No. 1, 1985, p. 146
  Vol. 21, No. 1, 1985, p. 222
Reisberg, Barry
  Vol. 21, No. 1, 1985, p. 101
Reisine, Terry
  Vol. 21, No. 3, 1985, p. 438
Renner, B. R.
  Vol. 21, No. 4, 1985, pp. 1053
Richardson, Mary Ann
  Vol. 21, No. 1, 1985, p. 130
Rickels, Karl
  Vol. 21, No. 1, 1985, p. 93
Rifkin, Arthur
  Vol. 21, No. 1, 1985, p. 114
  Vol. 21, No. 3, 1985, p. 533
Rinck, Chris
  Vol. 21, No. 2, 1985, p. 268
Risch, S. Craig
  Vol. 21, No. 3, 1985, p. 690
Robinson, Donald S.
  Vol. 21, No. 3, 1985, p. 562
Rosen, Jules P.
  Vol. 21, No. 3, 1985, p. 497
Rotatori, Anthony F.
  Vol. 21, No. 4, 1985, pp. 855
Rotrosen, John
  Vol. 21, No. 1, 1985, p. 136
Roy, Alec
  Vol. 21, No. 3, 1985, p. 694
Roy-Byrne, Peter P.
  Vol. 21, No. 3, 1985, pp. 546, 551
Rubinow, David R.
  Vol. 21, No. 3, 1985, p. 546
Rubinstein, Morton
  Vol. 21, No. 1, 1985, p. 136
Rudorfer, Matthew
  Vol. 21, No. 3, 1985, p. 389
Ruedrich, Stephen L.
  Vol. 21, No. 2, 1985, p. 316
Russell, Richard L.
  Vol. 21, No. 3, 1985, p. 623
Rutter, Michael
  Vol. 21, No. 4, 1985, p. 749

Sack, Robert L.
  Vol. 21, No. 3, 1985, p. 368
Safer, Daniel J.
  Vol. 21, No. 2, 1985, p. 212
Sameroff, Arnold J.
  Vol. 21, No. 4, 1985, p. 728
Sanders-Bush, Elaine
  Vol. 21, No. 3, 1985, p. 373
Scatton, B.
  Vol. 21, No. 3, 1985, p. 385
Schooler, Nina R.
  Vol. 21, No. 1, 1985, p. 136
Schopler, Erik
  Vol. 21, No. 4, 1985, pp. 1053
Schroeder, Stephen R.
  Vol. 21, No. 2, 1985, pp. 310, 323
Schwarcz, Glenn
  Vol. 21, No. 1, 1985, p. 77
Schwartz, Estelle
  Vol. 21, No. 4, 1985, pp. 1013
Seifer, R.
  Vol. 21, No. 4, 1985, p. 728
Shaffer, David
  Vol. 21, No. 4, 1985, pp. 747
Shapira, Baruch
  Vol. 21, No. 3, 1985, p. 705
Shavit, Yehuda
  Vol. 21, No. 3, 1985, p. 479
Shen, Yucun
  Vol. 21, No. 1, 1985, p. 59
Shu, Liang
  Vol. 21, No. 1, 1985, p. 59
Siever, Larry J.
  Vol. 21, No. 3, 1985, pp. 419, 599
Simson, Prudence Goodman
  Vol. 21, No. 3, 1985, p. 447
Singer, Clifford M.
  Vol. 21, No. 3, 1985, p. 368
Singh, Heminder
  Vol. 21, No. 3, 1985, p. 424

- Singh, Nirbhay N.
  - Vol. 21, No. 4, 1985, pp. 845
- Siris, Samual G.
  - Vol. 21, No. 1, 1985, p. 114
- Slade, Peter D.
  - Vol. 21, No. 4, 1985, pp. 1004
- Sleator, Esther K.
  - Vol. 21, No. 4, 1985, pp. 915, 1089
- Sloboda, Walter
  - Vol. 21, No. 1, 1985, p. 105
- Small, Arthur M.
  - Vol. 21, No. 1, 1985, p. 140
- Smith, Robert C.
  - Vol. 21, No. 1, 1985, p. 52
  - Vol. 21, No. 3, 1985, p. 588
- Spohn, Herbert E.
  - Vol. 21, No. 3, 1985, p. 582
- Sprague, Robert L.
  - Vol. 21, No. 4, 1985, pp. 915
- Spray, Judy
  - Vol. 21, No. 3, 1985, p. 582
- Spring, Bonnie
  - Vol. 21, No. 3, 1985, p. 509
- Stahl, Stephen M.
  - Vol. 21, No. 1, 1985, p. 43
  - Vol. 21, No. 3, 1985, pp. 393, 663
- Stanley, Barbara
  - Vol. 21, No. 1, 1985, p. 110
- Stanley, Michael
  - Vol. 21, No. 1, 1985, p. 110
- Stein, Judith
  - Vol. 21, No. 1, 1985, p. 110
- Steinbook, Richard M.
  - Vol. 21, No. 1, 1985, p. 97
- Steinhauer, Stuart R.
  - Vol. 21, No. 3, 1985, p. 513
- Stewart, Alistair W.
  - Vol. 21, No. 4, 1985, pp. 845
- Stewart, Jonathan W.
  - Vol. 21, No. 1, 1985, pp. 85, 107
  - Vol. 21, No. 3, 1985, pp. 555, 558
- Stokes, Peter
  - Vol. 21, No. 3, 1985, p. 579
- Sugrue, Michael F.
  - Vol. 21, No. 3, 1985, p. 619
- Sulser, Fridolin
  - Vol. 21, No. 3, 1985, p. 373
- Sunderland, Trey
  - Vol. 21, No. 3, 1985, p. 701
- Suneja, Sudhir
  - Vol. 21, No. 3, 1985, p. 595
- Swanson, H. Lee
  - Vol. 21, No. 4, 1985, pp. 877
- Swanson, James M.
  - Vol. 21, No. 4, 1985, pp. 887
- Sweeney, John
  - Vol. 21, No. 3, 1985, p. 698
- Sztaniszlav, Daniel
  - Vol. 21, No. 2, 1985, p. 345

- Takemori, A. E.
  - Vol. 21, No. 3, 1985, p. 464
- Targum, Steven
  - Vol. 21, No.3, 1985, p. 599
- Terman, Gregory W.
  - Vol. 21, No. 3, 1985, p. 479
- Thomas, John W.
  - Vol. 21, No. 3, 1985, p. 694
- Thompson, Mark
  - Vol. 21, No. 1, 1985, p. 77
- Tokola, Nancy S.
  - Vol. 21, No. 3, 1985, p. 599
- Transit, Roxanna-Pentland
  - Vol. 21, No. 1, 1985, p. 110
- Tricamo, Elaine
  - Vol. 21, No. 3, 1985, p. 558
- Tesing, E.
  - Vol. 21, No. 4, 1985, p. 969
- Tune, Larry
  - Vol. 21, No. 3, 1985, p. 595

- Uhde, Thomas W.
  - Vol. 21, No. 1, 1985, p. 10
  - Vol. 21, No. 3, 1985, pp. 546, 551, 599
- Ullmann, Rina K.
  - Vol. 21, No. 2, 1985, p. 339
  - Vol. 21, No. 4, 1985, pp. 915

- Van Kammen, Daniel P.
  - Vol. 21, No. 3, 1985, p. 497
- Van Kammen, Welmoet B.
  - Vol. 21, No. 3, 1985, p. 497
- Van Putten, Theodore
  - Vol. 21, No. 1, 1985, p. 69
- Vann, Felix H.
  - Vol. 21, No. 3, 1985, p. 686
- Varley, Christopher K.
  - Vol. 21, No. 2, 1985, p. 216
- Varney, Nils
  - Vol. 21, No. 1, 1985, p. 89
- Veridiano, Norma P.
  - Vol. 21, No. 3, 1985, p. 686

- Volterra, A.
  - Vol. 21, No. 3, 1985, p. 379
- Voss, Carlyle
  - Vol. 21, No. 3, 1985, p. 698

- Wagner, Henry N., Jr.
  - Vol. 21, No. 3, 1985, p. 595
- Wagner, Richard L.
  - Vol. 21, No. 1, 1985, p. 66
- Walsh, Timothy
  - Vol. 21, No. 4, 1985, pp. 1017
- Warner, Ken
  - Vol. 21, No. 3, 1985, p. 434
- Wegner, James
  - Vol. 21, No. 1, 1985, p. 123
- Weinhold, Paul
  - Vol. 21, No. 1, 1985, p. 136
- Weiss, Gabrielle
  - Vol. 21, No. 2, 1985, p. 169
- Weiss, Jay M.
  - Vol. 21, No. 3, 1985, p. 447
- Weissman, Myrna M.
  - Vol. 21, No. 3, 1985, pp. 538, 543
- Wells, Karen C.
  - Vol. 21, No. 4, 1985, p. 921
- Wender, Paul H.
  - Vol. 21, No. 1, 1985, p. 146
  - Vol. 21, No. 2, 1985, p. 222
  - Vol. 21, No. 4, 1985, pp. 927
- Whitehead, E. Douglas
  - Vol. 21, No. 3, 1985, p. 686
- Wilson, Alan A.
  - Vol. 21, No. 3, 1985, p. 595
- Wilson, Thomas F.
  - Vol. 21, No. 2, 1985, p. 316
- Winokur, Andrew
  - Vol. 21, No. 3, 1985, p. 579
- Woerner, Margaret
  - Vol. 21, No. 1, 1985, p. 136
  - Vol. 21, No. 3, 1985, p. 533
- Wolkowitz, Owen M.
  - Vol. 21, No. 3, 1985, p. 694
- Wong, Dean F.
  - Vol. 21, No. 3, 1985, P. 595
- Wood, David R.
  - Vol. 21, No. 1. 1985, p. 146
  - Vol. 21, No. 2, 1985, p. 222
- Wyatt, Richard Jed
  - Vol. 21, No. 1, 1985, p. 66

- Yeragani, Vikram
  - Vol. 21, No. 3, 1985, p. 434
- Yingling, Kevin
  - Vol. 21, No. 3, 1985, p. 562
- Young, Melinda
  - Vol. 21, No. 1, 1985, p. 77

- Zalcman, Steven
  - Vol. 21, No. 1, 1985, p. 66
- Zametkin, Alan
  - Vol. 21, No. 2, 1985, p. 232
- Zax, M.
  - Vol. 21, No. 4, 1985, p. 728
- Zhou, Dongfeng
  - Vol. 21, No. 1, 1985, p. 59
- Zivkovic, B.
  - Vol. 21, No. 3, 1985, p. 385
- Zohar, Joseph
  - Vol. 21, No. 3, 1985, p. 705
- Zubenko, George
  - Vol. 21, No. 3, 1985, pp. 631, 641
- Zubin, Joseph
  - Vol. 21, No. 3, 1985, p. 490

Psychopharmacology—A Recurring Bibliography

The bibliography below is offered to our readers to alert them to recent papers on psychopharmacology from the world literature. It was computer-generated by the Medical-Literature Analysis and Retrieval System (MEDLARS) of the National Library of Medicine, National Institutes of Health, and represents papers which were entered into the system during the 3 months before the *Bulletin* went to press.

The subject headings from Index Medicus were selected by the National Institute of Mental Health to reflect significant current interest of the international scientific community. Some nonrelevant citations may appear, and some relevant ones may be absent, but this is usual for machine-generated searches.

BIBLIOGRAPHY

ACEPROMAZINE

Increased mortality in gray wolves captured with acepromazine and etorphine hydrochloride in combination. Tobey RW, et al. **J Wildl Dis** 1985 Apr;21(2):188-90

ACETYLCHOLINE

Modulation of choline transport and acetylcholine synthesis in synaptosomes from different brain regions. Nordberg A, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Mar;56(3):193-8

Cadmium inhibition of [3H]acetylcholine secretion in guinea-pig ileum myenteric plexus. Alberts P, et al. **Acta Physiol Scand** 1985 Jun; 124(2):313-6

The effects of adenosine and of some adenosine analogues on the concanavalin A-or acetylcholine-induced histamine release from human adenoidal mast cells. Delmich K, et al. **Agents Actions** 1985 Apr; 16(3-4):141-3

Immunological modulation of cholinergic histamine release in isolated rat mast cells. Masini E, et al. **Agents Actions** 1985 Apr; 16(3-4):152-4

The modulation of acetylcholine release by noradrenaline, GABA and related compounds. Beani L, et al. **Ann Ist Super Sanita** 1984; 20(1):17-9

Acetylcholine and histamine interact supra-additively on bronchomotor tone in guinea-pigs in vivo: a possible consequence of the relationship between airways resistance and calibre. Stewart AG, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):33-46

Declining catecholamine secretion in adrenal medulla on prolonged stimulation with acetylcholine. Bevington A, et al. **Biochem Pharmacol** 1985 May 1;34(9):1497-500

Thyroliberin (TRH), 6-methyl-5-oxothiomorpholinyl-3-carbonyl histidylproline amide and histidylproline diketopiperazine do not affect the release of [3H]-acetyl choline and [3H]-choline from rat brain tissue cubes. Hedley D, et al. **Biochem Pharmacol** 1985 Apr 15; 34(8):1341-3

Blockade of the diazepam-induced increase in rat striatal acetylcholine content by the specific benzodiazepine antagonists ethyl-beta-carboline-3-carboxylate and Ro 15-1788. Kolasa K, et al. **Brain Res** 1985 Jun 17;336(2):342-5

Light evoked release of acetylcholine in response to a single flash: cholinergic amacrine cells receive ON and OFF input. Massey SC, et al. **Brain Res** 1985 Mar 4;328(2):374-7

Synthesis of acetylcholine and gamma-aminobutyric acid by dissociated cerebral cortical cells in vitro. Thomas WE. **Brain Res** 1985 Apr 15; 332(1):79-89

Acetylcholine release from rat atria can be regulated through an alpha 1-adrenergic receptor. Wetzel GT, et al. **Circ Res** 1985 May; 56(5):763-6

Effect of secretagogues on pancreatic exocrine secretion in the monkey and the dog. Iwatsuki K, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):67-72

Comparative actions of GABA and acetylcholine on the Xenopus laevis lateral line. Bobbin RP, et al. **Comp Biochem Physiol [C]** 1985; 80(2):313-8

Action of acetylcholine and antagonists on somata isolated from locust central neurons. Suter C, et al. **Comp Biochem Physiol [C]** 1985; 80(2):221-9

Neurochemical evidence for the release of acetylcholine from the guinea-pig ileum myenteric plexus by capsaicin. Barthó L, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):125-7

Real-time measurements of acetylcholine-induced release of ATP from bovine medullary chromaffin cells. Rojas E, et al. **FEBS Lett** 1985 Jun 17;185(2):323-7

Human pancreatic acinar cells: studies of stimulus-secretion coupling. Petersen OH, et al. **Gastroenterology** 1985 Jul;89(1):109-17

Mast cell heterogeneity in response to cholinergic stimulation. Masini E, et al. **Int Arch Allergy Appl Immunol** 1985;77(1-2):184-5

Rapid changes in synaptic vesicle cytochemistry after depolarization of cultured cholinergic sympathetic neurons. Johnson MI, et al. **J Cell Biol** 1985 Jul;101(1):217-26

Nimodipine has an inhibitory action on neurotransmitter release from human cerebral arteries. Porter ID, et al. **J Cereb Blood Flow Metab** 1985 Jun;5(2):338-42

Determination of choline and acetylcholine levels in rat brain regions by liquid chromatography with electrochemical detection. Ikarashi Y, et al. **J Chromatogr** 1985 Mar 29;322(1):191-9

Chromatographic analysis of choline and acetylcholine by UV visualization. Jones RS, et al. **J Chromatogr** 1985 Feb 20; 319(3):454-60

Modulation of the acetylcholine system in the superior cervical ganglion of rat: effects of GABA and hypoglossal nerve implantation after in vivo GABA treatment. Kása P, et al. **J Neurochem** 1985 May; 44(5):1363-72

Newly synthesized and preformed acetylcholine are released from Torpedo synaptosomes by different pathways. Luz S, et al. **J Neurochem** 1985 Jul;45(1):43-50

Changes in presynaptic release of acetylcholine during development of tolerance to the anticholinesterase. DFP. Russell RW, et al. **J Neurochem** 1985 Jul;45(1):293-9

High-affinity binding of [3H]acetylcholine to muscarinic cholinergic receptors. Kellar KJ, et al. **J Neurosci** 1985 Jun;5(6):1577-82

Pharmacological and ionic characterizations of the muscarinic receptors modulating [3H]acetylcholine release from rat cortical synaptosomes. Meyer EM, et al. **J Neurosci** 1985 May;5(5):1202-7

Bombesin evoked acetylcholine release from the guinea pig antrum. Kantoh M, et al. **Life Sci** 1985 Jun 24;36(25):2445-52

Oxidative metabolism and acetylcholine synthesis during acetylpyridine treatment. Gibson GE, et al. **Neurochem Res** 1985 Apr;10(4):453-67

The compartmentalized hypothalamo-neurohypophysial system: evidence for a neurohypophysial action of acetylcholine on vasopressin release. Gregg CM. **Neuroendocrinology** 1985 May;40(5):423-9

The modulation of cortical acetylcholine release by GABA, GABA-like drugs and benzodiazepines in freely moving guinea-pigs. Tanganelli S, et al. **Neuropharmacology** 1985 Apr;24(4):291-9

State of adrenergic and cholinergic systems in schizophrenia patients during psychopharmacotherapy. Krupenina LB, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):1-8

Acetylcholine-induced currents at plasma membrane of the frog oocyte. Toselli M, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):179-84

Acetylcholine stimulates a Ca2+-dependent C1- conductance in mouse lacrimal acinar cells. Findlay I, et al. **Pflugers Arch** 1985 Mar; 403(3):328-30

The biophysical pharmacology of calcium-dependent acetylcholine secretion. Silinsky EM. **Pharmacol Rev** 1985 Mar;37(1):81-132 (282 ref.)

Neurochemical basis for the photic control of circadian rhythms and seasonal reproductive cycles: role for acetylcholine. Earnest DJ, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4277-81

Is an acetylcholine transport system responsible for nonquantal release of acetylcholine at the rodent myoneural junction? Edwards C, et al. **Proc Natl Acad Sci USA** 1985 May;82(10):3514-8

Chronotropic effects of the reversed carboxyl (RC) analogue of acetylcholine (beta-homobetaine methylester) at defined intraluminal pressures on isolated right rabbit atria. Rossberg F, et al. **Res Exp Med (Berl)** 1985;185(2):139-44

Effects of secretagogues on membrane potential and input resistance of pancreatic acinar cells of sheep. Katoh K, et al. **Res Vet Sci** 1985 Mar; 38(2):250-1

Inhibitory effects of dopamine and isoprenaline on antral motor activity stimulated by acetylcholine or physostigmine in vitro. Ulvestad A, et al. **Scand J Gastroenterol** 1985 Mar;20(2):243-6

The release of acetylcholine. Dunant Y, et al. **Sci Am** 1985 Apr; 252(4):58-66

Immunocytochemical detection of acetylcholine in the rat central nervous system. Geffard M, et al. **Science** 1985 Jul 5;229(4708):77-9

[Relationship between cholinesterase activity and acetylcholine of the brains of mice acutely intoxicated with soman] Zhang X, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar;6(1):16-9 (Eng. Abstr.) **(Chi)**

[Regulation of the cell cycle of B-lymphocytes in mice by substances elevating the levels of intracellular cAMP and cGMP] Ado AD, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):455-8 (Eng. Abstr.) **(Rus)**

[Changes in the response to the extracellular application of acetylcholine during the intracellular perfusion of isolated neurons with biogenic amines] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985; 280(6):1495-8 **(Rus)**

[Effect of RNAse inhibitors and activators on acetylcholine interaction with the cholinoreceptor in a tissue extract] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985;281(2):500-2 **(Rus)**

[Catecholamine levels in pancreatic tissue after intraperitoneal administration of acetylcholine] Gal'kiv MA, et al. **Fiziol Zh** 1985 Mar-Apr;31(2):230-4 **(Rus)**

[Correlation between the plasticity of monosynaptic inputs of command neurons of Helix lucorum and the plastic properties of the chemoreceptive membrane during rhythmic stimulation] Norekian TP, et al. **Neirofiziologiia** 1985;17(2):279-82 (Eng. Abstr.) **(Rus)**

[The effect of acetylcholine and histamine on blood flow through the abdominal organs] Antal J, et al. **Bratisl Lek Listy** 1985 Mar; 83(3):218-28 (Eng. Abstr.) **(Slo)**

ACHIEVEMENT

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227-43

AFFECTIVE DISORDERS

Treatment of affective disorders. Lader MH. **Br J Clin Pharmacol** 1985; 19 Suppl 1:29S-30S

The relationship between antisocial behavior and affective illness. Reich J. **Compr Psychiatry** 1985 May-Jun;26(3):296-303 (47 ref.)

Consensus development summaries. Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health. **Conn Med** 1985 Mar;49(3):157-63

Compliance with outpatient lithium therapy. Connelly CE. **Perspect Psychiatr Care** 1984 Apr-Jun;22(2):44-50

AFFECTIVE DISORDERS, PSYCHOTIC

Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health Consensus Development Conference Statement. **Nat Inst Health Consensus Dev Conf Consensus Statement** 1984; 5(4):8 p.

AFFECTIVE SYMPTOMS

Nomifensine for 'emotional incontinence' of the pseudobulbar type [letter] Sandyk R. **J Am Geriatr Soc** 1985 May;33(5):375

AGGRESSION

Treatment of an aggressive, compulsive adolescent with sultopride [letter] Bucci L. **Am J Psychiatry** 1985 Jul;142(7):882-3

Differential effects of electroconvulsive shock on four models of experimentally-induced aggression in rats. Liou SY, et al. **Jpn J Pharmacol** 1985 Feb;37(2):167-72

Effects of chronic LiCl and RbCl on muricide induced by midbrain raphe lesions in rats. Yamamoto T, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):559-63

Target biting associated with a gustatory avoidance response. Wagner GC, et al. **Physiol Behav** 1985 Mar;34(3):465-9

Serotonergic control of experimental aggression. Valzelli L, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):495-503

Biogenic amine alterations in limbic brain regions of muricidal rats. Broderick PA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr; 48(1):3-15

AMINO ACIDS

Effects of jejunoileal bypass on food intake, amino acid levels, and indoleamine metabolism in rats. Herlin PM, et al. **Am J Surg** 1985 Jun; 149(6):739-44

Synthesis of side chain-protected amino acid phenylthiohydantoins and their use in quantitative solid-phase Edman degradation. Steiman DM, et al. **Anal Biochem** 1985 Feb 15;145(1):91-5

Effects of diazinon on nucleotide and amino acid contents of chick embryos. Teratogenic considerations. Kushaba-Rugaaju S, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1937-43

Aromatic amino acid metabolites as potential protein binding inhibitors in human uremic plasma. Tavares-Almeida I, et al. **Biochem Pharmacol** 1985 Jul 15;34(14):2431-8

Determination of the relative positions of amino acids by partial specific cleavages of end-labeled proteins. Jue RA, et al. **Biochemistry** 1985 Jan 1;24(1):162-70

Antagonism of inhibitory amino acids by the steroid derivative RU5135. Simmonds MA, et al. **Br J Pharmacol** 1985 Mar;84(3):631-5

Quantitative review of optimum amino acid intakes for young laying pullets. McDonald MW, et al. **Br Poult Sci** 1985 Apr;26(2):253-64 (32 ref.)

Effects of excitatory amino acids on calcium transport by brain membranes. Harris RA. **Brain Res** 1985 Jun 24;337(1):167-70

Modulatory effects of prostaglandin D2, E2 and F2 alpha on the postsynaptic actions of inhibitory and excitatory amino acids in cerebellar Purkinje cell dendrites in vitro. Kimura H, et al. **Brain Res** 1985 Mar 25;330(2):235-44

Isocratic separation of PTH-amino acids at picomole level by reverse-phase HPLC in the presence of sodium dodecylsulfate. Tsunasawa S, et al. **J Biochem (Tokyo)** 1985 Feb;97(2):701-4

Determination of neurotransmitter amino acids by high-performance liquid chromatography with fluorescence detection. Zecca L, et al. **J Chromatogr** 1985 Feb 8;337(2):391-6

An artifact in urinary amino acid analysis produced by tris(hydroxymethyl)aminomethane (THAM). Wilson WG, et al. **J Inherited Metab Dis** 1985;8(1):24

Orally active and potent inhibitors of gamma-aminobutyric acid uptake. Ali FE, et al. **J Med Chem** 1985 May;28(5):653-60

Synthesis and structure-activity studies on excitatory amino acids structurally related to ibotenic acid. Krogsgaard-Larsen P, et al. **J Med Chem** 1985 May;28(5):673-9

Ibotenic acid analogues. Synthesis, molecular flexibility, and in vitro activity of agonists and antagonists at central glutamic acid receptors. Lauridsen J, et al. **J Med Chem** 1985 May;28(5):668-72

An excitant amino acid projection from the medial prefrontal cortex to the anterior part of nucleus accumbens in the rat. Christie MJ, et al. **J Neurochem** 1985 Aug;45(2):477-82

Potassium-induced release of endogenous amino acids in the guinea pig cochlea. Jenison GL, et al. **J Neurochem** 1985 Jun;44(6):1845-53

Afferent facilitation induced by iontophoretic application of acidic amino acids in the ampullary electroreceptors of Plotosus. Nagai T, et al. **J Neurophysiol** 1985 Apr;53(4):853-67

Pharmacological characterization of postsynaptic receptors for excitatory amino acids in Purkinje cell dendrites in the guinea pig cerebellum. Kimura H, et al. **J Pharmacobiodyn** 1985 Feb;8(2):119-27

Release of endogenous dopamine, 3,4-dihydroxyphenylacetic acid, and amino acid transmitters from rat striatal slices. Flint RS, et al. **Neurochem Res** 1985 Apr;10(4):515-27

Transport of monoamine and amino acid neurotransmitters by primary astroglial cultures. Hansson E. **Neurochem Res** 1985 May; 10(5):667-75

Glutamine-induced alterations in the content of brain amino acid neurotransmitters in rats with different alcohol motivation. Ostrovsky SYu. **Subst Alcohol Actions Misuse** 1984;5(5):247-53

Electrophysiological studies on neuronal transmission in the frog's photosensory pineal organ. The effect of amino acids and biogenic amines. Meissl H, et al. **Vision Res** 1984;24(12):1727-34

[Observations on the use of amino-acid mixtures in severe burn patients] Wang QF, et al. **Chung Hua Wai Ko Tsa Chih** 1985 Feb; 23(2):69-71, 125 (Eng. Abstr.) **(Chi)**

[Biochemistry of the brain. b. Amino acids, polypeptides, and proteins] Nishimura T, et al. **Nippon Rinsho** 1985 Feb;43(2):253-7 (30 ref.) **(Jpn)**

[Differential spectrophotometry of iodinated proteins and amino acids in heavy water] Gussakovskii EE, et al. **Biofizika** 1985 Mar-Apr; 30(2):208-10 (Eng. Abstr.) **(Rus)**

AMITRIPTYLINE

Chlordiazepoxide toxicity in Limbitrol overdose [letter] Goethe JW, et al. **Am J Psychiatry** 1985 Jun;142(6):774

Comparison of the effects of binodaline and amitriptyline on peripheral autonomic functions in healthy volunteers. Longmore J, et al. **Br J Clin Pharmacol** 1985 Mar;19(3):295-300

A comparison of the cardiovascular effects and subjective tolerability of binedaline and amitriptylene in healthy volunteers. Joubert PH, et al. **Eur J Clin Pharmacol** 1985;27(6):667-70

Why is amitriptyline much weaker than desipramine at decreasing beta-adrenoceptor numbers? Wise H, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):137-41

Tricyclic antidepressants antagonize prostaglandin (PG) E2-induced contractions of the guinea pig ileum and hypomotility in the mouse. Tayo FM. **Experientia** 1985 Apr 15;41(4):474-6

Determination of cyclobenzaprine in plasma and urine using capillary gas chromatography with nitrogen-selective detection. Constanzer ML, et al. **J Chromatogr** 1985 May 3;339(2):414-8

Plasma levels of amitriptyline: effect of age and sex. Preskorn SH, et al. **J Clin Psychiatry** 1985 Jul;46(7):276-7

Amitriptyline and contact lenses [letter] Troiano G. **J Clin Psychiatry** 1985 May;46(5):199

Amitriptyline and hydroxylated metabolite plasma levels in depressed outpatients. Robinson DS, et al. **J Clin Psychopharmacol** 1985 Apr; 5(2):83-8

Comparison of limbitrol (chlordiazepoxide/amitriptyline) and amitriptyline alone as a single night-time dose for the treatment of depression with anxiety. James RT, et al. **J Int Med Res** 1985; 13(2):84-7

Inhibition of the retrograde axonal transport of acetylcholinesterase by the anti-calmodulin agents amitriptyline and desipramine. Tiberi M, et al. **J Neurobiol** 1985 May;16(3):245-8

Responsibilities of prescribing. Avery JK. **J Tenn Med Assoc** 1985 May; 78(5):297

Effects of acute and chronic treatment with amitryptyline on the sleep-wake activity of rats. Obál F Jr, et al. **Neuropharmacology** 1985 Mar;24(3):223-9

Mianserin versus amitriptyline for depression: a double-blind 6-week trial. Rabkin JG, et al. **Neuropsychobiology** 1984;12(4):224-8

AMOBARBITAL

[Attempted suicide with barbiturate after glue sniffing] Sami HO, et al. **Orv Hetil** 1985 Mar 31;126(13):781-3 (Eng. Abstr.) **(Hun)**

[Barbamyl distribution in human blood] Kudrin AN, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):113-5 (Eng. Abstr.) **(Rus)**

AMPHETAMINE

Pre-school children of amphetamine-addicted mothers. II. Environment and supportive social welfare. Eriksson M, et al. **Acta Paediatr Scand** 1985 Mar;74(2):185-90

Differential response to amphetamine in schizophrenia. Cesarec Z, et al. **Acta Psychiatr Scand** 1985 May;71(5):523-38

Effects of D- and L-amphetamine on dopamine metabolism and ascorbic acid levels in nucleus accumbens and olfactory tubercle as studied by in vivo differential pulse voltammetry. Louilot A, et al. **Brain Res** 1985 Jun 17;336(2):253-63

Single-reagent polarization fluoroimmunoassay for amphetamine in urine. Colbert DL, et al. **Clin Chem** 1985 Jul;31(7):1193-5

Opposite effects of sulpiride and metoclopramide on amphetamine-induced stereotypy. Robertson A, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):81-9

Liquid chromatographic determination of the enantiomeric composition of amphetamine and related drugs by diastereomeric derivatization. Barksdale JM, et al. **J Chromatogr Sci** 1985 Apr;23(4):176-80

Reserpine-induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31-8

Norepinephrine-dependent and independent mechanisms of persistent effects of amphetamine in rat cerebellum. Sorensen SM, et al. **Life Sci** 1985 Jun 24;36(25):2383-9

Hypothalamic involvement in the locomotor stimulant or satiety action of thyrotropin-releasing hormone and amphetamine. Shian LR, et al. **Pharmacology** 1985;30(5):259-65

Development of mouse activity, stimulus reactivity, habituation, and response to amphetamine and scopolamine. Alleva E, et al. **Physiol Behav** 1985 Apr;34(4):519-23

Amphetamine response and relapse risk after depot neuroleptic discontinuation. Angrist B, et al. **Psychopharmacology (Berlin)** 1985; 85(3):277-83

Specific opioid-amphetamine interactions in the caudate putamen. Woo SK, et al. **Psychopharmacology (Berlin)** 1985;85(3):371-6

The effect of previous d-amphetamine treatment on the disposition and lethality of fenfluramine in the rat. Hunsinger RN, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):236-45

[Comparative effect of the psychostimulants sidnocarb and fenamin on the tyrosine hydroxylase activity of the brain synaptosomes in rats] Ganiev MM, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):27-32 (Eng. Abstr.) **(Rus)**

[Effect of stable strontium on spontaneous and drug-induced motor activity in the rat] Escanero JF, et al. **Arch Farmacol Toxicol** 1985 Apr; 11(1):33-9 (Eng. Abstr.) **(Spa)**

[Is the combination of amphetamine and chloroquine the cause of unexpected psychological symptoms?] **Lakartidningen** 1985 May 22; 82(21):1962 **(Swe)**

AMPHETAMINES

4-Bromo-2,5-dimethoxyphenethylamine: identification of a new street drug. Ragan FA Jr, et al. **J Anal Toxicol** 1985 Mar-Apr;9(2):91-3

Board of Medicine proposes new amphetamine rules. **Mich Med** 1985 Feb;84(2):100-2

Psychobiological foundations of behaviors induced by amphetamines. Groves PM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:356-66

p-Chloroamphetamine: effect on sleep and respiration in the rat. DeMesquita S. **Pharmacol Biochem Behav** 1985 May;22(5):889-91

Structure-activity studies on methoxy-substituted phenylisopropylamines using drug discrimination methodology. Glennon RA, et al. **Pharmacol Biochem Behav** 1985 May;22(5):723-9

[Microanalysis of amphetamines III. Detection of amphetamines in the hair of monkeys treated with methamphetamine] Takahashi K, et al. **Eisei Shikenjo Hokoku** 1984;(102):21-4 (Eng. Abstr.) **(Jpn)**

ANOREXIA NERVOSA

Chlorpromazine-associated haemolysis in anorexia nervosa. Van der Weyden MB, et al. **Acta Haematol (Basel)** 1985;73(2):111-3

Activity measures in anorexia nervosa. Falk JR, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):811-4

Anorexia nervosa: aetiological theories and treatment methods. Bryant R, et al. **J Adolesc** 1985 Mar;8(1):93-103

Behavior therapy, pimozide treatment and prolactin secretion in anorexia nervosa. Weizman A, et al. **Psychother Psychosom** 1985;43(3):136-40

ANTIDEPRESSIVE AGENTS

1st Czechoslovak Conference on Biological Psychiatry. Karlovy Vary (Karlsbad), September 1983. Abstracts. **Act Nerv Super (Praha)** 1985 Mar;27(1):60-72

Alteration of histamine metabolism in the rat brain under influence of various antidepressive treatments. Zawilska J, et al. **Agents Actions** 1985 Apr;16(3-4):105-8

Qualitative and quantitative analysis of the action of typical and atypical antidepressants in the experimental animal. Kozlovskaya MM, et al. **Ann Ist Super Sanita** 1984;20(1):73-7

Effects of long-term drug treatments on the sensitivity of presynaptic receptors regulating neurotransmitter release. Raiteri M, et al. **Ann Ist Super Sanita** 1984;20(1):57-64

Membrane-related effects of atypical antidepressants. Valdman AV, et al. **Ann Ist Super Sanita** 1984;20(1):65-72

Resting metabolic rate is reduced in patients treated with antidepressants. Fernstrom MH, et al. **Biol Psychiatry** 1985 Jun;20(6):692-5

Comparison of the effects of binodaline and amitriptyline on peripheral autonomic functions in healthy volunteers. Longmore J, et al. **Br J Clin Pharmacol** 1985 Mar;19(3):295-300

Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: studies on the olfactory bulbectomized rat model of depression. O'Connor WT, et al. **Br J Clin Pharmacol** 1985;

19 Suppl 1:49S-56S

A comparison of the cardiovascular effects and subjective tolerability of binedaline and amitriptylene in healthy volunteers. Joubert PH, et al. **Eur J Clin Pharmacol** 1985;27(6):667-70

Interindividual differences in the binding of antidepressives to plasma proteins: the role of the variants of alpha 1-acid glycoprotein. Tinguely D, et al. **Eur J Clin Pharmacol** 1985;27(6):661-6

Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behavioural 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):253-6

Drug response as a predictor of transmission of non-bipolar major depression within families. Prusoff BA, et al. **J Affective Disord** 1985 Mar-Apr;8(2):171-6

1-Azacycloalkyl-1,4-benzodiazepin-2-ones with antianxiety-antidepressant actions. Sugasawa T, et al. **J Med Chem** 1985 Jun;28(6):699-707

Synthesis and antidepressant profiles of phenyl-substituted 2-amino- and 2-[(alkoxycarbonyl)amino]-1,4,5,6-tetrahydropyrimidines. Weinhardt K, et al. **J Med Chem** 1985 Jun;28(6):694-8

Neurochemical profile of Lu 19-005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615-22

5-Hydroxytryptamine-stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: pharmacological characterization and effects of antidepressants. Kendall DA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):473-9

Effects of clenbuterol and antidepressant drugs on beta adrenergic receptor/N-protein coupling in the cerebral cortex of the rat. O'Donnell JM, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):30-6

Enhanced signal transduction by adenylate cyclase in platelet membranes of patients showing antidepressant responses to alprazolam: preliminary data. Mooney JJ, et al. **J Psychiatr Res** 1985;19(1):65-75

Elevation of mood due to antidepressants [letter] Pearce PL. **JAMA** 1985 Jun 7;253(21):3091-2

On acute and chronic CNS effects of antidepressants in normals: neurophysiological, behavioral and pharmacokinetic studies with pirlindol. Saletu B, et al. **Methods Find Exp Clin Pharmacol** 1985 Mar; 7(3):137-51

Antidepressants and endogenous opioid peptide systems. Przewłocki R, et al. **Neuropeptides** 1985 Feb;5(4-6):575-8

Serotonin and antidepressant drugs antagonize melatonin-induced behavioural changes after injection into the nucleus accumbens of rats. Gaffori O, et al. **Neuropharmacology** 1985 Mar;24(3):237-44

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar; 24(3):217-22

The olfactory bulbectomized rat as a model of depression. Leonard BE. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):561-9 (30 ref.)

Characterization of the bupropion cue in the rat: lack of evidence for a dopaminergic mechanism. Blitzer RD, et al. **Psychopharmacology (Berlin)** 1985;85(2):173-7

The tail suspension test: a new method for screening antidepressants in mice. Steru L, et al. **Psychopharmacology (Berlin)** 1985;85(3):367-70

The activation of mice's behavior and reduction of brain beta-adrenergic receptor binding following repeated administration of antidepressant drugs. Nomura S, et al. **Yakubutsu Seishin Kodo** 1984 Nov; 4(3):237-41

[Effect of acute administration of antidepressive agents at 2 P.M. on plasma and pineal levels of melatonin in the rat] Mouren P, et al. **Encephale** 1985 Jan-Feb;11(1):29-30 (Eng. Abstr.) **(Fre)**

[Drug flush. Possible role of indalpine overdosage (letter)] Manigand G, et al. **Presse Med** 1985 Apr 13;14(15):841 **(Fre)**

[Therapeutic strategy in depression] Scotto JC, et al. **Rev Prat** 1985 May 11;35(27):1633-8 (Eng. Abstr.) **(Fre)**

[Action of indalpine on the pupil diameter in the healthy volunteer] Brion N, et al. **Therapie** 1985 Jan-Feb;40(1):9-11 (Eng. Abstr.) **(Fre)**

[Treatment of depressive syndrome with antidepressants] Woggon B, et al. **Med Monatsschr Pharm** 1985 May;8(5):130-6 **(Ger)**

[Inhibition of brain monoamine oxidase in the rat by multiple pyrazidol administration] Verevkina IV, et al. **Biull Eksp Biol Med** 1985 May; 99(5):583-4 (Eng. Abstr.) **(Rus)**

[Comparative study of the indices of the antidepressive activity of potassium orotate and piracetam] Karkishchenko NN, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):32-5 (Eng. Abstr.) **(Rus)**

[The effect of psychopharmacologic agents on the passive transport of Ca2+ induced by vanadate in human erythrocytes] Pogády J, et al. **Bratisl Lek Listy** 1985 Apr;83(4):345-52 (Eng. Abstr.) **(Slo)**

ANTISOCIAL PERSONALITY DISORDER

The relationship between antisocial behavior and affective illness. Reich J. **Compr Psychiatry** 1985 May-Jun;26(3):296-303 (47 ref.)

ANXIETY

A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. Davison K, et al. **Br J Clin Pharmacol** 1985;19 Suppl 1:37S-43S

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445-51

Brief review of published alprazolam clinical studies. Straw RN. **Br J Clin Pharmacol** 1985;19 Suppl 1:57S-59S (22 ref.)

Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety. Power KG, et al. **Br Med J [Clin Res]** 1985 Apr 27;290(6477):1246-8

Drugs in dentistry. Agents for anxiety disorders. Ciancio SG. **Dent Manage** 1985 Jun;25(6):66, 68, 70

Animal models for the study of anti-anxiety agents: a review. Treit D. **Neurosci Biobehav Rev** 1985 Summer;9(2):203-22

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: punished barpressing. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;85(2):244-51

[Clinical trial of the action of a benzodiazepine (Lexotan) on the behavior of the anxious patient in dental outpatient care] Debernardi G, et al. **Minerva Stomatol** 1985 Mar-Apr;34(2):323-8 (Eng. Abstr.) **(Ita)**

[Anxiolytic action of sodium valproate (possible role of gamma-aminobutyric acid in affective disorders)] Raevskii KS, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):574-9 (Eng. Abstr.) **(Rus)**

ANXIETY DISORDERS

Management of specific anxiety disorders in the elderly. Turnbull JM, et al. **Geriatrics** 1985 Aug;40(8):75-82

Emergency treatment of acute psychosis, agitation, and anxiety. Ellison JM. **Hosp Community Psychiatry** 1985 Apr;36(4):351-2

L-5-hydroxytryptophan in the treatment of anxiety disorders. Kahn RS, et al. **J Affective Disord** 1985 Mar-Apr;8(2):197-200

Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam. Ansseau M, et al. **Neuropsychobiology** 1984;12(4):255-9

Clinical pharmacology of benzodiazepines. Rickels K. **Pharmacopsychiatry** 1985 Jan;18(1):156-9

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167-70

New findings in anxiety. A synthesis for clinical practice in 1985. Curtis GC. **Psychiatr Clin North Am** 1985 Mar;8(1):169-75

Generalized anxiety disorder. Hoehn-Saric R, et al. **Psychiatr Clin North Am** 1985 Mar;8(1):73-88 (65 ref.)

Imipramine in the treatment of panic disorder and its complications. Liebowitz MR. **Psychiatr Clin North Am** 1985 Mar;8(1):37-47

APOMORPHINE

Effect of metoclopramide, domperidone and apomorphine on GH secretion in children and adolescents. Massara F, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):451-5

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196-201

Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Grace AA, et al. **Brain Res** 1985 May 6; 333(2):285-98

Antagonism of apomorphine-enhanced startle by alpha 1-adrenergic antagonists. Davis M, et al. **Eur J Pharmacol** 1985 Feb 5; 108(3):233-41

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349-54

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305-8

The supersensitivity of dopaminergic neurons to apomorphine in rats following chronic haloperidol. Vogelsang GD, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):267-9

Reserpine-induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31-8

Inhibitory effects of apomorphine and pergolide on neurogenic vasoconstriction in the hindquarters of the rat. Dupont AG, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):146-51

Effects of discriminant and non-discriminant dopamine antagonists on in vivo accumulation of 3H-N-propyl-norapomorphine in mouse striatum and tuberculum olfactorium. Gulat-Marnay C, et al.

Naunyn Schmiedebergs Arch Pharmacol 1985 Apr;329(2):117–22

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128–34

Effect of chronic haloperidol and quinacrine coadministration on striatal HVA levels and stereotypic behaviors in response to apomorphine in the rat. Deutsch SI, et al. **Neurochem Res** 1985 Apr;10(4):491–8

Antistereotypic effects of cholecystokinin octapeptide (CCK-8), ceruletide and related peptides on apomorphine-induced gnawing in sensitized mice. Zetler G. **Neuropharmacology** 1985 Mar;24(3):251–9

In vivo electrochemical monitoring of apomorphine penetration into the rat brain. Marcenac FM, et al. **Neurosci Lett** 1985 Apr 19; 55(3):305–10

The morphogenesis of stereotyped behavior induced by the dopamine receptor agonist apomorphine in the laboratory rat. Szechtman H, et al. **Neuroscience** 1985 Mar;14(3):783–98

Effect of chronic apomorphine on the development of denervation supersensitivity. Robin M, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):547–51

Effects of selective dopamine receptor agonists in rats trained to discriminate apomorphine from saline. Woolverton WL, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):577–81

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346–52

Increased or decreased locomotor response in rats following repeated administration of apomorphine depends on dosage interval. Castro R, et al. **Psychopharmacology (Berlin)** 1985;85(3):333–9

Influence of cimetidine, ranitidine and imidazole on the behavioral effects of (+/-) N-n-propylnorapomorphine in male rats. Ferrari F, et al. **Psychopharmacology (Berlin)** 1985;85(2):197–200

Increase in plasma ACTH after dopaminergic stimulation in rats. Ježová D, et al. **Psychopharmacology (Berlin)** 1985;85(2):201–3

Effects of apomorphine and haloperidol on 'spontaneous' stereotyped licking behaviour in the Cebus monkey. Korsgaard S, et al. **Psychopharmacology (Berlin)** 1985;85(2):240–3

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204–9

Studies on the stability of 3H-dopamine, 3H-apomorphine and 3H-ADTN: effects of sodium ascorbate and EDTA. Cabbat FS, et al. **Res Commun Chem Pathol Pharmacol** 1985 Mar;47(3):333–43

Circadian variation in the ambulation-increasing effect of apomorphine after repeated administration in mice. Kuribara H, et al. **Yakubutsu Seishin Kodo** 1984 Nov;4(3):231–6

APPETITE

d-Fenfluramine and salbutamol: two drugs causing anorexia through different neurochemical mechanisms. Garattini S, et al. **Int J Obes** 1984; 8 Suppl 1:151–7

The clinical pharmacology of appetite suppressant drugs. Silverstone T, et al. **Int J Obes** 1984;8 Suppl 1:23–33

AROUSAL

Are the anxiogenic effects of yohimbine mediated by its action at benzodiazepine receptors? Pellow S, et al. **Neurosci Lett** 1985 Mar 22; 55(1):5–9

Clinical pharmacology of benzodiazepines. Rickels K. **Pharmacopsychiatry** 1985 Jan;18(1):156–9

1.2-Anellated 1.4-benzodiazepine derivatives--a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174–7

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167–70

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49–55

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731–6

ATTENTION

Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178–93

A limiting factor in the 'normalization' of schizophrenic orienting response dysfunction. Bernstein AS, et al. **Schizophr Bull** 1985;11(2):230–54

ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY

Evaluating drug effectiveness in an office setting for children with attention deficit disorders. Ottinger DR, et al. **Clin Pediatr (Phila)** 1985 May;24(5):245–51

Oral pemoline kinetics in hyperactive children. Sallee F, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):606–9

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227–43

Stimulants and neuroleptics in hyperactive children [letter] Gualtieri CT, et al. **J Am Acad Child Psychiatry** 1985 May;24(3):363–4

Cardiovascular effects of desipramine in children and adolescents with attention deficit disorder. Biederman J, et al. **J Pediatr** 1985 Jun; 106(6):1017–20

Adolescent outcome of hyperactive children treated with stimulants in childhood: a review. Hechtman L. **Psychopharmacol Bull** 1985; 21(2):178–91 (15 ref.)

New drug trials in attention deficit disorder. Rapoport JL, et al. **Psychopharmacol Bull** 1985;21(2):232–6 (16 ref.)

A review of studies of drug treatment efficacy for attention deficit disorder with hyperactivity in adolescents. Varley CK. **Psychopharmacol Bull** 1985;21(2):216–21 (31 ref.)

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222–31

Methylphenidate: rate-dependent drug effects in hyperactive boys. Weber K. **Psychopharmacology (Berlin)** 1985;85(2):231–5

[Urinary 3-methoxy-4-hydroxyphenylglycol sulfate in school children with minimal brain dysfunction syndrome] Wang YF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Feb; 18(1):45–9 (Eng. Abstr.) **(Chi)**

AUTISM, INFANTILE

Vitamin B6, magnesium, and combined B6-Mg: therapeutic effects in childhood autism. Martineau J, et al. **Biol Psychiatry** 1985 May; 20(5):467–78

Serotonin relationships of autistic probands and their first-degree relatives. Kuperman S, et al. **J Am Acad Child Psychiatry** 1985 Mar; 24(2):186–90

AVOIDANCE LEARNING

Direct and indirect behavioral pathways to the social transmission of food avoidance. Galef BG Jr. **Ann NY Acad Sci** 1985;443:203–15

Introduction: physiological mechanisms in conditioned taste aversions. Grill HJ. **Ann NY Acad Sci** 1985;443:67–88

Conditioned food aversions and satiety signals. Kulkosky PJ. **Ann NY Acad Sci** 1985;443:330–47

Conditioned taste aversions: a behavioral index of toxicity. Riley AL, et al. **Ann NY Acad Sci** 1985;443:272–92

Glucocorticoid and other hormonal substrates of conditioned taste aversion. Smotherman WP. **Ann NY Acad Sci** 1985;443:126–44

Interfering with taste aversion learning in rats: the role of associative interference. Cannon DS, et al. **Appetite** 1985 Mar;6(1):1–19

Effects of tifluadom on passive avoidance behaviour in DBA/2 mice. Pavone F, et al. **Behav Brain Res** 1985 May;15(3):177–81

Response of the rat brain beta-endorphin system to novelty: importance of the fornix connection. Netto CA, et al. **Behav Neural Biol** 1985 Jan; 43(1):37–46

Central versus peripheral actions of Leu-enkephalin on acquisition of a one-way active avoidance response in rats. Martinez JL Jr, et al. **Brain Res** 1985 Feb 18;327(1-2):37–43

Aversive effects of subcutaneously injected vasopressin in the rat: independence of the ascending dorsal noradrenergic bundle. Tam FW, et al. **Brain Res** 1985 Jun 24;337(1):133–7

Spontaneous configuring in conditioned flavor aversion. Forbes DT, et al. **J Exp Psychol [Anim Behav]** 1985 Apr;11(2):224–40

Potentiation and overshadowing in preweanling and adult rats. Kucharski D, et al. **J Exp Psychol [Anim Behav]** 1985 Jan;11(1):15–34

2-Amino-4-phosphonobutyric acid selectively blocks two-way avoidance learning in the mouse. Sahai S, et al. **Neurosci Lett** 1985 May 14; 56(2):137–42

Dose-related effects of pentobarbital on the genetic differences seen between paired, Roman high- or low-avoidance rats in a shuttle box. Driscoll P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):435–9

Effects of psychotropic drugs on discrimination conditioning in olfactory bulbectomized rats. Gomita Y, et al. **Pharmacol Biochem Behav** 1985 May;22(5):717–22

Lithium effects on position learning with exploratory and aversive goal-box conditions. Hines G. **Pharmacol Biochem Behav** 1985 May; 22(5):695–8

Intracortical glutamate injection produces helpless-like behavior in the rat. Petty F, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):531–3

Passive avoidance after ibotenic acid and radio frequency lesions in the rat amygdala. Jellestad FK, et al. **Physiol Behav** 1985 Feb; 34(2):299-305

Conditioned taste aversion suppresses induction of delayed-type hypersensitivity immune reactions. Kelley KW, et al. **Physiol Behav** 1985 Feb;34(2):189-93

Target biting associated with a gustatory avoidance response. Wagner GC, et al. **Physiol Behav** 1985 Mar;34(3):465-9

Luteinizing-hormone-releasing hormone modifies retention of passive and active avoidance responses in rats. Mora S, et al. **Psychopharmacology (Berlin)** 1985;85(3):315-8

Anti-aversive role of serotonin in the dorsal periaqueductal grey matter. Schütz MT, et al. **Psychopharmacology (Berlin)** 1985;85(3):340-5

[3,6-disubstituted 1-lupinylquinoxalin-2(1H)-ones of pharmacological interest. Effect on acquisition and modification of a conditioned avoidance response in rats] Sparatore A, et al. **Farmaco [Sci]** 1985 May; 40(5):303-14 (Eng. Abstr.) **(Ita)**

AZEPINES

Differential modulation of gamma-aminobutyric acid receptors by caprolactam derivatives with central nervous system depressant or convulsant activity. Skerritt JH, et al. **Brain Res** 1985 Apr 8; 331(2):225-33

Pharmacological and neurochemical properties of 1,4-diazepines with two annelated heterocycles ('hetrazepines'). Weber KH, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):19-31

The dopamine autoreceptor agonist B-HT 920 markedly stimulates sexual behavior in male rats. Ferrari F, et al. **Experientia** 1985 May 15; 41(5):636-8

I.R. and N.M.R. spectroscopic studies of 1,4-thienodiazepinic drugs. Fernandez-Arciniega MA, et al. **Farmaco [Prat]** 1985 Apr; 40(4):124-30

Synthesis and interaction of 5-(substituted-phenyl)-3-methyl-6,7-dihydropyrazolo[4,3-e][1,4]diazepin-8(7H)-ones with benzodiazepine receptors in rat cerebral cortex. Baraldi PG, et al. **J Med Chem** 1985 May;28(5):683-5

The putative dopamine autoreceptor agonist B-HT 920 decreases nigral dopamine cell firing rate and prolactin release in rat. Eriksson E, et al. **Life Sci** 1985 May 13;36(19):1819-27

Effect of cetiedil on platelet aggregation and thromboxane synthesis. Yamaguchi A, et al. **Thromb Res** 1985 Feb 1;37(3):391-400

[Thin-layer densitometric determination of clotiazepam in tablets and blood plasma] Busch M, et al. **Arzneimittelforsch** 1985;35(2):547-51 (Eng. Abstr.) **(Ger)**

[The effect of dilazep on red cell survival] Saito H, et al. **Rinsho Ketsueki** 1985 Jan;26(1):15-9 (Eng. Abstr.) **(Jpn)**

[New derivatives of 7- and 8-member perhydrocyclic compounds. II. Studies on the effect on the central nervous system and circulatory system of new derivatives of perhydro-1,4-oxazepine, perhydro-1,4-diazepine, perhydro-1,4,5-oxadiazepine and perhydro-1,5-oxazocine containing the 2-guanidinoethyl group] Szadowska A, et al. **Acta Pol Pharm** 1985;42(1):55-60 (Eng. Abstr.) **(Pol)**

BEHAVIOR

Neuropharmacologic management of behavior sequelae in head injury: a case report. Haas JF, et al. **Arch Phys Med Rehabil** 1985 Jul; 66(7):472-4

No acute behavioural effects of exposure to styrene: a safe level of exposure? Edling C, et al. **Br J Ind Med** 1985 May;42(5):301-4

On acute and chronic CNS effects of antidepressants in normals: neurophysiological, behavioral and pharmacokinetic studies with pirlindol. Saletu B, et al. **Methods Find Exp Clin Pharmacol** 1985 Mar; 7(3):137-51

[Clinical trial of the action of a benzodiazepine (Lexotan) on the behavior of the anxious patient in dental outpatient care] Debernardi G, et al. **Minerva Stomatol** 1985 Mar-Apr;34(2):323-8 (Eng. Abstr.) **(Ita)**

BEHAVIOR, ANIMAL

The effects of aniracetam on primate behavior and EEG. Schwam E, et al. **Ann NY Acad Sci** 1985;444:482-4

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196-201

Some behavioral effects of early styrene intoxication in experimental animals. Husain R, et al. **Arch Toxicol** 1985 Apr;57(1):53-5

Catecholamine-blocking drugs injected at sites of amine accumulation reverse catecholamine degeneration associated deficits. Willis GL, et al. **Behav Brain Res** 1985 Apr;15(2):101-6

Ethanol preference behaviour and dopamine release in the rat. Schmidt J, et al. **Biomed Biochim Acta** 1984;43(12):1431-4

A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT1 and 5-HT2 receptors. Goodwin GM, et al. **Br J Pharmacol** 1985 Mar;84(3):743-53

Involvement of nigrostriatal dopamine neurons in the contraversive rotational behavior evoked by electrical stimulation of the lateral hypothalamus. Castañeda E, et al. **Brain Res** 1985 Feb 18; 327(1-2):143-51

Enhancement of some 5-HT-dependent behavioural responses following repeated immobilization in rats. Kennett GA, et al. **Brain Res** 1985 Mar 25;330(2):253-63

Amine accumulation in behavioural pathology. Willis GL, et al. **Brain Res** 1985 Jun;356(2):109-32 (302 ref.)

Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behavioural 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):253-6

Long-term behavioral effects of phenobarbital in suckling rats. McBride MC, et al. **Exp Neurol** 1985 Jul;89(1):59-70

Behavioral indications for phenothiazine and benzodiazepine tranquilizers in dogs. Hart BL. **J Am Vet Med Assoc** 1985 Jun 1;186(11):1192-4

Effect of immune complex-forming reactants on catecholamine-modulated behaviors in the rat hypothalamus. Schupf N, et al. **J Neuroimmunol** 1985 Jul;9(1-2):13-27

Characteristics of the cortical and hippocampal EEG power spectra of rabbits during normal behavioral states and after administration of CNS acting drugs. Yamamoto J. **Jpn J Pharmacol** 1985 Mar;37(3):227-34

Effects of bombesin on behavior. Cowan A, et al. **Life Sci** 1985 Jul 15; 37(2):135-45

Beta-endorphin-(10-16) antagonizes behavioral responses elicited by melatonin following injection into the nucleus accumbens of rats. Gaffori O, et al. **Life Sci** 1985 Jul 29;37(4):357-64

Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5-MeODMT or mCPP. Sills MA, et al. **Life Sci** 1985 Jul 1; 36(26):2463-9

Catecholamine-independent behavioral and neurochemical effects of cocaine in rats. Gale K. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:323-32

Psychobiological foundations of behaviors induced by amphetamines. Groves PM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:356-66

The continuity of dopamine receptor antagonism can dictate the long-term behavioural consequences of a mesolimbic infusion of dopamine. Costall B, et al. **Neuropharmacology** 1985 Mar;24(3):193-7

Serotonin and antidepressant drugs antagonize melatonin-induced behavioural changes after injection into the nucleus accumbens of rats. Gaffori O, et al. **Neuropharmacology** 1985 Mar;24(3):237-44

Effects of MET-ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):139-48

Specificity of nucleus accumbens to activities related to cholecystokinins in rats. Katsuura G, et al. **Peptides (Fayetteville)** 1985 Jan-Feb; 6(1):91-6

Altered responses to serotonergic agents in Fawn-Hooded rats. Gudelsky GA, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):489-92

Comparative behavioral effects of CNS cholinesterase inhibitors. Moss DE, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):479-82

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417-51 (238 ref.)

1,2-Anellated 1,4-benzodiazepine derivatives--a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174-7

Postnatal lead exposure and the cholinergic system. Alfano DP, et al. **Physiol Behav** 1985 Mar;34(3):449-55

8th congress of the Polish Pharmacological Society. Symposium II: Pharmacological implications for animal models of mental disorders. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):493-569

Some behavioral effects of microinjections of serotonin and noradrenaline into the limbic structures of the rat brain. Plaźnik A. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):541-54

Neurotropic drugs and brain development: effects on cell replication in vivo and in vitro. Patel AJ. **Prog Clin Biol Res** 1985;163C:301-5

Influence of cimetidine, ranitidine and imidazole on the behavioral effects of (+/-) N-n-propylnorapomorphine in male rats. Ferrari F, et al. **Psychopharmacology (Berlin)** 1985;85(2):197-200

Effects of some dibenzo-azepines on suppressed and nonsuppressed behavior of squirrel monkeys. Spealman RD. **Psychopharmacology (Berlin)** 1985;85(2):129-32

Chronic neuroleptic treatment and mesolimbic dopamine denervation induce behavioural supersensitivity to opiates. Stinus L, et al. **Psychopharmacology (Berlin)** 1985;85(3):323-8

Specific opioid-amphetamine interactions in the caudate putamen. Woo SK, et al. **Psychopharmacology (Berlin)** 1985;85(3):371-6

Behavioral effects of long-term neuroleptic treatment in Cebus monkeys. Casey DE. **Psychopharmacology [Suppl]** 1985;2:211-6

Functional classification of different dopamine receptors. Ungerstedt U, et al. **Psychopharmacology [Suppl]** 1985;2:19-30

An analysis of some behavioural effects of the vibration and noise components of transport in pigs. Stephens DB, et al. **Q J Exp Physiol** 1985 Apr;70(2):211-7

Biogenic amine alterations in limbic brain regions of muricidal rats. Broderick PA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr; 48(1):3-15

[Behavioral pharmacology of amantadine with special references to the effect on abnormal behavior in mice and rats] Fujiwara M, et al. **Nippon Yakurigaku Zasshi** 1985 Apr;85(4):259-74 (Eng. Abstr.) **(Jpn)**

[New derivatives of 7- and 8-member perhydrocyclic compounds. II. Studies on the effect on the central nervous system and circulatory system of new derivatives of perhydro-1,4-oxazepine, perhydro-1,4-diazepine, perhydro-1,4,5-oxadiazepine and perhydro-1,5-oxazocine containing the 2-guanidinoethyl group] Szadowska A, et al. **Acta Pol Pharm** 1985;42(1):55-60 (Eng. Abstr.) **(Pol)**

BENACTYZINE

Comparative effects of aprophen, atropine and benactyzine on central and peripheral cholinoceptors and on acetylcholinesterase. Dawson RM, et al. **Biochem Pharmacol** 1985 May 1;34(9):1577-9

BENZAZEPINES

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665-9

Inhibition of hepatic microsomal drug metabolism by the calcium channel blockers diltiazem and verapamil. Renton KW. **Biochem Pharmacol** 1985 Jul 15;34(14):2549-53

Haemodynamic and pharmacological effects of the converting enzyme inhibitor CGS 14824A in normal volunteers. Schaller MD, et al. **Eur J Clin Pharmacol** 1985;28(3):267-72

Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Creese I, et al. **Eur J Pharmacol** 1985 Feb 12; 109(1):127-8

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349-54

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305-8

Comparative studies of cardiovascular effects of a new dopamine agonist (SK&F 38393A) and dopamine. Tsai CS, et al. **Gen Pharmacol** 1985; 16(2):85-9

Effects of the calcium antagonist, diltiazem on in vitro and in vivo/in vitro bone resorption. Ly SY, et al. **Horm Metab Res** 1985 Mar; 17(3):152-5

Effects of SK&F 82526 and SK&F 83742 on the renal vascular dopamine receptor. Schmidt M, et al. **J Pharmacol** 1985 Jan-Mar;16(1):15-22

Do D 600 and diltiazem interact with serotonin receptors in rabbit vascular tissues? Ohashi M, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):830-5

SCH23390 causes persistent antidopaminergic effects in vivo: evidence for longterm occupation of receptors. Schulz DW, et al. **Life Sci** 1985 May 20;36(20):1941-8

Newer dopamine quinazolones as anti-parkinsonian agents. Kumar P, et al. **Pharmazie** 1985 Apr;40(4):267-8

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346-52

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

BENZODIAZEPINE TRANQUILIZERS

'Article-induced' dyscontrol [letter] Gardner DL, et al. **Am J Psychiatry** 1985 Jun;142(6):776

The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. Lauven PM, et al. **Anesthesiology** 1985 Jul;63(1):61-4

A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. Davison K, et al. **Br J Clin Pharmacol** 1985;19 Suppl 1:37S-43S

Pharmacokinetics and pharmacodynamics following single and repeated nightly administrations of loprazolam, a new benzodiazepine hypnotic. McInnes GT, et al. **Br J Clin Pharmacol** 1985 May;19(5):649-56

Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: studies on the olfactory bulbectomized rat model of depression. O'Connor WT, et al. **Br J Clin Pharmacol** 1985; 19 Suppl 1:49S-56S

Brief review of published alprazolam clinical studies. Straw RN. **Br J Clin Pharmacol** 1985;19 Suppl 1:57S-59S (22 ref.)

Drugs in dentistry. Agents for anxiety disorders. Ciancio SG. **Dent Manage** 1985 Jun;25(6):66, 68, 70

Intramuscular bioavailability of chlorazepate as compared to diazepam. Bertler A, et al. **Eur J Clin Pharmacol** 1985;28(2):229-30

Spontaneous and RO 15-1788-induced reversal of subsensitivity to GABA following chronic benzodiazepines. Gonsalves SF, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):163-70

On the spectrophotometric determination of estazolam using Ru(III) ion. Gallo N, et al. **Farmaco [Prat]** 1985 Mar;40(3):77-80

Behavioral indications for phenothiazine and benzodiazepine tranquilizers in dogs. Hart BL. **J Am Vet Med Assoc** 1985 Jun 1;186(11):1192-4

Alprazolam overdose: clinical findings and serum concentrations in two cases. McCormick SR, et al. **J Clin Psychiatry** 1985 Jun;46(6):247-8

Efficiency and cleanliness of ether extraction for benzodiazepines in blood samples treated with aqueous ammonia compared with other methods for the purpose of HPLC assay. Stevens HM. **J Forensic Sci Soc** 1985 Jan-Feb;25(1):67-79

Triazolam, an anomalous benzodiazepine receptor ligand: in vitro characterization of alprazolam and triazolam binding. Clow A, et al. **J Neurochem** 1985 Aug;45(2):621-5

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

Psychological treatment for benzodiazepine dependence [letter] Tyrer P, et al. **Lancet** 1985 May 4;1(8436):1042-3

Acute pharmacokinetic and pharmacodynamic comparison of two different formulations of temazepam. Mattila MJ, et al. **Med Biol** 1985; 63(1):21-7

Benzodiazepines produce contrasting effects on the active membrane properties of an invertebrate neuron. Tan KS, et al. **Neuropharmacology** 1985 Feb;24(2):91-4

The modulation of cortical acetylcholine release by GABA, GABA-like drugs and benzodiazepines in freely moving guinea-pigs. Tanganelli S, et al. **Neuropharmacology** 1985 Apr;24(4):291-9

Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory. Subhan Z, et al. **Neuropsychobiology** 1984;12(4):244-8

gamma-Aminobutyric acid modulation of benzodiazepine receptor binding in vitro does not predict the pharmacologic activity of all benzodiazepine receptor ligands. Chweh AY, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):173-7

Pharmacology of benzodiazepine antagonists. Haefely W. **Pharmacopsychiatry** 1985 Jan;18(1):163-6

Clinical pharmacology of benzodiazepines. Rickels K. **Pharmacopsychiatry** 1985 Jan;18(1):156-9

1.2-Anellated 1.4-benzodiazepine derivatives--a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174-7

The sedative effects of CL 218,872, like those of chlordiazepoxide, are reversed by benzodiazepine antagonists. File SE, et al. **Psychopharmacology (Berlin)** 1985;85(3):295-300

[Alprazolam (Tafil). A new benzodiazepine-with a new action profile?] Rasmussen SB, et al. **Ugeskr Laeger** 1985 Apr 29;147(18):1495-7 **(Dan)**

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[Characteristics of benzodiazepine consumption in patients hospitalized in an internal medicine department] Le Goc I, et al. **Encephale** 1985 Jan-Feb;11(1):1-6 (Eng. Abstr.) **(Fre)**

[Benzodiazepines: pharmacodynamic aspects] Jacqmin P, et al. **J Pharm Belg** 1985 Jan-Feb;40(1):35-54 (74 ref.) (Eng. Abstr.) **(Fre)**

[Clobazam and N-desmethylclobazam. Assay by HPLC. Application to a pharmacokinetic study] Biehler J, et al. **Therapie** 1985 May-Jun; 40(3):167-71 (Eng. Abstr.) **(Fre)**

[Possible disorders after withdrawal of prolonged treatment with benzodiazepines in man (drug addicts excluded)] Lagier G. **Therapie** 1985 Jan-Feb;40(1):51-7 (Eng. Abstr.) **(Fre)**

[Clinical trial of the action of a benzodiazepine (Lexotan) on the behavior of the anxious patient in dental outpatient care] Debernardi G, et al. **Minerva Stomatol** 1985 Mar-Apr;34(2):323-8 (Eng. Abstr.) **(Ita)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

BENZODIAZEPINONES

Effect of H2 receptor- and muscarine receptor antagonists and prostaglandin E1 analog on the gastric mucosal hemodynamics and oxygen sufficiency in rats. Sato N, et al. **Adv Exp Med Biol** 1984; 180:763-71

The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. Lauven PM, et al. **Anesthesiology** 1985 Jul;63(1):61-4

Pharmacokinetics and pharmacodynamics following single and repeated nightly administrations of loprazolam, a new benzodiazepine hypnotic. McInnes GT, et al. **Br J Clin Pharmacol** 1985 May;19(5):649-56

Blockade of the diazepam-induced increase in rat striatal acetylcholine content by the specific benzodiazepine antagonists ethyl-beta-carboline-3-carboxylate and Ro 15-1788. Kolasa K, et al. **Brain Res** 1985 Jun 17;336(2):342-5

Effects of pirenzepine on plasma insulin, glucagon and pancreatic polypeptide levels in normal man. Zaccaria M, et al. **Eur J Clin Pharmacol** 1985;27(6):701-5

The benzodiazepine antagonist Ro 15-1788 reverses the effect of methyl-beta-carboline-3-carboxylate but not of harmaline on cerebellar cGMP and motor performance in mice. Burkard WP, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):241-7

Spontaneous and RO 15-1788-induced reversal of subsensitivity to GABA following chronic benzodiazepines. Gonsalves SF, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):163-70

Kinetics and displacement of [11C]RO 15-1788, a benzodiazepine antagonist, studied in human brain in vivo by positron tomography. Samson Y, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):247-51

Comparative inhibitory effects of pirenzepine and atropine on cholinergic stimulation of exocrine and endocrine rat pancreas. Otsuki M, et al. **Gastroenterology** 1985 Aug;89(2):408-14

Plasma determination of 3-methylclonazepam by capillary gas chromatography. Coassolo P, et al. **J Chromatogr** 1985 Mar 22; 338(2):347-55

1-Azacycloalkyl-1,4-benzodiazepin-2-ones with antianxiety-antidepressant actions. Sugasawa T, et al. **J Med Chem** 1985 Jun;28(6):699-707

'Peripheral-type' binding sites for benzodiazepines in brain: relationship to the convulsant actions of Ro 5-4864. Weissman BA, et al. **J Neurochem** 1985 May;44(5):1494-9

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

The interaction of McN-A-343 with pirenzepine and other selective muscarine receptor antagonists at a prejunctional muscarine receptor. Choo LK, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb; 328(4):430-8

The effects of benzodiazepines on spinal homosynaptic depression. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):301-7

Information processing and benzodiazepines. Kleindienst-Vanderbeke G. **Neuropsychobiology** 1984;12(4):238-43

Clonazepam-induced hyperphagia in nondeprived rats: tests of pharmacological specificity with Ro5-4864, Ro5-3663, Ro15-1788 and CGS 9896. Cooper SJ, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):753-60

NMR analysis of an oligodeoxyribonucleotide-drug adduct: anthramycin-d(ATGCAT). Graves DE, et al. **Prog Clin Biol Res** 1985; 172B:193-205

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[Clobazam and N-desmethylclobazam. Assay by HPLC. Application to a pharmacokinetic study] Biehler J, et al. **Therapie** 1985 May-Jun; 40(3):167-71 (Eng. Abstr.) **(Fre)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

BIOGENIC AMINES

Changes in the brain biogenic monoamines of rats, induced by piracetam and aniracetam. Petkov VD, et al. **Acta Physiol Pharmacol Bulg** 1984; 10(4):6-15

Liquid chromatographic determination of free and conjugated 3-methoxy-4-hydroxyphenylethylene glycol with wide-ranging substances related to monoamine metabolism. Ishikawa K, et al. **Anal Biochem** 1985 Jun;147(2):441-50

Role of the spinal monoaminergic systems in suppression of ejaculation by alpha-methyldopa. Kimura Y, et al. **Andrologia** 1985 Mar-Apr; 17(2):166-71

Biogenic amine/metabolite response during in-flight emergencies. Krahenbuhl GS, et al. **Aviat Space Environ Med** 1985 Jun; 56(6):576-80

Monoamine metabolites: their relationship and lack of relationship to monoaminergic neuronal activity. Commissiong JW. **Biochem Pharmacol** 1985 Apr 15;34(8):1127-31

Effects of intraventricular injections of 6-hydroxydopamine on amine metabolites in rat brain and urine. Edwards DJ, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1255-63

Cerebrospinal fluid (CSF) and brain monoamine metabolites in the developing rat pup. Shaywitz BA, et al. **Brain Res** 1985 Jan; 349(1-2):225-32

Effect of styrene oxide on levels of biogenic amines and activity of monoamine oxidase in different parts of rat brain. Husain R, et al. **Bull Environ Contam Toxicol** 1985 May;34(5):722-9

Pharmacokinetics of oral moclobemide in healthy human subjects and effects on MAO-activity in platelets and excretion of urine monoamine metabolites. Wiesel FA, et al. **Eur J Clin Pharmacol** 1985; 28(1):89-95

Sex differences in long-term gonadectomized rats: monoamine levels and [3H]nitroimipramine binding in brain nuclei. Renner KJ, et al. **Exp Brain Res** 1985;58(1):198-201

Pharmacologic studies of central actions of zopiclone: influence on brain monoamines in rats under stressful condition. Sato K, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Apr;23(4):204-10

New high-performance liquid chromatography system for the separation of biogenic amines as their Dns derivatives. Hayman AR, et al. **J Chromatogr** 1985 Jun 7;325(2):462-6

Modulation by monoamines of somatostatin-sensitive adenylate cyclase on neuronal and glial cells from the mouse brain in primary cultures. Chneiweiss H, et al. **J Neurochem** 1985 Jun;44(6):1825-31

Role of monoamines in experimental spinal cord injury in rats. Relationship between Na+-K+-ATPase and lipid peroxidation. Kurihara M. **J Neurosurg** 1985 May;62(5):743-9

Relationships between drug-induced changes in tetrahydrobiopterin and biogenic amine concentrations in rat brain. Lee EH, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):141-6

Auto-tolerance to the endogenous opioids and sleep. Gillman MA, et al. **Med Hypotheses** 1985 Apr;16(4):393-5

Cardiovascular responses elicited by microinjection of monoamines into mesencephalic nucleus dorsalis raphe in cats. Saxena AK, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):141-5

Mechanisms of the central action of lithium. Sinitskii VN, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):81-8

Biogenic amine alterations in limbic brain regions of muricidal rats. Broderick PA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr; 48(1):3-15

Electrophysiological studies on neuronal transmission in the frog's photosensory pineal organ. The effect of amino acids and biogenic amines. Meissl H, et al. **Vision Res** 1984;24(12):1727-34

[Effect of electroconvulsive shock on brain monoamines] Kuang PG. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Feb; 18(1):41-4 (Eng. Abstr.) **(Chi)**

[A TRH analog (DN-1417). Effects on the levels of monoamines and the metabolites in the various brain regions in rats] Nagai Y, et al. **Nippon Yakurigaku Zasshi** 1985 Apr;85(4):209-20 (Eng. Abstr.) **(Jpn)**

[Changes in the response to the extracellular application of acetylcholine during the intracellular perfusion of isolated neurons with biogenic amines] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985; 280(6):1495-8 **(Rus)**

[Biogenic amine content of brain sections, blood and adrenals of rabbits exposed to vibration and noise] Minasian SM, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):439-45 (Eng. Abstr.) **(Rus)**

BIPOLAR DISORDER

Renal function in 153 manic-depressive patients treated with lithium for more than five years. Løkkegaard H, et al. **Acta Psychiatr Scand** 1985 Apr;71(4):347-55

Plasma lithium level and interepisode functioning in bipolar disorder. Goodnick PJ, et al. **Am J Psychiatry** 1985 Jun;142(6):761-2

Manic depression: a multiple hormone disorder? Skutsch GM. **Biol Psychiatry** 1985 Jun;20(6):662-8

Erythrocyte membrane sodium-potassium and magnesium ATPase in primary affective disorder. Thakar JH, et al. **Biol Psychiatry** 1985 Jul; 20(7):734-40

Methylene blue for MDI [letter] Turner WJ. **Biol Psychiatry** 1985 Jul; 20(7):815

Imipramine metabolism in recurrent depressive episodes. Tollefson G, et al. **J Affective Disord** 1985 Mar-Apr;8(2):183-6

Monoamine oxidase inhibitors in the treatment of atypical depression. Zisook S, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):131-7

Lithium therapy for mania and depression. Murray JB. **J Gen Psychol** 1985 Jan;112(1):5-33

Interdependency of lithium ratio, plasma lithium level and clinical state in patients with affective disorders. Elizur A, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(2):167-72

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

Bipolar disorder and social work practice. Sands RG. **Soc Work Health Care** 1985 Spring;10(3):91-105

[A case of simultaneous treatment of the manic syndrome and granulocytopenia with lithium salts] Greń K, et al. **Psychiatr Pol** 1984 May-Jun;18(3):285-8 **(Pol)**

BLOOD-BRAIN BARRIER

Blood-brain barrier permeability to leucine-enkephalin, D-alanine2-D-leucine5-enkephalin and their N-terminal amino acid (tyrosine). Zlokovic BV, et al. **Brain Res** 1985 Jun 10;336(1):125-32

Role of 5-HT on increased permeability of blood-brain barrier under heat stress. Sharma HS, et al. **Indian J Physiol Pharmacol** 1984 Oct-Dec;

28(4):259-67

[The hemato-encephalic barrier in emotional stress] Belova TI, et al. **Usp Fiziol Nauk** 1985 Apr-Jun;16(2):61-76 (105 ref.) **(Rus)**

BODY IMAGE

Dysmorphophobia [letter] Jenike MA. **Br J Psychiatry** 1985 Mar; 146:326

BRADYKININ

Stimulation of prostacyclin production in isolated rat adipocytes by angiotensin II, vasopressin, and bradykinin: evidence for two separate mechanisms of prostaglandin synthesis. Axelrod L, et al. **Endocrinology** 1985 Jun;116(6):2548-53

BUTYLAMINES

Metabolism of N-nitrodialkylamines. Suzuki E, et al. **IARC Sci Publ** 1984; (57):485-90

BUTYROPHENONE TRANQUILIZERS

Lipids and apolipoproteins in patients treated with major tranquilizers. Sasaki J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):684-7

[Haloperidol decanoate in replacing combinations of antipsychotic agents in the treatment of chronic schizophrenics] Youssef HA. **Acta Psiquiatr Psicol Am Lat** 1984 Dec;30(4):297-304 **(Spa)**

BUTYROPHENONES

Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Shenker A, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):427-9

Pergolide elevation of MHPG sulphate concentration in rat hypothalamus blocked by spiperone and mimicked by other dopamine agonists. Fuller RW, et al. **J Pharm Pharmacol** 1985 Apr;37(4):268-70

A comparison between centrifugation and filtration as a means to separate bound and unbound ligand during 3[H]-spiroperidol binding. Csernansky CA, et al. **J Pharmacol Methods** 1985 Jun;13(3):187-91

Binding of 3H-spiperone to human lymphocytes: a biological marker in schizophrenia? Bondy B, et al. **Psychiatry Res** 1985 May;15(1):41-8

Presynaptic stimulation of dopaminergic CNS structures in sheep as a mechanism of immobilising action of Immobyl (fentanyl + azaperone). Kania BF. **Res Vet Sci** 1985 Mar;38(2):179-83

[Binding of 3H-spiperone in the mouse brain after intraperitoneal injection] Zharkovskiĭ AM, et al. **Biull Eksp Biol Med** 1985 Mar; 99(3):314-5 (Eng. Abstr.) **(Rus)**

CARBAMAZEPINE

Lack of pharmacokinetic interaction of carbamazepine with tranylcypromine [letter] Joffe RT, et al. **Arch Gen Psychiatry** 1985 Jul; 42(7):738

Carbamazepine-induced thrombocytopenia in a young child. Bradley JM, et al. **Clin Pharm** 1985 Mar-Apr;4(2):221-3

The influence of cimetidine on single-dose carbamazepine pharmacokinetics. Dalton MJ, et al. **Epilepsia** 1985 Mar-Apr; 26(2):127-30

A study of some pharmacological actions of carbamazepine and sodium valproate. Mansuri SM, et al. **Indian J Physiol Pharmacol** 1984 Oct-Dec; 28(4):315-8

Bioavailability and central side effects of different carbamazepine tablets. Neuvonen PJ. **Int J Clin Pharmacol Ther Toxicol** 1985 Apr; 23(4):226-32

Differential mediation of the anticonvulsant effects of carbamazepine and diazepam. Weiss SR, et al. **Life Sci** 1985 Jun 24;36(25):2413-9

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

Erythromycin-carbamazepine interaction [letter] Kessler JM. **S Afr Med J** 1985 Jun 29;67(26):1038

Determination of total and free plasma carbamazepine concentrations by enzyme multiplied immunoassay: interference with the 10,11-epoxide metabolite. Contin M, et al. **Ther Drug Monit** 1985;7(1):46-50

Fallacious results from measuring salivary carbamazepine concentrations. Dickinson RG, et al. **Ther Drug Monit** 1985;7(1):41-5

Simultaneous plasma carbamazepine and carbamazepine-epoxide concentrations in pharmacokinetic and bioavailability studies. Hooper WD, et al. **Ther Drug Monit** 1985;7(1):36-40

[Responsibility of the physician in prescribing Tegretol [letter] Kamp JS. **Ned Tijdschr Geneeskd** 1985 Mar 30;129(13):607-8 **(Dut)**

[Tegretol] Benoit P, et al. **Soins Psychiatr** 1985 Feb;(52):I-II **(Fre)**

[Quantitative determination of carbamazepine in tablets by reverse phase HPLC] Mamolo MG, et al. **Boll Chim Farm** 1984 Dec; 123(12):591-9 (Eng. Abstr.) **(Ita)**

[Interaction of carbamacepine and tuberculostatic agents (letter)] Bastús JB. **Med Clin (Barc)** 1985 Apr 6;84(13):542-3 **(Spa)**

[Clinical pharmacology of carbamazepine--a comparison with phenytoin] Bertilsson L, et al. **Lakartidningen** 1985 Apr 10;82(15):1355-60 **(Swe)**

CARBIDOPA

Carbidopa effect on rat brain monoamine oxidase and pineal melatonin. McIntyre IM, et al. **Biol Psychiatry** 1985 Jul;20(7):809-11

CATATONIA

Severe prolonged catatonia with associated flushing reaction responsive to lithium carbonate. Pheterson AD, et al. **J Am Acad Child Psychiatry** 1985 Mar;24(2):235-7

CATECHOL ESTROGENS

Studies on the effects of catecholestrogens on prolactin secretion by cultured normal rat anterior pituitary cells. Lamberts SW, et al. **Endocrinology** 1985 Jun;116(6):2631-6

Effects of short-term exposure to catecholestrogens on serum concentrations of gonadotrophins and metabolism of catecholestrogens in ovariectomized rats. Ball P, et al. **Horm Metab Res** 1985 Apr; 17(4):184-8

CATECHOLAMINES

Catecholamines and contractility of the human myometrium at term: a possible role for prostaglandins. Wikland M, et al. **Acta Physiol Hung** 1985;65(3):331-4

Determinations of catecholamine half-lives and turnover rates in discrete catecholamine nerve terminal systems of the hypothalamus, the preoptic region and the forebrain by quantitative histofluorimetry. Andersson K, et al. **Acta Physiol Scand** 1985 Apr;123(4):411-26

Sub-aggregatory doses of catecholamines prevent prostacyclin-induced inhibition of platelet aggregation. Buttrick PM, et al. **Am Heart J** 1985 Jun;109(6):1258-63

Methodological considerations in the determination of plasma catecholamines by high-performance liquid chromatography with electrochemical detection. Bouloux P, et al. **Ann Clin Biochem** 1985 Mar;22 (Pt 2):194-203

Computer simulations of the conformations of catecholamine derivatives. Hassan M, et al. **Ann NY Acad Sci** 1985;446:185-98

Plasma norepinephrine, epinephrine, and dopamine levels in end-stage renal disease. Effect of hemodialysis. Elias AN, et al. **Arch Intern Med** 1985 Jun;145(6):1013-5

Brain catecholamines and memory modulation: effects of footshock, amygdala implantation, and stimulation. Welsh KA, et al. **Behav Neural Biol** 1985 Mar;43(2):119-31

Response of hepatic ornithine decarboxylase and polyamine concentration to surgical stress in the rat: evidence for a permissive effect of catecholamines on glucocorticoid action. Corti A, et al. **Biochem Biophys Res Commun** 1985 Jun 28;129(3):885-91

The phorbol ester TPA enhances A23187--but not carbachol- and high K+-induced catecholamine secretion from cultured bovine adrenal chromaffin cells. Morita K, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):511-6

Characterization of protein kinase C and its role in catecholamine secretion from bovine adrenal-medullary cells. Brocklehurst KW, et al. **Biochem J** 1985 May 15;228(1):35-42

Declining catecholamine secretion in adrenal medulla on prolonged stimulation with acetylcholine. Bevington A, et al. **Biochem Pharmacol** 1985 May 1;34(9):1497-500

Interaction of phenothiazine drugs with human ceruloplasmin. Relation between activation of catecholamine neurotransmitter oxidation and electron donating ability of phenothiazine drugs. de Mol NJ. **Biochem Pharmacol** 1985 Aug 1;34(15):2605-9

Affinity-dependent cross-linking to neurotoxin sites of the acetylcholine receptor mediated by catechol oxidation. Nickoloff BJ, et al. **Biochemistry** 1985 Feb 12;24(4):999-1007

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

Do catecholamines play a physiologic role in regulating corpus luteum function in the pseudopregnant rabbit? Gadsby JE, et al. **Biol Reprod** 1985 May;32(4):907-15

Hypothalamic epinephrine is released into hypophysial portal blood during stress. Gibbs DM. **Brain Res** 1985 Jun 3;335(2):360-4

Clonidine effects on catecholamine levels and turnover in discrete hypothalamic and extra-hypothalamic areas. Jhanwar-Uniyal M, et al. **Brain Res** 1985 Jun 24;337(1):109-16

Effects of catecholamines on spinal motoneurones and spinal reflex discharges in the isolated spinal cord of the newborn rat. Kitazawa T, et al. **Brain Res** 1985 Mar;351(1):31-6

Place preference conditioning with methylphenidate and nomifensine. Martin-Iverson MT, et al. **Brain Res** 1985 Apr 15;332(1):59-67

Cerebellum plus locus coeruleus in tissue culture: I. Catecholamine histofluorescence and extracellular electrophysiology. Seil FJ, et al. **Brain Res** 1985 Jan;349(1-2):165-70

BIBLIOGRAPHY

Intertectal neuronal plasticity in Xenopus laevis: persistence despite catecholamine depletion. Udin SB, et al. **Brain Res** 1985 Mar; 351(1):81-8

Microspectrofluorometric characterization of amine accumulation proximal to lateral hypothalamic lesions. Willis GL, et al. **Brain Res** 1985 May 20;334(2):344-7

Amine accumulation in behavioural pathology. Willis GL, et al. **Brain Res** 1985 Jun;356(2):109-32 (302 ref.)

Ultrastructural evidence of direct synaptic contact of catecholamine terminals with oxytocin-containing neurons in the parvocellular portion of the rat hypothalamic paraventricular nucleus. Yamano M, et al. **Brain Res** 1985 Jun 10;336(1):176-9

Catecholamine innervation of cervical dendrite bundles: possible phrenic nucleus innervation. Bellinger DL, et al. **Brain Res Bull** 1984 Dec; 13(6):701-7

MPTP alters central catecholamine neurons in addition to the nigrostriatal system. Gupta M, et al. **Brain Res Bull** 1984 Dec;13(6):737-42

Effect of delta 9-THC on brain and plasma catecholamine levels as measured by HPLC. Patel V, et al. **Brain Res Bull** 1985 Jan; 14(1):85-90

Plasticity of catecholaminergic neurons in aged rat brain: reinnervation and functional recovery after axotomy. Phelps CJ, et al. **Brain Res Bull** 1984 Dec;13(6):727-36

Early appearance of catecholaminergic neurons in the central nervous system of precocial and altricial avian species. A fluorescence-histochemical study. Guglielmone R, et al. **Cell Tissue Res** 1985;240(2):381-4

Cortisol and catecholamines response to venisection by humans with different blood groups. Locong AH, et al. **Clin Biochem** 1985 Feb; 18(1):67-9

Acetaminophen administration interferes with urinary metanephrine (and catecholamine) determinations [letter] Wilson SP, et al. **Clin Chem** 1985 Jun;31(6):1093-4

Receptor mechanisms in fish chromatophores—VIII. Mediated by beta adrenoceptors, catecholamines always act to disperse pigment in siluroid melanophores. Fujii R, et al. **Comp Biochem Physiol [C]** 1985; 81(1):1-6

Catecholamine hormones and the control of avian salt glands. Wilson JX, et al. **Comp Biochem Physiol [C]** 1985;81(1):77-9

Cardiovascular and catecholamine responses to hypoxemia in chemically sympathectomized fetal lambs. Lewis AB, et al. **Dev Pharmacol Ther** 1985;8(2):129-40

Effect of intravenous ketanserin on plasma catecholamines and renin activity in normal volunteers. Reimann IW, et al. **Eur J Clin Pharmacol** 1985;28(3):273-7

Pharmacological interference with the neurotoxic action of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on central catecholamine neurons in the mouse. Sundström E, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):293-9

Effects of intracerebroventricular 6-hydroxydopamine on catecholaminergic fibers in the rat hypothalamus. Hwang BH, et al. **Exp Neurol** 1985 May;88(2):336-48

Changes in the size of isolated chromaffin granules in ATP-evoked catecholamine release. Warashina A. **FEBS Lett** 1985 May 6; 184(1):87-9

Hormonal influence on the response of the uterus of the Brazilian marsupial Didelphis albiventris to adrenergic drugs. Rocha LR, et al. **Gen Comp Endocrinol** 1985 May;58(2):179-85

Immunohistochemical demonstration of catecholaminergic cell bodies in the spinal cord of the rat. Preliminary note. Dietl M, et al. **Histochemistry** 1985;82(4):385-9

Effect of phosphodiesterase regulators and catecholamines on motility of isolated pregnant rat uterus. Singh M, et al. **Indian J Exp Biol** 1984 Dec;22(12):645-8

Pharmacologic studies of the central action of zopiclone: effects on locomotor activity and brain monoamines in rats. Liu HJ, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):121-8

Brain catecholamines and the central control of food intake. Stricker EM, et al. **Int J Obes** 1984;8 Suppl 1:39-50 (64 ref.)

Sympathetic activity, plasma renin activity (PRA) and kininogen levels in patients haemodialysed with acetate and bicarbonate. Ksiażek A, et al. **Int Urol Nephrol** 1984;16(4):337-44

Exercise, dobutamine, and combined atropine, norepinephrine, and epinephrine compared. Haidet GC, et al. **J Appl Physiol** 1985 Jun; 58(6):2047-53

The effects of hypoxia on catecholamine dynamics in the rat carotid body. Brokaw JJ, et al. **J Auton Nerv Syst** 1985 May;13(1):35-47

Vasoactive amines modulate actin cables (stress fibers) and surface area in cultured bovine endothelium. Welles SL, et al. **J Cell Physiol** 1985 Jun;123(3):337-42

Simultaneous assay of 3,4-dihydroxyphenylalanine, catecholamines and O-methylated metabolites in human plasma using high-performance liquid chromatography. Ishimitsu T, et al. **J Chromatogr** 1985 Feb 8; 337(2):239-48

Catecholamine secretion as a function of perceived coping self-efficacy. Bandura A, et al. **J Consult Clin Psychol** 1985 Jun;53(3):406-14

Radioreceptor assay for beta-adrenergic receptor-reactive catecholamines in serum samples. Iwo K, et al. **J Lab Clin Med** 1985 Jun; 105(6):711-7

The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3-4):175-81

Direct fluorometric assay of catecholamine secretion from isolated bovine adrenal chromaffin cells. Lelkes PI, et al. **J Neurosci Methods** 1985 May;13(3-4):249-55

An improved technique for extracting catecholamines from body fluids. Macdonald IA, et al. **J Neurosci Methods** 1985 May;13(3-4):239-48

Photoaffinity labelling of MSH receptors on Anolis melanophores: effects of catecholamines, calcium and forskolin. Eberle AN, et al. **J Recept Res** 1985;5(1):59-81

Regional changes in catecholamine content of the pregnant uterus. Arkinstall SJ, et al. **J Reprod Fertil** 1985 Mar;73(2):547-57

Changes in dopamine-beta-hydroxylase, and copper, and catecholamine concentrations in human plasma with physical exercise. Ohno H, et al. **J Sports Med Phys Fitness** 1984 Dec;24(4):315-20

Glucose and insulin infusion directly after cardiac surgery: effects on systemic glucose uptake, catecholamine excretion, O2 consumption, and CO2 production. Nilsson F, et al. **JPEN** 1985 Mar-Apr;9(2):159-64

Effect of 2,4,6-trinitrophenol on catecholamine secretion from perfused bovine adrenal glands. Yamanaka K, et al. **Jpn J Pharmacol** 1985 Jan; 37(1):120-3

Hormonal control of renal potassium excretion. Field MJ, et al. **Kidney Int** 1985 Feb;27(2):379-87 (86 ref.)

The effects of a single acute dose of dexamethasone on monoamine and metabolite levels in rat brain. Rothschild AJ, et al. **Life Sci** 1985 Jul 1;36(26):2491-501

The effects of acute and chronic treatment with triiodothyronine and thyroxine on the hypothalamic and telencephalic catecholamine nerve terminal systems of the hypophysectomized male rat. Chronic treatment modulates catecholamine utilization in discrete catecholamine nerve terminal systems. Andersson K, et al. **Neuroendocrinology** 1985 May; 40(5):398-408

Influences of catecholamines on growth hormone release in female goldfish, Carassius auratus. Chang JP, et al. **Neuroendocrinology** 1985 Jun;40(6):463-70

A combined autoradiographic and immunocytochemical study of 3H-corticosterone target neurons and catecholamine neurons in rat and mouse lower brain stem. Duncan GE, et al. **Neuroendocrinology** 1985 Mar;40(3):262-71

Central and peripheral catecholamine innervation of the rat intermediate and posterior pituitary lobes. Saavedra JM. **Neuroendocrinology** 1985 Apr;40(4):281-4

Comparison of the changes in central catecholamine systems following short- and long-term lithium treatment and the consequences of lithium withdrawal. Ahluwalia P, et al. **Neuropsychobiology** 1984; 12(4):217-23

State of adrenergic and cholinergic systems in schizophrenia patients during psychopharmacotherapy. Krupenina LB, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):1-8

Morphological evidence that serotonin-immunoreactive neurons in the nucleus dorsomedialis hypothalami could be under catecholaminergic influence. Arezki F, et al. **Neurosci Lett** 1985 May 14;56(2):161-6

Reflex changes in sympatho-adrenal medullary functions in response to various thermal cutaneous stimulations in anesthetized rats. Kurosawa M, et al. **Neurosci Lett** 1985 May 14;56(2):149-54

Effects of gonadal steroids on catecholamine levels in the brain of the oyster toadfish. Pennypacker KR, et al. **Neurosci Lett** 1985 Apr 9; 55(2):203-6

Effects of intravenously administered 6-hydroxydopamine on the content of monoamines in the median eminence and neurointermediate lobe of the rat. Sheward WJ, et al. **Neurosci Lett** 1985 Apr 9;55(2):141-4

Chlordecone interaction with catecholamine binding and uptake in rat brain synaptosomes. Desaiah D. **Neurotoxicology (Little Rock Ar)** 1985 Spring;6(1):159-65

Effect of dialysate sodium on the dopamine, adrenaline and noradrenaline concentration in haemodialysis patients. Ksiażek A, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985;21:225-9

Prostaglandins, catecholamines, and differentiation of the secondary palate. Greene RM, et al. **Prog Clin Biol Res** 1985;163C:277-81

Effects of ketamine on the catecholamine containing cells of the adrenal gland of the lizard Podarcis s. sicula Raf. Varano L, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr;48(1):145-8

Effects of nicotinic an muscarinic stimulation on calcium flux and catecholamine secretion in primary cultures of adrenal medullary cells. Watanabe J. **Tokushima J Exp Med** 1984 Dec;31(3-4):79-84

[Central neurotransmitters and cardiovascular activity] Xia Y. **Sheng Li Ko Hsueh Chin Chan** 1985 Jan;16(1):27-31 (50 ref.) **(Chi)**

[Expression of the adrenergic phenotype by dorsal root ganglion cells of the quail in culture in vitro] Xue ZG, et al. **C R Acad Sci [III]** 1985;300(13):483-8 (Eng. Abstr.) **(Fre)**

[Concentrations of catecholamines in CSF and plasma, and cardiovascular effects following epidural administration of 2 mg epinephrine] Nakajima

J. **Masui** 1985 Feb;34(2):144–51 (Eng. Abstr.) **(Jpn)**

[Neuro-intestinal peptides and peptide-producing cells--immunohistocytochemistry of catecholamines and opioid peptides in the hamster adrenal medulla] Kobayashi S, et al. **Nippon Heikatsukin Gakkai Zasshi** 1984 Oct;20(5):393–9 **(Jpn)**

[Catecholamine content in the human adrenal gland] Nakada T, et al. **Nippon Hinyokika Gakkai Zasshi** 1985 Feb;76(2):239–43 (Eng. Abstr.) **(Jpn)**

[A study on catecholamine contents of the canine upper urinary tract] Nishimoto T. **Nippon Hinyokika Gakkai Zasshi** 1985 Jan;76(1):56–64 (Eng. Abstr.) **(Jpn)**

[Spatial reorganization of the organelles of catecholamine-synthesizing group A1 neurons during emotional stress] Zhigadlo BA, et al. **Arkh Anat Gistol Embriol** 1985 Feb;88(2):11–6 (Eng. Abstr.) **(Rus)**

[Catecholamine levels in pancreatic tissue after intraperitoneal administration of acetylcholine] Gal'kiv MA, et al. **Fiziol Zh** 1985 Mar–Apr;31(2):230–4 **(Rus)**

[Cardiomyocytes in monolayer culture and the effect on them of catecholamines and hypoxia] Gurevich MI, et al. **Fiziol Zh** 1985 May–Jun;31(3):267–72 (Eng. Abstr.) **(Rus)**

[Biogenic amine content of various parts of the brain under the stimulation of interoceptors of the gastrointestinal tract] Kravets SV, et al. **Fiziol Zh** 1985 Mar–Apr;31(2):216–9 **(Rus)**

[Changes in blood monoamine and 11-hydroxycorticosteroid levels in rats under the action of stress] Ugarova OP. **Fiziol Zh** 1985 Mar–Apr; 31(2):224–7 **(Rus)**

[Effect of gamma-aminobutyric acid, taurine and catecholamines on the synaptic processes in Lorenzini's ampules in Black Sea skates] Akoev GN, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):466–71 (Eng. Abstr.) **(Rus)**

[Cytophotometric study of catecholamines and acetylcholinesterase in neurons of the intramural plexus of the urinary bladder of the cat in controls and animals exposed to experimental conditions] Lapsha VI, et al. **Neirofiziologiia** 1985;17(2):263–70 (Eng. Abstr.) **(Rus)**

CENTRAL NERVOUS SYSTEM AGENTS

Characteristics of the cortical and hippocampal EEG power spectra of rabbits during normal behavioral states and after administration of CNS acting drugs. Yamamoto J. **Jpn J Pharmacol** 1985 Mar;37(3):227–34

Drugs and chemicals that act on the central nervous system: interpretation of experimental evidence. Kellogg CK. **Prog Clin Biol Res** 1985; 163C:147–53 (27 ref.)

CHILD BEHAVIOR DISORDERS

Treatment of an aggressive, compulsive adolescent with sultopride [letter] Bucci L. **Am J Psychiatry** 1985 Jul;142(7):882–3

CHILD DEVELOPMENT DISORDERS

Understanding and treatment of childhood depression. Aylward GP. **J Pediatr** 1985 Jul;107(1):1–9

CHLORAMINES

A possible origin of chemiluminescence in phagocytosing neutrophils. Reaction between chloramines and H2O2. Zgliczyński JM, et al. **Int J Biochem** 1985;17(4):515–9

Generation of free radical intermediates from foreign compounds by neutrophil-derived oxidants. Kalyanaraman B, et al. **J Clin Invest** 1985 May;75(5):1618–22

[In vitro antibacterial activity of chloramide] Farina C, et al. **G Ital Chemioter** 1984 Sep–Dec;31(3):215–8 (Eng. Abstr.) **(Ita)**

CHLORDIAZEPOXIDE

Chlordiazepoxide toxicity in Limbitrol overdose [letter] Goethe JW, et al. **Am J Psychiatry** 1985 Jun;142(6):774

Comparison of limbitrol (chlordiazepoxide/amitriptyline) and amitriptyline alone as a single night-time dose for the treatment of depression with anxiety. James RT, et al. **J Int Med Res** 1985; 13(2):84–7

Brain amines and effects of chlordiazepoxide on motor activity in response to stress. Freeman GB, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):665–70

The effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats. Evenden JL, et al. **Psychopharmacology (Berlin)** 1985;85(3):361–6

The sedative effects of CL 218,872, like those of chlordiazepoxide, are reversed by benzodiazepine antagonists. File SE, et al. **Psychopharmacology (Berlin)** 1985;85(3):295–300

A comparison between chlordiazepoxide and CL 218,872--a synthetic nonbenzodiazepine ligand for benzodiazepine receptors on spontaneous locomotor activity in rats. McElroy JF, et al. **Psychopharmacology (Berlin)** 1985;85(2):224–6

[Effect of stable strontium on spontaneous and drug-induced motor activity in the rat] Escanero JF, et al. **Arch Farmacol Toxicol** 1985 Apr; 11(1):33-9 (Eng. Abstr.) **(Spa)**

P-CHLOROPHENYLALANINE

Decreased serotonin content of embryonic raphe neurons following maternal administration of p-chlorophenylalanine: a quantitative immunocytochemical study. Lauder JM, et al. **Brain Res** 1985 May; 352(1):107–14

CHLORPROMAZINE

Chlorpromazine-associated haemolysis in anorexia nervosa. Van der Weyden MB, et al. **Acta Haematol (Basel)** 1985;73(2):111–3

Comparison of inhibitory actions of chlorpromazine or its 7,8-dihydroxy and 7,8-dioxo-didesmethyl analogs on DA-sensitive adenylate cyclase and calmodulin activation of phosphodiesterase in rat striatum. Palmer GC, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):202–11

Effects of chlorpromazine and its dihydroxy metabolite on calcium movement and electrical activity in superior cervical ganglia. Guzman-Harty M, et al. **Arch Toxicol** 1985 Feb;56(4):272–8

Inhibitory effect of chlorpromazine on bone formation in vivo and in vitro. Komoda T, et al. **Biochem Pharmacol** 1985 Jul 1; 34(13):2389–91

Drug-protein interactions: binding of chlorpromazine to calmodulin, calmodulin fragments, and related calcium binding proteins. Marshak DR, et al. **Biochemistry** 1985 Jan 1;24(1):144–50

Chlorpromazine inhibition of electron transport in Azotobacter vinelandii membranes. Wong TY, et al. **Biochim Biophys Acta** 1985 May 31; 807(3):320–3

The mechanism of intestinal transport of sulfamethoxazole and the effect of chlorpromazine in rat everted intestine. Chung YH, et al. **J Pharmacobiodyn** 1985 Feb;8(2):142–9

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984–85;22(6):573–9

Effect of chlorpromazine on peritoneal clearances. Indraprasit S, et al. **Nephron** 1985;40(3):341–3

Effect of centrally acting drugs on ethanol detoxification enzymes in distinct rat brain regions. Messiha FS. **Neurobehav Toxicol Teratol** 1985 Mar–Apr;7(2):181–4

Drug interactions and vasoconstrictors used in local anesthetic solutions. Yagiela JA, et al. **Oral Surg Oral Med Oral Pathol** 1985 Jun; 59(6):565–71

Temperature dependent modification of radiosensitivity following hypoxic cytocidal action of chlorpromazine. Shenoy MA, et al. **Radiat Environ Biophys** 1985;24(2):113–7

Thorazine injected; pt. dies: criminal charges. Case in point: people v. Nygren (696 P. 2d 270--CO). Tammelleo AD. **Regan Rep Nurs Law** 1985 May;25(12):2

[Effects of haloperidol, chlorpromazine, metoclopramide and ascorbic acid on adrenergic salivation and lacrimation in mice at an ambient temperature of 30 degrees C] Li BH, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar;6(1):24–6 (Eng. Abstr.) **(Chi)**

[A simple phosphorimetric method for the determination of chlorpromazine] Huang RH, et al. **Yao Hsueh Hsueh Pao** 1984 Aug; 19(8):606–10 (Eng. Abstr.) **(Chi)**

[Biotransformation of Chlorphenethazin (Elroquil, Marophen)] Pfeifer S, et al. **Pharmazie** 1985 Jan;40(1):37–9 (Eng. Abstr.) **(Ger)**

CHLORPROTHIXENE

Determination of chlorprothixene and its sulfoxide metabolite in plasma by high-performance liquid chromatography with ultraviolet and amperometric detection. Brooks MA, et al. **J Chromatogr** 1985 Feb 8;337(2):351–62

Tetracyclic pyridazines as potential psychopharmacological agents. Ross BS, et al. **J Med Chem** 1985 Jul;28(7):870–5

CHOICE BEHAVIOR

The effects of delaying reward on choice preference in rats with hippocampal or selective septal lesions. Rawlins JN, et al. **Behav Brain Res** 1985 May;15(3):191–203

Differential effects of pimozide on response-rate and choice accuracy in a self-stimulation paradigm in mice. Bowers W, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):521–6

CLOMIPRAMINE

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128–34

Role of the serotonin uptake carrier in the neurochemical response to methamphetamine: effects of citalopram and chlorimipramine. Schmidt CJ, et al. **Neurochem Res** 1985 May;10(5):637–48

Clomipramine and imipramine in obsessive-compulsive disorder. Volavka J, et al. **Psychiatry Res** 1985 Jan;14(1):85-93

[Treatment of obsessive compulsive neurosis] Greenberg D, et al. **Harefuah** 1985 Mar 1;108(5):231-5 (Eng. Abstr.) **(Heb)**

COCAINE

Atomizer modification for nasal administration of cocaine and other drugs. Rector FT, et al. **Anesth Analg** 1985 Jul;64(7):739-41

Carl Koller: the man and the drug. McAuley JE. **Br Dent J** 1985 May 11;158(9):339-42

Frequency-related, bidirectional limbic responses to cocaine: comparisons with amphetamine and lidocaine. Lesse H, et al. **Brain Res** 1985 May 27;335(1):21-31

Cocaine increases EEG beta: a replication and extension of Hans Berger's historic experiments. Herning RI, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):470-7

Platelet responsiveness and biosynthesis of thromboxane and prostacyclin in response to in vitro cocaine treatment. Togna C, et al. **Haemostasis** 1985;15(2):100-7

An epidemic of cocaine associated deaths in Utah. Sander R, et al. **J Forensic Sci** 1985 Apr;30(2):478-84

The danger of cocaine [editorial] Pollin W. **JAMA** 1985 Jul 5; 254(1):98

Bromocriptine as treatment of cocaine abuse [letter] Dackis CA, et al. **Lancet** 1985 May 18;1(8438):1151-2

Catecholamine-independent behavioral and neurochemical effects of cocaine in rats. Gale K. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 54:323-32

Sensitization of rotational behavior produced by a single exposure to cocaine. Guan LC, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):901-3

[A brief review on cocaine] Renggli R. **Schweiz Med Wochenschr** 1985 Mar 30;115(13):426-30 (15 ref.) (Eng. Abstr.) **(Ger)**

[Fatal cocaine poisoning] Kisser W. **Z Rechtsmed** 1985;94(2):155-8 (Eng. Abstr.) **(Ger)**

COGNITION

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

Information processing and benzodiazepines. Kleindienst-Vanderbeke G. **Neuropsychobiology** 1984;12(4):238-43

COMPULSIVE BEHAVIOR

Treatment of an aggressive, compulsive adolescent with sultopride [letter] Bucci L. **Am J Psychiatry** 1985 Jul;142(7):882-3

CONDITIONING (PSYCHOLOGY)

Associative conditioning analog selectively increases cAMP levels of tail sensory neurons in Aplysia. Ocorr KA, et al. **Proc Natl Acad Sci USA** 1985 Apr;82(8):2548-52

Anxiolytic drugs and the acquisition of conditioned fear in mice. Sanger DJ, et al. **Psychopharmacology (Berlin)** 1985;85(3):284-8

CONDITIONING, CLASSICAL

Direct and indirect behavioral pathways to the social transmission of food avoidance. Galef BG Jr. **Ann NY Acad Sci** 1985;443:203-15

Introduction: physiological mechanisms in conditioned taste aversions. Grill HJ. **Ann NY Acad Sci** 1985;443:67-88

GABA effect on conditioned reflex responses in teleost. Ivanuš J, et al. **Ann NY Acad Sci** 1985;444:543-6

Conditioned food aversions and satiety signals. Kulkosky PJ. **Ann NY Acad Sci** 1985;443:330-47

Conditioned taste aversions: a behavioral index of toxicity. Riley AL, et al. **Ann NY Acad Sci** 1985;443:272-92

Glucocorticoid and other hormonal substrates of conditioned taste aversion. Smotherman WP. **Ann NY Acad Sci** 1985;443:126-44

Interfering with taste aversion learning in rats: the role of associative interference. Cannon DS, et al. **Appetite** 1985 Mar;6(1):1-19

Potentiation and overshadowing in preweanling and adult rats. Kucharski D, et al. **J Exp Psychol [Anim Behav]** 1985 Jan;11(1):15-34

Conditioned taste aversion suppresses induction of delayed-type hypersensitivity immune reactions. Kelley KW, et al. **Physiol Behav** 1985 Feb;34(2):189-93

CONDITIONING, OPERANT

Arginine vasopressin inoculates against age-related changes in temporal memory. Meck WH, et al. **Ann NY Acad Sci** 1985;444:453-6

Physostigmine reverses memory deficits produced by pretraining electrical stimulation of the dorsal hippocampus in mice. Micheau J, et al. **Behav Brain Res** 1985 Apr;15(2):75-81

Effects of acute oral administration of lithium compounds on multiple schedule performance in rats. Chrislip DW, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):39-42

Differential effects of pimozide on response-rate and choice accuracy in a self-stimulation paradigm in mice. Bowers W, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):521-6

Neuroleptic-induced deficits in operant responding for temperature reinforcement. Ettenberg A, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):761-7

Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. Gramling SE, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):541-5

Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Picker M, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):389-93

Haloperidol and nonreinforcement produce different patterns of response slowing in a food reinforced runway task. Wirtshafter D, et al. **Pharmacol Biochem Behav** 1985 May;22(5):661-3

The effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats. Evenden JL, et al. **Psychopharmacology (Berlin)** 1985;85(3):361-6

Methylphenidate: rate-dependent drug effects in hyperactive boys. Weber K. **Psychopharmacology (Berlin)** 1985;85(2):231-5

CONFLICT (PSYCHOLOGY)

Prenatal stress impairs maternal behavior in a conflict situation and reduces hippocampal benzodiazepine receptors. Fride E, et al. **Life Sci** 1985 Jun 3;36(22):2103-9

CORTICOSTERONE

Pharmacology of the steroid regulation of transmitter choice in cultured rat sympathetic ganglia. McLennan IS, et al. **Aust J Exp Biol Med Sci** 1984 Oct;62 (Pt 5):627-39

Phospholipids, sterol carrier protein2 and adrenal steroidogenesis. Vahouny GV, et al. **Biochim Biophys Acta** 1985 May 17; 834(3):324-30

Effect of fetal decapitation on unbound rat plasma corticosterone concentration at the end of pregnancy. Cohen A, et al. **Biol Neonate** 1985;47(3):163-9

Corticosterone modulation of neurotransmitter receptors in rat hippocampus: a quantitative autoradiographic study. Biegon A, et al. **Brain Res** 1985 Apr 22;332(2):309-14

The development of the glucocorticoid receptor system in the rat limbic brain. I. Ontogeny and autoregulation. Meaney MJ, et al. **Brain Res** 1985 Feb;350(1-2):159-64

The development of the glucocorticoid receptor system in the rat limbic brain. III. Negative-feedback regulation. Sapolsky RM, et al. **Brain Res** 1985 Feb;350(1-2):169-73

Effects of steroid hormones on the neuropil of the hypothalamic paraventricular nucleus of male chickens. Panzica GC, et al. **Cell Tissue Res** 1985;240(1):169-74

Effects of corticotropin-releasing factor (CRF) on aldosterone and 18-hydroxycorticosterone secretion. Maser-Gluth C, et al. **Clin Exp Hypertens** [A] 1984;6(10-11):2097-100

Cytochemical and cytophysiological studies of gonadotropin-releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396-404

Androstenedione or corticosterone treatment during pregnancy alters estrous cycle of adult female offspring in mice. Harvey PW, et al. **Experientia** 1985 Apr 15;41(4):492-4

Effects of chronic changes in dietary electrolytes and acute stress on plasma levels of corticosterone and aldosterone in the duck (Anas platyrhynchos). Klingbeil CK. **Gen Comp Endocrinol** 1985 Apr; 58(1):10-9

Changes in hormone levels in relation to breeding behavior in male bullfrogs (Rana catesbeiana) at the individual and population levels. Mendonça MT, et al. **Gen Comp Endocrinol** 1985 May;58(2):270-9

Inhibition of the ACTH adrenal response to stress by treatment with hydrocortisone, prednisolone and dexamethasone in the rat. Baumann JB, et al. **Horm Res** 1985;21(4):254-60

Alterations in the activities of subcellular fractions marker enzymes in rat liver and brain by hydrocortisone and corticosterone treatment. Garcia MV, et al. **Int J Biochem** 1985;17(2):203-8

The stimulation of lipogenesis in white adipose tissue from fed rats by corticosterone. Minshull M, et al. **Int J Biochem** 1985;17(4):529-32

In vitro metabolism of [3H] corticosterone by mammary glands from lactating rats. Isolation and identification of 21-acyl[3H]corticosterone. Pearlman WH, et al. **J Biol Chem** 1985 May 10;260(9):5296-301

Thymosin fraction 5 causes increased serum corticosterone in rodents in vivo. McGillis JP, et al. **J Immunol** 1985 Jun;134(6):3952-5

Muscarinic receptor subclasses in the chick embryo retina: influence of corticosterone treatment. Gremo F, et al. **J Neurochem** 1985 Aug; 45(2):345-51

Eighteen-deoxyaldosterone and other less polar forms of 18-hydroxycorticosterone as aldosterone precursors in rat adrenals.

Cozza EN, et al. **J Steroid Biochem** 1985 May;22(5):665-72

Comparison of the distribution kinetics and metabolism to acid end-products of corticosterone and 11-deoxycorticosterone in BALB/c mice. Marandici A, et al. **J Steroid Biochem** 1985 Apr;22(4):539-45

Dissociation between adrenocorticotropin and corticosterone responses to restraint after previous chronic exposure to stress. Armario A, et al. **Life Sci** 1985 Jun 3;36(22):2085-92

A combined autoradiographic and immunocytochemical study of 3H-corticosterone target neurons and catecholamine neurons in rat and mouse lower brain stem. Duncan GE, et al. **Neuroendocrinology** 1985 Mar;40(3):262-71

ACTH and corticosterone secretion in rats following removal of the neurointermediate lobe of the pituitary gland. Fagin KD, et al. **Neuroendocrinology** 1985 Apr;40(4):352-62

Involvement of the sensory cortex in adrenocortical responses following photic and acoustic stimulation in the rat. Feldman S, et al. **Neurosci Lett** 1985 Apr 9;55(2):249-53

The effect of adrenalectomy and corticosterone on homotypic collateral sprouting of serotonergic fibers in hippocampus. Zhou FC, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):111-6

Effects of emotional stress on the immune system. Miller NE. **Pavlov J Biol Sci** 1985 Apr-Jun;20(2):47-52

Comparative biochemical responses of rats to different stressful stimuli. Odio MR, et al. **Physiol Behav** 1985 Apr;34(4):595-9

Maturation of the diurnal rhythm of corticosterone in female domestic fowl. Webb ML, et al. **Poult Sci** 1985 Apr;64(4):744-50

Increase in plasma ACTH after dopaminergic stimulation in rats. Ježová D, et al. **Psychopharmacology (Berlin)** 1985;85(2):201-3

In vivo effects of glucocorticoids on serum corticosterone levels in rats. Yamada K, et al. **Res Commun Chem Pathol Pharmacol** 1985 Mar; 47(3):441-4

[Appraisal of ultradian components in the ethosecretogram of rat] Shiraishi I. **Hokkaido Igaku Zasshi** 1985 Jan;60(1):66-81 (Eng. Abstr.) **(Jpn)**

[Development of a photoperiod-controllable clean rack for rats: circadian rhythms of water intake and blood corticosterone levels] Torii R, et al. **Jikken Dobutsu** 1985 Jan;34(1):57-62 (Eng. Abstr.) **(Jpn)**

CORTICOTROPIN

The effect of nifedipine on CRF-41 and AVP-induced ACTH release in vitro. Murakami K, et al. **Acta Endocrinol (Copenh)** 1985 May; 109(1):32-6

Opiomelanocorticotropic-like hormones in Vipera aspis pituitary. Uva B, et al. **Acta Histochem (Jena)** 1985;76(1):81-7

Somatostatin inhibition of cyclic AMP accumulation and adrenocorticotropin release from mouse anterior pituitary tumor cells: mode of action and self-regulation. Reisine TD. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:169-77

Distribution of the pro-opiomelanocortin derived peptides, adrenocorticotrope hormone, alpha-melanocyte-stimulating hormone and beta-endorphin (ACTH, alpha-MSH, beta-END) in the rat hypothalamus. Mezey E, et al. **Brain Res** 1985 Mar 4;328(2):341-7

Blood pressure responses to ACTH and adrenaline infusions in dogs. Anderson WP, et al. **Clin Exp Hypertens [A]** 1985;7(4):525-37

Acute and chronic effects of ACTH on thermogenesis and brown adipose tissue in the rat. Rothwell NJ, et al. **Comp Biochem Physiol [A]** 1985; 81(1):99-102

Re-evaluation of 'frontal deafferentation' studies on the regulation of ACTH secretion in the light of CRF immunohistology. Lengvári I, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):3-9

Changes induced in rabbit plasma and aqueous humour by ACTH4-10 and ACTH1-24. Stárka L, et al. **Endocrinol Exp (Bratisl)** 1985 Mar; 19(1):25-8

Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. Young EA, et al. **Endocrinology** 1985 Jul;117(1):23-30

Inhibition of the ACTH adrenal response to stress by treatment with hydrocortisone, prednisolone and dexamethasone in the rat. Baumann JB, et al. **Horm Res** 1985;21(4):254-60

Bacterial lipopolysaccharide induction of leukocyte-derived corticotropin and endorphins. Harbour-McMenamin D, et al. **Infect Immun** 1985 Jun; 48(3):813-7

Lack of renal effects of DOCA, ACTH, spironolactone, and angiotensin II in Squalus acanthias. Churchill PC, et al. **J Exp Zool** 1985 Apr; 234(1):17-22

Dissociation between adrenocorticotropin and corticosterone responses to restraint after previous chronic exposure to stress. Armario A, et al. **Life Sci** 1985 Jun 3;36(22):2085-92

ACTH and corticosterone secretion in rats following removal of the neurointermediate lobe of the pituitary gland. Fagin KD, et al. **Neuroendocrinology** 1985 Apr;40(4):352-62

Development of hypothalamic opioid neurons: a combined immunocytochemical and [3H]thymidine autoradiographic study. Khachaturian H, et al. **Neuropeptides** 1985 Feb;5(4-6):477-80

Changes in releasability of ACTH and beta-endorphin with chronic stress. Young E, et al. **Neuropeptides** 1985 Feb;5(4-6):545-8

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417-51 (238 ref.)

Ultrashort-loop positive feedback of corticotropin (ACTH)-releasing factor to enhance ACTH release in stress. Ono N, et al. **Proc Natl Acad Sci USA** 1985 May;82(10):3528-31

Loss of sensitivity to ACTH of adrenocortical cells isolated from maturing domestic fowl. Carsia RV, et al. **Proc Soc Exp Biol Med** 1985 Jul; 179(3):279-82

Increase in plasma ACTH after dopaminergic stimulation in rats. Ježová D, et al. **Psychopharmacology (Berlin)** 1985;85(2):201-3

ACTH-releasing activity of urotensin I and ovine CRF: interactions with arginine vasotocin, isotocin and arginine vasopressin. Fryer J, et al. **Regul Pept** 1985 May;11(1):11-5

[Corticotropin releasing factor] Conte-Devolx B, et al. **Presse Med** 1985 Mar 30;14(13):737-41 (Eng. Abstr.) **(Fre)**

[Effect of an introductory dose of etomidate, methohexital and midazolam on adrenal cortex function before and after ACTH-stimulation] Börner U, et al. **Dtsch Med Wochenschr** 1985 May 10;110(19):750-2 (Eng. Abstr.) **(Ger)**

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

[Brain blood supply and beta-endorphin and corticotropin content on exposure to thyroliberin] Mirozoian RS, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):318-20 (Eng. Abstr.) **(Rus)**

[Participation of gamma-aminobutyric acid in regulating corticotropin secretion in rats] Mishunina TM, et al. **Fiziol Zh** 1985 May-Jun; 31(3):321-6 (Eng. Abstr.) **(Rus)**

CORTICOTROPIN RELEASING HORMONE

The distribution of corticotrophin-releasing factor immunoreactivity in various ovine tissues. Kawai K, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):433-9

The effect of nifedipine on CRF-41 and AVP-induced ACTH release in vitro. Murakami K, et al. **Acta Endocrinol (Copenh)** 1985 May; 109(1):32-6

Studies on the site of origin and molecular form of the extrahypothalamic corticotrophin-releasing factor (CRF) in rats. Yasuda N, et al. **Acta Endocrinol (Copenh)** 1985 Jun;109(2):145-52

Corticotropin-releasing factor, sauvagine, and urotensin I: effects on blood flow. Lenz HJ, et al. **Am J Physiol** 1985 Jul;249(1 Pt 2):R85-90

Corticotropin-releasing factor inhibits insulin release from perfused rat pancreas. Moltz JH, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 1):E741-3

Corticotropin-releasing factor: a physiologic regulator of adrenal epinephrine secretion. Brown MR, et al. **Brain Res** 1985 Mar 4; 328(2):355-7

Corticotropin-releasing factor (CRF)-immunoreactive neurons in the mammillary body of the rat. Kovács M, et al. **Cell Tissue Res** 1985; 240(2):455-60

The origin and ultrastructural characteristics of corticotropin-releasing factor (CRF)-immunoreactive nerve fibers in the posterior pituitary of the rat. Lengvári I, et al. **Cell Tissue Res** 1985;240(2):467-71

Studies on peptides. CXXIV. Solution synthesis of the hentetracontapeptide amide corresponding to the entire amino acid sequence of human corticotropin releasing factor (hCRF). Fujii N, et al. **Chem Pharm Bull (Tokyo)** 1984 Dec;32(12):4797-805

Studies on peptides. CXXIII. Preparations of nine peptide fragments for the synthesis of human corticotropin releasing factor (hCRF). Fujii N, et al. **Chem Pharm Bull (Tokyo)** 1984 Dec;32(12):4786-96

Effects of corticotropin-releasing factor (CRF) on aldosterone and 18-hydroxycorticosterone secretion. Maser-Gluth C, et al. **Clin Exp Hypertens [A]** 1984;6(10-11):2097-100

Re-evaluation of 'frontal deafferentation' studies on the regulation of ACTH secretion in the light of CRF immunohistology. Lengvári I, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):3-9

Effects and pharmacokinetic properties of the rat/human corticotropin-releasing factor in rhesus monkeys. Schürmeyer TH, et al. **Endocrinology** 1985 Jul;117(1):300-6

Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. Young EA, et al. **Endocrinology** 1985 Jul;117(1):23-30

Relationship between pituitary responses to human corticotropin-releasing factor and thyrotropin-releasing hormone in depressives and normal controls. Holsboer F, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):153-4

Opposite regulation of pro-opiomelanocortin gene transcription by glucocorticoids and CRH. Gagner JP, et al. **Mol Cell Endocrinol** 1985 Apr;40(1):25-32

Co-localization of corticotropin releasing factor and vasopressin mRNA in neurones after adrenalectomy. Wolfson B, et al. **Nature** 1985 May 2-8;315(6014):59-61

Morphometrical analysis of the distribution of corticotrophin releasing factor, glucocorticoid receptor and phenylethanolamine-N-methyltransferase immunoreactive structures in the paraventricular hypothalamic nucleus of the rat. Agnati LF, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):147-52

CORTICOTROPIN

Anatomical and ontogenetic studies of the human paraventriculo-infundibular corticoliberin system. Bresson JL, et al. **Neuroscience** 1985 Apr;14(4):1077-90

Long-term suspension culture of isolated hypothalamic nuclei of the rat: morphological differentiation and release of substances influencing corticotropin and growth hormone secretion. Gyévai A, et al. **Neuroscience** 1985 Feb;14(2):519-33

Distribution of CRF- and tyrosine hydroxylase-immunoreactive neurons in the brainstem of the domestic fowl (Gallus domesticus). Knigge KM, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):97-101

Ultrashort-loop positive feedback of corticotropin (ACTH)-releasing factor to enhance ACTH release in stress. Ono N, et al. **Proc Natl Acad Sci USA** 1985 May;82(10):3528-31

Interaction of arginine vasopressin and corticotropin releasing factor demonstrated with an improved bioassay. Graf MV, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):303-8

ACTH-releasing activity of urotensin I and ovine CRF: interactions with arginine vasotocin, isotocin and arginine vasopressin. Fryer J, et al. **Regul Pept** 1985 May;11(1):11-5

[Corticotropin releasing factor] Conte-Devolx B, et al. **Presse Med** 1985 Mar 30;14(13):737-41 (Eng. Abstr.) **(Fre)**

DANSYL COMPOUNDS

pH dependence of phosphate transport across the red blood cell membrane after modification by dansyl chloride. Berghout A, et al. **Biochim Biophys Acta** 1985 May 14;815(2):281-6

Binding of N-dansylgalactosamine to the lectin from Erythrina cristagalli as followed by stopped-flow and pressure-jump relaxation kinetics. De Boeck H, et al. **Eur J Biochem** 1985 May 15;149(1):141-5

New high-performance liquid chromatography system for the separation of biogenic amines as their Dns derivatives. Hayman AR, et al. **J Chromatogr** 1985 Jun 7;325(2):462-6

DELUSIONS

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

DEMENTIA

Rational drug treatment of dementia? [editorial] Byrne J, et al. **Br Med J [Clin Res]** 1985 Jun 22;290(6485):1845-6

DEPRESSION

Plasma tryptophan, age and depression. Phipps DA, et al. **Age Ageing** 1985 Mar;14(2):71-5

Biochemical theories of schizophrenia and depression. Hollister LE. **Ann Acad Med Singapore** 1985 Jan;14(1):76-80

Brief review of published alprazolam clinical studies. Straw RN. **Br J Clin Pharmacol** 1985;19 Suppl 1:57S-59S (22 ref.)

DEPRESSIVE DISORDER

Qualitative and quantitative analysis of the action of typical and atypical antidepressants in the experimental animal. Kozlovskaya MM, et al. **Ann Ist Super Sanita** 1984;20(1):73-7

Can lithium carbonate prolong the antidepressant effect of sleep deprivation? [letter] Baxter LR Jr. **Arch Gen Psychiatry** 1985 Jun; 42(6):635

Internight variability of REM latency in major depression: implications for the use of REM latency as a biological correlate. Ansseau M, et al. **Biol Psychiatry** 1985 May;20(5):489-505

Resting metabolic rate is reduced in patients treated with antidepressants. Fernstrom MH, et al. **Biol Psychiatry** 1985 Jun;20(6):692-5

Animal models of depression: parallels and correlates to severe depression in humans. Jesberger JA, et al. **Biol Psychiatry** 1985 Jul; 20(7):764-84

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. Shapira B, et al. **Biol Psychiatry** 1985 May; 20(5):576-9

Platelet monoamine oxidase inhibition by deprenyl and tranylcypromine: implications for clinical use. Simpson GM, et al. **Biol Psychiatry** 1985 Jun;20(6):684-7

Factor analytic derivation of the MHPG/NM ratio: implications for studying the link between physical fitness and depression. Sothmann MS, et al. **Biol Psychiatry** 1985 May;20(5):579-83

Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: studies on the olfactory bulbectomized rat model of depression. O'Connor WT, et al. **Br J Clin Pharmacol** 1985; 19 Suppl 1:49S-56S

Relationship between pituitary responses to human corticotropin-releasing factor and thyrotropin-releasing hormone in depressives and normal controls. Holsboer F, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):153-4

A clinical and pharmacological study of the antidepressant activity of viloxazine in adult and elderly patients. Tosca P, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 May;23(5):270-3

Neuroticism and personality disorder in depression. Davidson J, et al. **J Affective Disord** 1985 Mar-Apr;8(2):177-82

The influence of mania and depression on the pharmacokinetics of lithium. A longitudinal single-case study. Kukopoulos A, et al. **J Affective Disord** 1985 Mar-Apr;8(2):159-66

Plasma nortriptyline and clinical response in depression. Murphy GE, et al. **J Affective Disord** 1985 Mar-Apr;8(2):123-9

Drug response as a predictor of transmission of non-bipolar major depression within families. Prusoff BA, et al. **J Affective Disord** 1985 Mar-Apr;8(2):171-6

Imipramine metabolism in recurrent depressive episodes. Tollefson G, et al. **J Affective Disord** 1985 Mar-Apr;8(2):183-6

Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. Feighner JP, et al. **J Clin Psychiatry** 1985 Jun;46(6):206-9

Trimipramine and maprotiline: antidepressant, anxiolytic, and cardiotoxic comparison. Pecknold JC, et al. **J Clin Psychiatry** 1985 May; 46(5):166-71

Thyroxine binding and TSH in recurrent depressive episodes. Tollefson G, et al. **J Clin Psychiatry** 1985 Jul;46(7):267-72

Peripheral edema associated with trazodone: a report of ten cases. Barrnett J, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):161-4

Child and adolescent nortriptyline single dose kinetics predict steady state plasma levels and suggested dose: preliminary data. Geller B, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):154-8

Amitriptyline and hydroxylated metabolite plasma levels in depressed outpatients. Robinson DS, et al. **J Clin Psychopharmacol** 1985 Apr; 5(2):83-8

Monoamine oxidase inhibitors in the treatment of atypical depression. Zisook S, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):131-7

Stress and immunomodulation: the role of depression and neuroendocrine function. Stein M, et al. **J Immunol** 1985 Aug; 135(2 Suppl):827s-833s

Comparison of limbitrol (chlordiazepoxide/amitriptyline) and amitriptyline alone as a single night-time dose for the treatment of depression with anxiety. James RT, et al. **J Int Med Res** 1985; 13(2):84-7

Two cases of obsessive-compulsive disorder with depression responsive to trazodone. Baxter LR Jr. **J Nerv Ment Dis** 1985 Jul;173(7):432-3

Understanding and treatment of childhood depression. Aylward GP. **J Pediatr** 1985 Jul;107(1):1-9

Enhanced signal transduction by adenylate cyclase in platelet membranes of patients showing antidepressant responses to alprazolam: preliminary data. Mooney JJ, et al. **J Psychiatr Res** 1985;19(1):65-75

Cholinomimetic drug RS 86, REM sleep, and depression [letter] Berger M, et al. **Lancet** 1985 Jun 15;1(8442):1385-6

Mianserin versus amitriptyline for depression: a double-blind 6-week trial. Rabkin JG, et al. **Neuropsychobiology** 1984;12(4):224-8

KUSTA (Kurz-Skala Stimmung/Aktivierung): a daily self-rating scale for depressive patients. Wendt G, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):118-22

Studies on the locus coeruleus system in an animal model for antidepressive activity. Kostowski W, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):523-30

The olfactory bulbectomized rat as a model of depression. Leonard BE. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):561-9 (30 ref.)

Trazodone in endogenous depressed patients: a negative report and a critical evaluation of the pertaining literature. Klein HE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(2):173-86

Delta-sleep inducing peptide in cerebrospinal fluid from schizophrenics, depressives and healthy volunteers. Lindström LH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):83-90

The cortisol response to desipramine in endogenous depressives and normal controls: preliminary findings. Asnis GM, et al. **Psychiatry Res** 1985 Mar;14(3):225-33

Elevated plasma homovanillic acid in depressed females with melancholia and psychosis. Devanand DP, et al. **Psychiatry Res** 1985 May; 15(1):1-4

The effect of clorgyline on noradrenergic function. Ross RJ, et al. **Psychopharmacology (Berlin)** 1985;85(2):227-30

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

'Pseudo-allergy': treatment with an MAO inhibitor. Ulwelling W **Psychosomatics** 1985 Jun;26(6):535-6

A preliminary report on anti-depressant therapy and its effects on hope and immunity. Udelman DL, et al. **Soc Sci Med** 1985; 20(10):1069-72

[Alprazolam (Tafil). A new benzodiazepine-with a new action profile?] Rasmussen SB, et al. **Ugeskr Laeger** 1985 Apr 29;147(18):1495-7 **(Dan)**

[Comparison of various tools for evaluating depression apropos of a study on Athymil 30 mg] Lempérière T, et al. **Ann Med Psychol (Paris)** 1984 Nov;142(9):1206-14 **(Fre)**

[Selective study of sulfate and glucuronide conjugates of urinary MHPG in nervous depression. Peripheral and central influences] Peyrin L, et al. **Encephale** 1985 Jan-Feb;11(1):19-24 (Eng. Abstr.) **(Fre)**

[Depressive states and biological markers] Boyer P. **Rev Prat** 1985 May 11;35(27):1627-32 (Eng. Abstr.) **(Fre)**

[Refractory depressions and their treatment] Jouvent R, et al. **Rev Prat** 1985 May 11;35(27):1647-53 (Eng. Abstr.) **(Fre)**

[Therapeutic strategy in depression] Scotto JC, et al. **Rev Prat** 1985 May 11;35(27):1633-8 (Eng. Abstr.) **(Fre)**

[Treatment of depressive conditions with viloxazine by the general practitioner] Haehn KD. **Fortschr Med** 1985 Apr 18;103(15):408-12 (Eng. Abstr.) **(Ger)**

[Treatment of depressive syndrome with antidepressants] Woggon B, et al. **Med Monatsschr Pharm** 1985 May;8(5):130-6 **(Ger)**

[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**

[Various aspects of the differential therapy of circular depressions] Prokhorova IS. **Zh Nevropatol Psikhiatr** 1985;85(4):570-4 (Eng. Abstr.) **(Rus)**

[Sleep deprivation as a method of treating endogenous depression] Vovin RIa, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):560-5 (Eng. Abstr.) **(Rus)**

DESIPRAMINE

Comparison of the effects of chronic administration of ciclazindol and desipramine on pupillary responses to tyramine, methoxamine and pilocarpine in healthy volunteers. Kerr FA, et al. **Br J Clin Pharmacol** 1985 May;19(5):639-47

Effect of chronic desipramine treatment on adrenoceptor modulation of [3H]dopamine release from rat nucleus accumbens slices. Nurse B, et al. **Brain Res** 1985 May 20;334(2):235-42

Effect of chronic reserpine and desmethylimipramine treatment on CRF-like immunoreactivity of discrete brain areas of rat. Tizabi Y, et al. **Brain Res** 1985 Jun 3;335(2):389-91

Why is amitriptyline much weaker than desipramine at decreasing beta-adrenoceptor numbers? Wise H, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):137-41

Tricyclic antidepressants antagonize prostaglandin (PG) E2-induced contractions of the guinea pig ileum and hypomotility in the mouse. Tayo FM. **Experientia** 1985 Apr 15;41(4):474-6

Interethnic dissociation between debrisoquine and desipramine hydroxylation. Rudorfer MV, et al. **J Clin Psychopharmacol** 1985 Apr; 5(2):89-92

Inhibition of the retrograde axonal transport of acetylcholinesterase by the anti-calmodulin agents amitriptyline and desipramine. Tiberi M, et al. **J Neurobiol** 1985 May;16(3):245-8

Cardiovascular effects of desipramine in children and adolescents with attention deficit disorder. Biederman J, et al. **J Pediatr** 1985 Jun; 106(6):1017-20

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

The effect of prolonged treatment with tricyclic antidepressants on the actions of 5-hydroxytryptamine in the hippocampal slice of the rat. Rowan MJ, et al. **Neuropharmacology** 1985 Feb;24(2):131-7

Drug interactions and vasoconstrictors used in local anesthetic solutions. Yagiela JA, et al. **Oral Surg Oral Med Oral Pathol** 1985 Jun; 59(6):565-71

Studies on the locus coeruleus system in an animal model for antidepressive activity. Kostowski W, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):523-30

The cortisol response to desipramine in endogenous depressives and normal controls: preliminary findings. Asnis GM, et al. **Psychiatry Res** 1985 Mar;14(3):225-33

Dose-dependent growth hormone, prolactin and cortisol stimulation after i.v. administration of desimipramine in human subjects. Laakmann G, et al. **Psychoneuroendocrinology** 1985;10(1):83-93

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

DESOXYCORTICOSTERONE

Effect of hydrocortisone and desoxycorticosterone on some reductases, esterases and synthetases. Tancheva L, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):59-63

Mineralocorticoid regulation of apical cell membrane Na+ and K+ transport of the cortical collecting duct. Sansom SC, et al. **Am J Physiol** 1985 Jun;248(6 Pt 2):F858-68

Lack of renal effects of DOCA, ACTH, spironolactone, and angiotensin II in Squalus acanthias. Churchill PC, et al. **J Exp Zool** 1985 Apr; 234(1):17-22

Sodium-dependent modulation of the renal Na-K-ATPase: influence of mineralocorticoids on the cortical collecting duct. O'Neil RG, et al. **J Membr Biol** 1985;85(2):169-79

Effects of angiotensin or carbachol on sodium intake and excretion in adrenalectomized or deoxycorticosterone-treated rats. Fitzsimons JT, et al. **J Physiol (Lond)** 1985 Feb;359:447-58

Comparison of the distribution kinetics and metabolism to acid end-products of corticosterone and 11-deoxycorticosterone in BALB/c mice. Marandici A, et al. **J Steroid Biochem** 1985 Apr;22(4):539-45

DEXTROAMPHETAMINE

Effects of some motion sickness suppressants on static and dynamic tracking performance. Schroeder DJ, et al. **Aviat Space Environ Med** 1985 Apr;56(4):344-50

Association of the mesencephalic locomotor region with locomotor activity induced by injections of amphetamine into the nucleus accumbens. Brudzyński SM, et al. **Brain Res** 1985 May 13; 334(1):77-84

6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233-41

Nigral reticulata neurons: potentiation of responsiveness to amphetamine with long-term treatment. Kamata K, et al. **Brain Res** 1985 Apr 15; 332(1):188-93

Frequency-related, bidirectional limbic responses to cocaine: comparisons with amphetamine and lidocaine. Lesse H, et al. **Brain Res** 1985 May 27;335(1):21-31

Effects of D- and L-amphetamine on dopamine metabolism and ascorbic acid levels in nucleus accumbens and olfactory tubercle as studied by in vivo differential pulse voltammetry. Louilot A, et al. **Brain Res** 1985 Jun 17;336(2):253-63

An investigation of amphetamine-induced release of 5-HT from rat hippocampal slices. Balfour DJ, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):395-9

Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. Feighner JP, et al. **J Clin Psychiatry** 1985 Jun;46(6):206-9

Amphetamine induced release of endogenous dopamine in vitro is not reduced following pretreatment with reserpine. Niddam R et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):123-7

The effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats. Evenden JL, et al. **Psychopharmacology (Berlin)** 1985;85(3):361-6

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

DIAZEPAM

Foot shock-induced decrease of low affinity GABA receptors in the rat brain: antagonism by diazepam. Concas A, et al. **Ann Ist Super Sanita** 1984;20(1):53-6

The influence of cyclobarbital and diazepam on drug metabolism in vitro and their binding to cytochrome P-450. Wierzba W, et al. **Biomed Biochim Acta** 1984;43(12):1425-30

The effects of age and smoking on the plasma protein binding of lignocaine and diazepam. Davis D, et al. **Br J Clin Pharmacol** 1985 Feb; 19(2):261-5

A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. Davison K, et al. **Br J Clin Pharmacol** 1985;19 Suppl 1:37S-43S

Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety. Power KG, et al. **Br Med J [Clin Res]** 1985 Apr 27;290(6477):1246-8

Blockade of the diazepam-induced increase in rat striatal acetylcholine content by the specific benzodiazepine antagonists ethyl-beta-carboline-3-carboxylate and Ro 15-1788. Kolasa K, et al. **Brain Res** 1985 Jun 17;336(2):342-5

Prenatal exposure to diazepam results in enduring reductions in brain receptors and deep slow wave sleep. Livezey GT, et al. **Brain Res** 1985 May 20;334(2):361-5

Pre-natal administration of diazepam improves radial maze learning in mice. Benton D, et al. **Comp Biochem Physiol [C]** 1985;80(2):273-5

Intramuscular bioavailability of chlorazepate as compared to diazepam. Bertler A, et al. **Eur J Clin Pharmacol** 1985;28(2):229-30

Pharmacological evidence that the non-neuronal diazepam binding site in primary cultures of glial cells is associated with a calcium channel. Bender AS, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):287-8

Extraction, separation, and detections of 14C-diazepam and 14C-metabolites from brain tissue of mature and old rats. Komiskey HL, et al. **J Anal Toxicol** 1985 May-Jun;9(3):131-3

Increased sensitivity of the elderly to the central depressant effects of diazepam. Pomara N, et al. **J Clin Psychiatry** 1985 May;46(5):185-7

3-Amino-beta-carboline derivatives and the benzodiazepine receptor. Synthesis of a selective antagonist of the sedative action of diazepam. Dodd RH, et al. **J Med Chem** 1985 Jun;28(6):824-8

Some long-lasting neurochemical effects of prenatal or early postnatal exposure to diazepam. Frieder B, et al. **J Neurochem** 1985 Jul; 45(1):37-42

Solubilization by cosolvents III: Diazepam and benzocaine in binary solvents. Rubino JT, et al. **J Parenter Sci Technol** 1985 May-Jun; 39(3):106-11

Responsibilities of prescribing. Avery JK. **J Tenn Med Assoc** 1985 May; 78(5):297

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

Differential mediation of the anticonvulsant effects of carbamazepine and diazepam. Weiss SR, et al. **Life Sci** 1985 Jun 24;36(25):2413-9

Patterns of diazepam prescribing in primary care: a case control study. Mulvihill MN, et al. **Mt Sinai J Med (NY)** 1985 Apr;52(4):276-80

The effects of benzodiazepines on spinal homosynaptic depression. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):301-7

Evidence that 2-phenylpyrazolo[4,3-c]-quinolin-3(5H)-one antagonises pharmacological, electrophysiological and biochemical effects of diazepam in rats. Santi M, et al. **Neuropharmacology** 1985 Feb; 24(2):99-105

Evidence that tolerance develops to the anxiolytic effect of diazepam in rats. Treit D. **Pharmacol Biochem Behav** 1985 Mar;22(3):383-7

Role of neurotransmitters and teratogens on palate development. Zimmerman EF, et al. **Prog Clin Biol Res** 1985;163C:405-8

The effects of intravenous diazepam and hyoscine upon human memory. Frith CD, et al. **Q J Exp Psychol** [A] 1984 Feb;36(1):133-44

Concentration independent accumulation of diazepam by rat liver slices. Effect of human serum albumin. Blaese U, et al. **Res Commun Chem Pathol Pharmacol** 1985 Feb;47(2):313-6

Generic Valiums clear another hurdle at FDA [news] Sun M. **Science** 1985 Jul 26;229(4711):369

Benzodiazepines inhibit human platelet activation: comparison of the mechanism of antiplatelet actions of flurazepam and diazepam. Romstedt K, et al. **Thromb Res** 1985 May 15;38(4):361-74

[Intravenous sedation before endoscopic interventions. Comparative study of lormetazepam and diazepam in oil] Tolksdorf W, et al. **Fortschr Med** 1985 Mar 7;103(9):249-52 (Eng. Abstr.) **(Ger)**

[Harman-induced changes in the anxiolytic effect of diazepam] Zin'kovskaia LIa, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):21-3 (Eng. Abstr.) **(Rus)**

[Effect of sodium valproate on brain levels of diazepam and N-desmethyldiazepam in the rat] Gómez Luque A, et al. **Arch Farmacol Toxicol** 1985 Apr;11(1):13-8 (Eng. Abstr.) **(Spa)**

DIBENZAZEPINES

Trimipramine and maprotiline: antidepressant, anxiolytic, and cardiotoxic comparison. Pecknold JC, et al. **J Clin Psychiatry** 1985 May; 46(5):166-71

Mianserin versus amitriptyline for depression: a double-blind 6-week trial. Rabkin JG, et al. **Neuropsychobiology** 1984;12(4):224-8

Mianserin [letter] Edwards IR. **NZ Med J** 1985 May 8;98(778):350

Effects of some dibenzo-azepines on suppressed and nonsuppressed behavior of squirrel monkeys. Spealman RD. **Psychopharmacology (Berlin)** 1985;85(2):129-32

Differential alteration of striatal D-1 and D-2 receptors induced by the long-term administration of haloperidol, sulpiride or clozapine to rats. Jenner P, et al. **Psychopharmacology [Suppl]** 1985;2:174-81

[Comparison of various tools for evaluating depression apropos of a study on Athymil 30 mg] Lempérière T, et al. **Ann Med Psychol (Paris)** 1984 Nov;142(9):1206-14 **(Fre)**

[Immunoallergic febrile reaction with hypereosinophilia after ingestion of metapramine (letter)] Gentric A, et al. **Presse Med** 1985 Jun 8; 14(23):1290 **(Fre)**

DIBENZOTHIEPINS

Possible relationship between antimanic effect and activity of zotepine to 5HT1 receptor. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):473-80

Delayed gastric emptying with dothiepin. Woodhouse KW, et al. **Hum Toxicol** 1985 Jan;4(1):67-70

Decreased 5-HT2 but not 5-HT1 receptor binding in cortex of rat after chronic administration of dothiepin. Application of the Woolf plot to analysis of binding parameters. Diggory GL, et al. **Neuropharmacology** 1985 Apr;24(4):275-8

DIBENZOXAZEPINES

Pharmacokinetics of amoxapine and its active metabolites. Calvo B, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Apr;23(4):180-5

Amoxapine-associated acute renal failure [letter] Chu CC, et al. **South Med J** 1985 Jun;78(6):761

DIETHYLAMINES

Dietary phenolics and betel nut extracts as modifiers of N-nitrosation in rat and man. Stich HF, et al. **IARC Sci Publ** 1984;(57):213-22

Metabolism of N-nitrodialkylamines. Suzuki E, et al. **IARC Sci Publ** 1984; (57):485-90

[Gas-chromatographic analysis of beta-diethylaminoethylchloride and beta-diethylaminoethylacetate ether in the air of work areas] Bake MIa. **Gig Tr Prof Zabol** 1985 Feb;(2):54-6 **(Rus)**

DIIODOTYROSINE

[Ultrastructural changes in thyrocytes exposed to the antithyroid preparations betazin and diiodotyrosine] Trunov VI, et al. **Tsitol Genet** 1985 Jan-Feb;19(1):13-7 (Eng. Abstr.) **(Rus)**

DISCRIMINATION (PSYCHOLOGY)

Effects of selective dopamine receptor agonists in rats trained to discriminate apomorphine from saline. Woolverton WL, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):577-81

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

DISCRIMINATION LEARNING

Effects of psychotropic drugs on discrimination conditioning in olfactory bulbectomized rats. Gomita Y, et al. **Pharmacol Biochem Behav** 1985 May;22(5):717-22

DOPA

Simultaneous assay of 3,4-dihydroxyphenylalanine, catecholamines and O-methylated metabolites in human plasma using high-performance liquid chromatography. Ishimitsu T, et al. **J Chromatogr** 1985 Feb 8; 337(2):239-48

[Enzymatic synthesis of 3,4-dihydroxyphenyl-L-alanine by free and immobilized Citrobacter freundii cells] Voivodov KI, et al. **Prikl Biokhim Mikrobiol** 1985 Mar-Apr;21(2):161-6 (Eng. Abstr.) **(Rus)**

DOPAMINE

Catecholamine microfluorometry of nigral perikarya and tyrosine hydroxylase assay in some telencephalic structures of rats exposed to different behavioral situations. Divac I, et al. **Acta Neurobiol Exp (Warsz)** 1984;44(6):262-72

Growth hormone releasing factor (GRF) and dopamine coexist in hypothalamic arcuate neurons. Meister B, et al. **Acta Physiol Scand** 1985 May;124(1):133-6

3H-dopamine clearance from the intravascular compartment of the maternal and fetal rhesus monkey. Phillippe M, et al. **Am J Obstet Gynecol** 1985 Jul 1;152(5):599-601

Clearance of 3H-dopamine from the amniotic fluid in the rhesus monkey. Phillippe M, et al. **Am J Obstet Gynecol** 1985 Jul 1;152(5):601-2

Central effects of angiotensin II and dopamine in sodium-depleted sheep. Huang BS, et al. **Am J Physiol** 1985 May;248(5 Pt 2):R541-8

The renal effects of dopamine [letter] Cramolini GM. **Anesthesiology** 1985 Jun;62(6):844

Physiologic and pharmacologic characterization of a novel group of substantia nigra zona reticulata neurons involved in striatal dopamine regulation. Chan SH. **Ann Acad Med Singapore** 1985 Jan;14(1):153-7

On the role of dopamine receptors in aldosterone secretion. Frisina N, et al. **Ann Endocrinol (Paris)** 1984;45(6):387-91

Mechanisms involved in the release of dopamine from the tuberoinfundibular system in vitro. Amoroso S, et al. **Ann Ist Super Sanita** 1984;20(1):109-11

Effect of dopamine on the threshold of the voltage-dependent ionic channels in the rat brain. Bernardi G, et al. **Ann Ist Super Sanita** 1984; 20(1):1-4

6R-L-erythro-5,6,7,8-tetrahydrobiopterin as a regulator of dopamine and serotonin biosynthesis in the rat brain. Miwa S, et al. **Arch Biochem Biophys** 1985 May 15;239(1):234-41

Asymmetry in the effects of unilateral 6-OHDA lesions on eating and drinking evoked by hypothalamic stimulation. Mittleman G, et al. **Behav Brain Res** 1985 May;15(3):263-7

Catecholamine-blocking drugs injected at sites of amine accumulation reverse catecholamine degeneration associated deficits. Willis GL, et al. **Behav Brain Res** 1985 Apr;15(2):101-6

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665-9

Binding characteristics of the dopamine uptake inhibitor [3H]nomifensine to striatal membranes. Dubocovich ML, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1137-44

Selective increase in dopamine metabolism in the prefrontal cortex by the anxiogenic beta-carboline FG 7142. Tam SY, et al. **Biochem Pharmacol** 1985 May 1;34(9):1595-8

Effect of chronic postnatal hypoxia on dopamine uptake by synaptosomes from striatum of adult rats. Ihle W, et al. **Biomed Biochim Acta** 1985; 44(3):433-7

Dopamine-stimulated fucosylation of brain proteins in vitro is not inhibited by puromycin. Lössner B, et al. **Biomed Biochim Acta** 1985; 44(3):465-73

Ethanol preference behaviour and dopamine release in the rat. Schmidt J, et al. **Biomed Biochim Acta** 1984;43(12):1431-4

Dopamine autoreceptors and the effects of drugs on locomotion and dopamine synthesis. Brown F, et al. **Br J Pharmacol** 1985 Apr; 84(4):853-60

Rapid desensitization of presynaptic dopamine autoreceptors during exposure to exogenous dopamine. Arbilla S, et al. **Brain Res** 1985 Jun 24;337(1):11-7

Subchronic administration of GABAergic agonists elevates [3H]GABA binding and produces tolerance in striatal dopamine catabolism. Beart PM, et al. **Brain Res** 1985 May 27 335(1):169-73

Effects of inhibitors of Na+,K+-ATPase on the membrane potentials and neurotransmitter efflux in rat brain slices. Brosemer RW. **Brain Res** 1985 May 13;334(1):125-37

Association of the mesencephalic locomotor region with locomotor activity induced by injections of amphetamine into the nucleus accumbens. Brudzyński SM, et al. **Brain Res** 1985 May 13; 334(1):77-84

Dopaminergic mechanisms in subthalamic nucleus of rat: analysis using horseradish peroxidase and microiontophoresis. Campbell GA, et al. **Brain Res** 1985 May 6;333(2):261-70

Involvement of nigrostriatal dopamine neurons in the contraversive rotational behavior evoked by electrical stimulation of the lateral hypothalamus. Castañeda E, et al. **Brain Res** 1985 Feb 18; 327(1-2):143-51

Excitatory and inhibitory effects of dopamine on synaptic transmission in the rat olfactory cortex slice. Collins GG, et al. **Brain Res** 1985 May 6;333(2):237-45

Topographical analysis of nucleus accumbens sites at which cholecystokinin potentiates dopamine-induced hyperlocomotion in the rat. Crawley JN, et al. **Brain Res** 1985 Jun 3;335(2):337-41

The formation of deaminated metabolites of dopamine in the locus coeruleus depends upon noradrenergic neuronal activity. Curet O, et al. **Brain Res** 1985 Jun 3;335(2):297-301

The hypothalamohypophyseal system in vitro: electrophysiology of the pars intermedia and evidence for both excitatory and inhibitory inputs. Davis MD, et al. **Brain Res** 1985 May 13;334(1):97-104

The prefrontal 'cortex' in the pigeon. Biochemical evidence. Divac I, et al. **Brain Res** 1985 Apr 22;332(2):365-8

Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Grace AA, et al. **Brain Res** 1985 May 6; 333(2):285-98

Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. Grace AA, et al. **Brain Res** 1985 May 6;333(2):271-84

6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233-41

Effects of D- and L-amphetamine on dopamine metabolism and ascorbic acid levels in nucleus accumbens and olfactory tubercle as studied by in vivo differential pulse voltammetry. Louilot A, et al. **Brain Res** 1985 Jun 17;336(2):253-63

Quantification of lesion-induced dopaminergic supersensitivity using the rotational model in the mouse. Mandel RJ, et al. **Brain Res** 1985 Mar 25;330(2):358-63

Effect of chronic desipramine treatment on adrenoceptor modulation of [3H]dopamine release from rat nucleus accumbens slices. Nurse B, et al. **Brain Res** 1985 May 20;334(2):235-42

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Potential changes of frog afferent terminals in response to dopamine. Ryan GP, et al. **Brain Res** 1985 Mar 4;328(2):283-90

Dopamine depletion in a striatal subregion disrupts performance of a skilled motor task in the rat. Sabol KE, et al. **Brain Res** 1985 May 27;335(1):33-43

Spatial distribution of dopamine, methotrexate and antipyrine during continuous intracerebral microperfusion. Sendelbeck SL, et al. **Brain Res** 1985 Mar 4;328(2):251-8

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

Reactive capacity: a sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Spirduso WW, et al. **Brain Res** 1985 May 27;335(1):45-54

On the origin of dopamine and its metabolite in predominantly noradrenergic innervated brain areas. Westerink BH, et al. **Brain Res** 1985 Mar 18;330(1):164-6

Dopamine production by isolated glomeruli and tubules from rat kidneys. Baines AD, et al. **Can J Physiol Pharmacol** 1985 Feb;63(2):155-8

Estradiol increases dopamine turnover in intermediate and posterior pituitary lobes of ovariectomized rats. Saavedra JM, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):397-402

Study of the interrelationship between dopaminergic activity and potassium ion. Matsuda S, et al. **Clin Exp Hypertens [A]** 1984; 6(12):2249-61

Evaluation of the central dopaminergic activity in gestational hyperprolactinaemia by means of the electroretinographic technique. De Luca Brunori I, et al. **Clin Exp Obstet Gynecol** 1985; 12(1-2):13-5

Effect of secretagogues on pancreatic exocrine secretion in the monkey and the dog. Iwatsuki K, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):67-72

Dopamine: receptors and clinical applications. Goldberg LI. **Clin Physiol Biochem** 1985;3(2-3):120-6 (33 ref.)

Norepinephrine alone versus norepinephrine plus low-dose dopamine: enhanced renal blood flow with combination pressor therapy. Schaer GL, et al. **Crit Care Med** 1985 Jun;13(6):492-6

Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215-27

Strain differences in brain biogenic amines concentration in rats with different resistance to emotional stress. Sudakov KV, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):39-45

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

Prolactin metabolic clearance and resistance to dopaminergic suppression in acute uremia. McKenna TM, et al. **Endocrinology** 1985 May; 116(5):2003-7

Rapid effects of hyperprolactinemia on basal prolactin secretion and dopamine turnover in the medial and lateral median eminence. Selmanoff M. **Endocrinology** 1985 May;116(5):1943-52

The effect of dopamine administration on the activity of the renin-angiotensin-aldosterone system in sick preterm infants. Sulyok E, et al. **Eur J Pediatr** 1985 Jan;143(3):191-3

Striatal synaptosomal dopamine synthesis: evidence against direct regulation by an autoreceptor mechanism. Compton DR, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):157-62

Magnesium ions reveal nanomolar potency of dopamine at [3H]spiperone labelled D-2 receptors in rat corpus striatum. De Vries DJ, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):417-9

Dopamine preferentially stimulates postsynaptic alpha 2-adrenoceptors in the femoral vascular bed, but alpha 1-adrenoceptors in the renal vascular bed of the anaesthetised dog. Duval N, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):265-72

Pharmacological changes in dopaminergic systems induced by long-term administration of amantadine. Gianutsos G, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):357-61

Phencyclidine-induced inhibition of rat prolactin secretion: increased portal blood dopamine. Meltzer HY, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):143-6

Electrochemical, pharmacological and electrophysiological evidence of rapid dopamine release and removal in the rat caudate nucleus following electrical stimulation of the median forebrain bundle. Millar J, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):341-8

Role of the dopamine uptake carrier in the neurochemical response to methamphetamine: effects of amfonelic acid. Schmidt CJ, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):73-80

Differences in dopamine- and noradrenaline-induced amylase release from the rat parotid gland. Sundström S, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):355-61

Reduced sensitivity of synaptosomal dopamine autoreceptors following increase in synaptosomal dopamine synthesis. Tissari AH. **Eur J Pharmacol** 1985 Mar 12;109(3):433-4

Number of dopamine neurons predicts prolactin levels in two inbred mouse strains. Sved AF, et al. **Experientia** 1985 May 15;41(5):644-6

Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Hong JS, et al. **Fed Proc** 1985 Jun;44(9):2535-9

Pergolide mesylate inhibits exercise-induced prolactin release in man. De Meirleir K, et al. **Fertil Steril** 1985 Apr;43(4):628-31

Comparative studies of cardiovascular effects of a new dopamine agonist (SK&F 38393A) and dopamine. Tsai CS, et al. **Gen Pharmacol** 1985; 16(2):85-9

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr; 6(2):78-81

Dopamine stimulated increase of GTP levels in the rat retina. Schaeffer JM, et al. **J Biol Chem** 1985 Apr 25;260(8):4555-7

Analysis of the positive inotropic effect of ibopamine in the blood-perfused canine papillary muscle. Kawahara K, et al. **J Cardiovasc Pharmacol** 1985 Mar-Apr;7(2):316-20

BIBLIOGRAPHY

Levels of dopamine and thyrotrophin-releasing hormone in hypophysial stalk blood during an oestrogen-stimulated surge of prolactin in the ovariectomized rat. de Greef WJ, et al. **J Endocrinol** 1985 Apr; 105(1):107-12

Synthesis and central dopaminergic effects of N-(4,6-dimethyl-2-pyridinyl)benzamides. Bouhayat S, et al. **J Med Chem** 1985 May;28(5):555-9

Dopamine sulfoconjugation in the rat brain: regulation by monoamine oxidase. Buu NT. **J Neurochem** 1985 Aug;45(2):470-6

3,4-Dihydroxyphenylethylamine and 5-hydroxytryptamine metabolism in the rat: acidic metabolites in cisternal cerebrospinal fluid before and after giving probenecid. Curzon G, et al. **J Neurochem** 1985 Aug; 45(2):508-13

Neurochemical profile of Lu 19-005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615-22

Evidence that [3H]dopamine is taken up and released from nondopaminergic nerve terminals in the rat substantia nigra in vitro. Kelly E, et al. **J Neurochem** 1985 Jul;45(1):137-44

Dopamine uptake is differentially regulated in rat striatum and nucleus accumbens. Missale C, et al. **J Neurochem** 1985 Jul;45(1):51-6

Preparation and characterization of antisera and monoclonal antibodies to serotonergic and dopaminergic ligands. Flurkey K, et al. **J Neuroimmunol** 1985 May;8(2-3):115-27

Pergolide elevation of MHPG sulphate concentration in rat hypothalamus blocked by spiperone and mimicked by other dopamine agonists. Fuller RW, et al. **J Pharm Pharmacol** 1985 Apr;37(4):268-70

Acute and subchronic effects of MJ-13859, a potential antipsychotic drug, on rat brain dopaminergic function. McMillen BA. **J Pharmacol Exp Ther** 1985 May;233(2):369-75

Role of dopamine in the neurotoxic effects of methamphetamine. Schmidt CJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):539-44

Further studies of dopamine metabolism and function in Tetrahymena. Gundersen RE, et al. **J Protozool** 1985 Feb;32(1):25-31

Benztropine inhibits toxicity of MPTP in mice [letter] Bradbury AJ, et al. **Lancet** 1985 Jun 22;1(8443):1444-5

Dopamine inhibition of anterior pituitary adenylate cyclase is mediated through the high-affinity state of the D2 receptor. Borgundvaag B, et al. **Life Sci** 1985 Jul 29;37(4):379-86

In vivo electrochemical studies of rat striatal dopamine and serotonin release after morphine. Broderick PA. **Life Sci** 1985 Jun 17; 36(24):2269-75

Firing properties of substantia nigra dopaminergic neurons in freely moving rats. Freeman AS, et al. **Life Sci** 1985 May 20; 36(20):1983-94

D2-dopamine receptor-mediated inhibition of cyclic AMP formation in striatal neurons in primary culture. Weiss S, et al. **Mol Pharmacol** 1985 Jun;27(6):595-9

Pharmacology in vivo of the phenylindan derivative, Lu 19-005, a new potent inhibitor of dopamine, noradrenaline and 5-hydroxytryptamine uptake in rat brain. Arnt J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):101-7

Effects of discriminant and non-discriminant dopamine antagonists on in vivo accumulation of 3H-N-propyl-norapomorphine in mouse striatum and tuberculum olfactorium. Gulat-Marnay C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):117-22

Amphetamine induced release of endogenous dopamine in vitro is not reduced following pretreatment with reserpine. Niddam R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):123-7

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128-34

Unexpected potentiation by discriminant benzamide derivatives of stereotyped behaviours elicited by dopamine agonists in mice. Vasse M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):108-16

Comparison of release of endogenous dopamine and gamma-aminobutyric acid from rat caudate synaptosomes. Caudill WL, et al. **Neurochem Res** 1985 Mar;10(3):319-31

Release of endogenous dopamine, 3,4-dihydroxyphenylacetic acid, and amino acid transmitters from rat striatal slices. Flint RS, et al. **Neurochem Res** 1985 Apr;10(4):515-27

The uptake of serotonin and dopamine by homogenates of frozen rat and human brain tissue. Stenström A, et al. **Neurochem Res** 1985 May; 10(5):591-9

Electroacupuncture alters catecholamines in brain regions of rats. Sun AY, et al. **Neurochem Res** 1985 Feb;10(2):251-8

Hypoprolactinemia induced by hypophysectomy and long-term bromocriptine treatment decreases tuberoinfundibular dopaminergic neuronal activity and the responsiveness of these neurons to prolactin. Demarest KT, et al. **Neuroendocrinology** 1985 May;40(5):369-76

Dopamine-induced physical barrier to inhibit prolactin release in mammotrophs disappears during resumption of prolactin secretion. Reifel CW, et al. **Neuroendocrinology** 1985 May;40(5):438-43

Altered pharmacokinetics of L-dopa metabolism [letter] Melamed E, et al. **Neurology** 1985 Jun;35(6):939-41

Activation of muscarinic receptors on striatal synaptosomes increases the release of endogenous dopamine. Bonanno G, et al. **Neuropharmacology** 1985 Mar;24(3):261-4

The continuity of dopamine receptor antagonism can dictate the long-term behavioural consequences of a mesolimbic infusion of dopamine. Costall B, et al. **Neuropharmacology** 1985 Mar;24(3):193-7

Alterations in dopamine metabolism after chronic administration of haloperidol. Possible role of increased autoreceptor sensitivity. Saller CF, et al. **Neuropharmacology** 1985 Feb;24(2):123-9

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer; 9(2):261-82

Dopamine hyperpolarizes and reduces the light responses of rod ON-centre bipolar cells in the retina of the dogfish, Scyliorhinus canicula. Shiells RA, et al. **Neurosci Lett** 1985 Apr 19;55(3):331-6

Alteration of dopamine metabolism in different brain regions of the rabbit by estradiol and tamoxifen. Baksi SN, et al. **Neuroscience** 1985 Apr; 14(4):1053-9

Regulation of dopamine release by impulse flow and by autoreceptors as studied by in vivo voltammetry in the rat striatum. Gonon FG, et al. **Neuroscience** 1985 Mar;14(3):765-74

Effect of haloperidol and sulpiride on dopamine metabolism in nucleus accumbens and olfactory tubercle: a study by in vivo voltammetry. Louilot A, et al. **Neuroscience** 1985 Mar;14(3):775-82

Detection of homovanillic acid in vivo using microcomputer-controlled voltammetry: simultaneous monitoring of rat motor activity and striatal dopamine release. O'Neill RD, et al. **Neuroscience** 1985 Mar; 14(3):753-63

Morphological evidence for a dopaminergic terminal field in the hippocampal formation of young and adult rat. Verney C, et al. **Neuroscience** 1985 Apr;14(4):1039-52

Locomotor response of nialamide pretreated old rats to intraaccumbens dopamine. Cousin KM, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):461-8

Effects of phencyclidine (PCP)-like drugs on turning behavior, 3H-dopamine uptake, and 3H-PCP binding. Johnson KM, et al. **Pharmacol Biochem Behav** 1985 May;22(5):731-5

Suppression of male copulatory behavior by delta 9-THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415-20

Effects of ovariectomy and estrogen replacement on intrastriatal dopamine-elicited postural deviation. Smith RL, et al. **Pharmacol Biochem Behav** 1985 May;22(5):689-93

Dopamine decreases conductance of the electrical junctions between cultured retinal horizontal cells. Lasater EM, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):3025-9

Central inhibitory action of TRH on prolactin secretion in the rat. Ohta H, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):9-12

Neurotropic drugs and brain development: effects on cell replication in vivo and in vitro. Patel AJ. **Prog Clin Biol Res** 1985;163C:301-5

Chronic neuroleptic treatment and mesolimbic dopamine denervation induce behavioural supersensitivity to opiates. Stinus L, et al. **Psychopharmacology (Berlin)** 1985;85(3):323-8

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

Studies on the stability of 3H-dopamine, 3H-apomorphine and 3H-ADTN: effects of sodium ascorbate and EDTA. Cabbat FS, et al. **Res Commun Chem Pathol Pharmacol** 1985 Mar;47(3):333-43

Effects of amfonelic acid, alpha-methyltyrosine, Ro 4-1284 and haloperidol pretreatment on the depletion of striatal dopamine by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. Fuller RW, et al. **Res Commun Chem Pathol Pharmacol** 1985 Apr;48(1):17-25

Effect of dopamine and dopamine-receptor blockade on in vitro renin release, tissue renin content and tissue cyclic AMP content in the rat. López GA, et al. **Rev Esp Fisiol** 1985 Mar;41(1):95-100

Inhibitory effects of dopamine and isoprenaline on antral motor activity stimulated by acetylcholine or physostigmine in vitro. Ulvestad A, et al. **Scand J Gastroenterol** 1985 Mar;20(2):243-6

Regional brain dopamine metabolism: a marker for the speed, direction, and posture of moving animals. Freed CR, et al. **Science** 1985 Jul 5; 229(4708):62-5

[Fixed mydriasis in hemorrhagic shock treated with dopamine] Longhi A, et al. **Minerva Anestesiol** 1984 Nov;50(11):551-3 (Eng. Abstr.) **(Ita)**

[Dopamine-induced up-regulation of alpha 2-adrenoceptors in crude synaptic membranes of rat brain] Kohno Y, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):173-83 (Eng. Abstr.) **(Jpn)**

[TRH and its analog (DN-1417). Effects on central dopaminergic system-dependent behaviors in rats and mice] Miyamoto M, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):129-41 (Eng. Abstr.) **(Jpn)**

[Cyclic AMP content of autonomic ganglia as affected by catecholamines] Kniazeva LA, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):348-9 (Eng. Abstr.) **(Rus)**

[Effect of dopamine and its combination with furosemide on urination in the rat] Berkhin EB. **Farmakol Toksikol** 1985 Mar-Apr; 48(2):89-92 (Eng. Abstr.) **(Rus)**

[Effect of dimethoxy dichloro vinyl phosphate and fluorostigmine on the cyclic nucleotide content and dopamine level in the brain nigrostriatal system] Golovko AI, et al. **Farmakol Toksikol** 1985 Mar-Apr; 48(2):46-8 (Eng. Abstr.) **(Rus)**

[Normal values of dopamine, noradrenaline, adrenaline, and 5-hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb; 53(334):49-52 (Eng. Abstr.) **(Spa)**

DOPAMINE BETA-HYDROXYLASE

A monoclonal antibody to dopamine beta-monooxygenase: detection of biosynthetic intermediates. Nolan J, et al. **Arch Biochem Biophys** 1985 Jul;240(1):257-64

3-Phenylpropenes as mechanism-based inhibitors of dopamine beta-hydroxylase: evidence for a radical mechanism. Fitzpatrick PF, et al. **Biochemistry** 1985 Apr 23;24(9):2108-14

Secondary isotope effects and structure-reactivity correlations in the dopamine beta-monooxygenase reaction: evidence for a chemical mechanism. Miller SM, et al. **Biochemistry** 1985 Apr 23; 24(9):2114-27

Immunohistochemical evidence for phenylethanolamine-N-methyltransferase-positive/tyrosine hydroxylase-negative neurones in the retina and the posterior hypothalamus of the rat. Foster GA, et al. **Brain Res** 1985 Mar 18; 330(1):183-8

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

Study on the mechanism of the appearance of noise effects. Okada A, et al. **Eur J Applied Physiol** 1985;53(4):364-7

Sympathetic activity, plasma renin activity (PRA) and kininogen levels in patients haemodialysed with acetate and bicarbonate. Ksiażek A, et al. **Int Urol Nephrol** 1984;16(4):337-44

Dopamine beta-hydroxylase-like immunoreactivity in the rat and cat carotid body: a light and electron microscopic study. Chen IL, et al. **J Neurocytol** 1985 Feb;14(1):131-44

Changes in dopamine-beta-hydroxylase, and copper, and catecholamine concentrations in human plasma with physical exercise. Ohno H, et al. **J Sports Med Phys Fitness** 1984 Dec;24(4):315-20

Dopamine-beta-hydroxylase inhibitors, feeding and locomotor activity: reinstatement of feeding following central norepinephrine. Evans KR, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):535-40

DOXAPRAM

Antagonism of xylazine sedation with yohimbine, 4-aminopyridine, and doxapram in dogs. Hatch RC, et al. **Am J Vet Res** 1985 Feb; 46(2):371-5

Effects of doxapram on body temperature of the rat during radiofrequency irradiation. Jauchem JR, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):1-8

DOXEPIN

Effect of single and repeated doses of activated charcoal on the pharmacokinetics of doxepin. Scheinin M, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Jan;23(1):38-42

ELECTROCONVULSIVE THERAPY

Plasma catecholamines and ECT. Khan A, et al. **Biol Psychiatry** 1985 Jul;20(7):799-804

Electroconvulsive therapy and schizophrenia. Van Valkenburg C, et al. **Biol Psychiatry** 1985 Jul;20(7):699-700

[Effect of electroconvulsive shock on brain monoamines] Kuang PG. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Feb; 18(1):41-4 (Eng. Abstr.) **(Chi)**

ELECTROENCEPHALOGRAPHY

Effects of fentanyl citrate and droperidol on electroencephalographic findings in dogs. Katherman AE, et al. **Am J Vet Res** 1985 Apr; 46(4):974-6

The effects of aniracetam on primate behavior and EEG. Schwam E, et al. **Ann NY Acad Sci** 1985;444:482-4

Hippocampal-dentate theta disturbance after selective CA1 pyramidal cell damage in the rat. Monmaur P, et al. **Brain Res** 1985 Mar 4; 328(2):301-11

Cocaine increases EEG beta: a replication and extension of Hans Berger's historic experiments. Herning RI, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):470-7

Characteristics of the cortical and hippocampal EEG power spectra of rabbits during normal behavioral states and after administration of CNS acting drugs. Yamamoto J. **Jpn J Pharmacol** 1985 Mar;37(3):227-34

Quantitative electrocortical changes in the rat induced by phencyclidine and other stimulants. Neal H, et al. **Neuropharmacology** 1985 Apr; 24(4):317-23

ELECTROLYTES

Steroids alter ion transport and absorptive capacity in proximal and distal colon. Sellin JH, et al. **Am J Physiol** 1985 Jul;249(1 Pt 1):G113-9

The pharmacological modification of secretory responses. Miller RJ, et al. **Ciba Found Symp** 1985;112:155-74

Effects of chronic changes in dietary electrolytes and acute stress on plasma levels of corticosterone and aldosterone in the duck (Anas platyrhynchos). Klingbeil CK. **Gen Comp Endocrinol** 1985 Apr; 58(1):10-9

Electrolyte transport across the basolateral membrane of the parietal cells. Muallem S, et al. **J Biol Chem** 1985 Jun 10;260(11):6641-53

ELECTROSHOCK

Differential effects of electroconvulsive shock on four models of experimentally-induced aggression in rats. Liou SY, et al. **Jpn J Pharmacol** 1985 Feb;37(2):167-72

Chlorimipramine, electroconvulsive shock and combination thereof: differential effects of chronic treatment on apomorphine-induced behaviours and on striatal and mesocortical dopamine turnover. Spyraki C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):128-34

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

Increased sensitivity to serotonergic agonists after repeated electroconvulsive shock in rats. Wielosz M. **Pharmacol Biochem Behav** 1985 May;22(5):683-7

EMOTIONS

Elevation of mood due to antidepressants [letter] Pearce PL. **JAMA** 1985 Jun 7;253(21):3091-2

A preliminary report on anti-depressant therapy and its effects on hope and immunity. Udelman DL, et al. **Soc Sci Med** 1985; 20(10):1069-72

ENDORPHINS

Maternal and fetal beta-endorphin release in response to the stress of labor and delivery. Kofinas GD, et al. **Am J Obstet Gynecol** 1985 May 1;152(1):56-9

Endogenous opioid immunoreactivity in rat spinal cord following traumatic injury. Faden AI, et al. **Ann Neurol** 1985 Apr; 17(4):386-90

Response of the rat brain beta-endorphin system to novelty: importance of the fornix connection. Netto CA, et al. **Behav Neural Biol** 1985 Jan; 43(1):37-46

Modification of opioid ligand binding in the central and the peripheral nervous system by different buffers. Bourhim N, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):328-33

Ginseng saponin treatment does not alter brain or pituitary levels of beta-endorphin and dynorphin. Ho WK, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):2044-6

Nitrous oxide inhalation does not influence plasma concentrations of beta-endorphin or Met-enkephalin-like immunoreactivity. Evans SF, et al. **Br J Anaesth** 1985 Jun;57(6):624-8

Altered body temperature of rabbits after central injection of beta-endorphin and other peptides. Glyn-Ballinger JR, et al. **Brain Res** 1985 May 6;333(2):366-8

Distribution of the pro-opiomelanocortin derived peptides, adrenocorticotrope hormone, alpha-melanocyte-stimulating hormone and beta-endorphin (ACTH, alpha-MSH, beta-END) in the rat hypothalamus. Mezey E, et al. **Brain Res** 1985 Mar 4;328(2):341-7

Immunohistochemical localization of neurotensin and beta-endorphin in the rat anterior pituitary gland. Miyoshi R, et al. **Brain Res** 1985 Apr 8;331(2):386-8

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Modulation of lordosis behaviour in the female rat by corticotropin releasing factor, beta-endorphin and gonadotropin releasing hormone in the mesencephalic central gray. Sirinathsinghji DJ. **Brain Res** 1985 Jun 10;336(1):45-55

Ultrastructural evidence for beta-endorphin-like immunoreactivity in the nervous system of the rat duodenum. Wolter HJ. **Brain Res** 1985 May 13;334(1):194-9

Homeostatic alterations with major trauma. Arachidonic acid metabolites and endorphins. DeMajo WA. **Can Anaesth Soc J** 1985 May; 32(3 Pt 1):241-2

Occurrence of beta-endorphin-like immunoreactive cells in the neural complex of a protochordate. Pestarino M. **Cell Mol Biol** 1985; 31(1):27-31

Determination of beta-endorphin and beta-lipotropin in human cerebrospinal fluid. Laatikainen TJ, et al. **Clin Chim Acta** 1985 Feb 15;145(3):325-9

Endogenous opioids in marine invertebrates. Piccoli R, et al. **Comp Biochem Physiol** [C] 1985;80(2):237-40

Ovarian immunoreactive beta-endorphin and estrous cycle in the rat. Lolait SJ, et al. **Endocrinology** 1985 Jul;117(1):161-8

Changes in beta-endorphin-like immunoreactivity in pituitary portal blood during the estrous cycle and after ovariectomy in rats. Sarkar DK, et al. **Endocrinology** 1985 May;116(5):2075-9

Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. Young EA, et al. **Endocrinology** 1985 Jul;117(1):23-30

Plasma immunoreactive beta-endorphin and cortisol in the newborn infant after elective caesarean section and after spontaneous labour. Pohjavuori M, et al. **Eur J Obstet Gynecol Reprod Biol** 1985 Feb;19(2):67-74

Isolation and characterization of dipeptidyl peptidase IV from human meconium. Functional role of beta-casomorphins. Caporale C, et al. **FEBS Lett** 1985 May 20;184(2):273-7

The identification and characterization of alpha-N-acetylated beta-endorphin in the human pituitary gland. Smith AI, et al. **FEBS Lett** 1985 Jun 3;185(1):109-11

Endogenous opioid nomenclature: light at the end of the tunnel. Kitchen I. **Gen Pharmacol** 1985;16(2):79-84 (48 ref.)

Beta-endorphin and cold pressor test in the aged. Casale G, et al. **Gerontology** 1985;31(2):101-5

Temporal difference of thyrotropin-releasing hormone in prevention of testicular regression in golden hamsters exposed to short photoperiods: possible involvement of beta-endorphin. Chen HJ, et al. **Horm Res** 1985; 21(3):168-74

Bacterial lipopolysaccharide induction of leukocyte-derived corticotropin and endorphins. Harbour-McMenamin D, et al. **Infect Immun** 1985 Jun; 48(3):813-7

Preparation and properties of tritiated human [Tyr18, Trp27]-beta-endorphin. Hammonds RG Jr, et al. **Int J Pept Protein Res** 1985 Feb;25(2):149-54

Identification of N alpha-acetyl-alpha-endorphin and N alpha-acetyl-gamma-endorphin isolated from the neurointermediate lobe of the rat pituitary gland. Burbach JP, et al. **J Biol Chem** 1985 Jun 10;260(11):6663-9

beta-Casomorphin immunoreactive materials in cows' milk incubated with various bacterial species. Hamel U, et al. **J Dairy Res** 1985 Feb; 52(1):139-48

Opioid peptides of the pituitary and hypothalamus: changes in pregnant and lactating rats. Petraglia F, et al. **J Endocrinol** 1985 May; 105(2):239-45

Plasma beta-endorphin levels after exercise [letter] De Meirleir, et al. **J Endocrinol Invest** 1985 Feb;8(1):89

Preembedding colloidal gold immunostaining of hypothalamic neurons: light and electron microscopic localization of beta-endorphin-immunoreactive perikarya. Lamberts R, et al. **J Histochem Cytochem** 1985 Jun;33(6):499-507

Beta-endorphin-(10-16) antagonizes behavioral responses elicited by melatonin following injection into the nucleus accumbens of rats. Gaffori O, et al. **Life Sci** 1985 Jul 29;37(4):357-64

N alpha-Acetyl-gamma-endorphin is an endogenous non-opioid neuropeptide with biological activity. Wiegant VM, et al. **Life Sci** 1985 Jun 17;36(24):2277-85

Auto-tolerance to the endogenous opioids and sleep. Gillman MA, et al. **Med Hypotheses** 1985 Apr;16(4):393-5

The use of reverse-phase chromatographic procedures coupled with radioimmunoassay in studying regional distribution of beta h-endorphin in the human brain. Pasi A, et al. **Neurobehav Toxicol Teratol** 1985 Mar-Apr;7(2):199-201

Senescent change in tissue weight and immunoreactive beta-endorphin, enkephalin, and vasopressin in eight regions of C57BL/6J mouse brain and pituitary. Rogers J, et al. **Neurobiol Aging** 1985 Spring;6(1):1-9

Postnatal development of beta-endorphin immunoreactivity in the medulla oblongata of rat. Alessi NE, et al. **Neuropeptides** 1985 Feb; 5(4-6):473-6

Separate populations of opioid containing neurons in the guinea-pig intestine. Costa M, et al. **Neuropeptides** 1985 Feb;5(4-6):445-8

Action of neutral metalloendopeptidase ('enkephalinase') on beta-endorphin. Gráf L, et al. **Neuropeptides** 1985 Mar;6(1):13-9

Beta-endorphin processing in pituitary and brain is sensitive to haloperidol stimulation. Ham J, et al. **Neuropeptides** 1985 Feb;5(4-6):497-500

Postnatal development of opioid systems in rat brain. Loughlin SE, et al. **Neuropeptides** 1985 Feb;5(4-6):469-72

Differential modulation of the beta-endorphin and dynorphin systems by serotonergic stimulation in the rat. Majeed NH, et al. **Neuropeptides** 1985 Feb;5(4-6):563-6

A comparison of opioid peptide precursors in guinea pig, rat and bovine striata and guinea pig adrenal. Metters KM, et al. **Neuropeptides** 1985 Feb;5(4-6):521-4

The effect of morphine upon CSF opioids in dogs. Noel MA, et al. **Neuropeptides** 1985 Feb;5(4-6):429-32

Antidepressants and endogenous opioid peptide systems. Przewlocki R, et al. **Neuropeptides** 1985 Feb;5(4-6):575-8

Dermorphin-like immunoreactivity in guinea pig and rat stomach. Tsou K, et al. **Neuropeptides** 1985 Feb;5(4-6):449-52

How is kyotorphin (Tyr-Arg) generated in the brain? Ueda H, et al. **Neuropeptides** 1985 Feb;5(4-6):525-8

Enkephalins and endorphins: activation molecules for the immune system and natural killer activity? Wybran J. **Neuropeptides** 1985 Feb; 5(4-6):371-4

Changes in releasability of ACTH and beta-endorphin with chronic stress. Young E, et al. **Neuropeptides** 1985 Feb;5(4-6):545-8

The effect of surgery on plasma beta-endorphin and methionine-enkephalin. Smith R, et al. **Neurosci Lett** 1985 Mar 22; 55(1):17-21

Acupuncture analgesia [letter] Han JS. **Pain** 1985 Mar;21(3):307-10

Effects of intracranial self-stimulation on brain opioid peptides. Stein EA. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):67-73

Binding characteristics of dermorphin, and [dermorphin1-7]-beta c-endorphin in rat brain membranes. Westphal M, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):149-52

Stress produces opioid-like effects on investigatory behavior. Arnsten AF, et al. **Pharmacol Biochem Behav** 1985 May;22(5):803-9

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417-51 (238 ref.)

The effect of chronic estrogen treatment on immunoreactive beta-endorphin levels in intact female rats. Forman LJ, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):365-72

Glucocorticoid inhibition of immunoreactive beta-endorphin release from the anterior lobe of the rat pituitary: in vitro and in vivo studies. Mueller GP, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):338-47

Endogenous opioid activity in clinical hemorrhagic shock. Shatney CH, et al. **Surg Gynecol Obstet** 1985 Jun;160(6):547-51

[Endogenous opioids] Schulz R, et al. **Tierarztl Prax** 1985;13(1):11-27 (93 ref.) (Eng. Abstr.) **(Ger)**

[Stress and the endogenous opioid system. III. Classification of the opioid system in the process of adaptation] Nieber K, et al. **Z Gesamte Inn Med** 1985 Mar 1;40(5):133-6 (Eng. Abstr.) **(Ger)**

[Stress and the endogenous opioid system. II. Stress, stress models and endogenous opioid peptides] Nieber K, et al. **Z Gesamte Inn Med** 1985 Feb 1;40(3):61-5 (Eng. Abstr.) **(Ger)**

[Endorphins and pregnancy] Stoppelli I, et al. **Minerva Ginecol** 1984 Dec; 36(12):761-6 (Eng. Abstr.) **(Ita)**

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

[Neuro-intestinal peptides and peptide-producing cells--immunohistocytochemistry of catecholamines and opioid peptides in the hamster adrenal medulla] Kobayashi S, et al. **Nippon Heikatsukin Gakkai Zasshi** 1984 Oct;20(5):393-9 **(Jpn)**

[Brain blood supply and beta-endorphin and corticotropin content on exposure to thyroliberin] Mirozoian RS, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):318-20 (Eng. Abstr.) **(Rus)**

[Changes in the opioid peptide content of the adrenals of rats during immobilization stress] Val'dman AV, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):404-6 (Eng. Abstr.) **(Rus)**

[Immunoreactive beta-lipotropin and endorphins are secreted by the isolated alimentary complex of rats] Titov MI, et al. **Dokl Akad Nauk SSSR** 1985;281(2):497-9 **(Rus)**

ENKEPHALIN, LEUCINE

The stimulation of glycogenolysis in isolated hepatocytes by opioid peptides. Leach RP, et al. **Biochem J** 1985 Apr 1;227(1):191-7

The metabolism of neuropeptides. Endopeptidase-24.11 in human synaptic membrane preparations hydrolyses substance P. Matsas R, et al. **Biochem J** 1985 Jun 1;228(2):487-92

Central versus peripheral actions of Leu-enkephalin on acquisition of a one-way active avoidance response in rats. Martinez JL Jr, et al. **Brain Res** 1985 Feb 18;327(1-2):37-43

Blockade of cholinergic receptors in the C1 area abolishes hypertensive response to opiates in the A1 area of the ventrolateral medulla. Punnen S, et al. **Brain Res** 1985 Jun 10;336(1):180-6

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Blood-brain barrier permeability to leucine-enkephalin, D-alanine2-D-leucine5-enkephalin and their N-terminal amino acid (tyrosine). Zlokovic BV, et al. **Brain Res** 1985 Jun 10;336(1):125-32

Effect of hemorrhage on vasopressin, dynorphin A, and leu5-enkephalin in the hypothalamo-pituitary system of the rat. Feuerstein G, et al. **Clin Exp Hypertens** [A] 1984;6(10-11):1973-6

Influence of intracerebroventricular (ICV) GTP-electrolyte infusion on ICV (D-ALA2, D-LEU5) enkephalin (DADL)-induced cardiovascular effects in rats. McDonald W., et al. **Clin Exp Hypertens** [A] 1984;

6(10–11):1837–41

Effects of traumatic injury on dynorphin immunoreactivity in spinal cord. Cox BM, et al. **Neuropeptides** 1985 Feb;5(4–6):571–4

Studies in vitro with ICI 174,864, [D–Pen2, D–Pen5]–enkephalin (DPDPE) and [D–Ala2, NMePhe4, Gly–ol]–enkephalin (DAGO). Hirning LD, et al. **Neuropeptides** 1985 Feb;5(4–6):383–6

Localization and quantitation of proenkephalin–derived neuropeptides in the rat hippocampus. Hoffman DW, et al. **Neuropeptides** 1985 Feb; 5(4–6):437–40

Development of hypothalamic opioid neurons: a combined immunocytochemical and [3H]thymidine autoradiographic study. Khachaturian H, et al. **Neuropeptides** 1985 Feb;5(4–6):4[illegible]–80

Opiate receptor–mediated chemotaxis of human monocytes. Ruff MR, et al. **Neuropeptides** 1985 Feb;5(4–6):363–6

Characterization of a high molecular weight polypeptide from spinal cord with (Leu) enkephalin–immunoreactivity. Wahlström A, et al. **Neuropeptides** 1985 Feb;5(4–6):509–12

Dynorphinergic pathways of Leu–enkephalin production in the rat brain. Zamir N, et al. **Neuropeptides** 1985 Feb;5(4–6):441–4

A study of intracerebroventricular self–administration of leucine or methionine enkephalin by rats in response to intermittent electric shocks. Dib B. **Pain** 1985 May;22(1):49–57

A general procedure for analysis of proenkephalin B derived opioid peptides. Christensson–Nylander I, et al. **Regul Pept** 1985 May; 11(1):65–76

[The nature of cation–binding groups in binding sites for [[3H]Tyr1, D–Ala2, D–Leu5]enkephalin] Zaitsev SV, et al. **Bioorg Khim** 1985 Feb; 11(2):153–61 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, METHIONINE

Protected homocysteine peptides as precursors of labelled methionine peptides. Application in preparation of methionine–enkephalin. Någren K, et al. **Acta Chem Scand** [B] 1985;39(3):157–61

Enzyme–linked immunosorbent assay for Met–enkephalin using unconjugated enkephalin as a solid phase antigen. Takesue Y, et al. **Anal Biochem** 1985 Apr;146(1):35–9

The stimulation of glycogenolysis in isolated hepatocytes by opioid peptides. Leach RP, et al. **Biochem J** 1985 Apr 1;227(1):191–7

Nitrous oxide inhalation does not influence plasma concentrations of beta–endorphin or Met–enkephalin–like immunoreactivity. Evans SF, et al. **Br J Anaesth** 1985 Jun;57(6):624–8

Met–enkephalin–Arg6–Gly7–Leu8 in the organ of Corti: high performance liquid chromatography and immunoelectron microscopy. Eybalin M, et al. **Brain Res** 1985 Apr 8;331(2):389–95

Dopamine receptors regulate Met–enkephalin content in pituitary. George SR, et al. **Brain Res** 1985 May 13;334(1):187–9

Development of methionine–enkephalin in microdissected areas of the rabbit brain. Gingras–Leatherman JL, et al. **Brain Res** 1985 Jun 10; 336(1):73–80

The opioid octapeptide Met5–enkephalin–Arg6–Gly7–Leu8: characterization and distribution in rat spinal cord. Iadarola MJ, et al. **Brain Res** 1985 Mar 18;330(1):127–34

Evidence for the coexistence of acetylcholine and enkephalin in the sympathetic preganglionic neurons of rats. Kondo H, et al. **Brain Res** 1985 Jun 3;335(2):309–14

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358–62

Effects of enkephalin and 5–hydroxytryptamine on solitary tract neurones involved in respiration and respiratory reflexes. Sessle BJ, et al. **Brain Res** 1985 Feb 18;327(1–2):221–30

Occurrence of met–enkephalin, met–enkephalin–Arg6–Phe7 and met–enkephalin–Arg6–Gly7–Leu8 in gastrin cells of hog antral mucosa. Jönsson AC. **Cell Tissue Res** 1985;240(2):361–5

Potential role of met–enkephalin in short term regulation of blood pressure in anesthetized rabbits. Rhee HM, et al. **Clin Exp Hypertens [A]** 1984; 6(10–11):2063–7

Methionine enkephalin as a possible neuromodulator of regional cerebral blood flow. Blum K, et al. **Experientia** 1985 Jul 15;41(7):932–3

Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Hong JS, et al. **Fed Proc** 1985 Jun;44(9):2535–9

Evaluation of BW942C, a novel antidiarrheal agent, against enterotoxins of Escherichia coli and Vibrio cholerae. Morgan DR, et al. **Infect Immun** 1985 Jun;48(3):754–8

Methionine–enkephalin inhibits stress–induced increases in noradrenaline turnover in brain regions of rats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Jan;37(1):117–9

Characterization of rat brain opioid receptors by [Tyr–3,5–3H]1, D–Ala2, Leu5–enkephalin binding. Benyhe S, et al. **Neurochem Res** 1985 May; 10(5):627–35

Localization and quantitation of proenkephalin–derived neuropeptides in the rat hippocampus. Hoffman DW, et al. **Neuropeptides** 1985 Feb; 5(4–6):437–40

Release of high molecular weight forms of met5–enkephalin–arg6–gly7–leu8 from rat brain. Lindberg I, et al. **Neuropeptides** 1985 Feb;5(4–6):541–4

Prodynorphin immunoreactivity is located in different neurons than proenkephalin immunoreactivity in the cerebral cortex of rats. McGinty JF. **Neuropeptides** 1985 Feb;5(4–6):465–8

Adrenorphin immunoreactivity in rat brain. Miyata A, et al. **Neuropeptides** 1985 Feb;5(4–6):517–20

Release of synenkephalin from neuronal terminals in vitro. Rossier J, et al. **Neuropeptides** 1985 Feb;5(4–6):549–52

Astrocyte opioid receptors: activation modifies the noradrenaline–evoked increase in 2–[14C]deoxyglucose incorporation into glycogen. Pearce B, et al. **Neurosci Lett** 1985 Apr 9;55(2):157–60

The effect of surgery on plasma beta–endorphin and methionine–enkephalin. Smith R, et al. **Neurosci Lett** 1985 Mar 22; 55(1):17–21

Effect of histamine infusion on circulating methionine–enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289–92

Mesencephalic pathway to the retina exhibits enkephalin–like immunoreactivity. Weiler R. **Neurosci Lett** 1985 Mar 22;55(1):11–6

A study of intracerebroventricular self–administration of leucine or methionine enkephalin by rats in response to intermittent electric shocks. Dib B. **Pain** 1985 May;22(1):49–57

Effects of MET–ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan–Feb;6(1):139–48

Cardiovascular interactions between methionine–enkephalin and substance P in the conscious dog. Sander GE, et al. **Peptides (Fayetteville)** 1985 Jan–Feb;6(1):133–7

[Effect of an enkephalin analog on the endocrine system in man] Földes J, et al. **Orv Hetil** 1985 May 12;126(19):1145–8 (Eng. Abstr.) **(Hun)**

ENKEPHALINS

Enkephalin–degrading dipeptidyl carboxypeptidase in guinea pig serum: its properties and action on bioactive peptides. Kase R, et al. **Arch Biochem Biophys** 1985 Jul;240(1):330–6

Enkephalin neurons in the guinea pig proximal colon: an immunocytochemical study using an antiserum to methionine–enkephalin–Arg6–Gly7–Leu8. Kobayashi S, et al. **Arch Histol Jpn** 1985 Feb;48(1):27–44

Enkephalin metabolism and its inhibition. Gros C, et al. **Biochem Soc Trans** 1985 Feb;13(1):47–50

Identification of aminopeptidase M as an enkephalin–inactivating enzyme in rat cerebral membranes. Gros C, et al. **Biochemistry** 1985 Apr 23; 24(9):2179–85

Evidence for synenkephalin–like immunoreactivity in pontobulbar monoaminergic neurons of the cat. Charnay Y, et al. **Brain Res** 1985 May 27;335(1):160–4

Spinal parasympathetic enkephalin fibers: patterns and projections. Romagnano MA, et al. **Brain Res** 1985 May 27;335(1):174–81

An enkephalinergic projection from the hypothalamic paraventricular nucleus to the hypothalamic ventromedial nucleus of the rat: an experimental immunohistochemical study. Yamano M, et al. **Brain Res** 1985 Apr 1;331(1):25–33

Light– and electron–microscopic demonstration of enkephalin–like immunoreactivity in paraganglia of the human urinary bladder. Vaalasti A, et al. **Cell Tissue Res** 1985;239(3):683–7

Quantitation of proenkephalin A messenger RNA in bovine brain, pituitary and adrenal medulla: correlation between mRNA and peptide levels. Pittius CW, et al. **EMBO J** 1985 May;4(5):1257–60

Proenkephalin and prodynorphin related neuropeptides in the cochlea. Hoffman DW, et al. **Hear Res** 1985 Jan;17(1):47–50

Localization of enkephalins in adrenaline cells and the nerves innervating adrenaline cells in rat adrenal medulla. Pelto–Huikko M, et al. **Histochemistry** 1985;82(4):377–83

Selective regulation of carboxypeptidase peptide hormone–processing enzyme during enkephalin biosynthesis in cultured bovine adrenomedullary chromaffin cells. Hook VY, et al. **J Biol Chem** 1985 May 25;260(10):5991–7

Separation of enkephalins from their metabolites and precursor by a single pump gradient high–performance liquid chromatographic method. Hui KS, et al. **J Chromatogr** 1985 Jun 7;325(2):467–72

Immunological characterization of secretory proteins of chromaffin granules: chromogranins A, chromogranins B, and enkephalin–containing peptides. Fischer–Colbrie R, et al. **J Neurochem** 1985 Jun;44(6):1854–61

Characterization of membrane–bound aminopeptidases from rat brain: identification of the enkephalin–degrading aminopeptidase. Hersh LB. **J Neurochem** 1985 May;44(5):1427–35

Changes from enkephalin–like to gastrin/cholecystokinin–like immunoreactivity in snail neurons. Gesser BP, et al. **J Neurosci** 1985 Jun;5(6):1412–7

Nasal delivery of polypeptides I: nasal absorption of enkephalins in rats. Su KS, et al. **J Pharm Sci** 1985 Apr;74(4):394–8

Mu1: a very high affinity subtype of enkephalin binding sites in rat brain. Lutz RA, et al. **Life Sci** 1985 Jun 10;36(23):2233–8

Senescent change in tissue weight and immunoreactive beta–endorphin, enkephalin, and vasopressin in eight regions of C57BL/6J mouse brain and pituitary. Rogers J, et al. **Neurobiol Aging** 1985 Spring;6(1):1-9

Peripheral enkephalin hydrolysis in different animal species: a comparative study. Venturelli F, et al. **Neurochem Res** 1985 Mar;10(3):333-42

Substance P, enkephalins, somatostatin, cholecystokinin, oxytocin, and vasopressin in human spinal cord. Schoenen J, et al. **Neurology** 1985 Jun;35(6):881-90

Influence of acute, subchronic and chronic treatment with neuroleptic (haloperidol) on enkephalins and their precursors in the striatum of rat brain. Blanc D, et al. **Neuropeptides** 1985 Feb;5(4-6):567-70

Studies in vitro with ICI 174,864, [D-Pen2, D-Pen5]-enkephalin (DPDPE) and [D-Ala2, NMePhe4, Gly-ol]-enkephalin (DAGO). Hirning LD, et al. **Neuropeptides** 1985 Feb;5(4-6):383-6

Prodynorphin immunoreactivity is located in different neurons than proenkephalin immunoreactivity in the cerebral cortex of rats. McGinty JF. **Neuropeptides** 1985 Feb;5(4-6):465-8

Partial purification and characterisation of a 31 kDalton putative enkephalin precursor from guinea pig striatum. Metters KM, et al. **Neuropeptides** 1985 Feb;5(4-6):505-8

Identification of high molecular weight enkephalin percursor forms in human cerebrospinal fluid. Nyberg F, et al. **Neuropeptides** 1985 Feb; 5(4-6):537-40

Characterization of a new 23 kDalton enkephalin-containing protein in the bovine adrenal medulla. Patey G, et al. **Neuropeptides** 1985 Feb; 5(4-6):513-6

Release of synenkephalin from neuronal terminals in vitro. Rossier J, et al. **Neuropeptides** 1985 Feb;5(4-6):549-52

Leumorphin in human brain. Suda M, et al. **Neuropeptides** 1985 Feb; 5(4-6):461-4

The comparative distribution of enkephalin, dynorphin and substance P in the human globus pallidus and basal forebrain. Haber SN, et al. **Neuroscience** 1985 Apr;14(4):1011-24

Comparison of substance P and enkephalin distribution in rat brain: an overview using radioimmunocytochemistry. McLean S, et al. **Neuroscience** 1985 Mar;14(3):837-52

Sequence and expression of the rat prodynorphin gene. Civelli O, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4291-5

A general procedure for analysis of proenkephalin B derived opioid peptides. Christensson-Nylander I, et al. **Regul Pept** 1985 May; 11(1):65-76

[Enkephalin-noradrenaline interactions in synaptic transmission] Fan JZ, et al. **Sheng Li Ko Hsueh Chin Chan** 1985 Apr;16(2):158-60 **(Chi)**

[Enkephalins and hormonal-metabolic reactions in experimental stress of differing severity] Lishmanov IuB, et al. **Biull Eksp Biol Med** 1985 Mar; 99(3):269-71 (Eng. Abstr **(Rus)**

ENURESIS

[Catecholaminergic activity in children with nocturnal enuresis] Szewczyk L. **Pediatr Pol** 1984 Oct;59(10):841-5 (Eng. Abstr.) **(Pol)**

EPHEDRINE

Bioavailability assessment of a new liquid controlled-release pseudoephedrine product. Graves DA, et al. **Clin Pharm** 1985 Mar-Apr; 4(2):199-203

Aperistalsis of the vas deferens corrected with administration of ephedrine. Tiffany P, et al. **J Urol** 1985 Jun;133(6):1060-1

EPINEPHRINE

Effect of propranolol on post-traumatic hypophosphataemia and catecholamine secretion. Lovén L, et al. **Acta Chir Scand** 1985; 151(3):201-4

Changes in blood level of catecholamines during arterial blood pressure rise induced with sciatic nerve stimulation. Całkosiński I, et al. **Acta Physiol Pol** 1984 Jan-Feb;35(1):47-51

Seasonal changes in blood lipids, adrenaline, noradrenaline, glucose and insulin in Norwegian reindeer. Larsen TS, et al. **Acta Physiol Scand** 1985 May;124(1):53-9

Human platelet alpha 2-adrenergic receptors: effect of Na+ on interaction with the adenylate cyclase system and on epinephrine-stimulated platelet secretion. Limbird LE, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:235-42

Neural and transmitter influence on the capillary diameter in exteriorized frog mesentery. Dietrich HH, et al. **Adv Exp Med Biol** 1984; 180:701-9

Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. Stratton JR, et al. **Am J Cardiol** 1985 Jul 1;56(1):136-9

Intravascular lidocaine toxicity: influence of epinephrine and route of administration. Yagiela JA. **Anesth Prog** 1985 Mar-Apr;32(2):57-61

Effect of amines on fibrinogen synthesis. Roy AK, et al. **Arch Biochem Biophys** 1985 Jun;239(2):364-7

Depletion of adrenal catecholamines alters the amnestic effect of amygdala stimulation. Bennett C, et al. **Behav Brain Res** 1985 Apr;15(2):83-91

Peripheral epinephrine modulates the effects of post-training amygdala stimulation on memory. Liang KC, et al. **Behav Brain Res** 1985 Apr; 15(2):93-100

Stimulation of inositol trisphosphate formation in hepatocytes by vasopressin, adrenaline and angiotensin II and its relationship to changes in cytosolic free Ca2+. Charest R, et al. **Biochem J** 1985 Apr 1; 227(1):79-90

Effects of phorbol esters on alpha 1-adrenergic-mediated and glucagon-mediated actions in isolated rat hepatocytes. García-Sáinz JA, et al. **Biochem J** 1985 May 15;228(1):277-80

Hepatic thiol and glutathione efflux under the influence of vasopressin, phenylephrine and adrenaline. Sies H, et al. **Biochem J** 1985 Mar 1; 226(2):545-9

Effect of methyl palmoxirate, an oral hypoglycemic agent, on epinephrine-induced hyperglycemia in the rat. Tutwiler GF, et al. **Biochem Pharmacol** 1985 Jun 15;34(12):2217-20

The effect of catecholamines and adenosine deaminase on the glucose transport system in rat adipocytes. Gliemann J, et al. **Biochim Biophys Acta** 1985 Jun 30;845(3):373-9

Factor analytic derivation of the MHPG/NM ratio: implications for studying the link between physical fitness and depression. Sothmann MS, et al. **Biol Psychiatry** 1985 May;20(5):579-83

Catecholamine responses to changes in posture during human pregnancy. Whittaker PG, et al. **Br J Obstet Gynaecol** 1985 Jun;92(6):586-92

Corticotropin-releasing factor: a physiologic regulator of adrenal epinephrine secretion. Brown MR, et al. **Brain Res** 1985 Mar 4; 328(2):355-7

Epinephrine- and norepinephrine-evoked potential changes of frog primary afferent terminals: pharmacological characterization of alpha and beta components. Wohlberg CJ, et al. **Brain Res** 1985 Feb 18; 327(1-2):289-301

Acetaminophen administration interferes with urinary metanephrine (and catecholamine) determinations [letter] Wilson SP, et al. **Clin Chem** 1985 Jun;31(6):1093-4

Blood pressure responses to ACTH and adrenaline infusions in dogs. Anderson WP, et al. **Clin Exp Hypertens** [A] 1985;7(4):525-37

Alpha 1-adrenergic responsiveness of young adult and aged rat submandibular cells in vitro. Baum BJ, et al. **Comp Biochem Physiol** [C] 1985;81(1):121-4

Accumulation of intra-arterially administered [3H]adrenaline and [3H]noradrenaline in various tissues of the Atlantic cod, Gadus morhua. Ungell AL. **Comp Biochem Physiol** [C] 1985;81(1):25-8

Regulation of ketogenesis by epinephrine and norepinephrine in the overnight-fasted, conscious dog. Steiner KE, et al. **Diabetes** 1985 May; 34(5):425-32

Plasma glucagon and catecholamines during exhaustive short-term exercise. Näveri H, et al. **Eur J Applied Physiol** 1985;53(4):308-11

Normetanephrine and metanephrine oxidized by both types of monoamine oxidase. Suzuki O, et al. **Experientia** 1985 May 15;41(5):634-6

Enhancement of adrenaline plasma-levels shortens adrenaline half-life. Porta S, et al. **Horm Metab Res** 1985 May;17(5):264-5

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr; 6(2):78-81

Exercise, dobutamine, and combined atropine, norepinephrine, and epinephrine compared. Haidet GC, et al. **J Appl Physiol** 1985 Jun; 58(6):2047-53

Hemodynamic effects of epinephrine: concentration-effect study in humans. Stratton JR, et al. **J Appl Physiol** 1985 Apr;58(4):1199-206

Analysis of USP epinephrine injections for potency, impurities, degradation products, and d-enantiomer by liquid chromatography, using ultraviolet and electrochemical detectors. Kirchhoefer RD, et al. **J Assoc Off Anal Chem** 1985 Mar-Apr;68(2):163-5

Simple and fast analysis of adrenaline and noradrenaline in plasma on microbore high-performance liquid chromatography columns using fluorimetric detection. Kamperman G, et al. **J Chromatogr** 1985 Feb 8;337(2):384-90

High-performance liquid chromatographic analysis of epinephrine enantiomers using a UV detector in series with an optical activity detector. Scott BS, et al. **J Chromatogr** 1985 Feb 20;319(3):419-26

Circadian rhythms of epinephrine and norepinephrine in man. Linsell CR, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1210-5

(-)-Adrenaline-induced, calcium-dependent phosphorylation of proteins in human platelets. Block LH, et al. **J Clin Invest** 1985 May; 75(5):1600-7

Evidence for a beta-adrenoceptor-mediated regulation of human natural killer cells. Hellstrand K, et al. **J Immunol** 1985 Jun;134(6):4095-9

Decrease in hypothalamic epinephrine concentration and other neurochemical changes produced by quinpirole, a dopamine agonist, in rats. Fuller RW, et al. **J Neural Transm** 1985;61(3-4):161-73

Effects of intravenous glucose or epinephrine injection on plasma concentrations of potassium, magnesium and insulin in sheep. Yano H, et al. **J Nutr Sci Vitaminol (Tokyo)** 1984 Dec;30(6):535-40

Review and survey of medicaments used with gingival retraction cords. Donovan TE, et al. **J Prosthet Dent** 1985 Apr;53(4):525-31

Adrenaline, adenosine, and feedback [letter] Böhm M, et al. **Lancet** 1985 May 18;1(8438):1157

Effect of intravenous epinephrine infusion on plasma renin activity in adrenalectomized dogs. Johnson MD. **Life Sci** 1985 Jun 24; 36(25):2403-11

Subsensitive pituitary cyclic AMP response to stress following adrenalectomy is not caused by loss of adrenal epinephrine. Kant GJ, et al. **Life Sci** 1985 Jun 24;36(25):2421-8

Epinephrine and norepinephrine syntheses are regulated by a glucocorticoid receptor-mediated mechanism in the bovine adrenal medulla. Nawata H, et al. **Life Sci** 1985 May 20;36(20):1957-66

The effect of epinephrine and serotonin on hepatic poly(A)+ RNA synthesis. Roy AK, et al. **Life Sci** 1985 Jun 17;36(24):2301-7

Adrenaline and anaphylaxis [letter] Roberts-Thomson P, et al. **Med J Aust** 1985 Jun 24;142(13):708

Excretion of urinary catecholamines and plasma cortisol levels in female nurses on short-rotating shift. Panza G, et al. **Med Lav** 1985 Jan-Feb; 76(1):30-4

Effect of epinephrine on carbohydrate metabolism in exercising dogs. Issekutz B Jr. **Metabolism** 1985 May;34(5):457-64

Plasma catecholamines in arterial and capillary blood. Baumgartner H, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):461-3

Effect of histamine infusion on circulating methionine-enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289-92

Administering epinephrine in an emergency. Gever LN. **Nursing** 1985 Jun;15(6):65

Dissociation of epinephrine's hyperglycemic and anorectic effect. Langhans W, et al. **Physiol Behav** 1985 Mar;34(3):457-63

Airway responses to low concentrations of adrenaline and noradrenaline in normal subjects. Berkin KE, et al. **Q J Exp Physiol** 1985 Apr; 70(2):203-9

Relationship between sleep efficiency and urinary excretion of catecholamines in bed-rested humans. Nishihara K, et al. **Sleep** 1985; 8(2):110-7

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

[Effect of adrenaline and phenylephrine on milk extraction during the mechanical milking of cows] Bernabe J, et al. **Reprod Nutr Dev** 1985; 25(2):379-88 (Eng. Abstr.) **(Fre)**

[Animal experiment studies on the hemodynamic effect of adrenaline following intravenous and endobronchial administration] Hörnchen U, et al. **Anasth Intensivther Notfallmed** 1985 Apr;20(2):84-8 (Eng. Abstr.) **(Ger)**

[Electrocardiographic studies of the modification of cardiac activity in cattle by adrenaline and noradrenaline with and without vagolysis (atropine) and beta-receptor blockade (propranolol)] Mielke H, et al. **Arch Exp Veterinarmed** 1985 Mar;39(2):193-206 (Eng. Abstr.) **(Ger)**

[Concentrations of catecholamines in CSF and plasma, and cardiovascular effects following epidural administration of 2 mg epinephrine] Nakajima J. **Masui** 1985 Feb;34(2):144-51 (Eng. Abstr.) **(Jpn)**

[Urinary excretion of catecholamines in children with functional disorders of the digestive system] Szewczyk L, et al. **Pediatr Pol** 1984 Oct; 59(10):835-9 (Eng. Abstr.) **(Pol)**

[Catecholaminergic activity in children with nocturnal enuresis] Szewczyk L. **Pediatr Pol** 1984 Oct;59(10):841-5 (Eng. Abstr.) **(Pol)**

[Regulation of the cell cycle of B-lymphocytes in mice by substances elevating the levels of intracellular cAMP and cGMP] Ado AD, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):455-9 (Eng. Abstr.) **(Rus)**

[Circadian rhythms of adrenaline and noradrenaline excretion in man in normal conditions and after alcohol intake] Latenkov VP. **Biull Eksp Biol Med** 1985 Mar;99(3):344-6 (Eng. Abstr.) **(Rus)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

[Changes in adrenaline sensitivity during thermal adaptation] Kosenkov NI. **Fiziol Cheloveka** 1984 May-Jun;10(3):478-9 **(Rus)**

[Effect and aftereffect of adrenaline on the respiration of rat liver mitochondria] Babskii AM, et al. **Fiziol Zh** 1985 May-Jun; 31(3):301-6 (Eng. Abstr.) **(Rus)**

[Effect of resection and dissection of the distal portion of the small intestine on the adrenergic inhibition of gastric secretion] Trefilov AB. **Fiziol Zh SSSR** 1985 Feb;71(2):221-5 (Eng. Abstr.) **(Rus)**

[Normal values of dopamine, noradrenaline, adrenaline, and 5-hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb; 53(334):49-52 (Eng. Abstr.) **(Spa)**

[Radioimmunoanalysis of adrenaline and noradrenaline in the normal fetus at term] Martinez Alcalá FO, et al. **Ginecol Obstet Mex** 1983 Oct; 51(318):267-72 (Eng. Abstr.) **(Spa)**

ESCAPE REACTION

Intracortical glutamate injection produces helpless-like behavior in the rat. Petty F, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):531-3

The activation of mice's behavior and reduction of brain beta-adrenergic receptor binding following repeated administration of antidepressant drugs. Nomura S, et al. **Yakubutsu Seishin Kodo** 1984 Nov; 4(3):237-41

ESTRADIOL

The effects of testosterone and estrogen on the pituitary growth hormone response to growth hormone-releasing factor. Wehrenberg WB, et al. **Biol Reprod** 1985 Mar;32(2):369-75

The possible role of 2-hydroxyestradiol in the development of estrogen-induced striatal dopamine receptor hypersensitivity. Clopton JK, et al. **Brain Res** 1985 Apr 29;333(1):1-10

Estradiol benzoate decreases nigral GABAergic activity in male rats. Nicoletti F, et al. **Brain Res** 1985 Apr 15;332(1 :179-83

Estradiol increases dopamine turnover in intermediate and posterior pituitary lobes of ovariectomized rats. Saavedra JM, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):397-402

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893-8

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953-9

Hormonal influence on the response of the uterus of the Brazilian marsupial Didelphis albiventris to adrenergic drugs. Rocha LR, et al. **Gen Comp Endocrinol** 1985 May;58(2):179-85

Levels of dopamine and thyrotrophin-releasing hormone in hypophysial stalk blood during an oestrogen-stimulated surge of prolactin in the ovariectomized rat. de Greef WJ, et al. **J Endocrinol** 1985 Apr; 105(1):107-12

Changes in pulsatile LH secretion and the positive and negative feedback actions of oestradiol after administration of a GnRH agonist in the ovariectomized ewe. Fitzgerald BP, et al. **J Reprod Fertil** 1985 Mar; 73(2):433-40

Neurotensin enhances estradiol induced DNA synthesis in immature rat uterus. Mistry A, et al. **Life Sci** 1985 May 27;36(21):2063-7

Progesterone-induced LHRH release in vitro is an estrogen--as well as Ca++- and calmodulin-dependent secretory process. Drouva SV, et al. **Neuroendocrinology** 1985 Apr;40(4):325-31

Alteration of dopamine metabolism in different brain regions of the rabbit by estradiol and tamoxifen. Baksi SN, et al. **Neuroscience** 1985 Apr; 14(4):1053-9

The effect of chronic estrogen treatment on immunoreactive beta-endorphin levels in intact female rats. Forman LJ, et al. **Proc Soc Exp Biol Med** 1985 Jul;179(3):365-72

[Effect of the administration of thyroxine and estradiol on the morphology of the anterior lobe of the pituitary gland] Szczurek Z, et al. **Patol Pol** 1984 Oct-Dec;35(4):499-507 (Eng. Abstr.) **(Pol)**

ETHOLOGY

Automated measurement of multivariate locomotor behavior in rodents. Sanberg PR, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb; 7(1):87-94

EXPLORATORY BEHAVIOR

Response of the rat brain beta-endorphin system to novelty: importance of the fornix connection. Netto CA, et al. **Behav Neural Biol** 1985 Jan; 43(1):37-46

Sulpiride blocks postsynaptic dopamine receptors in the nucleus accumbens. Morgenstern R, et al. **J Neural Transm** 1985; 61(3-4):151-60

Stress produces opioid-like effects on investigatory behavior. Arnsten AF, et al. **Pharmacol Biochem Behav** 1985 May;22(5):803-9

Increased investigative activity after presynaptic dopaminergic stimulation measured by a fixed-interval recording procedure. Höglund AU, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):403-6

Development of mouse activity, stimulus reactivity, habituation, and response to amphetamine and scopolamine. Alleva E, et al. **Physiol Behav** 1985 Apr;34(4):519-23

Behavioral analysis of the effect of neurotensin injected into the ventral mesencephalon on investigatory and spontaneous motor behavior in the rat. Cador M, et al. **Psychopharmacology (Berlin)** 1985;85(2):187-96

[Effect of stable strontium on spontaneous and drug-induced motor activity in the rat] Escanero JF, et al. **Arch Farmacol Toxicol** 1985 Apr; 11(1):33-9 (Eng. Abstr.) **(Spa)**

EXTINCTION (PSYCHOLOGY)

Haloperidol and nonreinforcement produce different patterns of response slowing in a food reinforced runway task. Wirtshafter D, et al. **Pharmacol Biochem Behav** 1985 May;22(5):661-3

FEAR

Imipramine in the treatment of panic disorder and its complications. Liebowitz MR. **Psychiatr Clin North Am** 1985 Mar;8(1):37–47

Anxiolytic drugs and the acquisition of conditioned fear in mice. Sanger DJ, et al. **Psychopharmacology (Berlin)** 1985;85(3):284–8

FENFLURAMINE

Possible relationships between changes in body weight set-point and stress metabolism after treating rats chronically with D-fenfluramine. Effects of feeding rats acutely with fructose on the metabolism of corticosterone, glucose, fatty acids, glycerol and triacylglycerol. Brindley DN, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1265–71

d-Fenfluramine and salbutamol: two drugs causing anorexia through different neurochemical mechanisms. Garattini S, et al. **Int J Obes** 1984; 8 Suppl 1:151–7

Comparison of the effects of fenfluramine and other anorectic agents in different feeding and drinking paradigms in rats. Rowland NE, et al. **Life Sci** 1985 Jun 17;36(24):2295–300

The effect of previous d-amphetamine treatment on the disposition and lethality of fenfluramine in the rat. Hunsinger RN, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):236–45

[Ponderal Retard] de Longraye J. **Soins** 1985 Feb;(448):III-IV (Fre)

FK 33–824

Effect of dopamine receptor stimulation on the inhibition of LH pulsatility by a met-enkephaline (FK 33-824). del Pozo E, et al. **Acta Neurochir (Wien)** 1985;75(1–4):88–90

FLUPHENAZINE

Priapism resulting from fluphenazine hydrochloride treatment reversed by diphenhydramine. Fishbain DA. **Ann Emerg Med** 1985 Jun; 14(6):600–2

The effects of chronic neuroleptic treatment on neurotensin-like immunoreactivity in the rat central nervous system. Goedert M, et al. **Brain Res** 1985 Jun 3;335(2):334–6

Serum neuroleptic levels and clinical outcome in schizophrenic patients treated with fluphenazine decanoate. Brown WA, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):143–7

Double-blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. Kissling W, et al. **Pharmacopsychiatry** 1985 May;18(3):240–5

Serum and cerebrospinal fluid prolactin patterns during neuroleptic treatment in schizophrenic patients. Rimón R, et al. **Pharmacopsychiatry** 1985 May;18(3):252–4

Effects of thioridazine and fluphenazine on the pituitary, thyroid and adrenal functions in patients with paranoid schizophrenia. Horodnicki JM, et al. **Psychiatr Pol** 1984 May–Jun;18(3):205–11

[Social integration of long-term paraphrenic patients with low-dose depot neuroleptic medication] Lesch OM, et al. **Psychiatr Prax** 1985 Mar; 12(2):63–8 (Eng. Abstr.) (Ger)

FLURAZEPAM

GABA and benzodiazepine-induced modification of [14C]L-glutamic acid release from rat spinal cord slices. Vellucci SV, et al. **Brain Res** 1985 Mar 25;330(2):201–7

Benzodiazepines inhibit human platelet activation: comparison of the mechanism of antiplatelet actions of flurazepam and diazepam. Romstedt K, et al. **Thromb Res** 1985 May 15;38(4):361–74

FOOD DEPRIVATION

Effect of feed and water deprivation or force-feeding on plasma prolactin concentration in turkey hens. Zadworny D, et al. **Biol Reprod** 1985 Mar;32(2):241–7

Ontogenetic alterations in the effects of food and/or maternal deprivation on 5-HT, 5-HIAA and 5-HIAA/5-HT ratios. Spear LP, et al. **Brain Res** 1985 Feb;350(1–2):143–57

FSH

Possible site of negative and positive feedback action of oestrogen on gonadotrophin secretion in normal women. Nagahara Y, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):440–4

Long-term, pulsatile, low dose, subcutaneous luteinizing hormone-releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar–Apr;17(2):143–9

Changes in the isoelectric focusing profile of pituitary follicle-stimulating hormone in the developing male rat. Chappel SC, et al. **Biol Reprod** 1985 Apr;32(3):567–73

Dose-dependent inhibition of the preovulatory surges of gonadotropins and prolactin by the antiestrogen CI-628: possible sites of action. De Paolo LV. **Biol Reprod** 1985 May;32(4):745–52

Effect of gonadotropin-releasing hormone antagonists on serum follicle-stimulating hormone and luteinizing hormone under conditions of singular follicle-stimulating hormone secretion. Schwartz NB, et al. **Biol Reprod** 1985 Mar;32(2):391–8

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893–8

Follicle-stimulating hormone induction of Leydig cell maturation. Kerr JB, et al. **Endocrinology** 1985 Jun;116(6):2592–604

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953–9

Release of luteinizing hormone and follicle-stimulating hormone from pituitaries of lactating rats by gonadotropin-releasing hormone and high potassium concentration. Smith MS. **Endocrinology** 1985 May; 116(5):1826–34

Cytochemical and cytophysiological studies of gonadotropin-releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396–404

FSH and LH response to testosterone and gonadotropin-releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter; 10(4):183–7

Effects of short-term exposure to catecholestrogens on serum concentrations of gonadotrophins and metabolism of catecholestrogens in ovariectomized rats. Ball P, et al. **Horm Metab Res** 1985 Apr; 17(4):184–8

Effect of castration and steroid treatment on the release of gonadotropins by the rat pituitary-hypothalamus complex in vitro. Gill MK, et al. **Horm Metab Res** 1985 Mar;17(3):141–6

Hormonal responses to short term fasting in postmenopausal women. Beitins IZ, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1120–6

Heterogeneity of rat FSH by chromatofocusing: studies on serum FSH, hormone released in vitro and metabolic clearance rates of its various forms. Blum WF, et al. **J Endocrinol** 1985 Apr;105(1):29–37

Routine measurement of thyroid hormones and FSH in infertility not worthwhile [letter] Conway DI, et al. **Lancet** 1985 Apr 27; 1(8435):977–8

Differential suppression of follicle-stimulating hormone and luteinizing hormone secretion in vivo by a gonadotropin-releasing hormone antagonist. Grady RR, et al. **Neuroendocrinology** 1985 Mar; 40(3):246–52

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409–11 (Eng. Abstr.) (Fre)

GABA

Respiratory depression produced by injection of GABA into the fourth ventricle of the rabbit. Xiang JZ, et al. **Acta Acad Med Wuhan** 1985; 5(1):10–4

Inhibition of anaphylactic histamine release in vitro by GABA. Luzzi S, et al. **Agents Actions** 1985 Apr;16(3–4):160–2

The modulation of acetylcholine release by noradrenaline, GABA and related compounds. Beani L, et al. **Ann Ist Super Sanita** 1984; 20(1):17–9

Selectivity of [3H] GABA uptake and release in cells cultured from the rat cerebellum. Levi G, et al **Ann Ist Super Sanita** 1984;20(1):39–45

Drugs acting as modulators of neurochemical mechanisms of gabaergic synaptic transmission. Rayevsky KS, et al. **Ann Ist Super Sanita** 1984; 20(1):47–52

GABA effect on conditioned reflex responses in teleost. Ivanuš J, et al. **Ann NY Acad Sci** 1985;444:543–6

Inhibitory effect of GABA on sympathetic neurotransmission in rabbit ear artery. Manzini S, et al. **Arch Int Pharmacodyn Ther** 1985 Jan; 273(1):100–9

Response of the cockroach brain gamma-aminobutyric acid system to isonicotinic acid hydrazide and mercaptopropionic acid. Pandey A, et al. **Biochem Int** 1985 Feb;10(2):213–20

In vivo effects of aminooxyacetic acid and valproic acid on nerve terminal (synaptosomal) GABA levels in discrete brain areas of the rat. Correlation to pharmacological activities. Löscher W, et al. **Biochem Pharmacol** 1985 May 15;34(10):1747–56

gamma-Aminobutyric acid-mediated inhibition at cholinergic synapses formed by cultured retinal neurons. Agardh E, et al. **Brain Res** 1985 Mar 25;330(2):323–8

Subchronic administration of GABAergic agonists elevates [3H]GABA binding and produces tolerance in striatal dopamine catabolism. Beart PM, et al. **Brain Res** 1985 May 27;335(1):169–73

Effects of inhibitors of Na+,K+-ATPase on the membrane potentials and neurotransmitter efflux in rat brain slices. Brosemer RW. **Brain Res** 1985 May 13;334(1):125–37

Effects of glycine and GABA on the ganglion cels of the retina of the skate Raja erinacea. Cohen JL. **Brain Res** 1985 Apr 15; 332(1):169–73

Chemical activation of the mesencephalic locomotor region. Garcia-Rill

E, et al. **Brain Res** 1985 Mar 18;330(1):43-54

Immunohistochemistry of gamma-aminobutyric acid in the cat nucleus tractus solitarius. Maley B, et al. **Brain Res** 1985 Mar 25; 330(2):364-8

Effect of GABA and its antagonists, bicuculline and picrotoxin, on nerve cell discharges of the photosensory pineal organ of the frog, Rana esculenta. Meissl H, et al. **Brain Res** 1985 Apr 15;332(1):39-46

Specific [3H]gamma-aminobutyric acid binding to vestibular membranes of the chick inner ear. Meza G, et al. **Brain Res** 1985 Jun 24; 337(1):179-83

Estradiol benzoate decreases nigral GABAergic activity in male rats. Nicoletti F, et al. **Brain Res** 1985 Apr 15;332(1):179-83

Inhibitory influence of GABA on central serotonergic transmission. Involvement of the habenulo-raphé pathways in the GABAergic inhibition of ascending cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):81-90

Inhibitory influence of GABA on central serotonergic transmission. Raphé nuclei as the neuroanatomical site of the GABAergic inhibition of cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):91-103

The development of the dorsal root potential and the responsiveness of primary afferent fibers to gamma-aminobutyric acid in the spinal cord of rat fetuses. Seno N, et al. **Brain Res** 1985 Jan;349(1-2):11-6

Identified axo-axonic cells are immunoreactive for GABA in the hippocampus and visual cortex of the cat. Somogyi P, et al. **Brain Res** 1985 Apr 15;332(1):143-9

Synthesis of acetylcholine and gamma-aminobutyric acid by dissociated cerebral cortical cells in vitro. Thomas WE. **Brain Res** 1985 Apr 15; 332(1):79-89

GABA and benzodiazepine-induced modification of [14C]L-glutamic acid release from rat spinal cord slices. Vellucci SV, et al. **Brain Res** 1985 Mar 25;330(2):201-7

Neurochemical studies of the nucleus of the solitary tract, dorsal motor nucleus of the vagus and the hypoglossal nucleus in rat: topographical distribution of glutamate uptake, GABA uptake and glutamic acid decarboxylase activity. Simon JR, et al. **Brain Res Bull** 1985 Jan; 14(1):49-53

Interaction of penicillin and pentobarbital with inhibitory synaptic mechanisms in neocortex. Weiss DS, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):301-17

Inhibition of central angiotensin II induced drinking by GABA in the rat. Hutchinson JS, et al. **Clin Exp Hypertens [A]** 1984; 6(10-11):1777-80

Gamma aminobutyric acid (GABA) and hepatic bile flow in the adult rat. Minuk GY, et al. **Clin Invest Med** 1984;7(4):193-7

Comparative actions of GABA and acetylcholine on the Xenopus laevis lateral line. Bobbin RP, et al. **Comp Biochem Physiol [C]** 1985; 80(2):313-8

gamma-Amino butyric-N-acid sensitivity of mouse and human oocytes. Dolci S, et al. **Dev Biol** 1985 May;109(1):242-6

Study of ocular tissue changes, brain GABA and polyamine levels in rats exposed to carbon disulfide. Sefić M, et al. **G Ital Med Lav** 1984 May-Jul;6(3-4):127-9

GABA-ergic system in brain regions of glutamate-lesioned rats. Di Giorgio RM, et al. **Ital J Biochem** 1985 Jan-Feb;34(1):19-28

GABA neurons in the superficial layers of the rat dorsal cochlear nucleus: light and electron microscopic immunocytochemistry. Mugnaini E. **J Comp Neurol** 1985 May 1;235(1):61-81

Orally active and potent inhibitors of gamma-aminobutyric acid uptake. Ali FE, et al. **J Med Chem** 1985 May;28(5):653-60

gamma-Aminobutyric acid: temperature dependence in benzodiazepine receptor binding. Chweh AY, et al. **J Neurochem** 1985 Jul; 45(1):240-3

Modulation of the acetylcholine system in the superior cervical ganglion of rat: effects of GABA and hypoglossal nerve implantation after in vivo GABA treatment. Kása P, et al. **J Neurochem** 1985 May; 44(5):1363-72

A description of the GABAergic neurons and axon terminals in the motor nuclei of the cat thalamus. Kultas-Ilinsky K, et al. **J Neurosci** 1985 May;5(5):1346-69

A specific and sensitive determination of gamma aminobutyric acid in CSF and brain tissue by gas chromatography-mass spectrometry. Schaaf JM, et al. **J Neurosci Methods** 1985 May;13(3-4):257-65

GABAergic inhibition of hypertonic saline-induced vasopressin-dependent hypertension. Brennan TJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):663-71

Evidence for gamma-aminobutyric acid mediation of the sympathetic nerve inhibitory response to vagal afferent stimulation. Humphrey SJ, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):288-97

Possible inhibitory role of endogenous gamma-aminobutyric acid in the nonnicotinic functions of the dog cardiac sympathetic ganglia. Kushiku K, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):810-5

gamma-Aminobutyric-acid- and pentobarbitone-gated chloride currents in internally perfused frog sensory neurones. Akaike N, et al. **J Physiol (Lond)** 1985 Mar;360:367-86

Comparison of the action of baclofen with gamma-aminobutyric acid on rat hippocampal pyramidal cells in vitro. Newberry NR, et al. **J Physiol (Lond)** 1985 Mar;360:161-85

Effects of calcium hopantenate on neurotransmitter receptors in the rat brain. Ogawa N, et al. **Jpn J Pharmacol** 1985 Jan;37(1):45-50

Inhibitory effect on 3H-diazepam binding and potentiating action on GABA of ethyl loflazepate, a new minor tranquilizer. Sakai Y, et al. **Jpn J Pharmacol** 1985 Apr;37(4):373-9

The use of 3H-gamma-aminobutyric acid for transport studies with isolated nerve-terminals from rat brain. Halvarsson GB, et al. **Life Sci** 1985 Jul 22;37(3):209-16

Uptake of gamma-aminobutyric acid by human blood platelets: comparison with CNS uptake. Hambley JW, et al. **Life Sci** 1985 May 27;36(21):2053-62

Comparison of the pharmacological and biochemical profiles of valproic acid (VPA) and its cerebral metabolite (2-en-VPA) after oral administration in mice. Keane PE, et al. **Methods Find Exp Clin Pharmacol** 1985 Feb;7(2):83-6

Comparison of release of endogenous dopamine and gamma-aminobutyric acid from rat caudate synaptosomes. Caudill WL, et al. **Neurochem Res** 1985 Mar;10(3):319-31

Cimetidine-induced prolactin release: possible involvement of the GABA-ergic system. Sibilia V, et al. **Neuroendocrinology** 1985 Mar; 40(3):189-92

Chronic valproic acid therapy and synaptic markers of amino acid neurotransmission. Slevin JT, et al. **Neurology** 1985 May; 35(5):728-31

A GABAergic component in homosynaptic depression in the spinal monosynaptic pathway. A requirement for action of benzodiazepines. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):309-16

Inhibitory effect of cholesteryl gamma-aminobutyrate on evoked activity in rat hippocampal slices. Hesse GW, et al. **Neuropharmacology** 1985 Feb;24(2):139-46

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar; 24(3):217-22

The modulation of cortical acetylcholine release by GABA, GABA-like drugs and benzodiazepines in freely moving guinea-pigs. Tanganelli S, et al. **Neuropharmacology** 1985 Apr;24(4):291-9

gamma-Aminobutyric acid modulation of benzodiazepine receptor binding in vitro does not predict the pharmacologic activity of all benzodiazepine receptor ligands. Chweh AY, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):173-7

gamma-Aminobutyric acid enables synaptogenesis in the intact superior cervical ganglion of the adult rat. Dames W, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):159-64

gamma-Aminobutyric acid-induced depression of calcium currents of chick sensory neurons. Deisz RA, et al. **Neurosci Lett** 1985 May 14; 56(2):205-10

gamma-Aminobutyric acid decreases levels of messenger ribonucleic acid encoding prolactin in the rat pituitary. Loeffler JP, et al. **Neurosci Lett** 1985 Jan 7;53(1):121-5

gamma-Aminobutyric acid partly mediates the pentobarbitone depression of synaptic excitation in the guinea-pig olfactory cortex in vitro. Steel L, et al. **Neurosci Lett** 1985 May 1;56(1):33-8

Autoreceptors regulate gamma-[3H]aminobutyric acid release from the guinea pig small intestine. Taniyama K, et al. **Neurosci Lett** 1985 Apr 9;55(2):245-8

Distribution, ontogeny and projections of cholecystokinin-8, vasoactive intestinal polypeptide and gamma-aminobutyrate-containing neuron systems in the rat spinal cord: an immunohistochemical analysis. Fuji K, et al. **Neuroscience** 1985 Mar;14(3):881-94

Effects of octopamine on GABA-ergic transmission in rats. Jagiełło-Wójtowicz E, et al. **Pol J Pharmacol Pharm** 1984 Nov-Dec; 36(6):595-601

Influence of GABA mimetics and lithium on biochemical manifestations of striatal dopamine target cell hypersensitivity. Scatton B, et al. **Psychopharmacology [Suppl]** 1985;2:39-45

Actions of GABA and ethylenediamine on CA1 pyramidal neurones of the rat hippocampus. Blaxter TJ, et al. **Q J Exp Physiol** 1985 Jan; 70(1):75-93

Somatostatin and GABA correlate with cervical autonomic nerve activity. Tonoue T, et al. **Regul Pept** 1985 Apr;10(4):299-307

[Pre-synaptic inhibition and pentobarbital] Ohmura Y. **Masui** 1985 Jan; 34(1):2-8 (36 ref.) **(Jpn)**

[Drug activation of GABAergic transmission in the central nervous system: benzodiazepines and GABAergic agonists] Moura D, et al. **Acta Med Port** 1985 Feb;6(2):57-64 (46 ref.) (Eng. Abstr.) **(Por)**

[Action of neurotropic substances on gamma-aminobutyric acid release from brain synaptosomes during K+ depolarization] Maisov NI, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):451-3 (Eng. Abstr.) **(Rus)**

[Participation of gamma-aminobutyric acid in regulating corticotropin secretion in rats] Mishunina TM, et al. **Fiziol Zh** 1985 May-Jun; 31(3):321-6 (Eng. Abstr.) **(Rus)**

[Effects of microinjections of GABA into structures of the medulla oblongata on cardio- and hemodynamics indices] Shapoval LN, et al. **Fiziol Zh** 1985 Mar-Apr;31(2):219-23 **(Rus)**

[Effect of gamma-aminobutyric acid, taurine and catecholamines on the synaptic processes in Lorenzini's ampules in Black Sea skates] Akoev GN, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):466-71 (Eng. Abstr.) **(Rus)**

[Effect of hypothermia on reuptake of neuromediators by synaptosomes] Babiichuk GA, et al. **Ukr Biokhim Zh** 1985 Mar-Apr;57(2):87-9 (Eng. Abstr.) **(Rus)**

GLUCURONIDASE

Assay of beta-glucuronidase in bile following ion-pair extraction of pigments and bile acids. Kurtin WE, et al. **Anal Biochem** 1985 Jun; 147(2):511-6

beta-Glucuronidase activities of intestinal bacteria determined both in vitro and in vivo in gnotobiotic rats. Gadelle D, et al. **Appl Environ Microbiol** 1985 Mar;49(3):682-5

Evaluation and modification of spectrophotometric procedures for analysis of lactate dehydrogenase, beta-glucuronidase and arylsulphatase in human gingival crevicular fluid collected with filter-paper strips. Lamster IB, et al. **Arch Oral Biol** 1985; 30(3):235-42

Glucuronidase activity in Escherichia coli [letter] Nastasi A, et al. **Boll Ist Sieroter Milan** 1982;61(5):441

Human hepatic beta-glucuronidase: an enzyme kinetic study. Ho YC, et al. **Enzyme** 1985;33(1):9-17

Oligosaccharides generated by an endoglucuronidase are intermediates in the intracellular degradation of heparan sulfate proteoglycans. Kjellén L, et al. **J Biol Chem** 1985 Jul 15;260(14):8416-22

Effects of ammonia on processing and secretion of precursor and mature lysosomal enzyme from macrophages of normal and pale ear mice: evidence for two distinct pathways. Brown JA, et al. **J Cell Biol** 1985 Jun;100(6):1894-904

Lactate dehydrogenase, beta-glucuronidase and arylsulfatase activity in gingival crevicular fluid associated with experimental gingivitis in man. Lamster IB, et al. **J Periodontol** 1985 Mar;56(3):139-47

Nucleotide sequence of a regulatory region of the uidA gene in Escherichia coli K12. Blanco C, et al. **MGG** 1985;199(1):101-5

Mutagenicity of beta-glucuronidase in the Ames test. Cerná M. **Mutat Res** 1985 Jul;143(3):169-72

Enzyme histochemistry of the response by naive and sensitised macrophages to phagocytosis of collagen and latex particles. Pugh DI, et al. **Z Mikrosk Anat Forsch** 1985;99(1):14-24

GONADOTROPINS, PITUITARY

Hypothalamic gonadotrophin-releasing hormone and pituitary and plasma FSH and prolactin during photostimulation and photorefractoriness in intact and thyroidectomized starlings (Sturnus vulgaris). Dawson A, et al. **J Endocrinol** 1985 Apr;105(1):71-7

[Effect of veralipride on LH, FSH, and PRL levels and on the climacteric syndrome] De Cecco L, et al. **Rev Fr Gynecol Obstet** 1985 Feb 28; 80(3):152-5 (Eng. Abstr.) **(Fre)**

[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**

GUANETHIDINE

Guanethidine blocks the 2-deoxy-D-glucose-induced hypothalamic noradrenergic drive to hyperglycemia. Storlien LH, et al. **Brain Res** 1985 May 27;335(1):144-7

HABITUATION (PSYCHOPHYSIOLOGY)

Habituation to repeated stress is stressor specific. Kant GJ, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):631-4

HALOPERIDOL

Rapid formation of reduced haloperidol in guinea pigs following haloperidol administration. Korpi ER, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Feb;56(2):94-8

The interpretation of plasma haloperidol concentrations. Kirch DG, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):838-40

Plasma haloperidol levels: clinical response and fancy mathematics [letter] Van Putten T, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):835-8

Ontogeny of striatal unit activity and effects of single or repeated haloperidol administration in rats. Napier TC, et al. **Brain Res** 1985 Apr 29;333(1):35-44

Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Quirion R, et al. **Brain Res** 1985 Apr 8;331(2):358-62

Effect of duration of haloperidol treatment on DA receptor supersensitization in aging C57BL/6J mice. Randall PK, et al. **Brain Res** 1985 Apr 29;333(1):85-95

Chronic haloperidol does not alter agonist affinity for dopamine receptors in vitro. Meller E, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):389-94

The supersensitivity of dopaminergic neurons to apomorphine in rats following chronic haloperidol. Vogelsang GD, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):267-9

Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Hong JS, et al. **Fed Proc** 1985 Jun;44(9):2535-9

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

Effect of chronic haloperidol and quinacrine coadministration on striatal HVA levels and stereotypic behaviors in response to apomorphine in the rat. Deutsch SI, et al. **Neurochem Res** 1985 Apr;10(4):491-8

Influence of acute, subchronic and chronic treatment with neuroleptic (haloperidol) on enkephalins and their precursors in the striatum of rat brain. Blanc D, et al. **Neuropeptides** 1985 Feb;5(4-6):567-70

Beta-endorphin processing in pituitary and brain is sensitive to haloperidol stimulation. Ham J, et al. **Neuropeptides** 1985 Feb;5(4-6):497-500

Alterations in dopamine metabolism after chronic administration of haloperidol. Possible role of increased autoreceptor sensitivity. Saller CF, et al. **Neuropharmacology** 1985 Feb;24(2):123-9

Effect of haloperidol and sulpiride on dopamine metabolism in nucleus accumbens and olfactory tubercle: a study by in vivo voltammetry. Louilot A, et al. **Neuroscience** 1985 Mar;14(3):775-82

Haloperidol and nonreinforcement produce different patterns of response slowing in a food reinforced runway task. Wirtshafter D, et al. **Pharmacol Biochem Behav** 1985 May;22(5):661-3

Double-blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. Kissling W, et al. **Pharmacopsychiatry** 1985 May;18(3):240-5

Lateral ventricular enlargement and clinical response in schizophrenia. Smith RC, et al. **Psychiatry Res** 1985 Mar;14(3):241-53

Effect of benztropine on the diurnal prolactin responses to haloperidol. Nathan RS, et al. **Psychoneuroendocrinology** 1985;10(1):71-6

Effects of apomorphine and haloperidol on 'spontaneous' stereotyped licking behaviour in the Cebus monkey. Korsgaard S, et al. **Psychopharmacology (Berlin)** 1985;85(2):240-3

Chronic haloperidol during development attenuates dopamine autoreceptor function in striatal and mesolimbic brain regions of young and older adult rats. Scalzo FM, et al. **Psychopharmacology (Berlin)** 1985;85(3):271-6

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

Behavioral effects of long-term neuroleptic treatment in Cebus monkeys. Casey DE. **Psychopharmacology [Suppl]** 1985;2:211-6

Differential alteration of striatal D-1 and D-2 receptors induced by the long-term administration of haloperidol, sulpiride or clozapine to rats. Jenner P, et al. **Psychopharmacology [Suppl]** 1985;2:174-81

[Effects of haloperidol, chlorpromazine, metoclopramide and ascorbic acid on adrenergic salivation and lacrimation in mice at an ambient temperature of 30 degrees C] Li BH, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar;6(1):24-6 (Eng. Abstr.) **(Chi)**

[Bilateral dislocation of mandibular joints induced by haloperidol therapy--a case report] Liu ZZ. **Ssu Chuan I Hsueh Yuan Hsueh Pao** 1985 Mar;16(1):82-3 (Eng. Abstr.) **(Chi)**

[Continuous suppression of methamphetamine-induced supersensitivity by chronic haloperidol administration] Kashihara K, et al. **Seishin Shinkeigaku Zasshi** 1984;86(11):928-32 **(Jpn)**

[Role of serotonin and dopamine receptors in the mechanism of action of haloperidol and pirenperone] Maimets MO, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):15-8 (Eng. Abstr.) **(Rus)**

[Haloperidol decanoate in replacing combinations of antipsychotic agents in the treatment of chronic schizophrenics] Youssef HA. **Acta Psiquiatr Psicol Am Lat** 1984 Dec;30(4):297-304 **(Spa)**

[Malignant syndrome caused by neuroleptics. Rapid response to biperiden in a case of brief development (letter)] Castilla Cortázar A, et al. **Med Clin (Barc)** 1985 Apr 13;84(14):588 **(Spa)**

[Influence of nutritional status on intravenous pharmacokinetics of haloperidol in psychotic patients] Donoso A, et al. **Rev Med Chil** 1984 Aug;112(8):777-83 (Eng. Abstr.) **(Spa)**

HISTAMINE

Alteration of histamine metabolism in the rat brain under influence of various antidepressive treatments. Zawilska J, et al. **Agents Actions** 1985 Apr;16(3-4):105-8

Acetylcholine and histamine interact supra-additively on bronchomotor tone in guinea-pigs in vivo: a possible consequence of the relationship between airways resistance and calibre. Stewart AG, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):33-46

Effect of secretagogues on pancreatic exocrine secretion in the monkey and the dog. Iwatsuki K, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):67-72

Involvement of H1- and H2-receptors in triple response to histamine in human volunteers. Patwardhan MD, et al. **Indian J Physiol Pharmacol** 1984 Oct-Dec;28(4):335-7

Vasoactive amines modulate actin cables (stress fibers) and surface area in cultured bovine endothelium. Welles SL, et al. **J Cell Physiol** 1985 Jun;123(3):337-42

Effect of Ni2+ on the multiphasic positive inotropic responses to histamine mediated by H1-receptors in left atria of guinea pigs. Hattori Y, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):188-94

Effect of histamine infusion on circulating methionine-enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289-92

Possible involvement of central adrenergic and histaminergic systems in clonidine-induced inhibition of pinna reflex. Singh PP, et al. **Pharmacol Res Commun** 1985 Mar;17(3):261-9

Chemical mediators and the human heart. Marone G, et al. **Prog Biochem Pharmacol** 1985;20:38-54 (52 ref.)

[The effect of acetylcholine and histamine on blood flow through the abdominal organs] Antal J, et al. **Bratisl Lek Listy** 1985 Mar; 83(3):218-28 (Eng. Abstr.) **(Slo)**

HUNGER

The anorectic effect of satietin is unrelated to carbohydrate metabolism. Gyarmati S, et al. **Physiol Behav** 1985 Feb;34(2):167-70

HYDANTOINS

Synthesis of side chain-protected amino acid phenylthiohydantoins and their use in quantitative solid-phase Edman degradation. Steiman DM, et al. **Anal Biochem** 1985 Feb 15;145(1):91-5

Genetic polymorphism of mephenytoin p(4')-hydroxylation: difference between Orientals and Caucasians. Jurima M, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):483-7

Mephenytoin metabolism in vitro by human liver. Jurima M, et al. **Drug Metab Dispos** 1985 Mar-Apr;13(2):151-5

Isocratic separation of PTH-amino acids at picomole level by reverse-phase HPLC in the presence of sodium dodecylsulfate. Tsunasawa S, et al. **J Biochem (Tokyo)** 1985 Feb;97(2):701-4

Effect of structural modification of the hydantoin ring on anticonvulsant activity. Cortes S, et al. **J Med Chem** 1985 May;28(5):601-6

HYDRAZINES

Blot analyses of glycoconjugates: enzyme-hydrazide--a novel reagent for the detection of aldehydes. Gershoni JM, et al. **Anal Biochem** 1985 Apr; 146(1):59-63

Separation of dansyl hydrazine-derivatized oligosaccharides by liquid chromatography. Hull SR, et al. **Anal Biochem** 1985 Apr; 146(1):143-9

Enhancement of the horseradish peroxidase-catalyzed chemiluminescent oxidation of cyclic diacyl hydrazides by 6-hydroxybenzothiazoles. Thorpe GH, et al. **Anal Biochem** 1985 Feb 15;145(1):96-100

Phosphorus-nitrogen compounds. 26. Phosphaminimides. 2. 2,2'-Phosphinylidenebis(1,1,1-trimethylhydrazinium) iodide inner salts as agents affecting ganglionic transmission. Cates LA, et al. **J Med Chem** 1985 May;28(5):595-7

Effects of rifampicin and phenobarbital on the fate of isoniazid and hydrazine in vivo in rats. Noda A, et al. **Toxicol Lett** 1985 Jun; 25(3):313-7

HYDROXYBUTYRATES

Identification and quantitation of 1,4-butanediol in mammalian tissues: an alternative biosynthetic pathway for gamma-hydroxybutyric acid. Barker SA, et al. **Biochem Pharmacol** 1985 May 15;34(10):1849-52

Natural occurrence of trans-gamma hydroxycrotonic acid in rat brain. Vayer P, et al. **Biochem Pharmacol** 1985 Jul 1;34(13):2401-4

Effects of endogenous sugar acids on the ventromedial hypothalamic nucleus of the rat. Puthuraya KP, et al. **Brain Res** 1985 Apr 15; 332(1):165-8

Plasma levels of glucose, alanine, lactate, and beta-hydroxybutyrate in the unfed spiny dogfish shark (Squalus acanthias) after surgery and following mammalian insulin infusion. deRoos R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):28-43

Effects of propionate and methylmalonate on conversions of acetate, butyrate, and D(-)-3-hydroxybutyrate to fatty acids and carbon dioxide by mammary tissue slices of goats. Emmanuel B, et al. **J Dairy Sci** 1985 Mar;68(3):751-4

The effects of mild congenital methylmercury intoxication on the metabolism of 3-hydroxybutyrate and glucose in the brains of suckling rats. Menon NK, et al. **Neurotoxicology (Little Rock Ar)** 1985 Spring; 6(1):55-61

Ketone kinetics and D-(-)-3-hydroxybutyrate-induced inhibition of feeding in rats. Langhans W, et al. **Physiol Behav** 1985 Apr; 34(4):579-82

Effects of hyperketonemia on mouse embryonic and fetal glucose metabolism in vitro. Horton WE Jr, et al. **Teratology** 1985 Apr; 31(2):227-33

HYDROXYDOPAMINES

Effects of intraventricular injections of 6-hydroxydopamine on amine metabolites in rat brain and urine. Edwards DJ, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1255-63

6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233-41

Neonatal 6-hydroxydopamine lesion of spinal norepinephrine terminals fails to affect the ontogeny of swimming behavior. Ryan C, et al. **Brain Res** 1985 Jan;349(1-2):258-62

Effect of intracerebroventricular 6-hydroxydopamine (6-HODA) on the angiotensinogen concentration of the brain. Basso N, et al. **Clin Exp Hypertens [A]** 1984;6(10-11):1773-6

Meningeal cells are involved in foliation, lamination, and neurogenesis of the cerebellum: evidence from 6-hydroxydopamine-induced destruction of meningeal cells. Pehlemann FW, et al. **Dev Biol** 1985 Jul;110(1):136-46

Selective destruction of meningeal cells by 6-hydroxydopamine: a tool to study meningeal-neuroepithelial interaction in brain development. Sievers J, et al. **Dev Biol** 1985 Jul;110(1):127-35

Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215-27

Effects of chemical sympathectomy with 6-hydroxydopamine on cardiac output and its distribution in the rat. Nichols AJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):263-8

Effects of intracerebroventricular 6-hydroxydopamine on catecholaminergic fibers in the rat hypothalamus. Hwang BH, et al. **Exp Neurol** 1985 May;88(2):336-48

Cardiovascular effects of intracisternal 6-hydroxydopamine and of subsequent lesions of the ventrolateral medulla coinciding with the A1 group of noradrenaline cells in the rabbit. Elliott JM, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):117-30

Rapid changes in synaptic vesicle cytochemistry after depolarization of cultured cholinergic sympathetic neurons. Johnson MI, et al. **J Cell Biol** 1985 Jul;101(1):217-26

Neonatal 6-hydroxydopamine destroys spinal cord noradrenergic axons from the locus coeruleus, but not those from lateral tegmental cell groups. McBride RL, et al. **J Comp Neurol** 1985 May 15; 235(3):375-83

Cardiac postjunctional supersensitivity to beta-agonists after chronic chemical sympathectomy with 6-hydroxydopamine. Chess-Williams RG, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):162-6

6-Hydroxydopamine pretreatment effects on alpha- and beta-adrenergic receptor adaptation to clorgyline. Cohen RM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):158-61

Effects of intravenously administered 6-hydroxydopamine on the content of monoamines in the median eminence and neurointermediate lobe of the rat. Sheward WJ, et al. **Neurosci Lett** 1985 Apr 9;55(2):141-4

Ibotenic acid lesions of the lateral hypothalamus: comparison with 6-hydroxydopamine-induced sensorimotor deficits. Dunnett SB, et al. **Neuroscience** 1985 Feb;14(2):509-18

Supersensitivity to the anticonvulsant and proconvulsant activity of clonidine following noradrenaline depletion induced by 6-hydroxydopamine. Dalton JC, et al. **Psychopharmacology (Berlin)** 1985;85(3):319-22

Differential effects of dopamine D-1 and D-2 agonists and antagonists in 6-hydroxydopamine-lesioned rats. Arnt J. **Psychopharmacology [Suppl]** 1985;2:60-1

HYDROXYINDOLEACETIC ACID

Effects of jejunoileal bypass on food intake, amino acid levels, and indoleamine metabolism in rats. Herlin PM, et al. **Am J Surg** 1985 Jun; 149(6):739-44

Simultaneous determination of homovanillic acid, 3,4-dihydroxyphenylacetic acid and 5-hydroxyindoleacetic acid in brain tissue, using a double-column procedure. Moroji T, et al. **Arzneimittelforsch** 1985;35(2):478-80

Ontogenetic alterations in the effects of food and/or maternal deprivation on 5-HT, 5-HIAA and 5-HIAA/5-HT ratios. Spear LP, et al. **Brain Res** 1985 Feb;350(1-2):143-57

The influence of testosterone in the brain of the male rat on levels of serotonin (5-HT) and hydroxyindole-acetic acid (5-HIAA). Martinez-Conde E, et al. **Comp Biochem Physiol [C]** 1985; 80(2):411-4

The effects of amiflamine on cerebrospinal fluid amine metabolites in the rhesus monkey. Garrick NA, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):1-9

Does brain 5-HIAA indicate serotonin release or monoamine oxidase activity? Wolf WA, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):381-7

[Normal values of dopamine, noradrenaline, adrenaline, and 5-hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb;53(334):49-52 (Eng. Abstr.) **(Spa)**

HYDROXYTRYPTOPHAN

Antagonism by lisuride and 8-OH-DPAT of 5-HTP-induced prolongation of the performance of male rat sexual behavior. Ahlenius S, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):379-81

L-5-hydroxytryptophan in the treatment of anxiety disorders. Kahn RS, et al. **J Affective Disord** 1985 Mar-Apr;8(2):197-200

Pharmacology in vivo of the phenylindan derivative, Lu 19-005, a new potent inhibitor of dopamine, noradrenaline and 5-hydroxytryptamine uptake in rat brain. Arnt J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):101-7

HYDROXYZINE

[Atarax] Peutillot JF, et al. **Soins Psychiatr** 1985 Jan;(51):I-II **(Fre)**

HYPOCHONDRIASIS

Modification of disease phobia using a multifaceted exposure program. Tearnan BH, et al. **J Behav Ther Exp Psychiatry** 1985 Mar;16(1):57-61

IMIPRAMINE

Combined pharmacological and behavioral treatment for agoraphobia. Telch MJ, et al. **Behav Res Ther** 1985;23(3):325-35

Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. Shapira B, et al. **Biol Psychiatry** 1985 May;20(5):576-9

Regional distribution and elimination kinetics of imipramine in rat brain. Masada M, et al. **Chem Pharm Bull (Tokyo)** 1984 Nov;32(11):4678-81

Repeated treatment with imipramine decreased the number of [3H]piflutixol binding sites in the rat striatum. Klimek V, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):131-2

Sex differences in long-term gonadectomized rats: monoamine levels and [3H]nitroimipramine binding in brain nuclei. Renner KJ, et al. **Exp Brain Res** 1985;58(1):198-201

Imipramine metabolism in recurrent depressive episodes. Tollefson G, et al. **J Affective Disord** 1985 Mar-Apr;8(2):183-6

Psychophysiological outcome of behavioral and pharmacological treatments of agoraphobia. Michelson L, et al. **J Consult Clin Psychol** 1985 Apr;53(2):229-36

High- and low-affinity binding components for [3H]imipramine in rat cerebral cortex. Conway PG, et al. **J Neurochem** 1985 Jul;45(1):206-9

Possible artefacts in imipramine binding assays [letter] Reith ME. **J Neurochem** 1985 Aug;45(2):661-3

5-Methoxytryptoline, a competitive endocoid acting at [3H]imipramine recognition sites in human platelets. Segonzac A, et al. **J Neurochem** 1985 Jul;45(1):249-56

The effect of prolonged treatment with tricyclic antidepressants on the actions of 5-hydroxytryptamine in the hippocampal slice of the rat. Rowan MJ, et al. **Neuropharmacology** 1985 Feb;24(2):131-7

Imipramine in the treatment of panic disorder and its complications. Liebowitz MR. **Psychiatr Clin North Am** 1985 Mar;8(1):37-47

3H-Imipramine binding sites in platelets of hospitalized psychiatric patients. Gentsch C, et al. **Psychiatry Res** 1985 Mar;14(3):177-87

Clomipramine and imipramine in obsessive-compulsive disorder. Volavka J, et al. **Psychiatry Res** 1985 Jan;14(1):85-93

Occurrence of myeloid bodies in rats following two-year administration of imipramine hydrochloride. Spaet RH, et al. **Toxicol Pathol** 1983;11(1):3-11

[Antenatal effect of imipramine on the ontogeny of the imipramine receptors in the cerebral cortex of rats] Pirogova MV, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):35-8 (Eng. Abstr.) **(Rus)**

ISOCARBOXAZID

Monoamine oxidase inhibitors in the treatment of atypical depression. Zisook S, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):131-7

LACTATES

Plasma levels of glucose, alanine, lactate, and beta-hydroxybutyrate in the unfed spiny dogfish shark (Squalus acanthias) after surgery and following mammalian insulin infusion. deRoos R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):28-43

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr;6(2):78-81

Effect of 1,3-butanediol and short chain acids in sow gestation diets on maternal plasma metabolites and fetal energy storage. Spence CA, et al. **J Anim Sci** 1985 May;60(5):1280-7

Lactate transport through the blood-retinal and the blood-brain barrier in rats. Alm A, et al. **Ophthalmic Res** 1985;17(3):181-4

LEARNING

Interfering with taste aversion learning in rats: the role of associative interference. Cannon DS, et al. **Appetite** 1985 Mar;6(1):1-19

Central action of substance P: possible role in reward. Stäubli U, et al. **Behav Neural Biol** 1985 Jan;43(1):100-8

Pre-natal administration of diazepam improves radial maze learning in mice. Benton D, et al. **Comp Biochem Physiol [C]** 1985;80(2):273-5

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227-43

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer;9(2):261-82

Learning and memory deficits after lesions of the nucleus basalis magnocellularis: reversal by physostigmine. Murray CL, et al. **Neuroscience** 1985 Apr;14(4):1025-32

The effect of chronic vs. acute injection of vasopressin on animal learning and memory. Hamburger-Bar R, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):23-5

LEVODOPA

Effect of L-DOPA on glucose oxidation and incorporation into glycogen in discrete brain regions of the rat. Barash V, et al. **Brain Res** 1985 Jun 3;335(2):347-9

Altered pharmacokinetics of L-dopa metabolism [letter] Melamed E, et al. **Neurology** 1985 Jun;35(6):939-41

LH

Possible site of negative and positive feedback action of oestrogen on gonadotrophin secretion in normal women. Nagahara Y, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):440-4

Effect of dopamine receptor stimulation on the inhibition of LH pulsatility by a met-enkephaline (FK 33-824). del Pozo E, et al. **Acta Neurochir (Wien)** 1985;75(1-4):88-90

Long-term, pulsatile, low dose, subcutaneous luteinizing hormone-releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar-Apr;17(2):143-9

Control of steroidogenesis in Leydig cells: roles of Ca^{2+} and lipoxygenase products in LH and LHRH agonist action. Cooke BA, et al. **Ann NY Acad Sci** 1984;438:269-82

Is cAMP the obligatory second messenger in the action of lutropin on Leydig cell steroidogenesis. Themmen AP, et al. **Biochem Biophys Res Commun** 1985 May 16;128(3):1164-72

Dose-dependent inhibition of the preovulatory surges of gonadotropins and prolactin by the antiestrogen CI-628: possible sites of action. De Paolo LV. **Biol Reprod** 1985 May;32(4):745-52

Changes in luteinizing hormone-releasing hormone content of discrete hypothalamic areas associated with spontaneous and induced preovulatory luteinizing hormone surges in the domestic hen. Johnson AL, et al. **Biol Reprod** 1985 May;32(4):813-9

Effect of gonadotropin-releasing hormone antagonists on serum follicle-stimulating hormone and luteinizing hormone under conditions of singular follicle-stimulating hormone secretion. Schwartz NB, et al. **Biol Reprod** 1985 Mar;32(2):391-8

Study of the luteinizing hormone-induced increase of ovarian blood flow during the estrous cycle in the rat. Varga B, et al. **Biol Reprod** 1985 Apr;32(3):480-8

Successful treatment of infertile women with oligomenorrhoea using a combination of an LHRH agonist and exogenous gonadotrophins. Fleming R, et al. **Br J Obstet Gynaecol** 1985 Apr;92(4):369-73

A correlative radioimmunoassay and immunohistochemical study of LHRH-induced LH depletion in the anterior pituitary of male and female neonatal rats in vitro. Watanabe YG, et al. **Cell Tissue Res** 1985;240(1):95-100

Absence of effect of the peptide PHI-27 on LH release in vitro. Miyake A, et al. **Endocrinol Jpn** 1984 Dec;31(6):821-4

Increased gonadotropin-releasing hormone pulse frequency associated with estrogen-induced luteinizing hormone surges in ovariectomized ewes. Clarke IJ, et al. **Endocrinology** 1985 Jun;116(6):2376-83

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893-8

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953-9

Dynamic characteristics of luteinizing hormone release from perifused sheep anterior pituitary cells stimulated by combined pulsatile and continuous gonadotropin-releasing hormone. McIntosh RP, et al. **Endocrinology** 1985 Jul;117(1):169-79

Neurotransmitters involved in mediating the steroid-dependent suppression of pulsatile luteinizing hormone secretion in anestrous ewes: effects of receptor antagonists. Meyer SL, et al. **Endocrinology** 1985 May;116(5):2054-61

A rise in tonic luteinizing hormone secretion occurs during photoperiod-stimulated sexual maturation of the female ferret. Ryan KD, et al. **Endocrinology** 1985 May;116(5):2013-8

Tunicamycin and neuraminidase effects on luteinizing hormone (LH)-releasing hormone binding and LH release from rat pituitary cells in culture. Schvartz I, et al. **Endocrinology** 1985 Jun;116(6):2341-6

Release of luteinizing hormone and follicle-stimulating hormone from pituitaries of lactating rats by gonadotropin-releasing hormone and high potassium concentration. Smith MS. **Endocrinology** 1985 May;116(5):1826-34

Cytochemical and cytophysiological studies of gonadotropin-releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396-404

FSH and LH response to testosterone and gonadotropin-releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter;10(4):183-7

Seasonal variations in plasma luteinizing hormone and testosterone levels in the European badger Meles meles L. Audy MC, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):445-53

Seasonal variation in pituitary responsiveness to luteinizing hormone-releasing hormone of mallards and canvasbacks. Bluhm CK. **Gen Comp Endocrinol** 1985 Jun;58(3):491-7

Changes in hormone levels in relation to breeding behavior in male bullfrogs (Rana catesbeiana) at the individual and population levels. Mendonça MT, et al. **Gen Comp Endocrinol** 1985 May;58(2):270-9

Short-term changes in plasma levels of hormones during establishment and defense of a breeding territory in male song sparrows, Melospiza melodia. Wingfield JC. **Horm Behav** 1985 Jun;19(2):174-87

Effects of short-term exposure to catecholestrogens on serum concentrations of gonadotrophins and metabolism of catecholestrogens in ovariectomized rats. Ball P, et al. **Horm Metab Res** 1985 Apr;17(4):184-8

Effect of castration and steroid treatment on the release of gonadotropins by the rat pituitary-hypothalamus complex in vitro. Gill MK, et al. **Horm Metab Res** 1985 Mar;17(3):141-6

Prolonged suppression of plasma LH levels in male rats after a single injection of an LH-RH agonist in poly(DL-lactide-co-glycolide) microcapsules. Asch RH, et al. **J Androl** 1985 Mar-Apr;6(2):83-8

Hormonal responses to short term fasting in postmenopausal women. Beitins IZ, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1120-6

Radioimmunoassay of luteinizing hormone in the baboon (Papio hamadryas). Khan SA, et al. **J Med Primatol** 1985;14(3):143-57

GnRH pulse frequency determines LH pulse amplitude by altering the amount of releasable LH in the pituitary glands of ewes. Clarke IJ, et al. **J Reprod Fertil** 1985 Mar;73(2):425-31

Changes in pulsatile LH secretion and the positive and negative feedback actions of oestradiol after administration of a GnRH agonist in the ovariectomized ewe. Fitzgerald BP, et al. **J Reprod Fertil** 1985 Mar;73(2):433-40

Changes in pituitary and ovarian LHRH receptors after active immunization of female rats against LH or LHRH. Popkin RM, et al. **J Reprod Fertil** 1985 Mar;73(2):491-6

Increased gonadotrophin releasing hormone receptors on pituitary gonadotrophs: effect on subsequent LH secretion. Young LS, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):69-78

Diacylglycerols and protein kinase C. Potential amplifying mechanism for Ca2+-mediated gonadotropin-releasing hormone-stimulated luteinizing hormone release. Harris CE, et al. **Mol Pharmacol** 1985 May;27(5):532-6

Pineal melatonin mediates photoperiodic control of pulsatile luteinizing hormone secretion in the ewe. Bittman EL, et al. **Neuroendocrinology** 1985 May;40(5):409-18

Differential suppression of follicle-stimulating hormone and luteinizing hormone secretion in vivo by a gonadotropin-releasing hormone antagonist. Grady RR, et al. **Neuroendocrinology** 1985 Mar;40(3):246-52

Medial preoptic area involvement in norepinephrine-induced suppression of pulsatile luteinizing hormone release in ovariectomized rats. Leipheimer RE, et al. **Neuroendocrinology** 1985 Apr;40(4):345-51

Clinical value of biological activity of serum luteinizing hormone in patients with ovulatory failure. Kuramoto T. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 May;37(5):793-8

Leukotriene C4 as a mediator of luteinizing hormone release from rat anterior pituitary cells. Hulting AL, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3834-8

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[The effects of bromocriptine on anovulatory patients with high LH and euprolactinemia] Mori H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jan 20;61(1):48-55 (Eng. Abstr.) **(Jpn)**

[Biological and immunological characterization of human luteinizing hormone in plasma discharged by LH-RH infusion in normal adult women] Yano M. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 May;37(5):703-12 (Eng. Abstr.) **(Jpn)**

LH-FSH RELEASING HORMONE

Treatment of hypothalamic infertility with pulsatile GN-RH administration. Turla R, et al. **Acta Eur Fertil** 1984 Nov-Dec;15(6):445-8

Successful treatment of anovulatory sterility by use of pulsatile GN-RH application. Wiegand M, et al. **Acta Eur Fertil** 1984 Nov-Dec;15(6):467-8

Success and relapse rate after treatment of cryptorchidism with intranasal LHRH. Schwarz HP, et al. **Acta Paediatr Scand** 1985 Mar;74(2):274-80

Comparison between the steroidogenic responses after pulsatile and continuous administration of gonadotrophin releasing hormone to superfused rat follicles. Hedin L. **Acta Physiol Scand** 1985 Jun;124(2):269-76

Characteristics and bioefficacy of monoclonal antigonadotropin releasing hormone antibody. Gupta SK, et al. **Am J Reprod Immunol Microbiol** 1985 Mar;7(3):104-8

Long-term, pulsatile, low dose, subcutaneous luteinizing hormone-releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar-Apr;17(2):143-9

Control of steroidogenesis in Leydig cells: roles of Ca2+ and lipoxygenase products in LH and LHRH agonist action. Cooke BA, et al. **Ann NY Acad Sci** 1984;438:269-82

Studies on the identification of a LHRH-like peptide in the rat testis. Hedger MP, et al. **Ann NY Acad Sci** 1984;438:371-81

Molecular dynamics and minimum energy conformations of GnRH and analogs. A methodology for computer-aided drug design. Struthers RS, et al. **Ann NY Acad Sci** 1985;439:81-96

GnRH-like factors in the rat testis and human seminal plasma. Swerdloff RS, et al. **Ann NY Acad Sci** 1984;438:382-9

Luteinising hormone releasing hormone for incomplete descent of the testis. Klidjian AM, et al. **Arch Dis Child** 1985 Jun;60(6):568-71

Discrete hypothalamic distribution of luteinizing hormone-releasing hormone (LHRH) content and of LHRH-degrading activity in laying and nonlaying hens. Advis JP, et al. **Biol Reprod** 1985 May;32(4):820-7

Gonadotropin-releasing hormone stimulation of pituitary gonadotrope cells produces an increase in intracellular calcium. Clapper DL, et al. **Biol Reprod** 1985 Mar;32(2):269-78

Changes in luteinizing hormone-releasing hormone content of discrete hypothalamic areas associated with spontaneous and induced preovulatory luteinizing hormone surges in the domestic hen. Johnson AL, et al. **Biol Reprod** 1985 May;32(4):813-9

Effect of gonadotropin-releasing hormone antagonists on serum follicle-stimulating hormone and luteinizing hormone under conditions of singular follicle-stimulating hormone secretion. Schwartz NB, et al. **Biol Reprod** 1985 Mar;32(2):391-8

D-Ala6-des-Gly10-gonadotropin-releasing hormone ethylamide: absence of binding sites and lack of a direct effect in rabbit corpora lutea. Thorson JA, et al. **Biol Reprod** 1985 Mar;32(2):226-31

Biochemical transmethylation of lipids and neuropeptidergic stimulation of pituitary hormone secretion. Prasad C, et al. **Brain Res** 1985 May 13;334(1):41-6

Effects of prostaglandins and luteinizing hormone-releasing hormone on phosphatidic acid-phosphatidylinositol labeling in rat granulosa cells. Minegishi T, et al. **Can J Physiol Pharmacol** 1985 Apr;63(4):320-4

A correlative radioimmunoassay and immunohistochemical study of LHRH-induced LH depletion in the anterior pituitary of male and female neonatal rats in vitro. Watanabe YG, et al. **Cell Tissue Res** 1985;240(1):95-100

The effects of the GnRH agonist, [(imBzl)-D-His6, Pro9-NEt]-GnRH, on the response to stress in rats. Gibson MJ, et al. **Contraception** 1985 Jan;31(1):91-9

Distribution of luteinizing hormone-releasing hormone (LHRH) content and total LHRH-degrading activity (LHRH-DA) in the hypothalamus of the ewe. Advis JP, et al. **Endocrinology** 1985 Jun;116(6):2410-8

A role for extracellular copper in modulating prostaglandin E2 (PGE2) action: facilitation of PGE2 stimulation of the release of gonadotropin-releasing hormone (LHRH) from median eminence explants. Barnea A, et al. **Endocrinology** 1985 Jul;117(1):415-7

D-Trp-6-luteinizing hormone-releasing hormone inhibits hyperprolactinemia in female rats. Debeljuk L, et al. **Endocrinology** 1985 Jun;116(6):2227-31

Prostaglandin E2-induced luteinizing hormone-releasing hormone release involves mobilization of intracellular Ca+2. Ojeda SR, et al. **Endocrinology** 1985 May;116(5):1763-70

Tunicamycin and neuraminidase effects on luteinizing hormone

(LH)-releasing hormone binding and LH release from rat pituitary cells in culture. Schvartz I, et al. **Endocrinology** 1985 Jun;116(6):2341-6

Cytochemical and cytophysiological studies of gonadotropin-releasing hormone (GnRH) target cells in the male rat pituitary: differential effects of androgens and corticosterone on GnRH binding and gonadotropin release. Tibolt RE, et al. **Endocrinology** 1985 Jul;117(1):396-404

Exogenous progesterone for luteal support following gonadotropin-releasing hormone ovulation induction: case report. Berger NG, et al. **Fertil Steril** 1985 Jul;44(1):133-5

Does constant infusion of gonadotropin-releasing hormone agonist lead to greater suppression of gonadal function in man than its intermittent administration? Bhasin S, et al. **Fertil Steril** 1985 Jul;44(1):96-101

Immunoreactive luteinizing hormone-releasing hormone in the seminal plasma and human semen parameters. Izumi S, et al. **Fertil Steril** 1985 Apr;43(4):617-20

Effect on corpus luteum function of luteal phase administration of a potent gonadotropin-releasing hormone analog (nafarelin). Schriock ED, et al. **Fertil Steril** 1985 Jun;43(6):844-50

Seasonal variation in pituitary responsiveness to luteinizing hormone-releasing hormone of mallards and canvasbacks. Bluhm CK. **Gen Comp Endocrinol** 1985 Jun;58(3):491-7

Pimozide modulates the luteinizing hormone-releasing hormone effect on gonadotrophin release in the African catfish, Clarias lazera. de Leeuw R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):120-7

Structure-activity relationships of mammalian, chicken, and salmon gonadotropin releasing hormones in vivo in goldfish. Peter RE, et al. **Gen Comp Endocrinol** 1985 May;58(2):231-42

Seasonal effects of pimozide and des Gly10 [D-Ala6] LH-RH ethylamide on gonadotrophin secretion in goldfish. Sokolowska M, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):472-9

Seasonal changes in luteinizing hormone-releasing hormone concentrations in microdissected brain regions of male rough-skinned newts (Taricha granulosa). Zoeller RT, et al. **Gen Comp Endocrinol** 1985 May;58(2):222-30

Effect of gonadotropin releasing hormone on ventral prostate of rat. Raju VS, et al. **Horm Metab Res** 1985 May;17(5):241-3

Detection of prolactin and LH releasing activity in mid-term human fetal cerebrospinal fluid. Gilmore DP, et al. **Indian J Exp Biol** 1984 Nov;22(11):586-8

Immunological castration by a totally synthetic vaccine: modification of biological properties of LH-RH after conjugation to adjuvant-active muramyl peptide. Carelli C, et al. **Int J Immunopharmacol** 1985;7(2):215-24

Prolonged suppression of plasma LH levels in male rats after a single injection of an LH-RH agonist in poly(DL-lactide-co-glycolide) microcapsules. Asch RH, et al. **J Androl** 1985 Mar-Apr;6(2):83-8

The priming effect of LH-releasing hormone: effects of cold and involvement of new protein synthesis. Curtis A, et al. **J Endocrinol** 1985 May;105(2):163-8

Pituitary and gonadal response to exogenous LH-releasing hormone in the male domestic cat. Goodrowe KL, et al. **J Endocrinol** 1985 May;105(2):175-81

Immunocytochemistry of luteinizing hormone-releasing hormone during spontaneous and thyroxine-induced metamorphosis of bullfrogs. Whalen R, et al. **J Exp Zool** 1985 Apr;234(1):131-44

Improved antagonists of luteinizing hormone-releasing hormone modified in position 7. Hocart SJ, et al. **J Med Chem** 1985 Jul;28(7):967-70

Changes in pituitary and ovarian LHRH receptors after active immunization of female rats against LH or LHRH. Popkin RM, et al. **J Reprod Fertil** 1985 Mar;73(2):491-6

Induction of oestrus and ovulation by means of prostaglandin and gonadoliberin (GnRH) treatment in an old mare barren for two breeding seasons. Penzhorn BL, et al. **J S Afr Vet Assoc** 1985 Mar;56(1):53-4

Changes in plasma steroid levels after single administration of hCG or LHRH agonist analogue in dog and rat. Tremblay Y, et al. **J Steroid Biochem** 1985 Mar;22(3):315-20

Progesterone-induced LHRH release in vitro is an estrogen--as well as Ca++- and calmodulin-dependent secretory process. Drouva SV, et al. **Neuroendocrinology** 1985 Apr;40(4):325-31

Lipoxygenase products of arachidonic acid stimulate LHRH release from rat median eminence. Gerozissis K, et al. **Neuroendocrinology** 1985 Mar;40(3):272-6

Responsiveness of immature versus adult male rat hypothalami to dibutyryl cyclic AMP- and forskolin-induced LHRH release in vitro. Hartter DE, et al. **Neuroendocrinology** 1985 Jun;40(6):476-82

Glutamic acid decarboxylase-containing axons synapse on LHRH neurons in the rat medial preoptic area. Leranth C, et al. **Neuroendocrinology** 1985 Jun;40(6):536-9

Effects of progesterone on hypothalamic and plasma LHRH. Peduto JC, et al. **Neuroendocrinology** 1985 Mar;40(3):238-45

Apparent lack of involvement of cAMP as a mediator of LHRH stimulation of nuclear estrogen receptor activity in the rat anterior pituitary. Singh P, et al. **Neuroendocrinology** 1985 May;40(5):430-7

Shifts in gonadotropin storage in cultured gonadotropes following GnRH stimulation, in vitro. Childs GV. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):103-7

A new antiserum with conformational specificity for LHRH: usefulness for radioimmunoassay and immunocytochemistry. Ellinwood WE, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):45-52

D-Tryptophan-6 analog of luteinizing hormone-releasing hormone as a protective agent against testicular damage caused by cyclophosphamide in baboons. Lewis RW, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):2975-9

Possible negative ultra-short loop feedback of luteinizing hormone releasing hormone (LHRH) in the ovariectomized rat. Bedran de Castro JC, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):132-5

Induction of the self-priming effect of luteinizing hormone releasing hormone during the sexual maturation of the male rat. Nazian SJ. **Proc Soc Exp Biol Med** 1985 Jul;179(3):348-51

Luteinizing-hormone-releasing hormone modifies retention of passive and active avoidance responses in rats. Mora S, et al. **Psychopharmacology (Berlin)** 1985;85(3):315-8

[LHRH stimulates the secretion of an 87 K protein by cultured gonadotrophic cells] Hubert JF, et al. **C R Acad Sci [III]** 1985;300(16):613-6 (Eng. Abstr.) **(Fre)**

[Pulsatile treatment with LH-RH using a portable pump: a new modality for inducing ovulation and treating sterility] Thomas D, et al. **Rev Med Brux** 1985 May;6(5):325-33 (Eng. Abstr.) **(Fre)**

[Treatment of cryptorchism with LHRH nasal spray] Borkenstein M, et al. **Wien Klin Wochenschr** 1985 Apr 26;97(9):414-6 (Eng. Abstr.) **(Ger)**

[Effects of iontophoretically-applied LHRH, TRH, estrogen and clomiphene on thermo-sensitive neurons in the rat hypothalamus] Inagaki K, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Apr;37(4):611-8 (Eng. Abstr.) **(Jpn)**

[Biological and immunological characterization of human luteinizing hormone in plasma discharged by LH-RH infusion in normal adult women] Yano M. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 May;37(5):703-12 (Eng. Abstr.) **(Jpn)**

[Immunohistochemical research on the development of the LHRH system in the development of the rat] Ugriumov MV, et al. **Dokl Akad Nauk SSSR** 1985;280(6):1425-7 **(Rus)**

[Synthetic tripeptide miniluliberin and its biological activity] Babichev VN, et al. **Probl Endokrinol (Mosk)** 1985 Mar-Apr;31(2):47-9 (Eng. Abstr.) **(Rus)**

LIPOTROPIN

Determination of beta-endorphin and beta-lipotropin in human cerebrospinal fluid. Laatikainen TJ, et al. **Clin Chim Acta** 1985 Feb 15;145(3):325-9

[Immunoreactive beta-lipotropin and endorphins are secreted by the isolated alimentary complex of rats] Titov MI, et al. **Dokl Akad Nauk SSSR** 1985;281(2):497-9 **(Rus)**

LITHIUM

Renal function in 153 manic-depressive patients treated with lithium for more than five years. Løkkegaard H, et al. **Acta Psychiatr Scand** 1985 Apr;71(4):347-55

Plasma lithium level and interepisode functioning in bipolar disorder. Goodnick PJ, et al. **Am J Psychiatry** 1985 Jun;142(6):761-2

Lithium-selective polymeric membrane electrodes based on dodecylmethyl-14-crown-4. Kitazawa S, et al. **Analyst** 1985 Mar;110(3):295-9

A novel technique for assessing the sources of dietary sodium. Sanchez-Castillo CP, et al. **Ann Clin Res** 1984;16 Suppl 43:44-8

Can lithium carbonate prolong the antidepressant effect of sleep deprivation? [letter] Baxter LR Jr. **Arch Gen Psychiatry** 1985 Jun;42(6):635

Decreased myeloperoxidase activity of mice polymorphonuclear leukocytes by lithium carbonate treatment. Gómez-Estrada H, et al. **Arch Invest Med (Mex)** 1984 Oct-Dec;15(4):287-91 **(Eng, Spa)**

Automated determinations of K+ and Li+ with a microprocessor-controlled flame photometer [letter] Soltero RA. **Clin Chem** 1985 Jun;31(6):1094

Consensus development summaries. Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health. **Conn Med** 1985 Mar;49(3):157-63

The effect of sulindac on lithium therapy. Furnell MM, et al. **Drug Intell Clin Pharm** 1985 May;19(5):374-6

The effect of lithium carbonate administration on growth in the domestic fowl. Lozanoff S, et al. **Growth** 1985 Spring;49(1):91-104

Lithium-stimulated recovery of granulopoiesis after sublethal irradiation is not mediated via increased levels of colony stimulating factor (CSF). Gallicchio VS, et al. **Int J Radiat Biol** 1985 May;47(5):581-90

The influence of mania and depression on the pharmacokinetics of lithium. A longitudinal single-case study. Kukopoulos A, et al. **J Affective Disord** 1985 Mar-Apr;8(2):159-66

Mania. Diagnosis, state measurement and prediction of treatment response. Secunda SK, et al. **J Affective Disord** 1985 Mar-Apr;8(2):113-21

Severe prolonged catatonia with associated flushing reaction responsive to lithium carbonate. Pheterson AD, et al. **J Am Acad Child Psychiatry** 1985 Mar;24(2):235-7

Brain glycine levels following lithium toxicity: case report. Stanley M, et al. **J Clin Psychiatry** 1985 Jun;46(6):239

Treatment-resistant catatonic stupor and combined lithium-neuroleptic therapy: a case report. Climo LH. **J Clin Psychopharmacol** 1985 Jun; 5(3):166-70

A pharmacokinetic approach to the study of cell membrane lithium transport in vivo. Mallinger AG, et al. **J Clin Psychopharmacol** 1985 Apr;5(2):78-82

Lithium therapy for mania and depression. Murray JB. **J Gen Psychol** 1985 Jan;112(1):5-33

Na+ (Li+)-proline cotransport in Escherichia coli. Chen CC, et al. **J Membr Biol** 1985;84(2):157-64

The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3-4):175-81

Denervation supersensitivity of the rat pineal to norepinephrine-stimulated [3H]inositide turnover revealed by lithium and a convenient procedure. Zatz M. **J Neurochem** 1985 Jul; 45(1):95-100

Lithium-induced improvement of myotonia: relevance of prostaglandin E1 blockade by lithium [letter] Backon J. **J Neurol Neurosurg Psychiatry** 1985 Jun;48(6):606-7

Familial differences in lithium responsive versus lithium nonresponsive psychoses. Sautter F, et al. **J Psychiatr Res** 1985;19(1):1-8

Poor response when laboratory recommended range for serum lithium is changed [letter] Masterton G, et al. **Lancet** 1985 Apr 27; 1(8435):981

Mood disorders: pharmacologic prevention of recurrences. National Institutes of Health Consensus Development Conference Statement. **Nat Inst Health Consensus Dev Conf Consensus Statement** 1984; 5(4):8 p.

Effects of acute oral administration of lithium compounds on multiple schedule performance in rats. Chrislip DW, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):39-42

Effects of lithium in vitro on noradrenaline-induced cyclic AMP accumulation in rat cortical slices after reserpine-induced supersensitivity. Newman ME, et al. **Neuropharmacology** 1985 Apr; 24(4):353-5

Comparison of the changes in central catecholamine systems following short- and long-term lithium treatment and the consequences of lithium withdrawal. Ahluwalia P, et al. **Neuropsychobiology** 1984; 12(4):217-23

Mechanisms of the central action of lithium. Sinitskii VN, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):81-8

Compliance with outpatient lithium therapy. Connelly CE. **Perspect Psychiatr Care** 1984 Apr-Jun;22(2):44-50

Lithium effects on position learning with exploratory and aversive goal-box conditions. Hines G. **Pharmacol Biochem Behav** 1985 May; 22(5):695-8

Effects of chronic LiCl and RbCl on muricide induced by midbrain raphe lesions in rats. Yamamoto T, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):559-63

How does the patient prefer his lithium treatment? Vestergaard P. **Pharmacopsychiatry** 1985 May;18(3):223-4

Lithiated compounds of biological and oncological interest. Allen EB, et al. **Prog Clin Biol Res** 1985;172B:311-9

Interdependency of lithium ratio, plasma lithium level and clinical state in patients with affective disorders. Elizur A, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(2):167-72

Combined lithium and valproate treatment and subsequent withdrawal: serotonergic mechanism of their interaction in discrete brain regions. Shukla GS. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(2):153-6

Influence of GABA mimetics and lithium on biochemical manifestations of striatal dopamine target cell hypersensitivity. Scatton B, et al. **Psychopharmacology [Suppl]** 1985;2:39-45

Bipolar disorder and social work practice. Sands RG. **Soc Work Health Care** 1985 Spring;10(3):91-105

[Compartmental analysis of 6Li/7Li isotope exchange in equilibrium conditions in mouse plasma] Heurteaux C, et al. **C R Acad Sci [III]** 1985;300(14):529-34 (Eng. Abstr.) **(Fre)**

[Indications and monitoring of lithium treatment] Singer L, et al. **Rev Prat** 1985 May 11;35(27):1657-8, 1661-4 (Eng. Abstr.) **(Fre)**

[Effect of lithium on the proliferation of fibroblasts and tumor cell lines in vitro] Bruchelt G, et al. **Klin Padiatr** 1985 May-Jun; 197(3):249-52 (Eng. Abstr.) **(Ger)**

[Effect of lithium carbonate on the leukocyte count after exposure to ionizing radiation. 2. Influence of lithium carbonate on the leukocyte ratio in peripheral blood] Rose H, et al. **Radiobiol Radiother (Berl)** 1985; 26(1):103-7 (Eng. Abstr.) **(Ger)**

[Effect of lithium carbonate on the leukocyte count after exposure to ionizing radiation. 3. Influence of lithium carbonate on the leukocyte count in peripheral blood following fractionated caudal half-body irradiation] Rose H, et al. **Radiobiol Radiother (Berl)** 1985; 26(1):109-11 (Eng. Abstr.) **(Ger)**

[A case of simultaneous treatment of the manic syndrome and granulocytopenia with lithium salts] Greń K, et al. **Psychiatr Pol** 1984 May-Jun;18(3):285-8 **(Pol)**

[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**

[Lithium salts in the treatment of schizoaffective psychosis] Kopel A. **Psychiatr Pol** 1984 May-Jun;18(3):279-83 **(Pol)**

LORAZEPAM

Aminophylline is an antagonist of lorazepam. Wangler MA, et al. **Anesth Analg** 1985 Aug;64(8):834-6

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445-51

Clonidine in benzodiazepine withdrawal [letter] Keshavan MS, et al. **Lancet** 1985 Jun 8;1(8441):1325-6

Information processing and benzodiazepines. Kleindienst-Vanderbeke G. **Neuropsychobiology** 1984;12(4):238-43

[Intravenous sedation before endoscopic interventions. Comparative study of lormetazepam and diazepam in oil] Tolksdorf W, et al. **Fortschr Med** 1985 Mar 7;103(9):249-52 (Eng. Abstr.) **(Ger)**

MANIC DISORDER

A controlled clinical trial of L-tryptophan in acute mania. Chouinard G, et al. **Biol Psychiatry** 1985 May;20(5):546-57

The influence of mania and depression on the pharmacokinetics of lithium. A longitudinal single-case study. Kukopoulos A, et al. **J Affective Disord** 1985 Mar-Apr;8(2):159-66

Mania. Diagnosis, state measurement and prediction of treatment response. Secunda SK, et al. **J Affective Disord** 1985 Mar-Apr;8(2):113-21

Comparison of antimanic efficacy of clonidine and verapamil. Giannini AJ, et al. **J Clin Pharmacol** 1985 May-Jun;25(4):307-8

MATERNAL BEHAVIOR

Prenatal stress impairs maternal behavior in a conflict situation and reduces hippocampal benzodiazepine receptors. Fride E, et al. **Life Sci** 1985 Jun 3;36(22):2103-9

MEMORY

Catecholamine microfluorometry of nigral perikarya and tyrosine hydroxylase assay in some telencephalic structures of rats exposed to different behavioral situations. Divac I, et al. **Acta Neurobiol Exp (Warsz)** 1984;44(6):262-72

Mediation of storage and retrieval with two drugs that selectively modulate serotonergic neurotransmission. Altman HJ. **Ann NY Acad Sci** 1985;444:496-8

Lesions in nucleus basalis magnocellularis and medial septal area of rats produce similar memory impairments in appetitive and non-appetitive behavioral tasks. Hepler D, et al. **Ann NY Acad Sci** 1985;444:518-9

Peripheral and central adrenergic influences on brain systems involved in the modulation of memory storage. McGaugh JL. **Ann NY Acad Sci** 1985;444:150-61

Arginine vasopressin inoculates against age-related changes in temporal memory. Meck WH, et al. **Ann NY Acad Sci** 1985;444:453-6

Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178-93

AF64A produces long-term cognitive impairments following infusion into the lateral cerebral ventricles or the dorsal hippocampus: involvement of hippocampal cholinergic processes in learning and memory. Walsh TJ, et al. **Ann NY Acad Sci** 1985;444:538-40

Depletion of adrenal catecholamines alters the amnestic effect of amygdala stimulation. Bennett C, et al. **Behav Brain Res** 1985 Apr;15(2):83-91

Peripheral epinephrine modulates the effects of post-training amygdala stimulation on memory. Liang KC, et al. **Behav Brain Res** 1985 Apr; 15(2):93-100

Physostigmine reverses memory deficits produced by pretraining electrical stimulation of the dorsal hippocampus in mice. Micheau J, et al. **Behav Brain Res** 1985 Apr;15(2):75-81

Effects of tifluadom on passive avoidance behaviour in DBA/2 mice. Pavone F, et al. **Behav Brain Res** 1985 May;15(3):177-81

Brain catecholamines and memory modulation: effects of footshock, amygdala implantation, and stimulation. Welsh KA, et al. **Behav Neural Biol** 1985 Mar;43(2):119-31

Increased sensitivity of the elderly to the central depressant effects of diazepam. Pomara N, et al. **J Clin Psychiatry** 1985 May;46(5):185-7

Interaction of choline and scopolamine in human memory. Mohs RC, et al. **Life Sci** 1985 Jul 15;37(2):193-7

Effects of dietary choline on memory and brain chemistry in aged mice. Mizumori SJ, et al. **Neurobiol Aging** 1985 Spring;6(1):51-6

Learning and memory deficits after lesions of the nucleus basalis magnocellularis: reversal by physostigmine. Murray CL, et al. **Neuroscience** 1985 Apr;14(4):1025-32

The effect of chronic vs. acute injection of vasopressin on animal learning and memory. Hamburger-Bar R, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):23-5

Manipulations of 5-HT activity and memory in the rat. Lalonde R, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):377-82

The effects of intravenous diazepam and hyoscine upon human memory. Frith CD, et al. **Q J Exp Psychol [A]** 1984 Feb;36(1):133-44

MEMORY, SHORT-TERM

Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory. Subhan Z, et al. **Neuropsychobiology** 1984;12(4):244-8

MENTAL DISORDERS

1st Czechoslovak Conference on Biological Psychiatry. Karlovy Vary (Karlsbad), September 1983. Abstracts. **Act Nerv Super (Praha)** 1985 Mar;27(1):60-72

26th annual psychopharmacological meeting. Jesenik Spa, January 1984. Proceedings, 2nd part. Abstracts. **Act Nerv Super (Praha)** 1985 Mar; 27(1):26-72

The pharmacokinetization of psychiatry [editorial] Greenblatt DJ. **J Clin Pharmacol** 1985 May-Jun;25(4):239-40

Treatment characteristics of psychiatric programs that correlate with patient community adjustment. Collins JF, et al. **J Clin Psychol** 1985 May;41(3):299-308

Compliance issues in outpatient treatment. Kane JM. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):22S-27S

Behavioral rehabilitation for chronic mental patients. Liberman RP, et al. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):8S-14S

The young adult chronic patient: population overview. Pepper B. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):3S-7S

MAOIs and drug interactions--a proposal for a clearinghouse. Shader RI, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):A17

The chronic patient: issues and concerns. Shader RI, et al. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):1S-2S

Focal neuroleptization: an approach to optimal dosing for initial and continuing therapy. Tupin JP. **J Clin Psychopharmacol** 1985 Jun; 5(3 Suppl):15S-21S

The clinical significance of halopemide, a dopamine-blocker related to the butyrophenones. De Cuyper H, et al. **Neuropsychobiology** 1984; 12(4):211-6

Effects of psychotropic drugs on discrimination conditioning in olfactory bulbectomized rats. Gomita Y, et al. **Pharmacol Biochem Behav** 1985 May;22(5):717-22

Proceedings of the congress of the AGNP. Nuremberg, 1983. Abstracts. **Pharmacopsychiatry** 1985 Jan;18(1):1-177

8th congress of the Polish Pharmacological Society. Symposium II: Pharmacological implications for animal models of mental disorders. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):493-569

3H-Imipramine binding sites in platelets of hospitalized psychiatric patients. Gentsch C, et al. **Psychiatry Res** 1985 Mar;14(3):177-87

Thorazine injected; pt. dies: criminal charges. Case in point: people v. Nygren (696 P 2d 270--CO). Tammelleo AD. **Regan Rep Nurs Law** 1985 May;25(12):2

[Prescribing psychoactive drugs for children] Bläker F, et al. **Monatsschr Kinderheilkd** 1985 May;133(5):307-9 **(Ger)**

MEPROBAMATE

Meprobamate overdosage. Dennison J, et al. **Hum Toxicol** 1985 Mar; 4(2):215-7

[Responsibility of meprobamate in bone marrow aplasia (letter)] Evreux JC, et al. **Presse Med** 1985 Apr 6;14(14):793 **(Fre)**

METHOTRIMEPRAZINE

[Nozinan] Scottez B, et al. **Soins Psychiatr** 1985 Mar;(53):I-II **(Fre)**

[Clinico-humoral manifestations secondary to treatment with injectable Tisercin] Gheorghe M, et al. **Rev Med Interna [Neurol Psihiatr]** 1985 Jan-Mar;30(1):71-2 **(Rum)**

METHYLPHENIDATE

Place preference conditioning with methylphenidate and nomifensine. Martin-Iverson MT, et al. **Brain Res** 1985 Apr 15;332(1):59-67

Evaluating drug effectiveness in an office setting for children with attention deficit disorders. Ottinger DR, et al. **Clin Pediatr (Phila)** 1985 May;24(5):245-51

Methylphenidate in hyperactive children: differential effects of dose on academic, learning, and social behavior. Rapport MD, et al. **J Abnorm Child Psychol** 1985 Jun;13(2):227-43

Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. Feighner JP, et al. **J Clin Psychiatry** 1985 Jun;46(6):206-9

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222-31

Methylphenidate: rate-dependent drug effects in hyperactive boys. Weber K. **Psychopharmacology (Berlin)** 1985;85(2):231-5

METHYSERGIDE

Control of suckling and feeding by methysergide in weaning albino rats: a determination of Y-maze preferences. Stoloff ML, et al. **Dev Psychobiol** 1985 May;18(3):273-85

Effects of quipazine and methysergide on play in juvenile rats. Normansell L, et al. **Pharmacol Biochem Behav** 1985 May;22(5):885-7

MOTIVATION

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer; 9(2):261-82

Glutamine-induced alterations in the content of brain amino acid neurotransmitters in rats with different alcohol motivation. Ostrovsky SYu. **Subst Alcohol Actions Misuse** 1984;5(5):247-53

MOTOR ACTIVITY

Activity measures in anorexia nervosa. Falk JR, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):811-4

The effect of methyl parathion on susceptibility of bobwhite quail (Colinus virginianus) to domestic cat predation. Galindo JC, et al. **Behav Neural Biol** 1985 Jan;43(1):21-36

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665-9

Association of the mesencephalic locomotor region with locomotor activity induced by injections of amphetamine into the nucleus accumbens. Brudzyński SM, et al. **Brain Res** 1985 May 13; 334(1):77-84

Quantification of lesion-induced dopaminergic supersensitivity using the rotational model in the mouse. Mandel RJ, et al. **Brain Res** 1985 Mar 25;330(2):358-63

Neonatal 6-hydroxydopamine lesion of spinal norepinephrine terminals fails to affect the ontogeny of swimming behavior. Ryan C, et al. **Brain Res** 1985 Jan;349(1-2):258-62

Inhibition of central angiotensin II induced drinking by GABA in the rat. Hutchinson JS, et al. **Clin Exp Hypertens [A]** 1984; 6(10-11):1777-80

Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215-27

The benzodiazepine antagonist Ro 15-1788 reverses the effect of methyl-beta-carboline-3-carboxylate but not of harmaline on cerebellar cGMP and motor performance in mice. Burkard WP, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):241-7

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349-54

Dysfunction of the midbrain angular complex can accentuate or attenuate circling behaviour in the rat. Starr MS, et al. **Exp Brain Res** 1985; 58(1):45-55

Tricyclic antidepressants antagonize prostaglandin (PG) E2-induced contractions of the guinea pig ileum and hypomotility in the mouse. Tayo FM. **Experientia** 1985 Apr 15;41(4):474-6

Pharmacologic studies of the central action of zopiclone: effects on locomotor activity and brain monoamines in rats. Liu HJ, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):121-8

Sulpiride blocks postsynaptic dopamine receptors in the nucleus accumbens. Morgenstern R, et al. **J Neural Transm** 1985; 61(3-4):151-60

SCH23390 causes persistent antidopaminergic effects in vivo: evidence for longterm occupation of receptors. Schulz DW, et al. **Life Sci** 1985 May 20;36(20):1941-8

Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5-MeODMT or mCPP. Sills MA, et al. **Life Sci** 1985 Jul 1; 36(26):2463-9

Automating the measurement of locomotor activity. Beninger RJ, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):79-85

Automated measurement of multivariate locomotor behavior in rodents. Sanberg PR, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb; 7(1):87-94

Effect of gestational and neonatal styrene exposure on dopamine receptors. Zaidi NF, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):23-8

Effects of a thyrotropin releasing hormone analogue on locomotor and other motor activity in the rat. Clarke KA, et al. **Neuropeptides** 1985 Apr;6(2):101-12

The effects of neurotensin and [D-Tyr11]-NT on the hyperactivity induced by intra-accumbens administration of a potent dopamine receptor agonist. Jolicoeur FB, et al. **Neuropeptides** 1985 Apr; 6(2):143-56

Evidence that 2-phenylpyrazolo[4,3-c]-quinolin-3(5H)-one antagonises pharmacological, electrophysiological and biochemical effects of diazepam in rats. Santi M, et al. **Neuropharmacology** 1985 Feb; 24(2):99-105

Treatment of rats with the TRH analog MK-771. Down-regulation of TRH receptors and behavioral tolerance. Simasko SM, et al. **Neuropharmacology** 1985 Feb;24(2):157-65

Behavioral interaction of adenosine and trifluoperazine in mice. DeLong RE, et al. **Neurosci Lett** 1985 Jan 7;53(1):101-7

Detection of homovanillic acid in vivo using microcomputer-controlled voltammetry: simultaneous monitoring of rat motor activity and striatal dopamine release. O'Neill RD, et al. **Neuroscience** 1985 Mar; 14(3):753-63

Hypermotility induced by vasoactive intestinal peptide in the rat: its reciprocal action to cholecystokinin octapeptide. Itoh S, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):53-7

Specificity of nucleus accumbens to activities related to cholecystokinins in rats. Katsuura G, et al. **Peptides (Fayetteville)** 1985 Jan-Feb; 6(1):91-6

Locomotor response of nialamide pretreated old rats to intraaccumbens dopamine. Cousin KM, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):461-8

Dopamine-beta-hydroxylase inhibitors, feeding and locomotor activity: reinstatement of feeding following central norepinephrine. Evans KR, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):535-40

Brain amines and effects of chlordiazepoxide on motor activity in response to stress. Freeman GB, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):665-70

Sensitization of rotational behavior produced by a single exposure to cocaine. Guan LC, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):901-3

Effects of phencyclidine (PCP)-like drugs on turning behavior, 3H-dopamine uptake, and 3H-PCP binding. Johnson KM, et al. **Pharmacol Biochem Behav** 1985 May;22(5):731-5

Hypothalamic involvement in the locomotor stimulant or satiety action of thyrotropin-releasing hormone and amphetamine. Shian LR, et al. **Pharmacology** 1985;30(5):259-65

Development of mouse activity, stimulus reactivity, habituation, and response to amphetamine and scopolamine. Alleva E, et al. **Physiol Behav** 1985 Apr;34(4):519-23

Serotonin and schizophrenia: correlations between serotonergic activity and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Behavioral analysis of the effect of neurotensin injected into the ventral mesencephalon on investigatory and spontaneous motor behavior in the rat. Cador M, et al. **Psychopharmacology (Berlin)** 1985;85(2):187-96

Increased or decreased locomotor response in rats following repeated administration of apomorphine depends on dosage interval. Castro R, et al. **Psychopharmacology (Berlin)** 1985;85(3):333-9

A comparison between chlordiazepoxide and CL 218,872--a synthetic nonbenzodiazepine ligand for benzodiazepine receptors on spontaneous locomotor activity in rats. McElroy JF, et al. **Psychopharmacology (Berlin)** 1985;85(2):224-6

The tail suspension test: a new method for screening antidepressants in mice. Steru L, et al. **Psychopharmacology (Berlin)** 1985;85(3):367-70

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

Regional brain dopamine metabolism: a marker for the speed, direction, and posture of moving animals. Freed CR, et al. **Science** 1985 Jul 5; 229(4708):62-5

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

[Appraisal of ultradian components in the ethosecretogram of rat] Shiraishi I. **Hokkaido Igaku Zasshi** 1985 Jan;60(1):66-81 (Eng. Abstr.) **(Jpn)**

[TRH and its analog (DN-1417). Effects on central dopaminergic system-dependent behaviors in rats and mice] Miyamoto M, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):129-41 (Eng. Abstr.) **(Jpn)**

MOTOR SKILLS

Dopamine depletion in a striatal subregion disrupts performance of a skilled motor task in the rat. Sabol KE, et al. **Brain Res** 1985 May 27;335(1):33-43

Sensitivity changes to dopaminergic agents in fine motor control of rhesus monkeys after repeated methamphetamine administration. Ando K, et al. **Pharmacol Biochem Behav** 1985 May;22(5):737-43

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167-70

MSH

Distribution of the pro-opiomelanocortin derived peptides, adrenocorticotrope hormone, alpha-melanocyte-stimulating hormone and beta-endorphin (ACTH, alpha-MSH, beta-END) in the rat hypothalamus. Mezey E, et al. **Brain Res** 1985 Mar 4;328(2):341-7

Cyclic melanotropins. 9. 7-D-Phenylalanine analogues of the active-site sequence. Cody WL, et al. **J Med Chem** 1985 May;28(5):583-8

Photoaffinity labelling of MSH receptors on Anolis melanophores: effects of catecholamines, calcium and forskolin. Eberle AN, et al. **J Recept Res** 1985;5(1):59-81

Opiomelanocortins and behavioral adaptation. Bohus B. **Pharmacol Ther** 1984;26(3):417-51 (238 ref.)

NEUROREGULATORS

Catecholamine and opioid receptors, presynaptic inhibition of CNS neurotransmitter release, and adenylate cyclase. Mulder AH, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:273-86

Adenosine, adenylate cyclase, and transmitter release. Phillis JW, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:243-57 (81 ref.)

Neuroendocrinology and the ovulation cycle--advances and review. Schnatz PT. **Adv Psychosom Med** 1985;12:4-24

Psychoendocrinology and the menstrual cycle. Youngs DD, et al. **Adv Psychosom Med** 1985;12:25-34

Delta 1-pyrroline-5-carboxylate dehydrogenase, a possible regulatory enzyme in transmitter glutamic acid metabolism--a preliminary report. Wong PT, et al. **Ann Acad Med Singapore** 1985 Jan;14(1):143-6

Membrane-related effects of atypical antidepressants. Valdman AV, et al. **Ann Ist Super Sanita** 1984;20(1):65-72

Accumulation of inositol phosphates in sympathetic ganglia. Effects of depolarization and of amine and peptide neurotransmitters. Bone EA, et al. **Biochem J** 1985 Apr 1;227(1):263-9

Release of D-[3H]aspartic acid from the rat striatum. Effect of veratridine-evoked depolarization, fronto-parietal cortex ablation, and striatal lesions with kainic acid. Arqueros L, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1217-24

Monoamine metabolites: their relationship and lack of relationship to monoaminergic neuronal activity. Commissiong JW. **Biochem Pharmacol** 1985 Apr 15;34(8):1127-31

Interaction of phenothiazine drugs with human ceruloplasmin. Relation between activation of catecholamine neurotransmitter oxidation and electron donating ability of phenothiazine drugs. de Mol NJ. **Biochem Pharmacol** 1985 Aug 1;34(15):2605-9

Animal models of depression: parallels and correlates to severe depression in humans. Jesberger JA, et al. **Biol Psychiatry** 1985 Jul; 20(7):764-84

The role of substance P as a neurotransmitter in the reflexes of slow time courses in the neonatal rat spinal cord. Akagi H, et al. **Br J Pharmacol** 1985 Mar;84(3):663-73

Electrophysiological evidence that nipecotic acid can be used in vivo as a false transmitter. Lerma J, et al. **Brain Res** 1985 Jun 3; 335(2):377-80

Evidence for genetic influences on neurotransmitter content of identified neurones of Lymnaea stagnalis. Audesirk G, et al. **Comp Biochem Physiol [C]** 1985;81(1):57-60

Motor and behavioural effects induced by putative neurotransmitter injection into the optic lobe of the cuttlefish, Sepia officinalis. Chichery R, et al. **Comp Biochem Physiol [C]** 1985;80(2):415-9

The effects of putative amino acid neurotransmitters on somata isolated from neurons of the locust central nervous system. Giles D, et al. **Comp Biochem Physiol [C]** 1985;80(2):231-6

Neurotransmitter precursors and metabolites in CSF of human neonates. Anderson GM, et al. **Dev Med Child Neurol** 1985 Apr;27(2):207-14

Neurotransmitters involved in mediating the steroid-dependent suppression of pulsatile luteinizing hormone secretion in anestrous ewes: effects of receptor antagonists. Meyer SL, et al. **Endocrinology** 1985 May;116(5):2054-61

Evidence that ATP is involved as a co-transmitter in the hypogastric nerve supplying the seminal vesicle of the guinea-pig. Meldrum LA, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):363-6

Phorbol ester and calcium act synergistically to enhance neurotransmitter release by brain neurons in culture. Zurgil N, et al. **FEBS Lett** 1985 Jun 17;185(2):257-61

Arterial and cardiopulmonary reflexes in the regulation of the neurohumoral drive to the circulation. Bishop VS, et al. **Fed Proc** 1985 May;44(8):2377-81 (31 ref.)

Vasoactive intestinal peptide. Relaxant neurotransmitter in tenia coli of the guinea pig. Grider JR, et al. **Gastroenterology** 1985 Jul; 89(1):36-42

Identification of putative neurotransmitters in the lizard parietal eye. Engbretson GA, et al. **Invest Ophthalmol Vis Sci** 1985 May; 26(5):670-8

Blood pressure control by neurotransmitters in the medulla oblongata and spinal cord. Howe PR. **J Auton Nerv Syst** 1985 Feb-Mar; 12(2-3):95-115

Determination of neurotransmitter amino acids by high-performance liquid chromatography with fluorescence detection. Zecca L, et al. **J Chromatogr** 1985 Feb 8;337(2):391-6

Role of calcium and phosphoinositides in the actions of certain hormones and neurotransmitters. Exton JH. **J Clin Invest** 1985 Jun;75(6):1753–7 (59 ref.)

Fine structure of peptidergic and catecholaminergic nerve fibers in the anterior cerebral artery and their interrelationship: an immunoelectron microscopic study. Matsuyama T, et al. **J Comp Neurol** 1985 May 8;235(2):268–76

Immunohistochemical demonstration of some putative neurotransmitters in the lamprey spinal cord and spinal ganglia: 5-hydroxytryptamine-, tachykinin-, and neuropeptide-Y-immunoreactive neurons and fibers. Van Dongen PA, et al. **J Comp Neurol** 1985 Apr 22;234(4):501–22

Insect cardioactive peptides. II. Neurohormonal control of heart activity by two cardioacceleratory peptides in the tobacco hawkmoth, Manduca sexta. Tublitz NJ, et al. **J Exp Biol** 1985 Jan;114:381–95

Distribution of aminergic neurons in the brain of the sterlet, Acipenser ruthenus (Chondrostei, Actinopterygii). Kotrschal K, et al. **J Hirnforsch** 1985;26(1):65–72

Neuropeptides and other mediators in the central nervous system. Bloom FE. **J Immunol** 1985 Aug;135(2 Suppl):743s–745s

Noradrenergic and peptidergic innervation of lymphoid tissue. Felten DL, et al. **J Immunol** 1985 Aug;135(2 Suppl):755s–765s (73 ref.)

Evidence that thymosins and other biologic response modifiers can function as neuroactive immunotransmitters. Hall NR, et al. **J Immunol** 1985 Aug;135(2 Suppl):806s–811s

Cellular interactions at the central and peripheral terminals of primary sensory neurons. Jessell TM. **J Immunol** 1985 Aug;135(2 Suppl):746s–749s

Modulation of macrophage-mediated tumoricidal activity by neuropeptides and neurohormones. Koff WC, et al. **J Immunol** 1985 Jul;135(1):350–4

Neuroanatomic and neurotransmitter influences on immune function. Roszman TL, et al. **J Immunol** 1985 Aug;135(2 Suppl):769s–772s

Evolutionary origins of neuropeptides, hormones, and receptors: possible applications to immunology. Roth J, et al. **J Immunol** 1985 Aug;135(2 Suppl):816s–819s

An excitant amino acid projection from the medial prefrontal cortex to the anterior part of nucleus accumbens in the rat. Christie MJ, et al. **J Neurochem** 1985 Aug;45(2):477–82

Composite technique for regional neurochemical studies: measurement of energy and neurotransmitter metabolites in single tissue sample. Djuricic BM, et al. **J Neurochem** 1985 Jun;44(6):1920–4

Some long-lasting neurochemical effects of prenatal or early postnatal exposure to diazepam. Frieder B, et al. **J Neurochem** 1985 Jul;45(1):37–42

Rat serum contains a developmentally regulated cholinergic inducing activity. Wolinsky EJ, et al. **J Neurosci** 1985 Jun;5(6):1509–12

Expression of noradrenergic and cholinergic traits by sympathetic neurons cultured without serum. Wolinsky EJ, et al. **J Neurosci** 1985 Jun;5(6):1497–508

Profiles of evoked release along the length of frog motor nerve terminals. D'Alonzo AJ, et al. **J Physiol (Lond)** 1985 Feb;359:235–58

Long-term potentiation of transmitter release induced by repetitive presynaptic activities in bull-frog sympathetic ganglia. Koyano K, et al. **J Physiol (Lond)** 1985 Feb;359:219–33

Burn trauma induces anorexia and aberrations in CNS amine neurotransmitters. Chance WT, et al. **J Trauma** 1985 Jun;25(6):501–7

Modulation of receptor sensitivity and action potentials by transmitters in vertebrate neurones. Koketsu K. **Jpn J Physiol** 1984;34(6):945–60 (59 ref.)

Proctolin: a potent inhibitor of aminoenkephalinase. Hui KS, et al. **Life Sci** 1985 Jun 17;36(24):2309–15

Tuning in to neurotransmitters [news] Altman J. **Nature** 1985 Jun 13–19;315(6020):537

Pertussis toxin reverses adenosine inhibition of neuronal glutamate release. Dolphin AC, et al. **Nature** 1985 Jul 11–17;316(6024):148–50

Transport of monoamine and amino acid neurotransmitters by primary astroglial cultures. Hansson E. **Neurochem Res** 1985 May;10(5):667–75

Selective retrograde labeling in some afferents to the rabbit lateral geniculate nucleus following injections of tritiated neurotransmitter-related compounds. Matute C, et al. **Neurosci Lett** 1985 Jan 7;53(1):9–14

Simultaneous monitoring of voltammetric and ion-selective electrodes in mammalian brain. Nagy G, et al. **Neurosci Lett** 1985 Apr 9;55(2):119–24

Prolonged non-adrenergic inhibition of cardiac vagal action following sympathetic stimulation: neuromodulation by neuropeptide Y? Potter EK. **Neurosci Lett** 1985 Mar 15;54(2–3):117–21

Effects of chlordecone on neuroendocrine function of female rats. Uphouse L. **Neurotoxicology (Little Rock Ar)** 1985 Spring;6(1):191–210 (80 ref.)

Sympathetic neuron density differentially regulates transmitter phenotypic expression in culture. Adler JE, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4296–300

N-Acetylaspartylglutamate: possible role as the neurotransmitter of the lateral olfactory tract. Ffrench-Mullen JM, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3897–900

Intraterminal injection of synapsin I or calcium/calmodulin-dependent protein kinase II alters neurotransmitter release at the squid giant synapse. Llinás R, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):3035–9

Roles for neurotransmitters in development: possible interaction with drugs during the fetal and neonatal periods. Lauder JM. **Prog Clin Biol Res** 1985;163C:375–80

Neurotropic drugs and brain development: effects on cell replication in vivo and in vitro. Patel AJ. **Prog Clin Biol Res** 1985;163C:301–5

Role of neurotransmitters and teratogens on palate development. Zimmerman EF, et al. **Prog Clin Biol Res** 1985;163C:405–8

Biochemical hypotheses of premenstrual tension syndrome. Janowsky DS, et al. **Psychol Med** 1985 Feb;15(1):3–8

Glutamine-induced alterations in the content of brain amino acid neurotransmitters in rats with different alcohol motivation. Ostrovsky SYu. **Subst Alcohol Actions Misuse** 1984;5(5):247–53

Retinal neurotransmission. Pycock CJ. **Surv Ophthalmol** 1985 Mar–Apr;29(5):335–65

[Central neurotransmitters and cardiovascular activity] Xia Y. **Sheng Li Ko Hsueh Chin Chan** 1985 Jan;16(1):27–31 (50 ref.) **(Chi)**

[Recent advances in research on substance P and related neuropeptides] Kanazawa I. **No To Hattatsu** 1985 Mar;17(2):94–102 (17 ref.) **(Jpn)**

[Neurotransmitters and neuropeptides in schizophrenia] Toru M, et al. **Tanpakushitsu Kakusan Koso** 1984 Dec;29(14):1838–54 (150 ref.) **(Jpn)**

[Regulation of tetanus toxin-inhibited transmitter secretion in the neuromuscular junction in a calcium-free medium] Kryzhanovskii GN, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):407–9 (Eng. Abstr.) **(Rus)**

[Inherent morphofunctional effects of experimental procedures in studying the mechanism of transmitter release] Nikulin VG, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):373–6 (Eng. Abstr.) **(Rus)**

[Vasoactive hormones and mediators in the mechanism of the development of an aphthous process in the oral mucosa] Rybakov AI, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):424–5 (Eng. Abstr.) **(Rus)**

[Neuroendocrine mechanisms in immunoregulation] Bezedovskii GO, et al. **Fiziol Cheloveka** 1984 Mar–Apr;10(2):224–8 (14 ref.) **(Rus)**

[Neurohumoral regulation of immune homeostasis] Korneva EA, et al. **Fiziol Cheloveka** 1984 Mar–Apr;10(2):179–92 (38 ref.) **(Rus)**

[Distribution and functioning of mediator release sites in the neuromuscular junction of the frog] Zefirov AL. **Neirofiziologiia** 1985;17(2):152–60 (Eng. Abstr.) **(Rus)**

[Elements of the systems approach in studying the mechanisms of the neurohumoral regulation of immunological processes] Korneva EA. **Vestn Akad Med Nauk SSSR** 1985;(3):63–73 (60 ref.) (Eng. Abstr.) **(Rus)**

[Nervous system regulation of exocrine pancreatic secretion in the chicken] Salido GM, et al. **Rev Esp Fisiol** 1985 Mar;41(1):11–7 (Eng. Abstr.) **(Spa)**

NEUROTENSIN

Immunohistochemical localization of neurotensin in hamster adrenal medulla. Pelto-Huikko M, et al. **Anat Rec** 1985 Apr;211(4):458–64

Dopamine D2 receptors modulate neurotransmitter-regulated calcium ion gates. Memo M, et al. **Ann Ist Super Sanita** 1984;20(1):5–10

Neurotensin degradation by soluble and membrane-associated enzymes from the brain. Emson PC, et al. **Biochem Soc Trans** 1985 Feb;13(1):53–4

The effects of chronic neuroleptic treatment on neurotensin-like immunoreactivity in the rat central nervous system. Goedert M, et al. **Brain Res** 1985 Jun 3;335(2):334–6

The ontogenetic development of neurotensin-like immunoreactivity and neurotensin receptors in the cat striatum. Goedert M, et al. **Brain Res** 1985 May;352(1):127–31

Immunohistochemical localization of neurotensin and beta-endorphin in the rat anterior pituitary gland. Miyoshi R, et al. **Brain Res** 1985 Apr 8;331(2):386–8

A quantitative, immunochemical demonstration of the postnatal development of neurotensin in the medial preoptic area of the rat. Wolfson B, et al. **Brain Res** 1985 Feb;350(1–2):241–50

Vascular actions of VIP, substance P and neurotensin on the isolated perfused human fetal placenta. de Moura RS, et al. **Contrib Gynecol Obstet** 1985;13:174–5

Changes in neurotensin-like immunoreactivity during menopausal hot flashes. Kronenberg F, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1081–6

Neurotensin enhances estradiol induced DNA synthesis in immature rat uterus. Mistry A, et al. **Life Sci** 1985 May 27;36(21):2063–7

Ultrastructural immunocytochemical studies on CCK-and neurotensin-like immunoreactivity in the nucleus accumbens of the rat. Johansson O, et al. **Med Biol** 1984;62(6):318–22

The effects of neurotensin and [D-Tyr11]-NT on the hyperactivity induced by intra-accumbens administration of a potent dopamine receptor agonist. Jolicoeur FB, et al. **Neuropeptides** 1985 Apr;6(2):143–56

Release of mast cell mediators, vasoconstriction and edema in the isolated, perfused head of the rat following intracarotid infusion of neurotensin. Rioux F, et al. **Neuropeptides** 1985 Mar;6(1):1-12

Behavioral analysis of the effect of neurotensin injected into the ventral mesencephalon on investigatory and spontaneous motor behavior in the rat. Cador M, et al. **Psychopharmacology (Berlin)** 1985;85(2):187-96

Bombesin, neurotensin and pro-gamma-melanotropin immunoreactants in human milk. Ekman R, et al. **Regul Pept** 1985 Mar; 10(2-3):99-105

[Gastrointestinal hormones and related peptides. V. Neurotensin] Sadowska-Krowicka H, et al. **Postepy Hig Med Dosw** 1984 Jul-Aug; 38(4):535-52 (110 ref.) (Eng. Abstr.) **(Pol)**

[Cyclic AMP content of the blood, brain, stomach, adrenals and duodenum after administration of neurotensin and cholecystokinin] Andreanova MV, et al. **Fiziol Zh SSSR** 1985 Feb;71(2):258-61 **(Rus)**

[Effect of natural neurotensin and its analog on gastric secretion and levels of various peptides in dog blood] Barashkova GM, et al. **Fiziol Zh SSSR** 1985 Feb;71(2):200-5 (Eng. Abstr.) **(Rus)**

NEUROTIC DISORDERS

Neuroticism and personality disorder in depression. Davidson J, et al. **J Affective Disord** 1985 Mar-Apr;8(2):177-82

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

NIALAMIDE

Locomotor response of nialamide pretreated old rats to intraaccumbens dopamine. Cousin KM, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):461-8

NOREPINEPHRINE

Effect of propranolol on post-traumatic hypophosphataemia and catecholamine secretion. Lovén L, et al. **Acta Chir Scand** 1985; 151(3):201-4

Changes in blood level of catecholamines during arterial blood pressure rise induced with sciatic nerve stimulation. Całkosiński I, et al. **Acta Physiol Pol** 1984 Jan-Feb;35(1):47-51

Seasonal changes in blood lipids, adrenaline, noradrenaline, glucose and insulin in Norwegian reindeer. Larsen TS, et al. **Acta Physiol Scand** 1985 May;124(1):53-9

Noradrenergic modulation of cerebral cortical oxidative metabolism. LaManna JC, et al. **Adv Exp Med Biol** 1984;180:211-9

Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. Stratton JR, et al. **Am J Cardiol** 1985 Jul 1;56(1):136-9

Norepinephrine in cochlear microcirculation of guinea pigs. Matsunaga T, et al. **Am J Otolaryngol** 1985 May-Jun;6(3):226-30

Decidua-associated changes in guinea pig uterine blood flow and volume: relation to uterine norepinephrine concentrations. Garris DR, et al. **Anat Rec** 1985 Apr;211(4):410-13

The modulation of acetylcholine release by noradrenaline, GABA and related compounds. Beani L, et al. **Ann Ist Super Sanita** 1984; 20(1):17-9

Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178-93

Selective decrease of hypothalamic noradrenaline by cysteamine. Vecsei L, et al. **Arch Int Pharmacodyn Ther** 1985 Mar;274(1):125-8

Depletion of adrenal catecholamines alters the amnestic effect of amygdala stimulation. Bennett C, et al. **Behav Brain Res** 1985 Apr;15(2):83-91

Studies on the mechanism of inhibition of glucose-stimulated insulin secretion by noradrenaline in rat islets of Langerhans. Morgan NG, et al. **Biochem J** 1985 Mar 1;226(2):571-6

Catecholamine responses to changes in posture during human pregnancy. Whittaker PG, et al. **Br J Obstet Gynaecol** 1985 Jun;92(6):586-92

The formation of deaminated metabolites of dopamine in the locus coeruleus depends upon noradrenergic neuronal activity. Curet O, et al. **Brain Res** 1985 Jun 3;335(2):297-301

The prefrontal 'cortex' in the pigeon. Biochemical evidence. Divac I, et al. **Brain Res** 1985 Apr 22;332(2):365-8

Comparative effects of sciatic nerve stimulation, blood pressure, and morphine on the activity of A5 and A6 pontine noradrenergic neurons. Guyenet PG, et al. **Brain Res** 1985 Feb 18;327(1-2):191-201

Central noradrenergic involvement in yohimbine excitation of acoustic startle: effects of DSP4 and 6-OHDA. Kehne JH, et al. **Brain Res** 1985 Mar 18;330(1):31-41

Neonatal 6-hydroxydopamine lesion of spinal norepinephrine terminals fails to affect the ontogeny of swimming behavior. Ryan C, et al. **Brain Res** 1985 Jan;349(1-2):258-62

The postnatal development of norepinephrine-stimulated cyclic AMP accumulation in rat spinal cord. Simmons K, et al. **Brain Res** 1985 Feb; 350(1-2):306-10

Aversive effects of subcutaneously injected vasopressin in the rat: independence of the ascending dorsal noradrenergic bundle. Tam FW, et al. **Brain Res** 1985 Jun 24;337(1):133-7

Inputs from the A1 noradrenergic region to hypothalamic paraventricular neurons in the rat. Tanaka J, et al. **Brain Res** 1985 Jun 3; 335(2):368-71

Epinephrine- and norepinephrine-evoked potential changes of frog primary afferent terminals: pharmacological characterization of alpha and beta components. Wohlberg CJ, et al. **Brain Res** 1985 Feb 18; 327(1-2):289-301

Mechanisms of supersensitivity to sympathomimetic amines in the chronically denervated heart of the conscious dog. Vatner DE, et al. **Circ Res** 1985 Jul;57(1):55-64

Effect of intracerebroventricular 6-hydroxydopamine (6-HODA) on the angiotensinogen concentration of the brain. Basso N, et al. **Clin Exp Hypertens [A]** 1984;6(10-11):1773-6

Effects of angiotensin II and ACE inhibitors on electrically stimulated noradrenaline release from superfused rat brain slices. Schacht U. **Clin Exp Hypertens [A]** 1984;6(10-11):1847-51

Accumulation of intra-arterially administered [3H]adrenaline and [3H]noradrenaline in various tissues of the Atlantic cod, Gadus morhua. Ungell AL. **Comp Biochem Physiol [C]** 1985;81(1):25-8

Norepinephrine alone versus norepinephrine plus low-dose dopamine: enhanced renal blood flow with combination pressor therapy. Schaer GL, et al. **Crit Care Med** 1985 Jun;13(6):492-6

Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Emerich DF, et al. **Dev Psychobiol** 1985 May;18(3):215-27

Regulation of ketogenesis by epinephrine and norepinephrine in the overnight-fasted, conscious dog. Steiner KE, et al. **Diabetes** 1985 May; 34(5):425-32

Strain differences in brain biogenic amines concentration in rats with different resistance to emotional stress. Sudakov KV, et al. **Endocrinol Exp (Bratisl)** 1985 Mar;19(1):39-45

Plasma glucagon and catecholamines during exhaustive short-term exercise. Näveri H, et al. **Eur J Applied Physiol** 1985;53(4):308-11

Differences in dopamine- and noradrenaline-induced amylase release from the rat parotid gland. Sundström S, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):355-61

Response of phasically firing paraventricular neurons to A1 noradrenergic region stimulation and its attenuation by adrenoceptor antagonists. Tanaka J, et al. **Exp Neurol** 1985 Jun;88(3):714-25

Plasma catecholamine and blood lactate cumulation during incremental exhaustive exercise. Lehmann M, et al. **Int J Sports Med** 1985 Apr; 6(2):78-81

Heat acclimation: role of norepinephrine in the anterior hypothalamus. Christman JV, et al. **J Appl Physiol** 1985 Jun;58(6):1923-8

Exercise, dobutamine, and combined atropine, norepinephrine, and epinephrine compared. Haidet GC, et al. **J Appl Physiol** 1985 Jun; 58(6):2047-53

Cardiovascular effects of intracisternal 6-hydroxydopamine and of subsequent lesions of the ventrolateral medulla coinciding with the A1 group of noradrenaline cells in the rabbit. Elliott JM, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):117-30

Role of central nervous system monoamines in cardiopulmonary effects of Althesin in rabbit and man. Quail AW, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):159-74

Ambient temperature modulates the differentiated cardiorespiratory pattern generated by the central noradrenergic system, most likely via alterations of thyrotropin-releasing hormone (TRH) activity. Riedel W. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):145-57

Central nervous system 5-hydroxytryptamine and noradrenaline specificity of ear vascular and ventilation reflexes in thermoregulating rabbits. White SW, et al. **J Auton Nerv Syst** 1985 Feb-Mar; 12(2-3):131-44

Rapid changes in synaptic vesicle cytochemistry after depolarization of cultured cholinergic sympathetic neurons. Johnson MI, et al. **J Cell Biol** 1985 Jul;101(1):217-26

Pial artery responses to norepinephrine potentiated by endothelium removal. Sercombe R, et al. **J Cereb Blood Flow Metab** 1985 Jun; 5(2):312-7

Simultaneous assay of 3,4-dihydroxyphenylethylene glycol and norepinephrine in human plasma by high-performance liquid chromatography with electrochemical detection. Howes LG, et al. **J Chromatogr** 1985 Mar 22;338(2):401-3

Simple and fast analysis of adrenaline and noradrenaline in plasma on microbore high-performance liquid chromatography columns using fluorimetric detection. Kamperman G, et al. **J Chromatogr** 1985 Feb 8;337(2):384-90

Circadian rhythms of epinephrine and norepinephrine in man. Linsell CR, et al. **J Clin Endocrinol Metab** 1985 Jun;60(6):1210-5

Modulation of calcium channels by norepinephrine in internally dialyzed avian sensory neurons. Forscher P, et al. **J Gen Physiol** 1985 May; 85(5):743-63

Effect of norepinephrine on swelling-induced potassium transport in duck red cells. Evidence against a volume-regulatory decrease under physiological conditions. Haas M, et al. **J Gen Physiol** 1985 May; 85(5):649-67

BIBLIOGRAPHY

Norepinephrine as a possible transmitter involved in synaptic transmission in frog taste organs and Ca dependence of its release. Nagahama S, et al. **J Gen Physiol** 1985 Mar;85(3):431–42

Pressor responsiveness to norepinephrine in rabbits with adrenal perturbations. Siripaisarnpipat S, et al. **J Hypertens** 1985 Feb; 3(1):89–96

Neurochemical profile of Lu 19–005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615–22

Assessment of noradrenaline and 5–hydroxytryptamine uptake in intact rat brain. Wyllie MG, et al. **J Neurochem** 1985 Aug;45(2):456–60

Denervation supersensitivity of the rat pineal to norepinephrine–stimulated [3H]inositide turnover revealed by lithium and a convenient procedure. Zatz M. **J Neurochem** 1985 Jul; 45(1):95–100

Dopamine beta–hydroxylase–like immunoreactivity in the rat and cat carotid body: a light and electron microscopic study. Chen IL, et al. **J Neurocytol** 1985 Feb;14(1):131–44

Effect of immune complex–forming reactants on catecholamine–modulated behaviors in the rat hypothalamus. Schupf N, et al. **J Neuroimmunol** 1985 Jul;9(1–2):13–27

Measurement of noradrenaline synthesis in rat hippocampal synaptosomes using HPLC with ECD. Birch PJ, et al. **J Neurosci Methods** 1985 May; 13(3–4):231–8

A technique for the microinjection of macromolecules into viable chromaffin cells in culture. Kenigsberg RL, et al. **J Neurosci Methods** 1985 Apr;13(2):103–18

Inhibition by 5,6–dihydroxy–2–dimethylaminotetralin (M7) of noradrenergic neurotransmission in the rabbit hypothalamus: role of alpha–2 adrenoceptors and of dopamine receptors. Galzin AM, et al. **J Pharmacol Exp Ther** 1985 May;233(2):459–65

Adrenergic and possible nonadrenergic sources of adenosine 5'–triphosphate release from nerve varicosities isolated from ileal myenteric plexus. Al–Humayyd M, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):796–800

Inhibitory effects of norepinephrine, methoxamine and phenylephrine on renin release from rat kidney cortical slices. Matsumura Y, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):782–7

Chronic thyroxine treatment of rats down–regulates the noradrenergic cyclic AMP generating system in cerebral cortex. Schmidt BH, et al. **J Pharmacol Exp Ther** 1985 May;233(2):466–72

Demonstration of an alpha adrenoceptor–mediated inotropic effect of norepinephrine in human atria. Skomedal T, et al. **J Pharmacol Exp Ther** 1985 May;233(2):441–6

Reduction of the cyclic adenosine 3',5'–monophosphate response to catecholamines in rat brain slices after repeated restraint stress. Stone EA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):382–8

Noradrenaline hyperpolarization and depolarization in cat vesical parasympathetic neurones. Akasu T, et al. **J Physiol (Lond)** 1985 Apr; 361:165–84

Efflux of 5–hydroxytryptamine and noradrenaline into spinal cord superfusates during stimulation of the rat medulla. Hammond DL, et al. **J Physiol (Lond)** 1985 Feb;359:151–62

Methionine–enkephalin inhibits stress–induced increases in noradrenaline turnover in brain regions of rats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Jan;37(1):117–9

Inhibition of locus coeruleus neuronal activity by beta–phenylethylamine. Lundberg PA, et al. **Life Sci** 1985 May 13;36(19):1889–96

Epinephrine and norepinephrine syntheses are regulated by a glucocorticoid receptor–mediated mechanism in the bovine adrenal medulla. Nawata H, et al. **Life Sci** 1985 May 20;36(20):1957–66

Norepinephrine–dependent and independent mechanisms of persistent effects of amphetamine in rat cerebellum. Sorensen SM, et al. **Life Sci** 1985 Jun 24;36(25):2383–9

Enhancement of the pressor response to norepinephrine by angiotensin in the conscious rabbit. Weber MA, et al. **Life Sci** 1985 May 20; 36(20):1897–907

Excretion of urinary catecholamines and plasma cortisol levels in female nurses on short–rotating shift. Panza G, et al. **Med Lav** 1985 Jan–Feb; 76(1):30–4

Pharmacology in vivo of the phenylindan derivative, Lu 19–005, a new potent inhibitor of dopamine, noradrenaline and 5–hydroxytryptamine uptake in rat brain. Arnt J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):101–7

Plasma catecholamines in arterial and capillary blood. Baumgartner H, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):461–3

Effects of clorgyline and (–)deprenyl on the deamination of normetanephrine and noradrenaline in strips and homogenates of the canine saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):396–400

Influence of MAO A and MAO B on the inactivation of noradrenaline in the saphenous vein of the dog. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):401–6

Cardiac glycosides, calcium and the release of neurotransmitter from peripheral noradrenergic nerves. Tan CM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Mar;329(1):1–8

Electroacupuncture alters catecholamines in brain regions of rats. Sun AY, et al. **Neurochem Res** 1985 Feb;10(2):251–8

Medial preoptic area involvement in norepinephrine–induced suppression of pulsatile luteinizing hormone release in ovariectomized rats. Leipheimer RE, et al. **Neuroendocrinology** 1985 Apr;40(4):345–51

Effects of lithium in vitro on noradrenaline–induced cyclic AMP accumulation in rat cortical slices after reserpine–induced supersensitivity. Newman ME, et al. **Neuropharmacology** 1985 Apr; 24(4):353–5

Stress and brain noradrenaline: a review. Glavin GB. **Neurosci Biobehav Rev** 1985 Summer;9(2):233–43 (81 ref.)

The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Oades RD. **Neurosci Biobehav Rev** 1985 Summer; 9(2):261–82

Temporal relationship between noradrenaline release in the central amygdala and plasma noradrenaline secretion in rats and tree shrews. Dietl H. **Neurosci Lett** 1985 Mar 22;55(1):41–6

Astrocyte opioid receptors: activation modifies the noradrenaline–evoked increase in 2–[14C]deoxyglucose incorporation into glycogen. Pearce B, et al. **Neurosci Lett** 1985 Apr 9;55(2):157–60

Effect of histamine infusion on circulating methionine–enkephalin and catecholamine concentrations. Smith R, et al. **Neurosci Lett** 1985 Apr 19;55(3):289–92

Relative pre– and postjunctional roles of noradrenaline and adenosine 5'–triphosphate as neurotransmitters of the sympathetic nerves of guinea–pig and mouse vas deferens. Stjärne L, et al. **Neuroscience** 1985 Mar;14(3):929–46

alpha 1– and beta–adrenergic receptors are co–regulated during both noradrenergic denervation and hyperinnervation. Sutin J, et al. **Neuroscience** 1985 Apr;14(4):973–80

Dopamine–beta–hydroxylase inhibitors, feeding and locomotor activity: reinstatement of feeding following central norepinephrine. Evans KR, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):535–40

Effect of a low sodium medium, ouabain and noradrenaline on relaxation of the myocardium of the perfused rabbit heart. Fišer B, et al. **Physiol Bohemoslov** 1985;34(1):77–84

The influence of prazosin on E. coli lipopolysaccharide–induced fever and noradrenaline hyperthermia. Matuszek M, et al. **Pol J Pharmacol Pharm** 1984 Nov–Dec;36(6):585–93

Some behavioral effects of microinjections of serotonin and noradrenaline into the limbic structures of the rat brain. Płaźnik A. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):541–54

The effects of lesions of the locus coeruleus and treatment with drugs affecting brain noradrenergic neurotransmission on dominant–subordinate behavior in rats competing for water. Plewako M, et al. **Pol J Pharmacol Pharm** 1984 Sep–Oct;36(5):555–60

The role of the central noradrenaline system in regulating neuronal plasticity in the developing neocortex. Kasamatsu T. **Prog Clin Biol Res** 1985;163C:369–73

Hypophysectomy disturbs the noradrenergic feeding system of the paraventricular nucleus. Roland CR, et al. **Psychoneuroendocrinology** 1985;10(1):109–20

Supersensitivity to the anticonvulsant and proconvulsant activity of clonidine following noradrenaline depletion induced by 6–hydroxydopamine. Dalton JC, et al. **Psychopharmacology (Berlin)** 1985;85(3):319–22

The effect of clorgyline on noradrenergic function. Ross RJ, et al. **Psychopharmacology (Berlin)** 1985;85(2):227–30

Airway responses to low concentrations of adrenaline and noradrenaline in normal subjects. Berkin KE, et al. **Q J Exp Physiol** 1985 Apr; 70(2):203–9

Relationship between sleep efficiency and urinary excretion of catecholamines in bed–rested humans. Nishihara K, et al. **Sleep** 1985; 8(2):110–7

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731–6

[Enkephalin–noradrenaline interactions in synaptic transmission] Fan JZ, et al. **Sheng Li Ko Hsueh Chin Chan** 1985 Apr;16(2):158–60 **(Chi)**

[Electrocardiographic studies of the modification of cardiac activity in cattle by adrenaline and noradrenaline with and without vagolysis (atropine) and beta–receptor blockade (propranolol)] Mielke H, et al. **Arch Exp Veterinarmed** 1985 Mar;39(2):193–206 (Eng. Abstr.) **(Ger)**

[Direct observation on microcirculation of cochlea. I. Effects of ADP and norepinephrine injections upon blood flow of radiating arteriole in guinea pigs] Fuzisaki Y, et al. **Nippon Jibiinkoka Gakkai Kaiho** 1985 Feb;88(2):128–37 (Eng. Abstr.) **(Jpn)**

[Urinary excretion of catecholamines in children with functional disorders of the digestive system] Szewczyk L, et al. **Pediatr Pol** 1984 Oct; 59(10):835–9 (Eng. Abstr.) **(Pol)**

[Catecholaminergic activity in children with nocturnal enuresis] Szewczyk L. **Pediatr Pol** 1984 Oct;59(10):841–5 (Eng. Abstr.) **(Pol)**

[Cyclic AMP content of autonomic ganglia as affected by catecholamines] Kniazeva LA, et al. **Biull Eksp Biol Med** 1985 Mar;99(3):348–9 (Eng. Abstr.) **(Rus)**

[Circadian rhythms of adrenaline and noradrenaline excretion in man in normal conditions and after alcohol intake] Latenkov VP. **Biull Eksp Biol Med** 1985 Mar;99(3):344-6 (Eng. Abstr.) (Rus)

[Reactivity of the coronary vessels and adrenergic action] Lysenko LT, et al. **Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR** 1985; 8(1):82-8 (Rus)

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) (Rus)

[Effect of hypothermia on reuptake of neuromediators by synaptosomes] Babilchuk GA, et al. **Ukr Biokhim Zh** 1985 Mar-Apr;57(2):87-9 (Eng. Abstr.) (Rus)

[Normal values of dopamine, noradrenaline, adrenaline, and 5-hydroxyindoleacetic acid in pregnancies of different gestational ages] Lerdo de Tejada A, et al. **Ginecol Obstet Mex** 1985 Feb; 53(334):49-52 (Eng. Abstr.) (Spa)

[Radioimmunoanalysis of adrenaline and noradrenaline in the normal fetus at term] Martínez Alcalá FO, et al. **Ginecol Obstet Mex** 1983 Oct; 51(318):267-72 (Eng. Abstr.) (Spa)

NORMETANEPHRINE

Normetanephrine and metanephrine oxidized by both types of monoamine oxidase. Suzuki O, et al. **Experientia** 1985 May 15;41(5):634-6

Effects of clorgyline and (-)deprenyl on the deamination of normetanephrine and noradrenaline in strips and homogenates of the canine saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):396-400

NORTRIPTYLINE

Monitoring plasma concentration of nortriptyline. Methodological, pharmakokinetic and clinical aspects. Kragh-Sørensen P. **Dan Med Bull** 1985 Mar;32(1):29-53

Plasma nortriptyline and clinical response in depression. Murphy GE, et al. **J Affective Disord** 1985 Mar-Apr;8(2):123-9

Child and adolescent nortriptyline single dose kinetics predict steady state plasma levels and suggested dose: preliminary data. Geller B, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):154-8

Structural analysis of the epitope recognized by a monoclonal antibody directed against tricyclic antidepressants. Marullo S, et al. **J Immunol** 1985 Jul;135(1):471-7

OBSESSIVE-COMPULSIVE DISORDER

Two cases of obsessive-compulsive disorder with depression responsive to trazodone. Baxter LR Jr. **J Nerv Ment Dis** 1985 Jul;173(7):432-3

Obsessive-compulsive disorder. Insel TR. **Psychiatr Clin North Am** 1985 Mar;8(1):105-17 (85 ref.)

Clomipramine and imipramine in obsessive-compulsive disorder. Volavka J, et al. **Psychiatry Res** 1985 Jan;14(1):85-93

[Treatment of obsessive compulsive neurosis] Greenberg D, et al. **Harefuah** 1985 Mar 1;108(5):231-5 (Eng. Abstr.) (Heb)

ORGANIC MENTAL DISORDERS, SUBSTANCE-INDUCED

Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. Goldberg E. **Schizophr Bull** 1985;11(2):255-63

Tardive dysmentia : further comments. Jones BD. **Schizophr Bull** 1985; 11(2):187-9

OXAZEPAM

Protein binding of oxazepam and its glucuronide conjugates to human albumin. Boudinot FD, et al. **Biochem Pharmacol** 1985 Jun 15; 34(12):2115-21

Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam. Ansseau M, et al. **Neuropsychobiology** 1984;12(4):255-9

PARASYMPATHOMIMETICS

The mechanism by which adenosine and cholinergic agents reduce contractility in rat myocardium. Correlation with cyclic adenosine monophosphate and receptor densities. Linden J, et al. **Circ Res** 1985 May;56(5):728-35

Comparative inhibitory effects of pirenzepine and atropine on cholinergic stimulation of exocrine and endocrine rat pancreas. Otsuki M, et al. **Gastroenterology** 1985 Aug;89(2):408-14

Cholinomimetic drug RS 86, REM sleep, and depression [letter] Berger M, et al. **Lancet** 1985 Jun 15;1(8442):1385-6

Allosteric interactions between muscarinic agonist binding sites and effector sites demonstrated by the use of bisquaternary pyridinium oximes. Kloog Y, et al. **Life Sci** 1985 Jun 3;36(22):2127-36

Cholinergic stimulation of pancreatic amylase release and muscarinic receptors: effect of ionophore A23187. Larose L, et al. **Life Sci** 1985 Jul 22;37(3):255-61

Food and water intake of broiler chicks as affected by intracerebroventricular injections of cholinomimetics. Denbow DM, et al. **Poult Sci** 1985 May;64(5):991-4

Effects of nicotinic an muscarinic stimulation on calcium flux and catecholamine secretion in primary cultures of adrenal medullary cells. Watanabe J. **Tokushima J Exp Med** 1984 Dec;31(3-4):79-84

[Comparative sensitivity of the m-cholinoreceptors in various sites to cholinotropic agents] Angelova LA. **Farmakol Toksikol** 1985 Mar-Apr; 48(2):115-20 (Rus)

PARGYLINE

The metabolic fate of pargyline in rat liver microsomes. Weli AM, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1993-8

Localization in rat brain of binding sites for parkinsonian toxin MPTP: similarities with [3H]pargyline binding to monoamine oxidase. Rainbow TC, et al. **Brain Res** 1985 Mar 25;330(2):337-42

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222-31

PEMOLINE

Oral pemoline kinetics in hyperactive children. Sallee F, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):606-9

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222-31

PENTOBARBITAL

Interaction of penicillin and pentobarbital with inhibitory synaptic mechanisms in neocortex. Weiss DS, et al. **Cell Mol Neurobiol** 1984 Dec;4(4):301-17

Blood versus bone marrow pentobarbital concentrations. Winek CL, et al. **Forensic Sci Int** 1985 Jan;27(1):15-24

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

gamma-Aminobutyric-acid- and pentobarbitone-gated chloride currents in internally perfused frog sensory neurones. Akaike N, et al. **J Physiol (Lond)** 1985 Mar;360:367-86

Effect of pentobarbital dependence on adenylate cyclase activity and calmodulin levels in rat cerebral cortex. Piascik MT, et al. **Life Sci** 1985 Jul 8;37(1):55-62

gamma-Aminobutyric acid partly mediates the pentobarbitone depression of synaptic excitation in the guinea-pig olfactory cortex in vitro. Steel L, et al. **Neurosci Lett** 1985 May 1;56(1):33-8

Barbiturate-enhanced paired-pulse depression in neonatal rats. Wilson DA, et al. **Neurosci Lett** 1985 May 14;56(2):101-6

Dose-related effects of pentobarbital on the genetic differences seen between paired, Roman high- or low-avoidance rats in a shuttle box. Driscoll P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):435-9

Involvement of the serotonergic system in the prolongation of pentobarbital sleeping time produced by prostaglandin D2. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):365-70

[Pre-synaptic inhibition and pentobarbital] Ohmura Y. **Masui** 1985 Jan; 34(1):2-8 (36 ref.) (Jpn)

PEPTIDES

Isolation from calf brain of a polypeptide fraction affecting aminoacylation of tRNA. Brzuszkiewicz-Zarnowska H, et al. **Acta Biochim Pol** 1984; 31(4):397-400

Corticotropin-releasing factor, sauvagine, and urotensin I: effects on blood flow. Lenz HJ, et al. **Am J Physiol** 1985 Jul;249(1 Pt 2):R85-90

Synthesis of side chain-protected amino acid phenylthiohydantoins and their use in quantitative solid-phase Edman degradation. Steiman DM, et al. **Anal Biochem** 1985 Feb 15;145(1):91-5

LHRH-like substance in the rat testis. Arimura A, et al. **Ann NY Acad Sci** 1984;438:390-3

Beta-endorphin, Met-enkephalin, and calcitonin in human semen: evidence for a possible role in human sperm motility. Fraioli F, et al. **Ann NY Acad Sci** 1984;438:365-70

Studies on the identification of a LHRH-like peptide in the rat testis. Hedger MP, et al. **Ann NY Acad Sci** 1984;438:371-81

GnRH-like factors in the rat testis and human seminal plasma. Swerdloff RS, et al. **Ann NY Acad Sci** 1984;438:382-9

Vascular, plasma membrane aminopeptidase M. Metabolism of vasoactive peptides. Palmieri FE, et al. **Biochem Pharmacol** 1985 Jul 1; 34(13):2309-17

Poly(DL-proline), a synthetic polypeptide behaving as an ion channel across bilayer membranes. De Santis P, et al. **Biophys Chem** 1985 Mar; 21(3-4):211-5

Peptide homologs, isosteres, and isomers: a general approach to structure-activity relationships. Goodman M. **Biopolymers** 1985 Jan;

24(1):137-55

Substance K excites dopaminergic and non-dopaminergic neurons in rat substantia nigra. Innis RB, et al. **Brain Res** 1985 Jun 3;335(2):381-3

Vasoactive intestinal peptide and PHI stimulate somatostatin release from rat cerebral cortical and diencephalic cells in dispersed cell culture. Tapia-Arancibia L, et al. **Brain Res** 1985 Jun 10;336(1):67-72

Proopiomelanocortin peptide immunocytochemistry in rhesus monkey brain. Khachaturian H, et al. **Brain Res Bull** 1984 Dec; 13(6):785-800

Localization of somatostatin-, bombesin-, and serotonin-like immunoreactivity in the lung of the fetal rhesus monkey. Dayer AM, et al. **Cell Tissue Res** 1985;239(3):621-5

Studies on peptides. CXXIII. Preparations of nine peptide fragments for the synthesis of human corticotropin releasing factor (hCRF). Fujii N, et al. **Chem Pharm Bull (Tokyo)** 1984 Dec;32(12):4786-96

Electrophysiological studies of peptide actions on the excitability of cultured nerve and pituitary cells. Barker JL, et al. **Clin Exp Hypertens [A]** 1984;6(10-11):1701-16 (32 ref.)

Proximal tubular hydrolysis and transport of small peptides. Carone FA, et al. **Contrib Nephrol** 1984;42:1-9

Absence of effect of the peptide PHI-27 on LH release in vitro. Miyake A, et al. **Endocrinol Jpn** 1984 Dec;31(6):821-4

Mouse salivary glands secrete a glucagon-degrading enzyme, not glucagon. Baldissera FG, et al. **Endocrinology** 1985 Jul;117(1):84-7

Selective regulation of carboxypeptidase peptide hormone-processing enzyme during enkephalin biosynthesis in cultured bovine adrenomedullary chromaffin cells. Hook VY, et al. **J Biol Chem** 1985 May 25;260(10):5991-7

Multiple forms of somatostatin-like immunoreactivity in the hypothalamus and amygdala of the rat: selective localization of somatostatin-28 in the median eminence. Pierotti AR, et al. **J Endocrinol** 1985 Jun; 105(3):383-9

Inhibition of sodium transport in frog skin and iodination of tyrosine in vitro by a peptide of renal origin. Fregly MJ, et al. **Klin Wochenschr** 1985;63 Suppl 3:102-6

Effects of bombesin on behavior. Cowan A, et al. **Life Sci** 1985 Jul 15; 37(2):135-45

Effect of bombesin on feeding behavior. Gibbs J. **Life Sci** 1985 Jul 15; 37(2):147-53

Bombesin evoked acetylcholine release from the guinea pig antrum. Kantoh M, et al. **Life Sci** 1985 Jun 24;36(25):2445-52

Centrally-mediated bombesin effects on gastrointestinal motility. Porreca F, et al. **Life Sci** 1985 Jul 15;37(2):125-34

Central nervous system action of bombesin to inhibit gastric acid secretion. Tache Y, et al. **Life Sci** 1985 Jul 15;37(2):115-23 (43 ref.)

Characterization of a high molecular weight polypeptide from spinal cord with (Leu) enkephalin-immunoreactivity. Wahlström A, et al. **Neuropeptides** 1985 Feb;5(4-6):509-12

Cholecystokinin and bombesin suppress operant responding for food reward. Babcock AM, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):893-5

Biochemistry of peptide-secreting neurons. White JD, et al. **Physiol Rev** 1985 Jul;65(3):553-606 (313 ref.)

Cerebrospinal fluid cholecystokinin, bombesin and somatostatin in schizophrenia and normals. Gerner RH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):73-82

Physiological neuroendocrinology of peptides, steroids and other hormones in cerebrospinal fluid. Kee DB Jr, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):55-72 (131 ref.)

Distribution and vasomotor effects of peptide HI (PHI) in feline cerebral blood vessels in vitro and in situ. Edvinsson L, et al. **Regul Pept** 1985 Apr;10(4):345-56

Bombesin, neurotensin and pro-gamma-melanotropin immunoreactants in human milk. Ekman R, et al. **Regul Pept** 1985 Mar; 10(2-3):99-105

ACTH-releasing activity of urotensin I and ovine CRF: interactions with arginine vasotocin, isotocin and arginine vasopressin. Fryer J, et al. **Regul Pept** 1985 May;11(1):11-5

Effects of secretagogues on membrane potential and input resistance of pancreatic acinar cells of sheep. Katoh K, et al. **Res Vet Sci** 1985 Mar; 38(2):250-1

Effects of somatostatin-14 and somatostatin-28 on plasma hormonal and gastric secretory responses to cephalic and gastrointestinal stimulation in man. Konturek SJ, et al. **Scand J Gastroenterol** 1985 Jan; 20(1):31-8

[Effect of peptides on thermoregulation] He ZA. **Sheng Li Ko Hsueh Chin Chan** 1985 Jan;16(1):36-40 (33 ref.) **(Chi)**

[Stress and the endogenous opioid system. II. Stress, stress models and endogenous opioid peptides] Nieber K, et al. **Z Gesamte Inn Med** 1985 Feb 1;40(3):61-5 (Eng. Abstr.) **(Ger)**

PERSONALITY DISORDERS

Axis II personality disorders: diagnostic and treatment issues. Widiger TA, et al. **Hosp Community Psychiatry** 1985 Jun;36(6):619-27

Neuroticism and personality disorder in depression. Davidson J, et al. **J Affective Disord** 1985 Mar-Apr;8(2):177-82

PHENCYCLIDINE

Phencyclidine-induced inhibition of rat prolactin secretion: increased portal blood dopamine. Meltzer HY, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):143-6

Acute and chronic phencyclidine administration changes serotonin receptors in rat brain. Nabeshima T, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):129-30

Hemoperfusion of phencyclidine in the dog. Allen WR, et al. **Int J Artif Organs** 1985 Mar;8(2):101-4

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

Local anesthetic properties of opioids and phencyclidines: interaction with the voltage-dependent, batrachotoxin binding site in sodium channels. Creveling CR, et al. **Neuropeptides** 1985 Feb;5(4-6):253-6

Quantitative electrocortical changes in the rat induced by phencyclidine and other stimulants. Neal H, et al. **Neuropharmacology** 1985 Apr; 24(4):317-23

Effects of phencyclidine (PCP)-like drugs on turning behavior, 3H-dopamine uptake, and 3H-PCP binding. Johnson KM, et al. **Pharmacol Biochem Behav** 1985 May;22(5):731-5

PHENELZINE

Formation of beta-phenylethylamine from the antidepressant, beta-phenylethylhydrazine. Dyck LE, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1925-9

Drug interactions and vasoconstrictors used in local anesthetic solutions. Yagiela JA, et al. **Oral Surg Oral Med Oral Pathol** 1985 Jun; 59(6):565-71

'Pseudo-allergy': treatment with an MAO inhibitor. Ulwelling W. **Psychosomatics** 1985 Jun;26(6):535-6

PHENETHYLAMINES

Thermodynamics of agonist and antagonist binding to the alpha 1-adrenoceptor studied using [125I]BE 2254. Adams A, et al. **Biochem Biophys Res Commun** 1985 Apr 30;128(2):816-23

Formation of beta-phenylethylamine from the antidepressant, beta-phenylethylhydrazine. Dyck LE, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1925-9

Platelet monoamine oxidase inhibition by deprenyl and tranylcypromine: implications for clinical use. Simpson GM, et al. **Biol Psychiatry** 1985 Jun;20(6):684-7

The effects of amiflamine on cerebrospinal fluid amine metabolites in the rhesus monkey. Garrick NA, et al. **Eur J Pharmacol** 1985 Mar 26; 110(1):1-9

Selective inhibition of MAO-A but not MAO-B activity increases rat pineal melatonin. Oxenkrug GF, et al. **J Neural Transm** 1985; 61(3-4):265-70

m-Octopamine: normal occurrence with p-octopamine in mammalian sympathetic nerves. Ibrahim KE, et al. **J Neurochem** 1985 Jun; 44(6):1862-7

Inhibition of locus coeruleus neuronal activity by beta-phenylethylamine. Lundberg PA, et al. **Life Sci** 1985 May 13;36(19):1889-96

Effects of clorgyline and (-)deprenyl on the deamination of normetanephrine and noradrenaline in strips and homogenates of the canine saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):396-400

Cold-restraint stress and urinary endogenous beta-phenylethylamine excretion in rats. Snoddy AM, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):497-500

Pharmacological treatment of attention deficit disorder, residual type (ADD,RT, 'minimal brain dysfunction,' 'hyperactivity') in adults. Wender PH, et al. **Psychopharmacol Bull** 1985;21(2):222-31

PHENOBARBITAL

Monoclonal antibody directed isolation and amino-terminal sequence analysis of phenobarbital induced rat liver cytochromes P-450. Friedman FK, et al. **Biochem Biophys Res Commun** 1985 Jun 28; 129(3):926-33

Comparison of kidney, lung and liver coumarin 7-hydroxylases in phenobarbital pretreated DBA/2J and C57BL/6J mice. Kaipainen P, et al. **Biochem Pharmacol** 1985 Jun 1;34(11):1987-91

Induction of cytochrome P-450 by phenobarbital is mediated at the level of transcription. Pike SF, et al. **Biochem Pharmacol** 1985 Jul 15; 34(14):2489-94

Ultrastructural and immunohistochemical studies on non-ciliated cells of the tracheal epithelium of normal, phenobarbital-treated and 3-methylcholanthrene-treated mice. Ishimura K, et al. **Cell Tissue Res** 1985;240(2):501-4

Effect of peritoneal dialysis on serum concentrations of three drugs commonly used in pediatric patients. Chow-Tung E, et al. **Dev Pharmacol Ther** 1985;8(2):85-95

Diphenylbarbituric acid: its effects on neuromuscular and spinal cord function in the cat. Zavadil AP 3d, et al. **Epilepsia** 1985 Mar-Apr; 26(2):158-66

Long-term behavioral effects of phenobarbital in suckling rats. McBride MC, et al. **Exp Neurol** 1985 Jul;89(1):59-70

Response of meiotic chromosomes of mice to phenobarbitone. Subramanyam S, et al. **Indian J Exp Biol** 1984 Dec;22(12):666-9

On the mechanism of the inactivation of the major phenobarbital-inducible isozyme of rat liver cytochrome P-450 by chloramphenicol. Halpert JR, et al. **J Biol Chem** 1985 Jul 15; 260(14):8397-403

Gene structure of a major form of phenobarbital-inducible cytochrome P-450 in rat liver. Suwa Y, et al. **J Biol Chem** 1985 Jul 5; 260(13):7980-4

Kinetics of drug action in disease states. XIII. Effect of dialyzable component(s) of uremic blood on phenobarbital concentrations in rats at onset of loss of righting reflex. Hisaoka M, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):180-3

Effect of centrally acting drugs on ethanol detoxification enzymes in distinct rat brain regions. Messiha FS. **Neurobehav Toxicol Teratol** 1985 Mar-Apr;7(2):181-4

Stereological analysis of smooth endoplasmic reticulum and peroxisome proliferation in hepatocytes from neonatal and adult mice after phenobarbital administration. Kanai K, et al. **Okajimas Folia Anat Jpn** 1984 Dec;61(5):327-35

Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Picker M, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):389-93

The time course of [3H]PteGlu uptake and its incorporation into pteroylpolyglutamates in liver of phenobarbitone treated rats. Formiggini G, et al. **Pharmacol Res Commun** 1985 Feb;17(2):123-8

Biopharmaceutical investigation of rectal suppositories. Part 2(1): Pharmaceutical and biological availability of phenobarbital and phenobarbital-sodium. Minkov E, et al. **Pharmazie** 1985 Apr; 40(4):257-9

Neonatal phenobarbital imprinting of hepatic microsomal enzymes in adult rats: modulation by neonatal testosterone presence. Bagley DM, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):227-35

Inducible aldehyde dehydrogenases from rat liver cytosol. Simpson VJ, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):193-203

Reduction of ochratoxin A toxicity in mice treated with phenylalanine and phenobarbital. Moroi K, et al. **Toxicol Lett** 1985 Apr;25(1):1-5

Effects of rifampicin and phenobarbital on the fate of isoniazid and hydrazine in vivo in rats. Noda A, et al. **Toxicol Lett** 1985 Jun; 25(3):313-7

[Pharmacokinetics of injectable phenobarbital in the premature infant. Study of a new lyophilized form] Kossmann JC, et al. **Arch Fr Pediatr** 1985 Apr;42(4):317-20 (Eng. Abstr.) **(Fre)**

[Value of a charcoal column of our design for hemoperfusion in the treatment of experimental barbiturate poisoning] Bakula S, et al. **Pol Tyg Lek** 1985 Feb 25;40(8):217-9 (Eng. Abstr.) **(Pol)**

[Comparative study of zixoryn and phenobarbital as enzyme inducers of the liver mono-oxygenase system] Loginov AS, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):437-40 (Eng. Abstr.) **(Rus)**

[Immunomorphological study of cytochrome P-450PB induction in the liver of rat embryos and pregnant females after phenobarbital administration] Popova NV, et al. **Biull Eksp Biol Med** 1985 Mar; 99(3):366-8 (Eng. Abstr.) **(Rus)**

[Nomogram for phenobarbital dosage in children (letter)] Armijo JA, et al. **An Esp Pediatr** 1985 Apr 15;22(5):418-21 **(Spa)**

PHENOTHIAZINE TRANQUILIZERS

Lipids and apolipoproteins in patients treated with major tranquilizers. Sasaki J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):684-7

Behavioral indications for phenothiazine and benzodiazepine tranquilizers in dogs. Hart BL. **J Am Vet Med Assoc** 1985 Jun 1;186(11):1192-4

[Ecto-ATPases in leukocytes and its modification by drugs] Hehl EM, et al. **Allerg Immunol (Leipz)** 1985;31(1):17-23 (Eng. Abstr.) **(Ger)**

[Biotransformation of Chlorphenethazin (Elroquil, Marophen)] Pfeifer S, et al. **Pharmazie** 1985 Jan;40(1):37-9 (Eng. Abstr.) **(Ger)**

[Clinico-humoral manifestations secondary to treatment with injectable Tisercin] Gheorghe M, et al. **Rev Med Interna [Neurol Psihiatr]** 1985 Jan-Mar;30(1):71-2 **(Rum)**

PHENOTHIAZINES

Interaction of phenothiazine drugs with human ceruloplasmin. Relation between activation of catecholamine neurotransmitter oxidation and electron donating ability of phenothiazine drugs. de Mol NJ. **Biochem Pharmacol** 1985 Aug 1;34(15):2605-9

Reciprocal effects of phenothiazines and naphthalene sulfonamides on the external ATP-dependent permeability change in Chinese hamster ovary cells. Kitagawa T, et al. **Biochim Biophys Acta** 1985 Apr 26; 815(1):25-32

Selective effects of CAPP1-calmodulin on its target proteins. Newton D, et al. **Biochim Biophys Acta** 1985 Jun 30;845(3):533-9

Cimetidine inhibition of ethmozine metabolism. Biollaz J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):665-8

Pharmacokinetics of dixyrazine: low bioavailability, improved by food intake. Liedholm H, et al. **Drug Nutr Interact** 1985;3(2):87-92

The involvement of nucleosomes in Giemsa staining of chromosomes. A new hypothesis on the banding mechanism. van Duijn P, et al. **Histochemistry** 1985;82(4):363-76

Assessment of the potential pharmacokinetic interaction between digoxin and ethmozine. MacFarland RT, et al. **J Clin Pharmacol** 1985 Mar; 25(2):138-43

A versatile and simple method for staining nervous tissue using Giemsa dye. Iñiguez C, et al. **J Neurosci Methods** 1985 Mar;13(1):77-86

Application of Azure C for the extractive spectrophotometric determination of microgram amounts of penicillin. Gowda AT, et al. **J Pharmacol Methods** 1985 Jun;13(3):275-80

[Interaction of oxygen anion radicals with eye melanins and ommochromes] Lapina VA, et al. **Dokl Akad Nauk SSSR** 1985; 280(6):1463-5 **(Rus)**

PHENOXYBENZAMINE

Influence of intracerebroventricular phenoxybenzamine on the renal action of intracerebroventricular morphine. Kook YJ, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):289-98

PHENYLALANINE

Identification of peptides containing tryptophan, tyrosine, and phenylalanine using photodiode-array spectrophotometry. Yang CY, et al. **Anal Biochem** 1985 Feb 15;145(1):67-72

L-Phenylalanine and L-tyrosine catabolism by selected Streptomyces species. Pometto AL 3d, et al. **Appl Environ Microbiol** 1985 Mar; 49(3):727-9

Abilities of some tryptophan and phenylalanine derivatives to inhibit gastric acid secretion. Magous R, et al. **Biochim Biophys Acta** 1985 May 30;845(2):158-62

The effect of the intracellular sodium level on the activity of amino acid transport systems L and A in SV40 3T3 cells. Petronini PG, et al. **Biochim Biophys Acta** 1985 May 28;815(3):361-8

Clues from Xanthomonas campestris about the evolution of aromatic biosynthesis and its regulation. Whitaker RJ, et al. **J Mol Evol** 1984-85; 21(2):139-49

The effect of phenylalanine on intracellular pH and sodium activity in proximal convoluted tubule cells of the frog kidney. Messner G, et al. **Pflugers Arch** 1985 May;404(2):145-9

Reduction of ochratoxin A toxicity in mice treated with phenylalanine and phenobarbital. Moroi K, et al. **Toxicol Lett** 1985 Apr;25(1):1-5

PHENYLPROPANOLAMINE

Determination of phenylpropanolamine hydrochloride and acetaminophen in pharmaceutical preparations by Raman spectroscopy. King TH, et al. **J Pharm Sci** 1985 Apr;74(4):443-7

Effects of reserpine and adrenal demedullation on brown adipose tissue thermogenesis induced by dl-phenylpropanolamine. Wellman PJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Feb;47(2):211-20

Vascular effects of phenylpropanolamine on human nasal mucosa. Bende M, et al. **Rhinology** 1985 Mar;23(1):43-8

PHENYTOIN

Effects of ibuprofen on the disposition kinetics of phenytoin in pregnant rats. Cleveland PA, et al. **Biopharm Drug Dispos** 1985 Apr-Jun; 6(2):167-76

Audit of a monitoring service for free phenytoin. Peterson GM, et al. **Br J Clin Pharmacol** 1985 May;19(5):693-7

Effect of phenytoin on intracellular calcium and intracellular protein changes during pentylenetetrazole-induced bursting activity in snail neurons. Sugaya E, et al. **Brain Res** 1985 Feb 18;327(1-2):161-8

A theoretical and an in vitro experimental model for estimation of drug transfer through the human placenta. Mor L, et al. **Contrib Gynecol Obstet** 1985;13:155-7

Phenytoin clearance by continuous ambulatory peritoneal dialysis. Hays DP, et al. **Drug Intell Clin Pharm** 1985 Jun;19(6):429-31

Effects of phenytoin administration on vestibular function in the rat. Mameli O, et al. **Epilepsia** 1985 May-Jun;26(3):262-7

The effects of phenytoin on serum and organ concentrations of zinc and copper in cat. Palm R, et al. **Epilepsia** 1985 Mar-Apr;26(2):184-8

A rapid method for separation and estimation of free phenytoin in serum. Ahmad SN, et al. **Indian J Exp Biol** 1984 Nov;22(11):605-7

Phenytoin bioavailability assessed by steady state serum concentrations. Halkin H, et al. **Isr J Med Sci** 1985 Apr;21(4):327-30

Phenytoin pharmacokinetics in therapeutic plasmapheresis. Nasca TJ, et al. **J Clin Pharmacol** 1985 May-Jun;25(4):302-4

The use of a monosaccharide linkage group in a heterologous solid-phase enzyme immunoassay for phenytoin. Hinds JA, et al. **J Immunol Methods** 1985 Jun 25;80(2):239-53

Expanding physician duties and patients rights in wrongful life: Harbeson

v. Parke-Davis, Inc. Skolnick M. **Med Law** 1985;4(3):283-98

Mutagenic potential of anticonvulsant diphyenylhydantoin (DPH) on human lymphocytes in vitro. Maurya AK, et al. **Methods Find Exp Clin Pharmacol** 1985 Mar;7(3):109-12

Preparation of a phenytoin beta-cyclodextrin complex and evaluation of a suspension and a tablet dosage form prepared from the complex. Hegde RP, et al. **Pharm Acta Helv** 1985;60(2):53-7

Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Picker M, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):389-93

Phenytoin and trimethadione: pharmacokinetics, embryotoxicity, and maternal toxicity. Khera KS. **Prog Clin Biol Res** 1985;163C:317-22

Phenytoin teratogenicity and effects on embryonic and maternal folate metabolism. Hansen DK, et al. **Teratology** 1985 Jun;31(3):363-71

The water, DNA, collagen and noncollagen protein contents in embryos after maternal administration of a teratogenic dose of phenytoin. Hicks HE, et al. **Toxicol Lett** 1985 Apr;25(1):41-6

[Study on phenytoin-selective electrode] Yao SZ, et al. **Yao Hsueh Hsueh Pao** 1984 Jun;19(6):455-60 (Eng. Abstr.) **(Chi)**

[Effects of diphenylhydantoin on thyroid function] Giroud M, et al. **Therapie** 1985 Mar-Apr;40(2):119-22 (Eng. Abstr.) **(Fre)**

[Experimental study of the effects of diphenylhydantoins and estrogens in rats. I. Microbiological aspects of changes in the gingival flora of rats treated with diphenylhydantoins] Bascones A, et al. **Rev Esp Estomatol** 1984 May-Jun;32(3):147-54 **(Spa)**

[Clinical pharmacology of carbamazepine--a comparison with phenytoin] Bertilsson L, et al. **Lakartidningen** 1985 Apr 10;82(15):1355-60 **(Swe)**

PHOBIC DISORDERS

Agoraphobia. Horn TL. **Am Fam Physician** 1985 Jul;32(1):165-73

Combined pharmacological and behavioral treatment for agoraphobia. Telch MJ, et al. **Behav Res Ther** 1985;23(3):325-35

Dysmorphophobia [letter] Jenike MA. **Br J Psychiatry** 1985 Mar; 146:326

Agoraphobia. Pyke JM, et al. **Can Nurse** 1985 Jun;81(6):18-21

Modification of disease phobia using a multifaceted exposure program. Tearnan BH, et al. **J Behav Ther Exp Psychiatry** 1985 Mar; 16(1):57-61

Catecholamine secretion as a function of perceived coping self-efficacy. Bandura A, et al. **J Consult Clin Psychol** 1985 Jun;53(3):406-14

Psychophysiological outcome of behavioral and pharmacological treatments of agoraphobia. Michelson L, et al. **J Consult Clin Psychol** 1985 Apr;53(2):229-36

[Agoraphobia] Pyke JM, et al. **Infirm Can** 1985 Jun;27(6):24-7 **(Fre)**

PHYSOSTIGMINE

Antagonism of physostigmine induced lethality by a combination of scopolamine and methscopolamine. Janowsky DS, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Feb;56(2):154-7

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196-201

Physostigmine reverses memory deficits produced by pretraining electrical stimulation of the dorsal hippocampus in mice. Micheau J, et al. **Behav Brain Res** 1985 Apr;15(2):75-81

Physostigmine effects on serotonin uptake in human blood platelets. Rausch JL, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):91-6

Determination of physostigmine in plasma and brain by HPLC. Somani SM, et al. **J Anal Toxicol** 1985 Mar-Apr;9(2):71-5

Plasma physostigmine concentrations after oral administration [letter] Sharpless NS, et al. **Lancet** 1985 Jun 15;1(8442):1397-8

Inhibitory effects of dopamine and isoprenaline on antral motor activity stimulated by acetylcholine or physostigmine in vitro. Ulvestad A, et al. **Scand J Gastroenterol** 1985 Mar;20(2):243-6

[The acute toxicity of eserine, VX and paraoxon for the establishment of a mathematical model for extrapolation to humans] Leblic C, et al. **Arch Belg** 1984;Suppl:226-42 (Eng. Abstr.) **(Fre)**

[Stabilization of physostigmine salicylate injection solutions] Trose D, et al. **Pharmazie** 1985 Feb;40(2):124-6 (Eng. Abstr.) **(Ger)**

PILOCARPINE

Characteristics of yawning behavior induced by apomorphine, physostigmine and pilocarpine. Ushijima I, et al. **Arch Int Pharmacodyn Ther** 1985 Feb;273(2):196-201

Prevention of intraocular pressure elevation following neodymium-YAG laser posterior capsulotomy. Richter CU, et al. **Arch Ophthalmol** 1985 Jul;103(7):912-5

Comparison of the effects of chronic administration of ciclazindol and desipramine on pupillary responses to tyramine, methoxamine and pilocarpine in healthy volunteers. Kerr FA, et al. **Br J Clin Pharmacol** 1985 May;19(5):639-47

[The stability of pilocarpine hydrochloride in eyedrops] Porst H, et al. **Pharmazie** 1985 Jan;40(1):23-9 (Eng. Abstr.) **(Ger)**

PITUITARY HORMONE RELEASING HORMONES

Gonadotropin releasing hormone stimulates the formation of inositol phosphates in rat anterior pituitary tissue. Schrey MP. **Biochem J** 1985 Mar 1;226(2):563-9

Modulation of lordosis behaviour in the female rat by corticotropin releasing factor, beta-endorphin and gonadotropin releasing hormone in the mesencephalic central gray. Sirinathsinghji DJ. **Brain Res** 1985 Jun 10;336(1):45-55

Mechanisms of gonadotropin-releasing hormone and prostaglandin action on luteal cells. Leung PC. **Can J Physiol Pharmacol** 1985 Mar; 63(3):249-56 (79 ref.)

Increased gonadotropin-releasing hormone pulse frequency associated with estrogen-induced luteinizing hormone surges in ovariectomized ewes. Clarke IJ, et al. **Endocrinology** 1985 Jun;116(6):2376-83

Longitudinal study of the surge of gonadotropins induced by exogenous hormones in prepuberal gilts. Fleming MW, et al. **Endocrinology** 1985 May;116(5):1893-8

The frequency of gonadotropin-releasing hormone stimulation determines the number of pituitary gonadotropin-releasing hormone receptors. Katt JA, et al. **Endocrinology** 1985 May;116(5):2113-5

Release of luteinizing hormone and follicle-stimulating hormone from pituitaries of lactating rats by gonadotropin-releasing hormone and high potassium concentration. Smith MS. **Endocrinology** 1985 May; 116(5):1826-34

FSH and LH response to testosterone and gonadotropin-releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter; 10(4):183-7

Influence of the frequency of gonadotropin-releasing hormone (GnRH) administration on ovulatory responses in women with anovulation. Bringer J, et al. **Fertil Steril** 1985 Jul;44(1):42-8

Structure-activity relationships of mammalian, chicken, and salmon gonadotropin releasing hormones in vivo in goldfish. Peter RE, et al. **Gen Comp Endocrinol** 1985 May;58(2):231-42

Successful pregnancy following ovulation induction with pulsatile GnRH. O'Herlihy C, et al. **Ir Med J** 1985 May;78(5):133-4, 136

Hypothalamic gonadotrophin-releasing hormone and pituitary and plasma FSH and prolactin during photostimulation and photorefractoriness in intact and thyroidectomized starlings (Sturnus vulgaris). Dawson A, et al. **J Endocrinol** 1985 Apr;105(1):71-7

Diacylglycerols and protein kinase C. Potential amplifying mechanism for Ca2+-mediated gonadotropin-releasing hormone-stimulated luteinizing hormone release. Harris CE, et al. **Mol Pharmacol** 1985 May; 27(5):532-6

Differential suppression of follicle-stimulating hormone and luteinizing hormone secretion in vivo by a gonadotropin-releasing hormone antagonist. Grady RR, et al. **Neuroendocrinology** 1985 Mar; 40(3):246-52

[Pulsatile administration of gonadoliberin by subcutaneous route in the induction of ovulation (letter)] Fenichel P, et al. **Presse Med** 1985 Apr 13;14(15):846 **(Fre)**

[The effect of blood serum on GnRH-loaded multilayer liposomes: proof of a correlation between their size and the inclusion stability of the peptide hormones] Schäfer H, et al. **Pharmazie** 1985 Feb;40(2):131-2 **(Ger)**

PITUITARY HORMONES, ANTERIOR

Ketanserin without effects on basal anterior pituitary hormone secretion in healthy subjects. Gordin A, et al. **J Endocrinol Invest** 1985 Feb; 8(1):73-5

Idiopathic premature ovarian failure. A clinical and biochemical study. Naidoo C, et al. **S Afr Med J** 1985 Jul 20;68(2):91-4

PROGESTERONE

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

Phorbol ester regulation of rat granulosa cell prostaglandin and progesterone accumulation. Kawai Y, et al. **Endocrinology** 1985 Jun; 116(6):2320-6

Relation of circulating estradiol and progesterone to gonadotropin secretion and estrous cyclicity in aging female rats. Lu JK, et al. **Endocrinology** 1985 May;116(5):1953-9

Exogenous progesterone for luteal support following gonadotropin-releasing hormone ovulation induction: case report. Berger NG, et al. **Fertil Steril** 1985 Jul;44(1):133-5

Hormonal influence on the response of the uterus of the Brazilian marsupial Didelphis albiventris to adrenergic drugs. Rocha LR, et al. **Gen Comp Endocrinol** 1985 May;58(2):179-85

Progesterone-induced LHRH release in vitro is an estrogen--as well as Ca++- and calmodulin-dependent secretory process. Drouva SV, et al. **Neuroendocrinology** 1985 Apr;40(4):325-31

Effects of progesterone on hypothalamic and plasma LHRH. Peduto JC, et al. **Neuroendocrinology** 1985 Mar;40(3):238-45

PROLACTIN

Age-related changes in prolactin and growth hormone release from pituitary glands in vitro. Hall TR, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):479-84

Plasma prolactin in the rat during suckling without prior separation from pups. Mattheij JA, et al. **Acta Endocrinol (Copenh)** 1985 Apr; 108(4):468-74

Temporary increase in the circulating prolactin levels during and after consecutive administration of bromocriptine-mesilate (CB-154) in female mice. Mori T, et al. **Acta Endocrinol (Copenh)** 1985 Jun; 109(2):208-13

Neuro-endocrine effects of isotheoline. Zhelyazkov D, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):53-8

Serum concentrations of thyroxine, 3,5,3'-triiodothyronine, thyrotropin, and prolactin in dogs before and after thyrotropin-releasing hormone administration. Kaufman J, et al. **Am J Vet Res** 1985 Feb; 46(2):486-92

Dopamine D2 receptors modulate neurotransmitter-regulated calcium ion gates. Memo M, et al. **Ann Ist Super Sanita** 1984;20(1):5-10

Effect of prolactin and bromocriptine administration on testicular metabolism in albino rats. Dhananjaya Reddy Y, et al. **Arch Int Physiol Biochim** 1985 May;93(1):19-23

Dose-dependent inhibition of the preovulatory surges of gonadotropins and prolactin by the antiestrogen CI-628: possible sites of action. De Paolo LV. **Biol Reprod** 1985 May;32(4):745-52

The proestrous surge of prolactin enhances sexual receptivity in the rat. Witcher JA, et al. **Biol Reprod** 1985 May;32(4):834-9

Effect of feed and water deprivation or force-feeding on plasma prolactin concentration in turkey hens. Zadworny D, et al. **Biol Reprod** 1985 Mar;32(2):241-7

Intolerance of bromocriptine: is metergoline a satisfactory alternative? Casson IF, et al. **Br Med J [Clin Res]** 1985 Jun 15; 290(6484):1783-4

Effects of prostaglandin F2 alpha on prolactin secretion in the fowl. Hall TR, et al. **Br Poult Sci** 1985 Apr;26(2):239-45

The effect of long-term diethylstilbestrol treatment or hyperprolactinemia on the response of the tuberoinfundibular dopamine neurons to elevated prolactin. Morgan WW, et al. **Brain Res** 1985 Jun 3;335(2):330-3

Evaluation of the central dopaminergic activity in gestational hyperprolactinaemia by means of the electroretinographic technique. De Luca Brunori I, et al. **Clin Exp Obstet Gynecol** 1985; 12(1-2):13-5

p-Tyramine, a natural amine, inhibits prolactin release in vivo. Becú-Villalobos D, et al. **Endocrinology** 1985 May;116(5):2044-8

In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. Bression D, et al. **Endocrinology** 1985 May;116(5):1905-11

D-Trp-6-luteinizing hormone-releasing hormone inhibits hyperprolactinemia in female rats. Debeljuk L, et al. **Endocrinology** 1985 Jun;116(6):2227-31

5-Hydroxyeicosatetraenoic acid increases prolactin release from rat anterior pituitary cells. Koike K, et al. **Endocrinology** 1985 May; 116(5):1813-7

Studies on the effects of catecholestrogens on prolactin secretion by cultured normal rat anterior pituitary cells. Lamberts SW, et al. **Endocrinology** 1985 Jun;116(6):2631-6

Prolactin metabolic clearance and resistance to dopaminergic suppression in acute uremia. McKenna TM, et al. **Endocrinology** 1985 May; 116(5):2003-7

Rapid effects of hyperprolactinemia on basal prolactin secretion and dopamine turnover in the medial and lateral median eminence. Selmanoff M. **Endocrinology** 1985 May;116(5):1943-52

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

Phencyclidine-induced inhibition of rat prolactin secretion: increased portal blood dopamine. Meltzer HY, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):143-6

Inhibition by antiserum to vasoactive intestinal polypeptide (VIP) of prolactin secretion induced by serotonin in the rat. Ohta H, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):409-12

Number of dopamine neurons predicts prolactin levels in two inbred mouse strains. Sved AF, et al. **Experientia** 1985 May 15;41(5):644-6

Pergolide mesylate inhibits exercise-induced prolactin release in man. De Meirleir K, et al. **Fertil Steril** 1985 Apr;43(4):628-31

Hyperprolactinaemia and testosterone production. Observations in 2 men on long-term dialysis. Stegmayr B, et al. **Horm Res** 1985; 21(4):224-8

Chronic treatment with 2-alpha-bromocriptine in women with the hyperprolactinemic syndrome. Eshel A, et al. **Int J Fertil** 1984; 29(4):247-53

Effects of induced hypoprolactinemia on testicular function during gonadal maturation in the rat. Suescun MO, et al. **J Androl** 1985 Mar-Apr;6(2):77-82

Levels of dopamine and thyrotrophin-releasing hormone in hypophysial stalk blood during an oestrogen-stimulated surge of prolactin in the ovariectomized rat. de Greef WJ, et al. **J Endocrinol** 1985 Apr; 105(1):107-12

Possible role of prolactin in the inhibitory effect of testosterone on the hypothalamic-pituitary-testicular axis in the rat. Tresguerres JA, et al. **J Endocrinol** 1985 Jun;105(3):423-7

The putative dopamine autoreceptor agonist B-HT 920 decreases nigral dopamine cell firing rate and prolactin release in rat. Eriksson E, et al. **Life Sci** 1985 May 13;36(19):1819-27

The mechanism of action of cyproheptadine on prolactin release by cultured anterior pituitary cells. Lamberts SW, et al. **Life Sci** 1985 Jun 10;36(23):2257-62

Adrenalectomy does not prevent the hyperprolactinemic, induced sexual behavior deficits in CDF male rats. Shrenker P, et al. **Life Sci** 1985 May 13;36(19):1881-8

Calcium mobilization potentiates prolactin release induced by protein kinase C activators. Koike K, et al. **Mol Cell Endocrinol** 1985 May; 40(2-3):137-43

Hypoprolactinemia induced by hypophysectomy and long-term bromocriptine treatment decreases tuberoinfundibular dopaminergic neuronal activity and the responsiveness of these neurons to prolactin. Demarest KT, et al. **Neuroendocrinology** 1985 May;40(5):369-76

Dopamine-induced physical barrier to inhibit prolactin release in mammotrophs disappears during resumption of prolactin secretion. Reifel CW, et al. **Neuroendocrinology** 1985 May;40(5):438-43

Cimetidine-induced prolactin release: possible involvement of the GABA-ergic system. Sibilia V, et al. **Neuroendocrinology** 1985 Mar; 40(3):189-92

gamma-Aminobutyric acid decreases levels of messenger ribonucleic acid encoding prolactin in the rat pituitary. Loeffler JP, et al. **Neurosci Lett** 1985 Jan 7;53(1):121-5

Serum and cerebrospinal fluid prolactin patterns during neuroleptic treatment in schizophrenic patients. Rimón R, et al. **Pharmacopsychiatry** 1985 May;18(3):252-4

Cyproheptadine stimulated prolactin release in the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Poult Sci** 1985 May; 64(5):1038-40

Central inhibitory action of TRH on prolactin secretion in the rat. Ohta H, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):9-12

Dose-dependent growth hormone, prolactin and cortisol stimulation after i.v. administration of desimipramine in human subjects. Laakmann G, et al. **Psychoneuroendocrinology** 1985;10(1):83-93

Effect of benztropine on the diurnal prolactin responses to haloperidol. Nathan RS, et al. **Psychoneuroendocrinology** 1985;10(1):71-6

Behavior therapy, pimozide treatment and prolactin secretion in anorexia nervosa. Weizman A, et al. **Psychother Psychosom** 1985;43(3):136-40

[Activity of clobazam on plasma prolactin and gonadotropins after administration of sulpiride in the male rat] Valli M, et al. **Ann Endocrinol (Paris)** 1984;45(6):409-11 (Eng. Abstr.) **(Fre)**

[The mechanism of induction of ovulation by bromocriptine in euprolactinemic anovulation--the role of occult hyperprolactinemia in anovulation] Mori H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jan 20;61(1):38-47 (Eng. Abstr.) **(Jpn)**

[The effects of bromocriptine on anovulatory patients with high LH and euprolactinemia] Mori H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jan 20;61(1):48-55 (Eng. Abstr.) **(Jpn)**

[Specific proteases which degrade prolactin in the mammary glands; subcellular localization and inhibitory analysis] Marinchenko GV. **Biokhimiia** 1985 Feb;50(2):200-10 (Eng. Abstr.) **(Rus)**

[Lactation and re-induction of lactation] Vargas W. **GEN** 1983 Jan-Jun; 37(1-2):16-28 **(Spa)**

PROMETHAZINE

Effects of some motion sickness suppressants on static and dynamic tracking performance. Schroeder DJ, et al. **Aviat Space Environ Med** 1985 Apr;56(4):344-50

Changes in the disposition of promethazine during multiple dosing in the rabbit. Taylor G, et al. **J Pharm Pharmacol** 1985 Apr;37(4):243-7

[Attempted suicide with barbiturate after glue sniffing] Sami HO, et al. **Orv Hetil** 1985 Mar 31;126(13):781-3 (Eng. Abstr.) **(Hun)**

PROPANEDIOLS

Propylene glycol-induced heparin resistance during nitroglycerin infusion. Col J, et al. **Am Heart J** 1985 Jul;110(1 Pt 1):171-3

Solubilization by cosolvents I: organic solutes in propylene glycol-water mixtures. Yalkowsky SH, et al. **J Pharm Sci** 1985 Apr;74(4):416-21

PROPERICIAZINE

Measurement of propericiazine in plasma by capillary gas chromatography and selected ion monitoring detection. De Leenheer AP, et al. **Biomed Mass Spectrom** 1985 Jan;12(1):25-9

PROPRANOLOL

Effect of propranolol on post-traumatic hypophosphataemia and catecholamine secretion. Lovén L, et al. **Acta Chir Scand** 1985; 151(3):201-4

Perturbations of sarcolemmal and microsomal enzymes by amphiphilic lipids and drugs. Weglicki WB, et al. **Adv Myocardiol** 1985;6:127-36

Effects of cardioselective and nonselective beta-adrenergic blockade on the performance of highly trained runners. Anderson RL, et al. **Am J Cardiol** 1985 Apr 26;55(10):149D-154D

Effect of selective and nonselective beta-adrenoceptor blockade on thermoregulation during prolonged exercise in heat. Gordon NF. **Am J Cardiol** 1985 Apr 26;55(10):74D-78D

Cardiovascular and pharmacokinetic consequences of combined administration of verapamil and propranolol in dogs. Hamann SR, et al. **Am J Cardiol** 1985 Jul 1;56(1):147-56

Effects of intravenous infusion of esmolol and propranolol on biventricular performance at rest and during exercise as assessed by quantitative radionuclide angiography. Iskandrian AS, et al. **Am J Cardiol** 1985 May 1;55(11):1287-92

Beta blockade in the compensation for bed-rest cardiovascular deconditioning: physiologic and pharmacologic observations. Sandler H, et al. **Am J Cardiol** 1985 Apr 26;55(10):114D-119D

Exercise training during long-term beta-blockade treatment in healthy subjects. Savin WM, et al. **Am J Cardiol** 1985 Apr 26; 55(10):101D-109D

Cardiorespiratory alterations consequent to endurance exercise training during chronic beta-adrenergic blockade with atenolol and propranolol. Wilmore JH, et al. **Am J Cardiol** 1985 Apr 26;55(10):142D-148D

Acute response to submaximal and maximal exercise consequent to beta-adrenergic blockade: implications for the prescription of exercise. Wilmore JH, et al. **Am J Cardiol** 1985 Apr 26;55(10):135D-141D

Effects of aspirin and propranolol alone and in combination on hemostatic determinants in the healthy cat. Allen DG, et al. **Am J Vet Res** 1985 Mar;46(3):660-3

Effect of propranolol on human spermatozoal in vitro hamster ova penetration. Chan SY, et al. **Arch Androl** 1984;12 Suppl:79-82

Renin response to captopril in conscious dogs pretreated with indomethacin or propranolol. Kamijo T, et al. **Arch Int Pharmacodyn Ther** 1985 Mar;274(1):56-64

Modification of propranolol binding to alpha-1-acid glycoprotein by serum albumin. Chauvelot-Moachon L, et al. **Biochem Pharmacol** 1985 May 1;34(9):1591-4

Reduced hepatic uptake of propranolol in rats with acute renal failure. Hori R, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2679-83

Adrenergic ligand binding in human serum. Sager G, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2812-5

Semi-empirical conformational analysis of propranolol interacting with dipalmitoylphosphatidylcholine. Brasseur R, et al. **Biochim Biophys Acta** 1985 May 28;815(3):341-50

Penbutolol and propranolol: a comparison of their effects on antipyrine clearance in man. Bax ND, et al. **Br J Clin Pharmacol** 1985 May; 19(5):593-6

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445-51

The effects of propranolol and digoxin on the acute vascular responses to frusemide in normal man. Johnston GD, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):417-21

Pre-dosing plasma concentrations and beta-adrenoceptor blocking effects during repeated once daily dosing with 160 mg sustained-release propranolol (Inderal LA) and 16/260 oxprenolol Oros to healthy volunteers. Moppert J, et al. **Br J Clin Pharmacol** 1985; 19 Suppl 2:197S-201S

Comparative effects of adimolol, labetalol and propranolol on heart rate and blood pressure in man. Riddell JG, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):405-10

Ethnic differences in human lymphocytic cyclic AMP production after isoprenaline stimulation and propranolol blockade. Venter CP, et al. **Br J Clin Pharmacol** 1985 Feb;19(2):187-90

Enhancement of the antiaggregatory activity of prostacyclin by propranolol in human platelets. Callahan KS, et al. **Circulation** 1985 Jun;71(6):1237-46

Propranolol: pooled Michaelis-Menten parameters and the effect of input rate on bioavailability. Wagner JG. **Clin Pharmacol Ther** 1985 May; 37(5):481-7

Quantitative account of propranolol metabolism in urine of normal man. Walle T, et al. **Drug Metab Dispos** 1985 Mar-Apr;13(2):204-9

Comparative beta-adrenoceptor blocking effect and pharmacokinetics of bucindolol and propranolol in man. Maury M, et al. **Eur J Clin Pharmacol** 1985;27(6):649-56

Effects of propranolol during pregnancy and development of rats. II. Adverse effects on development. Schoenfeld N, et al. **Eur J Pediatr** 1985 Jan;143(3):194-5

The contribution of vasopressin and angiotensin to the maintenance of blood pressure after autonomic blockade. Hiwatari M, et al. **Hypertension** 1985 Jul-Aug;7(4):547-53

Lack of influence of aluminum hydroxide on the bioavailability and beta-adrenoceptor blocking activity of propranolol. Hong CY, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 May;23(5):244-6

Impairment of isoniazid clearance by propranolol. Santoso B. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):134-6

Comparative pharmacokinetics of intravenous propranolol in black and white volunteers [letter] Venter CP, et al. **J Cardiovasc Pharmacol** 1985 Mar-Apr;7(2):409-10

Augmentation by propranolol of growth hormone-releasing hormone-(1-44)-NH2-induced growth hormone release in normal short and normal children. Chihara K, et al. **J Clin Endocrinol Metab** 1985 Aug;61(2):229-33

Plasma concentration-response relationships of two formulations of propranolol. DeLeve LD, et al. **J Clin Pharmacol** 1985 Apr; 25(3):182-6

Synthesis of 4'-hydroxypropranolol sulfate, a major non-beta-blocking propranolol metabolite in man. Oatis JE Jr, et al. **J Med Chem** 1985 Jun;28(6):822-4

Effect of the sialylation state of alpha 1-acid glycoprotein on propranolol binding. Primozic S, et al. **J Pharm Sci** 1985 Apr;74(4):473-5

Reduced extraction of l-propranolol by perfused rat liver in the presence of uremic blood. Terao N, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):277-84

Effect of chronic treatment of propranolol on lipid metabolism in spontaneously hypertensive rats (SHR). Tonooka M, et al. **Jpn J Pharmacol** 1985 Apr;37(4):335-44

Competitive binding of quinidine, propranolol, and 4-OH-propranolol to human plasma very low-density (VLDL) and low-density (LDL) lipoproteins. Ho Ngoc-Ta Trung A, et al. **Pharm Acta Helv** 1985; 60(4):106-9

The effects of d-propranolol and captopril on post-ischaemic acute renal failure in rats. Ishigami M, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985;21:843-8

[Effect of the central action of propranolol on coronary circulation in dogs] Xie BZ, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Mar; 6(1):33-6 (Eng. Abstr.) **(Chi)**

[Electrocardiographic studies of the modification of cardiac activity in cattle by adrenaline and noradrenaline with and without vagolysis (atropine) and beta-receptor blockade (propranolol)] Mielke H, et al. **Arch Exp Veterinarmed** 1985 Mar;39(2):193-206 (Eng. Abstr.) **(Ger)**

[The anticonvulsant action of propranolol in pentylenetetrazole-induced convulsions] Lasek R, et al. **Pharmazie** 1985 Apr;40(4):271-2 **(Ger)**

PROSTAGLANDINS

Catecholamines and contractility of the human myometrium at term: a possible role for prostaglandins. Wikland M, et al. **Acta Physiol Hung** 1985;65(3):331-4

Effects of prostaglandins on vasoconstrictor action in isolated renal arterioles. Edwards RM. **Am J Physiol** 1985 Jun; 248(6 Pt 2):F779-84

Carbon tetrachloride-induced eicosanoid synthesis and enzyme release from rat peritoneal leucocytes. Lynch TJ, et al. **Biochem Pharmacol** 1985 May 1;34(9):1515-22

Modulatory effects of prostaglandin D2, E2 and F2 alpha on the postsynaptic actions of inhibitory and excitatory amino acids in cerebellar Purkinje cell dendrites in vitro. Kimura H, et al. **Brain Res** 1985 Mar 25;330(2):235-44

Mechanisms of gonadotropin-releasing hormone and prostaglandin action on luteal cells. Leung PC. **Can J Physiol Pharmacol** 1985 Mar; 63(3):249-56 (79 ref.)

Phorbol ester regulation of rat granulosa cell prostaglandin and progesterone accumulation. Kawai Y, et al. **Endocrinology** 1985 Jun; 116(6):2320-6

Effect of verapamil & lignocaine on prostaglandin induced contractions in isolated rat uterus. Kothekar V, et al. **Indian J Med Res** 1985 Jan; 81:79-82

Role of calcium in prostaglandin induced contractile activity in rat uterus. Reddy G, et al. **Indian J Med Res** 1984 Oct;80:491-3

Beclobrinic acid--a new hypolipidemic agent--inhibits in vitro human platelet activation by blocking prostaglandin synthesis. Anwer K, et al. **Life Sci** 1985 Jul 8;37(1):63-70

Prostaglandins, catecholamines, and differentiation of the secondary palate. Greene RM, et al. **Prog Clin Biol Res** 1985;163C:277-81

Evidence against prostaglandin-mediation of somatostatin-inhibition of gastric secretions. Albinus M, et al. **Regul Pept** 1985 Mar; 10(2-3):259-66

[Physiological and pharmacological actions of prostaglandins and related substances on the endocrine system] Kasai Y, et al. **Nippon Rinsho** 1985 Mar;43(3):507-13 (38 ref.) **(Jpn)**

PSYCHIATRIC STATUS RATING SCALES

Mania. Diagnosis, state measurement and prediction of treatment response. Secunda SK, et al. **J Affective Disord** 1985 Mar-Apr;8(2):113-21

KUSTA (Kurz-Skala Stimmung/Aktivierung): a daily self-rating scale for depressive patients. Wendt G, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):118-22

[Comparison of various tools for evaluating depression apropos of a study on Athymil 30 mg] Lempérière T, et al. **Ann Med Psychol (Paris)** 1984 Nov;142(9):1206-14 **(Fre)**

PSYCHIATRY

Data-based psychiatric consultation: applying mainframe computer capability to consultation. Popkin MK, et al. **Gen Hosp Psychiatry** 1985 Apr;7(2):109-12

PSYCHOLOGICAL TESTS

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

PSYCHOMOTOR AGITATION

Emergency treatment of acute psychosis, agitation, and anxiety. Ellison JM. **Hosp Community Psychiatry** 1985 Apr;36(4):351-2

PSYCHOMOTOR PERFORMANCE

Effects of some motion sickness suppressants on static and dynamic tracking performance. Schroeder DJ, et al. **Aviat Space Environ Med** 1985 Apr;56(4):344-50

Evaluation of antimotion sickness drug side effects on performance. Wood CD, et al. **Aviat Space Environ Med** 1985 Apr;56(4):310-6

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance. File SE, et al. **Br J Clin Pharmacol** 1985 Apr;19(4):445-51

Increased sensitivity of the elderly to the central depressant effects of diazepam. Pomara N, et al. **J Clin Psychiatry** 1985 May;46(5):185-7

Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Roache JD, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):120-33

Ibotenic acid lesions of the lateral hypothalamus: comparison with 6-hydroxydopamine-induced sensorimotor deficits. Dunnett SB, et al. **Neuroscience** 1985 Feb;14(2):509-18

PSYCHOPHARMACOLOGY

Fifth Italo-Soviet symposium on neuropsychopharmacology. Proceedings. Florence, November 25-26, 1983. **Ann Ist Super Sanita** 1984;20(1):1-122

Automating the measurement of locomotor activity. Beninger RJ, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):79-85

Automated measurement of multivariate locomotor behavior in rodents. Sanberg PR, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb; 7(1):87-94

Proceedings of the congress of the AGNP. Nuremberg, 1983. Abstracts. **Pharmacopsychiatry** 1985 Jan;18(1):1-177

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204-9

PSYCHOPHYSIOLOGIC DISORDERS

Psychoendocrinology and the menstrual cycle. Youngs DD, et al. **Adv Psychosom Med** 1985;12:25-34

[Auto-erythrocyte sensitization] Inbal A, et al. **Harefuah** 1984 Dec 16; 107(12):385-7 (Eng. Abstr.) **(Heb)**

[Urinary excretion of catecholamines in children with functional disorders of the digestive system] Szewczyk L, et al. **Pediatr Pol** 1984 Oct; 59(10):835-9 (Eng. Abstr.) **(Pol)**

PSYCHOSES, SUBSTANCE-INDUCED

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

[Is the combination of amphetamine and chloroquine the cause of unexpected psychological symptoms?] **Lakartidningen** 1985 May 22; 82(21):1962 **(Swe)**

PSYCHOTHERAPY

Psychological treatment for benzodiazepine dependence [letter] Tyrer P, et al. **Lancet** 1985 May 4;1(8436):1042-3

PSYCHOTIC DISORDERS

Clinical characteristics of hospitalized psychotic patients who refuse antipsychotic drug therapy. Zito JM, et al. **Am J Psychiatry** 1985 Jul; 142(7):822-6

Antipsychotic and prophylactic effects of acetazolamide (Diamox) on atypical psychosis. Inoue H, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):425-36

Emergency treatment of acute psychosis, agitation, and anxiety. Ellison JM. **Hosp Community Psychiatry** 1985 Apr;36(4):351-2

Familial differences in lithium responsive versus lithium nonresponsive psychoses. Sautter F, et al. **J Psychiatr Res** 1985;19(1):1-8

Acutely psychotic patients: a treatment approach. Wagemaker H, et al. **South Med J** 1985 Jul;78(7):833-7

[Classification of chronic psychoses types I and II and platelet serotonin levels. Apropos of 38 cases] Boudjema F, et al. **Encephale** 1985 Jan-Feb; 11(1):39-42 (Eng. Abstr.) **(Fre)**

[Lithium salts in the treatment of schizoaffective psychosis] Kopel A. **Psychiatr Pol** 1984 May-Jun;18(3):279-83 **(Pol)**

[Influence of nutritional status on intravenous pharmacokinetics of haloperidol in psychotic patients] Donoso A, et al. **Rev Med Chil** 1984 Aug;112(8):777-83 (Eng. Abstr.) **(Spa)**

QUINIDINE

Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers. Relationship to potassium and cycle length. Roden DM, et al. **Circ Res** 1985 Jun; 56(6):857-67

Kinetics and electrocardiographic changes after oral 3-OH-quinidine in healthy subjects. Vožeh S, et al. **Clin Pharmacol Ther** 1985 May; 37(5):575-81

Pharmacokinetics and pharmacodynamics of quinidine and its metabolite, quinidine-N-oxide, in beagle dogs. Rakhit A, et al. **Eur J Drug Metab Pharmacokinet** 1984 Oct-Dec;9(4):315-24

Elimination kinetic of high polar metabolites pool of quinidine from human serum. Camsonne R, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Feb;23(2):74-5

Quinidine-digoxin interaction: are the pharmacokinetics of both drugs altered? Rameis H. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar; 23(3):145-53

Competitive binding of quinidine, propranolol, and 4-OH-propranolol to human plasma very low-density (VLDL) and low-density (LDL) lipoproteins. Ho Ngoc-Ta Trung A, et al. **Pharm Acta Helv** 1985; 60(4):106-9

REACTION TIME

Reactive capacity: a sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Spirduso WW, et al. **Brain Res** 1985 May 27;335(1):45-54

RECEPTORS, ADRENERGIC

Peripheral and central adrenergic influences on brain systems involved in the modulation of memory storage. McGaugh JL. **Ann NY Acad Sci** 1985;444:150-61

Noradrenergic modulation of selective attention: its role in memory retrieval. Sara SJ. **Ann NY Acad Sci** 1985;444:178-93

Effect of chronic desipramine treatment on adrenoceptor modulation of [3H]dopamine release from rat nucleus accumbens slices. Nurse B, et al. **Brain Res** 1985 May 20;334(2):235-42

Beta 1 and beta 2 adrenergic receptors: their role in the regulation of paradoxical sleep in the rat. Lanfumey L, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):558-67

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar; 24(3):217-22

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

[Role of hypothalamic adrenoreactive structures in regulating the protective reaction to plasmin] Kalishevskaia TM, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):418-21 (Eng. Abstr.) **(Rus)**

RECEPTORS, ADRENERGIC, ALPHA

Human platelet alpha 2-adrenergic receptors: effect of Na+ on interaction with the adenylate cyclase system and on epinephrine-stimulated platelet secretion. Limbird LE, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:235-42

Catecholamine and opioid receptors, presynaptic inhibition of CNS neurotransmitter release, and adenylate cyclase. Mulder AH, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:273-86

Alpha 2-adrenoceptor antagonism of vasopressin-induced changes in sodium excretion. Smyth DD, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 2):F767-72

Thermodynamics of agonist and antagonist binding to the alpha 1-adrenoceptor studied using [125I]BE 2254. Adams A, et al. **Biochem Biophys Res Commun** 1985 Apr 30;128(2):816-23

Comparison of postnatal changes in alpha 1-adrenoceptor binding and adrenergic stimulation of phosphoinositide hydrolysis in rat cerebral cortex. Schoepp DD, et al. **Biochem Pharmacol** 1985 Aug 1; 34(15):2705-11

Platelet alpha-2-adrenergic dysfunction in negative symptom schizophrenia: a preliminary study. Rosen J, et al. **Biol Psychiatry** 1985 May;20(5):539-45

Acetylcholine release from rat atria can be regulated through an alpha 1-adrenergic receptor. Wetzel GT, et al. **Circ Res** 1985 May; 56(5):763-6

Alpha 1-adrenergic responsiveness of young adult and aged rat submandibular cells in vitro. Baum BJ, et al. **Comp Biochem Physiol** [C] 1985;81(1):121-4

Trials of serotonin, substance P and alpha 2-adrenergic receptor effects on the equine large colon. Sellers AF, et al. **Cornell Vet** 1985 Apr; 75(2):319-23

Evidence for alpha 1-adrenergic stimulatory control of in vitro release of immunoreactive thyrotropin-releasing hormone from rat median eminence: in vivo corroboration. Tapia-Arancibia L, et al. **Endocrinology** 1985 Jun;116(6):2314-9

Dopamine preferentially stimulates postsynaptic alpha 2-adrenoceptors in the femoral vascular bed, but alpha 1-adrenoceptors in the renal vascular bed of the anaesthetised dog. Duval N, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):265-72

Inhibition by 5,6-dihydroxy-2-dimethylaminotetralin (M7) of noradrenergic neurotransmission in the rabbit hypothalamus: role of alpha-2 adrenoceptors and of dopamine receptors. Galzin AM, et al. **J Pharmacol Exp Ther** 1985 May;233(2):459-65

Demonstration of an alpha adrenoceptor-mediated inotropic effect of norepinephrine in human atria. Skomedal T, et al. **J Pharmacol Exp Ther** 1985 May;233(2):441-6

Modulation of a transient outward current in serotonergic neurones by alpha 1-adrenoceptors. Aghajanian GK. **Nature** 1985 Jun 6-12; 315(6019):501-3

6-Hydroxydopamine pretreatment effects on alpha- and beta-adrenergic receptor adaptation to clorgyline. Cohen RM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):158-61

alpha 1- and beta-adrenergic receptors are co-regulated during both noradrenergic denervation and hyperinnervation. Sutin J, et al. **Neuroscience** 1985 Apr;14(4):973-80

[Dopamine-induced up-regulation of alpha 2-adrenoceptors in crude synaptic membranes of rat brain] Kohno Y, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):173-83 (Eng. Abstr.) **(Jpn)**

RECEPTORS, ADRENERGIC, BETA

Increase in serotonin2 receptor density in rat cerebral cortex slices by stimulation of beta-adrenergic receptors. Scott JA, et al. **Biochem Pharmacol** 1985 May 1;34(9):1585-8

Mechanisms of supersensitivity to sympathomimetic amines in the chronically denervated heart of the conscious dog. Vatner DE, et al. **Circ Res** 1985 Jul;57(1):55-64

Receptor mechanisms in fish chromatophores--VIII. Mediated by beta adrenoceptors, catecholamines always act to disperse pigment in siluroid melanophores. Fujii R, et al. **Comp Biochem Physiol** [C] 1985; 81(1):1-6

Why is amitriptyline much weaker than desipramine at decreasing beta-adrenoceptor numbers? Wise H, et al. **Eur J Pharmacol** 1985 Mar 26;110(1):137-41

The effect of age on beta-adrenergic function in man: a review. Ebstein RP, et al. **Isr J Med Sci** 1985 Mar;21(3):302-11

Evidence for a beta-adrenoceptor-mediated regulation of human natural killer cells. Hellstrand K, et al. **J Immunol** 1985 Jun;134(6):4095-9

Radioreceptor assay for beta-adrenergic receptor-reactive catecholamines in serum samples. Iwo K, et al. **J Lab Clin Med** 1985 Jun; 105(6):711-7

Effects of clenbuterol and antidepressant drugs on beta adrenergic receptor/N-protein coupling in the cerebral cortex of the rat. O'Donnell JM, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):30-6

Chronic thyroxine treatment of rats down-regulates the noradrenergic cyclic AMP generating system in cerebral cortex. Schmidt BH, et al. **J Pharmacol Exp Ther** 1985 May;233(2):466-72

Effects of beta-adrenoceptor antagonist administration on beta 2-adrenoceptor density in human lymphocytes. The role of the 'intrinsic sympathomimetic activity'. Brodde OE, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):417-22

6-Hydroxydopamine pretreatment effects on alpha- and beta-adrenergic receptor adaptation to clorgyline. Cohen RM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):158-61

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

alpha 1- and beta-adrenergic receptors are co-regulated during both noradrenergic denervation and hyperinnervation. Sutin J, et al. **Neuroscience** 1985 Apr;14(4):973-80

The activation of mice's behavior and reduction of brain beta-adrenergic receptor binding following repeated administration of antidepressant drugs. Nomura S, et al. **Yakubutsu Seishin Kodo** 1984 Nov; 4(3):237-41

RECEPTORS, CHOLINERGIC

Comparative effects of aprophen, atropine and benactyzine on central and peripheral cholinoceptors and on acetylcholinesterase. Dawson RM, et al. **Biochem Pharmacol** 1985 May 1;34(9):1577-9

Affinity-dependent cross-linking to neurotoxin sites of the acetylcholine receptor mediated by catechol oxidation. Nickoloff BJ, et al. **Biochemistry** 1985 Feb 12;24(4):999-1007

Blockade of cholinergic receptors in the C1 area abolishes hypertensive response to opiates in the A1 area of the ventrolateral medulla. Punnen S, et al. **Brain Res** 1985 Jun 10;336(1):180-6

Cholinergic-muscarinic receptors do not mediate growth hormone release in response to baclofen, a gamma-aminobutyric acid agonist, in humans. Coiro V, et al. **Horm Metab Res** 1985 May;17(5):260-1

High-affinity binding of [3H]acetylcholine to muscarinic cholinergic receptors. Kellar KJ, et al. **J Neurosci** 1985 Jun;5(6):1577-82

[Effect of RNAse inhibitors and activators on acetylcholine interaction with the cholinoreceptor in a tissue extract] Turpaev TM, et al. **Dokl Akad Nauk SSSR** 1985;281(2):500-2 **(Rus)**

[Possible participation of slow Na+--Ca++ channels in realizing cholinergic effects on the cardiac pacemaker] Sukhova GS, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):506-9 (Eng. Abstr.) **(Rus)**

RECEPTORS, DOPAMINE

Effect of metoclopramide, domperidone and apomorphine on GH secretion in children and adolescents. Massara F, et al. **Acta Endocrinol (Copenh)** 1985 Apr;108(4):451-5

Effect of dopamine receptor stimulation on the inhibition of LH pulsatility by a met-enkephaline (FK 33-824). del Pozo E, et al. **Acta Neurochir (Wien)** 1985;75(1-4):88-90

Age-related changes in rat brain dopaminergic receptors. Petkov VV, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):16-27

On the role of dopamine receptors in aldosterone secretion. Frisina N, et al. **Ann Endocrinol (Paris)** 1984;45(6):387-91

Dopamine D2 receptors modulate neurotransmitter-regulated calcium ion gates. Memo M, et al. **Ann Ist Super Sanita** 1984;20(1):5-10

SCH 23390 may alter dopamine-mediated motor behaviour via striatal D-1 receptors. Boyce S, et al. **Biochem Pharmacol** 1985 May 15; 34(10):1665-9

Dopamine autoreceptors and the effects of drugs on locomotion and dopamine synthesis. Brown F, et al. **Br J Pharmacol** 1985 Apr; 84(4):853-60

Rapid desensitization of presynaptic dopamine autoreceptors during exposure to exogenous dopamine. Arbilla S, et al. **Brain Res** 1985 Jun 24;337(1):11-7

The possible role of 2-hydroxyestradiol in the development of estrogen-induced striatal dopamine receptor hypersensitivity. Clopton JK, et al. **Brain Res** 1985 Apr 29;333(1):1-10

Effects of pertussis toxin on D2-dopamine receptor in rat striatum: evidence for coupling of Ni regulatory protein with D2-receptor. Fujita N, et al. **Brain Res** 1985 May 6;333(2):231-6

Dopamine receptors regulate Met-enkephalin content in pituitary. George SR, et al. **Brain Res** 1985 May 13;334(1):187-9

Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Grace AA, et al. **Brain Res** 1985 May 6; 333(2):285-98

Effect of duration of haloperidol treatment on DA receptor supersensitization in aging C57BL/6J mice. Randall PK, et al. **Brain Res** 1985 Apr 29;333(1):85-95

Regional sensitivity of neuroleptic receptors to sub-acute soman intoxication. Valdes JJ, et al. **Brain Res Bull** 1985 Feb;14(2):117-21

Dopamine: receptors and clinical applications. Goldberg LI. **Clin Physiol Biochem** 1985;3(2-3):120-6 (33 ref.)

An investigation of amphetamine-induced release of 5-HT from rat hippocampal slices. Balfour DJ, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):395-9

Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behavioural 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):253-6

Striatal synaptosomal dopamine synthesis: evidence against direct regulation by an autoreceptor mechanism. Compton DR, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):157-62

Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Creese I, et al. **Eur J Pharmacol** 1985 Feb 12; 109(1):127-8

Magnesium ions reveal nanomolar potency of dopamine at [3H]spiperone labelled D-2 receptors in rat corpus striatum. De Vries DJ, et al.

Eur J Pharmacol 1985 Mar 12;109(3):417-9

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

N-methyl,N-propargyl-2-aminotetralins:novel dopamine agonists with monoamine oxidase inhibiting properties. Hazelhoff B, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):229-40

Effect of the dopamine D-1 antagonist SCH 23390 on rotational behaviour induced by apomorphine and pergolide in 6-hydroxy-dopamine denervated rats. Herrera-Marschitz M, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):349-54

Chronic haloperidol does not alter agonist affinity for dopamine receptors in vitro. Meller E, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):389-94

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305-8

Dopamine receptor subtypes: in vivo biochemical evidence for functional interaction. Saller CF, et al. **Eur J Pharmacol** 1985 Feb 26; 109(2):297-300

Reduced sensitivity of synaptosomal dopamine autoreceptors following increase in synaptosomal dopamine synthesis. Tissari AH. **Eur J Pharmacol** 1985 Mar 12;109(3):433-4

The supersensitivity of dopaminergic neurons to apomorphine in rats following chronic haloperidol. Vogelsang GD, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):267-9

The dopamine autoreceptor agonist B-HT 920 markedly stimulates sexual behavior in male rats. Ferrari F, et al. **Experientia** 1985 May 15; 41(5):636-8

Resolution of 5,6-dihydroxy-2-(N,N-di-n-propylamino)tetralin in relation to the structural and stereochemical requirements for centrally acting dopamine agonists. Grol CJ, et al. **J Med Chem** 1985 May; 28(5):679-83

Sulpiride blocks postsynaptic dopamine receptors in the nucleus accumbens. Morgenstern R, et al. **J Neural Transm** 1985; 61(3-4):151-60

Effects of SK&F 82526 and SK&F 83742 on the renal vascular dopamine receptor. Schmidt M, et al. **J Pharmacol** 1985 Jan-Mar;16(1):15-22

Computer imaging and analysis of dopamine (D2) and serotonin (S2) binding sites in rat basal ganglia or neocortex labeled by [3H]spiroperidol. Altar CA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):527-38

Inhibition by 5,6-dihydroxy-2-dimethylaminotetralin (M7) of noradrenergic neurotransmission in the rabbit hypothalamus: role of alpha-2 adrenoceptors and of dopamine receptors. Galzin AM, et al. **J Pharmacol Exp Ther** 1985 May;233(2):459-65

Acute and subchronic effects of MJ-13859, a potential antipsychotic drug, on rat brain dopaminergic function. McMillen BA. **J Pharmacol Exp Ther** 1985 May;233(2):369-75

Inactivation of D1 and D2 dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vivo: selective protection by neuroleptics. Meller E, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):656-62

D-2 dopamine receptors in aging mouse striatum: determination of high- and low-affinity agonist binding sites. Severson JA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):361-8

Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1984-85;22(6):573-9

Dopamine inhibition of anterior pituitary adenylate cyclase is mediated through the high-affinity state of the D2 receptor. Borgundvaag B, et al. **Life Sci** 1985 Jul 29;37(4):379-86

Reserpine-induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31-8

The putative dopamine autoreceptor agonist B-HT 920 decreases nigral dopamine cell firing rate and prolactin release in rat. Eriksson E, et al. **Life Sci** 1985 May 13;36(19):1819-27

Dopamine receptor antagonists inhibit the natriuretic response to atrial natriuretic factor (ANF). Marin-Grez M, et al. **Life Sci** 1985 Jun 3; 36(22):2171-6

SCH23390 causes persistent antidopaminergic effects in vivo: evidence for longterm occupation of receptors. Schulz DW, et al. **Life Sci** 1985 May 20;36(20):1941-8

D2-dopamine receptor-mediated inhibition of cyclic AMP formation in striatal neurons in primary culture. Weiss S, et al. **Mol Pharmacol** 1985 Jun;27(6):595-9

Unexpected potentiation by discriminant benzamide derivatives of stereotyped behaviours elicited by dopamine agonists in mice. Vasse M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):108-16

Effect of gestational and neonatal styrene exposure on dopamine receptors. Zaidi NF, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):23-8

The effects of neurotensin and [D-Tyr11]-NT on the hyperactivity induced by intra-accumbens administration of a potent dopamine receptor agonist. Jolicoeur FB, et al. **Neuropeptides** 1985 Apr; 6(2):143-56

The continuity of dopamine receptor antagonism can dictate the long-term behavioural consequences of a mesolimbic infusion of dopamine. Costall B, et al. **Neuropharmacology** 1985 Mar;24(3):193-7

Striatal topography of D-2 receptors correlates with indexes of cholinergic neuron localization. Joyce JN, et al. **Neurosci Lett** 1985 Jan 7;53(1):127-31

Lack of effect of intranigral administration of a dopamine analogue, (+/-)-3-(3-hydroxyphenyl)-N,n-propylpiperidine [(+/-)-3-PPP], on nigrostriatal dopamine neurones. Kelly E, et al. **Neurosci Lett** 1985 May 1;56(1):57-62

Regulation of dopamine release by impulse flow and by autoreceptors as studied by in vivo voltammetry in the rat striatum. Gonon FG, et al. **Neuroscience** 1985 Mar;14(3):765-74

Increased investigative activity after presynaptic dopaminergic stimulation measured by a fixed-interval recording procedure. Höglund AU, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):403-6

Effect of chronic apomorphine on the development of denervation supersensitivity. Robin M, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):547-51

Effects of selective dopamine receptor agonists in rats trained to discriminate apomorphine from saline. Woolverton WL, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):577-81

Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. Farde L, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3863-7

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346-52

Characterization of the bupropion cue in the rat: lack of evidence for a dopaminergic mechanism. Blitzer RD, et al. **Psychopharmacology (Berlin)** 1985;85(2):173-7

Chronic haloperidol during development attenuates dopamine autoreceptor function in striatal and mesolimbic brain regions of young and older adult rats. Scalzo FM, et al. **Psychopharmacology (Berlin)** 1985;85(3):271-6

Differential effects of dopamine D-1 and D-2 agonists and antagonists in 6-hydroxydopamine-lesioned rats. Arnt J. **Psychopharmacology [Suppl]** 1985;2:60-1

Intermittent treatment with droperidol, a short-acting neuroleptic, increases behavioral dopamine receptor sensitivity. Belmaker RH, et al. **Psychopharmacology [Suppl]** 1985;2:194-9

Pharmacological differentiation of dopamine D-1 and D-2 antagonists after single and repeated administration. Christensen AV, et al. **Psychopharmacology [Suppl]** 1985;2:182-90

Receptor-binding profiles of neuroleptics. Hyttel J, et al. **Psychopharmacology [Suppl]** 1985;2:9-18

Differential alteration of striatal D-1 and D-2 receptors induced by the long-term administration of haloperidol, sulpiride or clozapine to rats. Jenner P, et al. **Psychopharmacology [Suppl]** 1985;2:174-81

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

Influence of GABA mimetics and lithium on biochemical manifestations of striatal dopamine target cell hypersensitivity. Scatton B, et al. **Psychopharmacology [Suppl]** 1985;2:39-45

Functional classification of different dopamine receptors. Ungerstedt U, et al. **Psychopharmacology [Suppl]** 1985;2:19-30

Effect of dopamine and dopamine-receptor blockade on in vitro renin release, tissue renin content and tissue cyclic AMP content in the rat. López GA, et al. **Rev Esp Fisiol** 1985 Mar;41(1):95-100

[Continuous suppression of methamphetamine-induced supersensitivity by chronic haloperidol administration] Kashihara K, et al. **Seishin Shinkeigaku Zasshi** 1984;86(11):928-32 **(Jpn)**

[Role of serotonin and dopamine receptors in the mechanism of action of haloperidol and pirenperone] Maimets MO, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):15-8 (Eng Abstr.) **(Rus)**

RECEPTORS, DRUG

Synthesis and structure-activity studies on excitatory amino acids structurally related to ibotenic acid. Krogsgaard-Larsen P, et al. **J Med Chem** 1985 May;28(5):673-9

RECEPTORS, ENDOGENOUS SUBSTANCES

Adenosine, adenylate cyclase, and transmitter release. Phillis JW, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:243-57 (81 ref.)

Endocrine-mediated parallel changes in hepatic glucocorticoid and prolactin receptors. Dave JR, et al. **Biochim Biophys Acta** 1985 May 30;845(2):276-82

Regulation of infant and developing rat testicular gonadotropin and prolactin receptors and steroidogenesis by treatments with human chorionic gonadotropin, gonadotropin-releasing hormone analogs, bromocriptine, prolactin, and estrogen. Huhtaniemi IT, et al. **Biol Reprod** 1985 May;32(4):721-32

Somatostatin-14 and somatostatin-28 pretreatment down-regulate somatostatin-14 receptors and have biphasic effects on forskolin-stimulated cyclic adenosine, 3',5'-monophosphate synthesis and adrenocorticotropin secretion in mouse anterior pituitary tumor cells. Heisler S, et al. **Endocrinology** 1985 Jul;117(1):217-25

The frequency of gonadotropin-releasing hormone stimulation determines the number of pituitary gonadotropin-releasing hormone receptors. Katt JA, et al. **Endocrinology** 1985 May;116(5):2113-5

Tunicamycin and neuraminidase effects on luteinizing hormone (LH)-releasing hormone binding and LH release from rat pituitary cells in culture. Schvartz I, et al. **Endocrinology** 1985 Jun;116(6):2341-6

Interaction of growth hormone-releasing factor (GRF) and 14 GRF analogs with vasoactive intestinal peptide (VIP) receptors of rat pancreas. Discovery of (N-Ac-Tyr1,D-Phe2)-GRF(1-29)-NH2 as a VIP antagonist. Waelbroeck M, et al. **Endocrinology** 1985 Jun; 116(6):2643-9

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

3,5,3'-Triiodothyronine receptors and thyroxine 5'-monodeiodinating activity in thyroid hormone-insensitive amphibia. Galton VA. **Gen Comp Endocrinol** 1985 Mar;57(3):465-71

A unique control mechanism in the regulation of insulin secretion. Secretagogue-induced somatostatin receptor recruitment. Draznin B, et al. **J Clin Invest** 1985 May;75(5):1510-6

Neuropeptides and their receptors: a psychosomatic network. Pert CB, et al. **J Immunol** 1985 Aug;135(2 Suppl):820s-826s

Evolutionary origins of neuropeptides, hormones, and receptors: possible applications to immunology. Roth J, et al. **J Immunol** 1985 Aug; 135(2 Suppl):816s-819s

Localization of somatostatin receptors in secretion vesicles in anterior pituitary cells and pancreatic islets. Draznin B, et al. **J Recept Res** 1985; 5(1):83-103

Photoaffinity labelling of MSH receptors on Anolis melanophores: effects of catecholamines, calcium and forskolin. Eberle AN, et al. **J Recept Res** 1985;5(1):59-81

Changes in pituitary and ovarian LHRH receptors after active immunization of female rats against LH or LHRH. Popkin RM, et al. **J Reprod Fertil** 1985 Mar;73(2):491-6

Newborn and immature rat testes contain gonadotropin-releasing hormone (GnRH) receptors, and their testosterone production is stimulated by a GnRH agonist in vitro. Huhtaniemi IT, et al. **Mol Cell Endocrinol** 1985 Apr;40(1):41-4

Receptor-mediated degradation of human growth hormone in rat adipocytes and cultured human lymphocytes (IM-9). Weyer B, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):85-92

Increased gonadotrophin releasing hormone receptors on pituitary gonadotrophs: effect on subsequent LH secretion. Young LS, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):69-78

Treatment of rats with the TRH analog MK-771. Down-regulation of TRH receptors and behavioral tolerance. Simasko SM, et al. **Neuropharmacology** 1985 Feb;24(2):157-65

Products of cholecystokinin (CCK)-octapeptide proteolysis interact with central CCK receptors. Steardo L, et al. **Neurosci Lett** 1985 Mar 15; 54(2-3):319-25

Somatostatin analogs: correlation of receptor affinity with inhibition of cyclic AMP formation in pancreatic acinar cells. Taparel D, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):109-14

Up-regulation of thyrotropin-releasing hormone (TRH) receptors in rat spinal cord after codepletion of serotonin and TRH. Ogawa N, et al. **Regul Pept** 1985 Mar;10(2-3):85-90

RECEPTORS, ENDORPHIN

Catecholamine and opioid receptors, presynaptic inhibition of CNS neurotransmitter release, and adenylate cyclase. Mulder AH, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:273-86

Effects of tifluadom on passive avoidance behaviour in DBA/2 mice. Pavone F, et al. **Behav Brain Res** 1985 May;15(3):177-81

Modification of opioid ligand binding in the central and the peripheral nervous system by different buffers. Bourhim N, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):328-33

Central nervous system opiate and 5-hydroxytryptamine influences on baroreflex control of the coronary circulation. Moore PG, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):185-94

Mu1: a very high affinity subtype of enkephalin binding sites in rat brain. Lutz RA, et al. **Life Sci** 1985 Jun 10;36(23):2233-8

Characterization of rat brain opioid receptors by [Tyr-3,5-3H]1, D-Ala2, Leu5-enkephalin binding. Benyhe S, et al. **Neurochem Res** 1985 May; 10(5):627-35

Studies in vitro with ICI 174,864, [D-Pen2. D-Pen5]-enkephalin (DPDPE) and [D-Ala2, NMePhe4, Gly-ol]-enkephalin (DAGO). Hirning LD, et al. **Neuropeptides** 1985 Feb;5(4-6):383-6

Postnatal development of opioid systems in rat brain. Loughlin SE, et al. **Neuropeptides** 1985 Feb;5(4-6):469-72

The interaction of the two isomers of the opioid benzodiazepine tifluadom with mu-, delta-, and kappa-binding sites and their analgesic and intestinal effects in rats. Petrillo P, et al. **Neuropeptides** 1985 Feb; 5(4-6):403-6

Opiate receptor-mediated chemotaxis of human monocytes. Ruff MR, et al. **Neuropeptides** 1985 Feb;5(4-6):363-6

Opiate and histamine H1 receptors are present on some substance P-containing dorsal root ganglion cells. Ninkovic M, et al. **Neurosci Lett** 1985 Jan 7;53(1):133-7

Astrocyte opioid receptors: activation modifies the noradrenaline-evoked increase in 2-[14C]deoxyglucose incorporation into glycogen. Pearce B, et al. **Neurosci Lett** 1985 Apr 9;55(2):157-60

Acupuncture analgesia [letter] Han JS. **Pain** 1985 Mar;21(3):307-10

Binding characteristics of dermorphin, and [dermorphin1-7]-beta c-endorphin in rat brain membranes. Westphal M, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):149-52

[The nature of cation-binding groups in binding sites for [[3H]Tyr1, D-Ala2, D-Leu5]enkephalin] Zaitsev SV, et al. **Bioorg Khim** 1985 Feb; 11(2):153-61 (Eng. Abstr.) **(Rus)**

RECEPTORS, GABA-BENZODIAZEPINE

Foot shock-induced decrease of low affinity GABA receptors in the rat brain: antagonism by diazepam. Concas A, et al. **Ann Ist Super Sanita** 1984;20(1):53-6

Central effects of nicotinamide and inosine which are not mediated through benzodiazepine receptors. Bold JM, et al. **Br J Pharmacol** 1985 Mar;84(3):689-96

Prenatal exposure to diazepam results in enduring reductions in brain receptors and deep slow wave sleep. Livezey GT, et al. **Brain Res** 1985 May 20;334(2):361-5

Specific [3H]gamma-aminobutyric acid binding to vestibular membranes of the chick inner ear. Meza G, et al. **Brain Res** 1985 Jun 24; 337(1):179-83

Differential modulation of gamma-aminobutyric acid receptors by caprolactam derivatives with central nervous system depressant or convulsant activity. Skerritt JH, et al. **Brain Res** 1985 Apr 8; 331(2):225-33

Heterogeneity of brain benzodiazepine receptors: effects of physiological conditions. Lippa AS, et al. **Brain Res Bull** 1985 Feb;14(2):189-95

Pharmacological evidence that the non-neuronal diazepam binding site in primary cultures of glial cells is associated with a calcium channel. Bender AS, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):287-8

Benzodiazepine receptor photoaffinity labeling: correlation of function with binding. Gibbs TT, et al. **Eur J Pharmacol** 1985 Apr 2; 110(2):171-80

Spontaneous and RO 15-1788-induced reversal of subsensitivity to GABA following chronic benzodiazepines. Gonsalves SF, et al. **Eur J Pharmacol** 1985 Apr 2;110(2):163-70

Synthesis and interaction of 5-(substituted-phenyl)-3-methyl-6,7-dihydropyrazolo[4,3-e] [1,4]diazepin-8(7H)-ones with benzodiazepine receptors in rat cerebral cortex. Baraldi PG, et al. **J Med Chem** 1985 May;28(5):683-5

3-Amino-beta-carboline derivatives and the benzodiazepine receptor. Synthesis of a selective antagonist of the sedative action of diazepam. Dodd RH, et al. **J Med Chem** 1985 Jun;28(6):824-8

gamma-Aminobutyric acid: temperature dependence in benzodiazepine receptor binding. Chweh AY, et al. **J Neurochem** 1985 Jul; 45(1):240-3

Triazolam, an anomalous benzodiazepine receptor ligand: in vitro characterization of alprazolam and triazolam binding. Clow A, et al. **J Neurochem** 1985 Aug;45(2):621-5

Differential degradation of different benzodiazepine binding proteins by incubation of membranes from cerebellum or hippocampus with trypsin. Eichinger A, et al. **J Neurochem** 1985 Jul;45(1):219-26

Radiation inactivation studies of the benzodiazepine/gamma-aminobutyric acid/chloride ionophore receptor complex. Schwartz RD, et al. **J Neurochem** 1985 Jul;45(1):108-15

'Peripheral-type' binding sites for benzodiazepines in brain: relationship to the convulsant actions of Ro 5-4864. Weissman BA, et al. **J Neurochem** 1985 May;44(5):1494-9

Effects of acute and chronic treatment on the pro- and anti-convulsant actions of CL 218, 872, PK 8165 and PK 9084, putative ligands for the benzodiazepine receptor. File SE, et al. **J Pharm Pharmacol** 1985 Apr;37(4):252-6

Daily rhythms of benzodiazepine receptor numbers in frontal lobe and cerebellum of the rat. Brennan MJ, et al. **Life Sci** 1985 Jun 17; 36(24):2333-7

Prenatal stress impairs maternal behavior in a conflict situation and reduces hippocampal benzodiazepine receptors. Fride E, et al. **Life Sci** 1985 Jun 3;36(22):2103-9

Reduction of GABAB receptor binding induced by climbing fiber degeneration in the rat cerebellum. Kato K, et al. **Life Sci** 1985 Jul 22;37(3):279-88

The effects of benzodiazepines on spinal homosynaptic depression. Davies MF, et al. **Neuropharmacology** 1985 Apr;24(4):301-7

The influence of bicarbonate ions on the GABA-mimetic activity of ethylenediamine. Hill DR. **Neuropharmacology** 1985 Feb;24(2):147-55

Parallel changes in the sensitivity of gamma-aminobutyric acid and noradrenergic receptors following chronic administration of antidepressant and GABAergic drugs. A possible role in affective disorders. Suzdak PD, et al. **Neuropharmacology** 1985 Mar; 24(3):217-22

gamma-Aminobutyric acid modulation of benzodiazepine receptor binding in vitro does not predict the pharmacologic activity of all benzodiazepine receptor ligands. Chweh AY, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):173-7

Are the anxiogenic effects of yohimbine mediated by its action at benzodiazepine receptors? Pellow S, et al. **Neurosci Lett** 1985 Mar 22; 55(1):5-9

Autoreceptors regulate gamma-[3H]aminobutyric acid release from the guinea pig small intestine. Taniyama K, et al. **Neurosci Lett** 1985 Apr 9;55(2):245-8

On the location of gamma-aminobutyrate and benzodiazepine receptors in the cerebellum of the normal C3H and Lurcher mutant mouse. Fry JP, et al. **Neuroscience** 1985 Apr;14(4):1091-101

Pharmacology of benzodiazepine antagonists. Haefely W. **Pharmacopsychiatry** 1985 Jan;18(1):163-6

The anxiolytic activity of beta-carboline derivatives in mice, and its separation from ataxic properties. Stephens DN, et al. **Pharmacopsychiatry** 1985 Jan;18(1):167-70

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: punished barpressing. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;85(2):244-51

RECEPTORS, SEROTONIN

Increase in serotonin2 receptor density in rat cerebral cortex slices by stimulation of beta-adrenergic receptors. Scott JA, et al. **Biochem Pharmacol** 1985 May 1;34(9):1585-8

Tryptamine-induced vasoconstrictor responses in rat caudal arteries are mediated predominantly via 5-hydroxytryptamine receptors. Bradley PB, et al. **Br J Pharmacol** 1985 Apr;84(4):919-25

A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT1 and 5-HT2 receptors. Goodwin GM, et al. **Br J Pharmacol** 1985 Mar;84(3):743-53

Serotonin release in human cerebral cortex and its modulation via serotonin receptors. Schlicker E, et al. **Brain Res** 1985 Apr 8; 331(2):337-41

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

A molecular theory of recognition and activation at a 5-HT receptor based on a quantum chemical approach to structure activity relationships. Osman R, et al. **Clin Physiol Biochem** 1985;3(2-3):80-8

Acute and chronic phencyclidine administration changes serotonin receptors in rat brain. Nabeshima T, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):129-30

Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Shenker A, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):427-9

The enteric neural receptor for 5-hydroxytryptamine. Gershon MD, et al. **Experientia** 1985 Jul 15;41(7):863-8

Evidence that phospholipid turnover is the signal transducing system coupled to serotonin-S2 receptor sites. de Chaffoy de Courcelles D, et al. **J Biol Chem** 1985 Jun 25;260(12):7603-8

5-Hydroxytryptamine stimulates inositol phosphate production in a cell-free system from blowfly salivary glands. Evidence for a role of GTP in coupling receptor activation to phosphoinositide breakdown. Litosch I, et al. **J Biol Chem** 1985 May 10;260(9):5464-71

Bioactive conformation of 1-arylpiperazines at central serotonin receptors. Huff JR, et al. **J Med Chem** 1985 Jul;28(7):945-8

Cardiovascular effects in the Sprague-Dawley rat of 8-hydroxy-2(di-N-propylamino) tetralin, a selective 5-hydroxytryptamine receptor agonist. Gradin K, et al. **J Pharm Pharmacol** 1985 Apr;37(4):263-5

Computer imaging and analysis of dopamine (D2) and serotonin (S2) binding sites in rat basal ganglia or neocortex labeled by [3H]spiroperidol. Altar CA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):527-38

5-Hydroxytryptamine receptor in isolated rabbit aorta: characterization with tryptamine analogs. Clancy BM, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):761-9

5-Hydroxytryptamine-stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: pharmacological characterization and effects of antidepressants. Kendall DA, et al. **J Pharmacol Exp Ther** 1985 May; 233(2):473-9

Do D 600 and diltiazem interact with serotonin receptors in rabbit vascular tissues? Ohashi M, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):830-5

Receptor-binding properties in vitro and in vivo of ritanserin: A very potent and long acting serotonin-S2 antagonist. Leysen JE, et al. **Mol Pharmacol** 1985 Jun;27(6):600-11

Decreased 5-HT2 but not 5-HT1 receptor binding in cortex of rat after chronic administration of dothiepin. Application of the Woolf plot to analysis of binding parameters. Diggory GL, et al. **Neuropharmacology** 1985 Apr;24(4):275-8

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

[Central serotonin receptors] Fillion G. **Pathol Biol (Paris)** 1985 Apr; 33(4):221-6 (56 ref.) **(Fre)**

[Structure of the binding center of the serotonin S2 receptor] Kats MM. **Biol Nauki** 1985;(3):19-24 (Eng. Abstr.) **(Rus)**

[pH changes in the matrix of serotonin organelles of stimulated thrombocytes] Kozlov VK, et al. **Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR** 1985; 8(1):77-82 (Eng. Abstr.) **(Rus)**

[Role of serotonin and dopamine receptors in the mechanism of action of haloperidol and pirenperone] Maimets MO, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):15-8 (Eng. Abstr.) **(Rus)**

REFLEX

Anterior hypothalamic lesions impair reflex bradycardia selectively in rats. Miyajima E, et al. **Am J Physiol** 1985 Jun;248(6 Pt 2):H937-44

The role of substance P as a neurotransmitter in the reflexes of slow time courses in the neonatal rat spinal cord. Akagi H, et al. **Br J Pharmacol** 1985 Mar;84(3):663-73

Attenuation of the reflex pressor response to muscular contraction by a substance P antagonist. Kaufman MP, et al. **Brain Res** 1985 Apr 29; 333(1):182-4

Effects of catecholamines on spinal motoneurones and spinal reflex discharges in the isolated spinal cord of the newborn rat. Kitazawa T, et al. **Brain Res** 1985 Mar;351(1):31-6

Effects of enkephalin and 5-hydroxytryptamine on solitary tract neurones involved in respiration and respiratory reflexes. Sessle BJ, et al. **Brain Res** 1985 Feb 18;327(1-2):221-30

Arterial and cardiopulmonary reflexes in the regulation of the neurohumoral drive to the circulation. Bishop VS, et al. **Fed Proc** 1985 May;44(8):2377-81 (31 ref.)

Central nervous system opiate and 5-hydroxytryptamine influences on baroreflex control of the coronary circulation. Moore PG, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):185-94

Central nervous system 5-hydroxytryptamine and noradrenaline specificity of ear vascular and ventilation reflexes in thermoregulating rabbits. White SW, et al. **J Auton Nerv Syst** 1985 Feb-Mar; 12(2-3):131-44

Kinetics of drug action in disease states. XIII. Effect of dialyzable component(s) of uremic blood on phenobarbital concentrations in rats at onset of loss of righting reflex. Hisaoka M, et al. **J Pharmacol Exp Ther** 1985 Jul;234(1):180-3

Reflex changes in sympatho-adrenal medullary functions in response to various thermal cutaneous stimulations in anesthetized rats. Kurosawa M, et al. **Neurosci Lett** 1985 May 14;56(2):149-54

Effects of glutamate, substance P and eledoisin-related peptide on solitary tract neurones involved in respiration and respiratory reflexes. Henry JL, et al. **Neuroscience** 1985 Mar;14(3):863-73

Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. Gramling SE, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):541-5

Possible involvement of central adrenergic and histaminergic systems in clonidine-induced inhibition of pinna reflex. Singh PP, et al. **Pharmacol Res Commun** 1985 Mar;17(3):261-9

[Role of hypothalamic adrenoreactive structures in regulating the protective reaction to plasmin] Kalishevskaia TM, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):418-21 (Eng. Abstr.) **(Rus)**

[Analysis of the factors affecting cardiac output in exclusion of the sino-carotid reflexogenic area] Osadchii LI, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):500-5 (Eng. Abstr.) **(Rus)**

RESERPINE

Effects of reserpine and isoproterenol on elemental distribution in submandibular gland of rat. Müller RM, et al. **Acta Physiol Scand** 1985 Apr;123(4):383-91

The chronically reserpinized rat: decreased glycolytic activity in the submandibular gland. Bardon A, et al. **Biochem Med** 1985 Feb; 33(1):99-103

Effect of chronic reserpine and desmethylimipramine treatment on CRF-like immunoreactivity of discrete brain areas of rat. Tizabi Y, et al. **Brain Res** 1985 Jun 3;335(2):389-91

Catecholamine hormones and the control of avian salt glands. Wilson JX, et al. **Comp Biochem Physiol [C]** 1985;81(1):77-9

Reserpine toxicosis in a horse. Lloyd KC, et al. **J Am Vet Med Assoc** 1985 May 1;186(9):980-1

Reserpine-induced hypothermia and its reversal by dopamine agonists. Danielson TJ, et al. **Life Sci** 1985 Jul 8;37(1):31-8

Amphetamine induced release of endogenous dopamine in vitro is not

best copy available

reduced following pretreatment with reserpine. Niddam R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr;329(2):123-7

Effects of lithium in vitro on noradrenaline-induced cyclic AMP accumulation in rat cortical slices after reserpine-induced supersensitivity. Newman ME, et al. **Neuropharmacology** 1985 Apr; 24(4):353-5

Developmental status of sympathetic innervation in relation to calcium accumulation by submandibular gland following reserpine, surgical sympathectomy or cyclocytidine. Schneyer CA, et al. **Proc Soc Exp Biol Med** 1985 Jun;179(2):143-6

Effects of reserpine and adrenal demedullation on brown adipose tissue thermogenesis induced by dl-phenylpropanolamine. Wellman PJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Feb;47(2):211-20

RUBIDIUM

Stimulus-secretion coupling of parathyroid hormone release: studies of 45Ca and 86Rb fluxes. Wallfelt C, et al. **Acta Physiol Scand** 1985 Jun; 124(2):239-45

Occlusion of Rb+ by detergent-solubilized (Na+ + K+)-ATPase from shark salt glands. Esmann M. **Biochim Biophys Acta** 1985 May 14; 815(2):196-202

Effects of chronic LiCl and RbCl on muricide induced by midbrain raphe lesions in rats. Yamamoto T, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):559-63

SCHIZOPHRENIA

Differential response to amphetamine in schizophrenia. Cesarec Z, et al. **Acta Psychiatr Scand** 1985 May;71(5):523-38

Biochemical theories of schizophrenia and depression. Hollister LE. **Ann Acad Med Singapore** 1985 Jan;14(1):76-80

Creatine phosphokinase and schizophrenia in Singapore. Tsoi WF, et al. **Ann Acad Med Singapore** 1985 Jan;14(1):84-6

The interpretation of plasma haloperidol concentrations. Kirch DG, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):838-40

Plasma haloperidol levels: clinical response and fancy mathematics [letter] Van Putten T, et al. **Arch Gen Psychiatry** 1985 Aug;42(8):835-8

Ceruletide for schizophrenia: a double-blind study. Mattes JA, et al. **Biol Psychiatry** 1985 May;20(5):533-8

Platelet alpha-2-adrenergic dysfunction in negative symptom schizophrenia: a preliminary study. Rosen J, et al. **Biol Psychiatry** 1985 May;20(5):539-45

Electroconvulsive therapy and schizophrenia. Van Valkenburg C, et al. **Biol Psychiatry** 1985 Jul;20(7):699-700

Schizophrenia with good and poor outcome. I: Early clinical features, response to neuroleptics and signs of organic dysfunction. Kolakowska T, et al. **Br J Psychiatry** 1985 Mar;146:229-39

Schizophrenia with good and poor outcome. II: Cerebral ventricular size and its clinical significance. Williams AO, et al. **Br J Psychiatry** 1985 Mar;146:239-46

Lipids and apolipoproteins in patients treated with major tranquilizers. Sasaki J, et al. **Clin Pharmacol Ther** 1985 Jun;37(6):684-7

Bioavailability of oral and intramuscular molindone hydrochloride in schizophrenic patients. Zetin M, et al. **Clin Ther** 1985;7(2):169-75

Platelet monoamine-oxidase activity in schizophrenia. Relation to genetic load of the illness and treatment with antipsychotic drugs. Kemali D, et al. **Encephale** 1985 Jan-Feb;11(1):31-4

Abnormal phosphatidylinositol-cycle of platelet membrane in schizophrenia--a preliminary study. Kaiya H, et al. **Folia Psychiatr Neurol Jpn** 1984;38(4):437-41

Positron emission tomography in schizophrenic patients with and without neuroleptic medication. DeLisi LE, et al. **J Cereb Blood Flow Metab** 1985 Jun;5(2):201-6

Drugs and the quality of life: the patient's point of view. Diamond R. **J Clin Psychiatry** 1985 May;46(5 Pt 2):29-35

Serum neuroleptic levels and clinical outcome in schizophrenic patients treated with fluphenazine decanoate. Brown WA, et al. **J Clin Psychopharmacol** 1985 Jun;5(3):143-7

Problems in classification of schizophrenics as neuroleptic responders and nonresponders. Csernansky JG, et al. **J Nerv Ment Dis** 1985 Jun; 173(6):325-31 (93 ref.)

Lower CSF level of dynorphin(1-8) immunoreactivity in schizophrenic patients. Zhang AZ, et al. **Neuropeptides** 1985 Feb;5(4-6):553-6

State of adrenergic and cholinergic systems in schizophrenia patients during psychopharmacotherapy. Krupenina LB, et al. **Neurosci Behav Physiol** 1985 Jan-Feb;15(1):1-8

One-year outcome of schizophrenic patients--the interaction of chronicity and neuroleptic treatment. Gaebel W, et al. **Pharmacopsychiatry** 1985 May;18(3):235-9

Double-blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. Kissling W, et al. **Pharmacopsychiatry** 1985 May;18(3):240-5

Serum and cerebrospinal fluid prolactin patterns during neuroleptic treatment in schizophrenic patients. Rimón R, et al. **Pharmacopsychiatry** 1985 May;18(3):252-4

Cerebrospinal fluid cholecystokinin, bombesin and somatostatin in schizophrenia and normals. Gerner RH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):73-82

Delta-sleep inducing peptide in cerebrospinal fluid from schizophrenics, depressives and healthy volunteers. Lindström LH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):83-90

Binding of 3H-spiperone to human lymphocytes: a biological marker in schizophrenia? Bondy B, et al. **Psychiatry Res** 1985 May;15(1):41-8

Serotonin and schizophrenia: correlations between serotonergic activity and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Lateral ventricular enlargement and clinical response in schizophrenia. Smith RC, et al. **Psychiatry Res** 1985 Mar;14(3):241-53

Amphetamine response and relapse risk after depot neuroleptic discontinuation. Angrist B, et al. **Psychopharmacology (Berlin)** 1985; 85(3):277-83

A limiting factor in the 'normalization' of schizophrenic orienting response dysfunction. Bernstein AS, et al. **Schizophr Bull** 1985;11(2):230-54

Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. Goldberg E. **Schizophr Bull** 1985;11(2):255-63

[Treatment of schizophrenia without symptoms with viloxazine (letter)] Kornhuber HH, et al. **Dtsch Med Wochenschr** 1985 Apr 26; 110(17):698 **(Ger)**

[Social integration of long-term paraphrenic patients with low-dose depot neuroleptic medication] Lesch OM, et al. **Psychiatr Prax** 1985 Mar; 12(2):63-8 (Eng. Abstr.) **(Ger)**

[Neurotransmitters and neuropeptides in schizophrenia] Toru M, et al. **Tanpakushitsu Kakusan Koso** 1984 Dec;29(14):1838-54 (150 ref.) **(Jpn)**

[Asymmetry of cholinesterase activity in cortical centers of human cerebral hemispheres] Kononenko VS, et al. **Fiziol Zh** 1985 Mar-Apr; 31(2):134-8 (Eng. Abstr.) **(Rus)**

SCHIZOPHRENIA, CATATONIC

Treatment-resistant catatonic stupor and combined lithium-neuroleptic therapy: a case report. Climo LH. **J Clin Psychopharmacol** 1985 Jun; 5(3):166-70

SCHIZOPHRENIA, PARANOID

Effects of thioridazine and fluphenazine on the pituitary, thyroid and adrenal functions in patients with paranoid schizophrenia. Horodnicki JM, et al. **Psychiatr Pol** 1984 May-Jun;18(3):205-11

[Haloperidol decanoate in replacing combinations of antipsychotic agents in the treatment of chronic schizophrenics] Youssef HA. **Acta Psiquiatr Psicol Am Lat** 1984 Dec;30(4):297-304 **(Spa)**

SELF STIMULATION

6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Hand TH, et al. **Brain Res** 1985 Mar 4;328(2):233-41

Comparison of deficits in electrical self-stimulation after ibotenic acid lesion of the lateral hypothalamus and the medial prefrontal cortex. Nassif S, et al. **Brain Res** 1985 Apr 22;332(2):247-57

Lateral hypothalamic self-stimulation persists in rats after destruction of lateral hypothalamic neurons by kainic acid or ibotenic acid. Sprick U, et al. **Neurosci Lett** 1985 May 14;56(2):211-6

Effects of intracranial self-stimulation on brain opioid peptides. Stein EA. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):67-73

Differential effects of pimozide on response-rate and choice accuracy in a self-stimulation paradigm in mice. Bowers W, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):521-6

The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: effects of d-amphetamine, morphine, and haloperidol. Schaefer GJ, et al. **Psychopharmacology (Berlin)** 1985; 85(3):289-94

SEROTONIN

Patency of saphenous veins used for aortocoronary bypass grafting: effects of platelet-derived mediators. Chiavarelli M, et al. **Adv Prostaglandin Thromboxane Leukotriene Res** 1985;13:311-4

The effect of stimulation and blocking of histamine H2 receptors on the turnover of the serotonin in different parts of the alimentary tract and the brain of the rat. Skrzydlo-Radomańska B, et al. **Agents Actions** 1985 Apr;16(3-4):183-6

An immunohistochemical study of serotonin development in the opossum cerebellum. Bishop GA, et al. **Anat Embryol (Berl)** 1985; 171(3):325-38

Mediation of storage and retrieval with two drugs that selectively modulate serotonergic neurotransmission. Altman HJ. **Ann NY Acad Sci** 1985;444:496-8

6R-L-erythro-5,6,7,8-tetrahydrobiopterin as a regulator of dopamine and serotonin biosynthesis in the rat brain. Miwa S, et al. **Arch Biochem Biophys** 1985 May 15;239(1):234-41

Effect of amines on fibrinogen synthesis. Roy AK, et al. **Arch Biochem Biophys** 1985 Jun;239(2):364-7

Influence of chronic stellectomy on reactivity to serotonin in the dog external carotid bed. Mena MA, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):110-6

Human prostatic endocrine-paracrine (APUD) cells. Distributional analysis with a comparison of serotonin and neuron-specific enolase immunoreactivity and silver stains. di Sant'Agnese PA, et al. **Arch Pathol Lab Med** 1985 Jul;109(7):607-12

Differential release of serotonin without comparable histamine under diverse conditions in the rat mast cell. Theoharides TC, et al. **Biochem Pharmacol** 1985 May 1;34(9):1389-98

Endogenous platelet serotonin release monitored during aggregation by means of a new electrochemical technique. Marcenac F, et al. **Biochim Biophys Acta** 1985 Jul 5;840(3):377-82

The distribution and origin of serotonin immunoreactivity in the rat cerebellum. Bishop GA, et al. **Brain Res** 1985 Apr 8;331(2):195-207

Differential responses of serotonergic and non-serotonergic neurons in nucleus raphe magnus to systemic morphine in rats. Chiang CY, et al. **Brain Res** 1985 Jun 24;337(1):146-50

Ontogenetic development of serotoninergic neurons in the brain of a teleost, the three-spined stickleback. An immunohistochemical analysis. Ekstrom P, et al. **Brain Res** 1985 Jan;349(1-2):209-24

Serotonin depolarizes type A and C primary afferents: an intracellular study in bullfrog dorsal root ganglion. Holz IV GG, et al. **Brain Res** 1985 Feb 18;327(1-2):71-9

Enhancement of some 5-HT-dependent behavioural responses following repeated immobilization in rats. Kennett GA, et al. **Brain Res** 1985 Mar 25;330(2):253-63

Decreased serotonin content of embryonic raphe neurons following maternal administration of p-chlorophenylalanine: a quantitative immunocytochemical study. Lauder JM, et al. **Brain Res** 1985 May;352(1):107-14

Inhibitory influence of GABA on central serotonergic transmission. Raphe nuclei as the neuroanatomical site of the GABAergic inhibition of cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):91-103

Inhibitory influence of GABA on central serotonergic transmission. Involvement of the habenulo-raphe pathways in the GABAergic inhibition of ascending cerebral serotonergic neurons. Nishikawa T, et al. **Brain Res** 1985 Apr 1;331(1):81-90

Serotonin release in human cerebral cortex and its modulation via serotonin receptors. Schlicker E, et al. **Brain Res** 1985 Apr 8;331(2):337-41

Effects of enkephalin and 5-hydroxytryptamine on solitary tract neurones involved in respiration and respiratory reflexes. Sessle BJ, et al. **Brain Res** 1985 Feb 18;327(1-2):221-30

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

Ontogenetic alterations in the effects of food and/or maternal deprivation on 5-HT, 5-HIAA and 5-HIAA/5-HT ratios. Spear LP, et al. **Brain Res** 1985 Feb;350(1-2):143-57

Characterization of sodium-dependent, high-affinity serotonin uptake in rat spinal cord synaptosomes. Stauderman KA, et al. **Brain Res** 1985 Mar 18;330(1):11-20

Denervation supersensitivity to 5-hydroxytryptamine in the rat spinal cord is not due to the absence of 5-hydroxytryptamine. Tremblay LE, et al. **Brain Res** 1985 Mar 18;330(1):174-7

Immunocytochemical and radioautographic study of serotonin projections to cerebral ventricles of perinatal rats. Ugrumov MV, et al. **Brain Res** 1985 Feb;350(1-2):225-30

A comparison of the effects of serotonin, substance P and thyrotropin-releasing hormone on excitability of rat spinal motoneurons in vivo. White SR. **Brain Res** 1985 May 27;335(1):63-70

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

Postnatal development of serotonin in adrenal medullary cells. Holzwarth MA, et al. **Brain Res Bull** 1985 Jan;14(1):15-23

Localization of somatostatin-, bombesin-, and serotonin-like immunoreactivity in the lung of the fetal rhesus monkey. Dayer AM, et al. **Cell Tissue Res** 1985;239(3):621-5

Immunocytochemical demonstration of neuropeptides and serotonin in the tapeworm Diphyllobothrium dendriticum. Gustafsson MK, et al. **Cell Tissue Res** 1985;240(2):255-60

Immunocytochemical localization of serotonin in the brain and pituitary gland of the platyfish, Xiphophorus maculatus. Margolis-Kazan H, et al. **Cell Tissue Res** 1985;240(2):311-4

Unsaturated 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholines (unsaturated platelet-activating factor): aggregation of human platelets after incubation with indomethacin, creatinephosphate/creatinephosphokinase, xylocain and hirudine, and serotonin release after incubation with indomethacin. Korth R, et al. **Chem Phys Lipids** 1985 Jan;36(3):209-14

Removal of the endothelium potentiates canine large coronary artery constrictor responses to 5-hydroxytryptamine in vivo. Lamping KG, et al. **Circ Res** 1985 Jul;57(1):46-54

Liquid chromatography of serotonin and adenine nucleotides in blood platelets, illustrated by evaluation of functional integrity of platelet preparations. Ingebretsen OC, et al. **Clin Chem** 1985 May;31(5):695-8

Further studies on the effects of adrenal steroids in the active transport of serotonin into rat platelets. Lee PH, et al. **Clin Exp Pharmacol Physiol** 1985 Jan-Feb;12(1):43-50

Intraplatelet serotonin (I5HT) in children with the hemolytic uremic syndrome. Edefonti A, et al. **Clin Nephrol** 1985 Apr;23(4):207-11

A molecular theory of recognition and activation at a 5-HT receptor based on a quantum chemical approach to structure activity relationships. Osman R, et al. **Clin Physiol Biochem** 1985;3(2-3):80-8

The influence of testosterone in the brain of the male rat on levels of serotonin (5-HT) and hydroxyindole-acetic acid (5-HIAA). Martinez-Conde E, et al. **Comp Biochem Physiol [C]** 1985;80(2):411-4

The uptake and metabolism of 5-hydroxytryptamine by tissue slices of the cestode Hymenolepis diminuta. Webb RA. **Comp Biochem Physiol [C]** 1985;80(2):305-12

Trials of serotonin, substance P and alpha 2-adrenergic receptor effects on the equine large colon. Sellers AF, et al. **Cornell Vet** 1985 Apr;75(2):319-23

Scheduled feeding and 24-hour rhythms of N-acetylserotonin and melatonin in rats. Ho AK, et al. **Endocrinology** 1985 May;116(5):1858-62

Serotonergic elements of the mammalian pituitary. Payette RF, et al. **Endocrinology** 1985 May;116(5):1933-42

An investigation of amphetamine-induced release of 5-HT from rat hippocampal slices. Balfour DJ, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):395-9

Age-related changes in 5HT uptake and [3H]imipramine binding sites in rat cerebral cortex. Brunello N, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):393-4

Inhibition by antiserum to vasoactive intestinal polypeptide (VIP) of prolactin secretion induced by serotonin in the rat. Ohta H, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):409-12

Physostigmine effects on serotonin uptake in human blood platelets. Rausch JL, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):91-6

Does brain 5-HIAA indicate serotonin release or monoamine oxidase activity? Wolf WA, et al. **Eur J Pharmacol** 1985 Mar 12;109(3):381-7

Activity of serotonin-containing neurons in nucleus raphe magnus in freely moving cats. Fornal C, et al. **Exp Neurol** 1985 Jun;88(3):590-608

The enteric neural receptor for 5-hydroxytryptamine. Gershon MD, et al. **Experientia** 1985 Jul 15;41(7):863-8

Effect of various excitatory agonists on the secretion of 5-hydroxytryptamine from permeabilised human platelets induced by Ca2+ in the presence or absence of GTP. Knight DE, et al. **FEBS Lett** 1985 Apr 22;183(2):417-22

Endothelial serotonin uptake and mediation of prostanoid secretion and stress fiber formation. Shepro D, et al. **Fed Proc** 1985 Jul;44(10):2616-9

Evidence for negative feedback control of the release of [3H]serotonin from superfused mouse cerebellum slices induced by electrical field stimulation. Figueroa HR, et al. **Gen Pharmacol** 1985;16(2):103-8

Subcellular localization of serotonin immunoreactivity in rat enterochromaffin cells. Nilsson O, et al. **Histochemistry** 1985;82(4):351-5

Immunohistological studies of masked indoleamine cells in the area postrema of the rat. Nishida K, et al. **Histochemistry** 1985;82(2):101-6

Role of 5-HT on increased permeability of blood-brain barrier under heat stress. Sharma HS, et al. **Indian J Physiol Pharmacol** 1984 Oct-Dec;28(4):259-67

Cloned mouse mast cells and normal mouse peritoneal mast cells. Determination of serotonin content and ability to synthesize serotonin in vitro. Weitzman G, et al. **Int Arch Allergy Appl Immunol** 1985;77(1-2):189-91

Pharmacologic studies of the central action of zopiclone: effects on locomotor activity and brain monoamines in rats. Liu HJ, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Mar;23(3):121-8

Effects of pinealectomy on regional brain serotonin metabolism. Aldegunde M, et al. **Int J Neurosci** 1985 Apr;26(1-2):9-13

d-Fenfluramine and salbutamol: two drugs causing anorexia through different neurochemical mechanisms. Garattini S, et al. **Int J Obes** 1984;8 Suppl 1:151-7

Two novel agents affecting eating through an action on monoaminergic systems. Roncucci R, et al. **Int J Obes** 1984;8 Suppl 1:103-17

Serotonin relationships of autistic probands and their first-degree relatives. Kuperman S, et al. **J Am Acad Child Psychiatry** 1985 Mar;24(2):186-90

Central nervous system opiate and 5-hydroxytryptamine influences on

baroreflex control of the coronary circulation. Moore PG, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):185-94

Role of central nervous system monoamines in cardiopulmonary effects of Althesin in rabbit and man. Quail AW, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):159-74

Central nervous system 5-hydroxytryptamine and noradrenaline specificity of ear vascular and ventilation reflexes in thermoregulating rabbits. White SW, et al. **J Auton Nerv Syst** 1985 Feb-Mar;12(2-3):131-44

Evidence that phospholipid turnover is the signal transducing system coupled to serotonin-S2 receptor sites. de Chaffoy de Courcelles D, et al. **J Biol Chem** 1985 Jun 25;260(12):7603-8

Thrombin induces serotonin secretion and aggregation independently of inositol phospholipids hydrolysis and protein phosphorylation in human platelets permeabilized with saponin. Lapetina EG, et al. **J Biol Chem** 1985 Jun 10;260(11):7078-83

5-Hydroxytryptamine stimulates inositol phosphate production in a cell-free system from blowfly salivary glands. Evidence for a role of GTP in coupling receptor activation to phosphoinositide breakdown. Litosch I, et al. **J Biol Chem** 1985 May 10;260(9):5464-71

Vasoactive amines modulate actin cables (stress fibers) and surface area in cultured bovine endothelium. Welles SL, et al. **J Cell Physiol** 1985 Jun;123(3):337-42

Nimodipine has an inhibitory action on neurotransmitter release from human cerebral arteries. Porter ID, et al. **J Cereb Blood Flow Metab** 1985 Jun;5(2):338-42

Localization of serotonin immunoreactivity in the opossum cerebellum. Bishop GA, et al. **J Comp Neurol** 1985 May 15;235(3):301-21

Possible target neurons of 5-hydroxytryptamine fibers in the lamprey spinal cord: immunohistochemistry combined with intracellular staining with Lucifer yellow. Van Dongen PA, et al. **J Comp Neurol** 1985 Apr 22;234(4):523-35

Serotoninlike immunoreactivity in the cestode Hymenolepis diminuta. Webb RA, et al. **J Comp Neurol** 1985 Apr 22;234(4):431-40

Ultrastructural analysis of central serotoninergic neurons immunolabeled by silver-gold-intensified diaminobenzidine chromogen. Completion of immunocytochemistry with X-ray microanalysis. Liposits Z, et al. **J Histochem Cytochem** 1985 Jun;33(6):604-10

Sprouting and functional regeneration of an identified serotonergic neuron following axotomy. Murphy AD, et al. **J Neurobiol** 1985 Mar;16(2):137-51

3,4-Dihydroxyphenylethylamine and 5-hydroxytryptamine metabolism in the rat: acidic metabolites in cisternal cerebrospinal fluid before and after giving probenecid. Curzon G, et al. **J Neurochem** 1985 Aug;45(2):508-13

Neurochemical profile of Lu 19-005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonin. Hyttel J, et al. **J Neurochem** 1985 May;44(5):1615-22

Tryptamine concentrations in areas of 5-hydroxytryptamine terminal innervation after electrolytic lesions of midbrain raphe nuclei. Juorio AV, et al. **J Neurochem** 1985 Aug;45(2):422-6

Assessment of noradrenaline and 5-hydroxytryptamine uptake in intact rat brain. Wyllie MG, et al. **J Neurochem** 1985 Aug;45(2):456-60

Localization of 5-hydroxytryptamine to neurons and endoneurial mast cells in rat sensory ganglia. Kai-Kai MA, et al. **J Neurocytol** 1985 Feb;14(1):63-78

Preparation and characterization of antisera and monoclonal antibodies to serotonergic and dopaminergic ligands. Flurkey K, et al. **J Neuroimmunol** 1985 May;8(2-3):115-27

Effect of prostaglandin F2 alpha on brain and stomach 5-hydroxytryptamine. Sanyal AK, et al. **J Pharm Pharmacol** 1985 Apr;37(4):274-5

5-Hydroxytryptamine-stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: pharmacological characterization and effects of antidepressants. Kendall DA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):473-9

Efflux of 5-hydroxytryptamine and noradrenaline into spinal cord superfusates during stimulation of the rat medulla. Hammond DL, et al. **J Physiol (Lond)** 1985 Feb;359:151-62

A calcium-dependent reversible permeability increase in microvessels in frog brain, induced by serotonin. Olesen SP. **J Physiol (Lond)** 1985 Apr;361:103-13

In vivo electrochemical studies of rat striatal dopamine and serotonin release after morphine. Broderick PA. **Life Sci** 1985 Jun 17;36(24):2269-75

Differential effects of isoproterenol injections on the levels of pineal N-acetyltransferase, serum N-acetylserotonin and melatonin. Ho AK, et al. **Life Sci** 1985 Jun 3;36(22):2137-43

Differential regulation of the brain and gut immunoreactive dynorphin by the serotonin system. Majeed NH, et al. **Life Sci** 1985 Jul 29;37(4):339-43

The effect of epinephrine and serotonin on hepatic poly(A)+ RNA synthesis. Roy AK, et al. **Life Sci** 1985 Jun 17;36(24):2301-7

Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5-MeODMT or mCPP. Sills MA, et al. **Life Sci** 1985 Jul 1;36(26):2463-9

Modulation of a transient outward current in serotonergic neurones by alpha 1-adrenoceptors. Aghajanian GK. **Nature** 1985 Jun 6-12;315(6019):501-3

The depolarizing action of 5-hydroxytryptamine on rabbit vagal primary afferent and sympathetic neurones and its selective blockade by MDL 72222. Azami J, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):423-9

Effect of triamterene on 5-hydroxytryptamine biosynthesis in different brain areas. Steinberg P, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Mar;329(1):42-4

Role of the serotonin uptake carrier in the neurochemical response to methamphetamine: effects of citalopram and chlorimipramine. Schmidt CJ, et al. **Neurochem Res** 1985 May;10(5):637-48

The uptake of serotonin and dopamine by homogenates of frozen rat and human brain tissue. Stenström A, et al. **Neurochem Res** 1985 May;10(5):591-9

Opiate regulation of mesolimbic serotonin release: in vivo semiderivative electrochemical analyses. Broderick PA. **Neuropeptides** 1985 Feb;5(4-6):587-90

Differential modulation of the beta-endorphin and dynorphin systems by serotonergic stimulation in the rat. Majeed NH, et al. **Neuropeptides** 1985 Feb;5(4-6):563-6

Serotonin and antidepressant drugs antagonize melatonin-induced behavioural changes after injection into the nucleus accumbens of rats. Gaffori O, et al. **Neuropharmacology** 1985 Mar;24(3):237-44

Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. Nimgaonkar VL, et al. **Neuropharmacology** 1985 Apr;24(4):279-83

The effect of prolonged treatment with tricyclic antidepressants on the actions of 5-hydroxytryptamine in the hippocampal slice of the rat. Rowan MJ, et al. **Neuropharmacology** 1985 Feb;24(2):131-7

Morphological evidence that serotonin-immunoreactive neurons in the nucleus dorsomedialis hypothalami could be under catecholaminergic influence. Arezki F, et al. **Neurosci Lett** 1985 May 14;56(2):161-6

Immunohistochemical and biochemical detection of serotonin in the guinea pig celiac-superior mesenteric plexus. Ma RC, et al. **Neurosci Lett** 1985 May 14;56(2):107-12

Membrane responses and changes in cAMP levels in Aplysia sensory neurons produced by serotonin, tryptamine, FMRFamide and small cardioactive peptideB (SCPB). Ocorr KA, et al. **Neurosci Lett** 1985 Apr 9;55(2):113-8

The effect of adrenalectomy and corticosterone on homotypic collateral sprouting of serotonergic fibers in hippocampus. Zhou FC, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):111-6

Distribution of serotonergic neurons and processes in the lamprey spinal cord. Harris-Warrick RM, et al. **Neuroscience** 1985 Apr;14(4):1127-40

A serotonin-containing pathway from the area postrema to the parabrachial nucleus in the rat. Lança AJ, et al. **Neuroscience** 1985 Apr;14(4):1117-26

Serotonergic terminals in the neural sheath of the blowfly nervous system: electron microscopical immunocytochemistry and 5,7-dihydroxytryptamine labelling. Nässel DR, et al. **Neuroscience** 1985 May;15(1):293-307

Altered responses to serotonergic agents in Fawn-Hooded rats. Gudelsky GA, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):489-92

Involvement of the serotonergic system in the prolongation of pentobarbital sleeping time produced by prostaglandin D2. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):365-70

The effects produced by prostaglandin D2 on serotonin turnover and release and tryptophan uptake. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):371-5

Manipulations of 5-HT activity and memory in the rat. Lalonde R, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):377-82

Effects of quipazine and methysergide on play in juvenile rats. Normansell L, et al. **Pharmacol Biochem Behav** 1985 May;22(5):885-7

Suppression of male copulatory behavior by delta 9-THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415-20

Increased sensitivity to serotonergic agonists after repeated electroconvulsive shock in rats. Wielosz M. **Pharmacol Biochem Behav** 1985 May;22(5):683-7

Some behavioral effects of microinjections of serotonin and noradrenaline into the limbic structures of the rat brain. Plaznik A. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):541-54

Serotonergic control of experimental aggression. Valzelli L, et al. **Pol J Pharmacol Pharm** 1984 Sep-Oct;36(5):495-503

Combined lithium and valproate treatment and subsequent withdrawal: serotonergic mechanism of their interaction in discrete brain regions. Shukla GS. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(2):153-6

Serotonin and schizophrenia: correlations between serotonergic activity

and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Anti-aversive role of serotonin in the dorsal periaqueductal grey matter. Schütz MT, et al. **Psychopharmacology (Berlin)** 1985;85(3):340-5

Inhibition of platelet function by contrast media: iopamidol and ioxaglate versus iothalamate. Work in progress. Rao AK, et al. **Radiology** 1985 Aug;156(2):311-3

Up-regulation of thyrotropin-releasing hormone (TRH) receptors in rat spinal cord after codepletion of serotonin and TRH. Ogawa N, et al. **Regul Pept** 1985 Mar;10(2-3):85-90

High-performance liquid chromatographic assay of serotonin in human plasma. Marasini B, et al. **Ric Clin Lab** 1985 Jan-Mar;15(1):63-9

The effects of vagal nerve stimulation on endoluminal release of serotonin and substance P into the feline small intestine. Grønstad KO, et al. **Scand J Gastroenterol** 1985 Mar;20(2):163-9

High-affinity uptake of serotonin into immunocytochemically identified astrocytes. Kimelberg HK, et al. **Science** 1985 May 17; 228(4701):889-91

Diurnal rhythms of N-acetylserotonin and serotonin in cerebrospinal fluid of monkeys. Taylor PA, et al. **Science** 1985 May 17;228(4701):900

Serotonin-induced platelet aggregation in whole blood and the effects of ketanserin and mepyramine. Bevan J, et al. **Thromb Res** 1985 Apr 15;38(2):189-94

Platelet-mediated vascular permeability in the rat: a predominant role for 5-hydroxytryptamine. De Clerck F, et al. **Thromb Res** 1985 May 15;38(4):321-39

[Stimulatory control by oxytocin (or an analog peptide) of the pituitary intermediate lobe in rabbits. Inhibitory role of serotonin] Schimchowitsch S, et al. **C R Acad Sci [III]** 1985;300(7):283-6 (Eng. Abstr.) **(Fre)**

[Classification of chronic psychoses types I and II and platelet serotonin levels. Apropos of 38 cases] Boudjema F, et al. **Encephale** 1985 Jan-Feb; 11(1):39-42 (Eng. Abstr.) **(Fre)**

[Central serotonin receptors] Fillion G. **Pathol Biol (Paris)** 1985 Apr; 33(4):221-6 (56 ref.) **(Fre)**

[Preliminary observations on the distribution of serotoninergic and cerebellar-projecting neurons of the raphe nuclei of the brain stem] De Leo F, et al. **Boll Soc Ital Biol Sper** 1985 Feb 28;61(2):229-33 (Eng. Abstr.) **(Ita)**

[Structure of the binding center of the serotonin S2 receptor] Kats MM. **Biol Nauki** 1985;(3):19-24 (Eng. Abstr.) **(Rus)**

[pH changes in the matrix of serotonin organelles of stimulated thrombocytes] Kozlov VK, et al. **Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR** 1985; 8(1):77-82 (Eng. Abstr.) **(Rus)**

[Effect of cold on the brain serotonin system and the corticosteroid level of the blood in different strains of mice] Koriakina LA, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):422-7 (Eng. Abstr.) **(Rus)**

SEX BEHAVIOR, ANIMAL

The proestrous surge of prolactin enhances sexual receptivity in the rat. Witcher JA, et al. **Biol Reprod** 1985 May;32(4):834-9

Modulation of lordosis behaviour in the female rat by corticotropin releasing factor, beta-endorphin and gonadotropin releasing hormone in the mesencephalic central gray. Sirinathsinghji DJ. **Brain Res** 1985 Jun 10;336(1):45-55

Progesterone stimulates sexual behaviour in female rats by increasing 5-HT activity on 5-HT2 receptors. Wilson CA, et al. **Brain Res** 1985 May 6;333(2):223-9

Antagonism by lisuride and 8-OH-DPAT of 5-HTP-induced prolongation of the performance of male rat sexual behavior. Ahlenius S, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):379-81

The dopamine autoreceptor agonist B-HT 920 markedly stimulates sexual behavior in male rats. Ferrari F, et al. **Experientia** 1985 May 15; 41(5):636-8

Changes in hormone levels in relation to breeding behavior in male bullfrogs (Rana catesbeiana) at the individual and population levels. Mendonça MT, et al. **Gen Comp Endocrinol** 1985 May;58(2):270-9

Adrenalectomy does not prevent the hyperprolactinemic, induced sexual behavior deficits in CDF male rats. Shrenker P, et al. **Life Sci** 1985 May 13;36(19):1881-8

Neuroendocrine regulation of seasonal reproductive activity in the male golden hamster. Steger RW, et al. **Neurosci Biobehav Rev** 1985 Summer; 9(2):191-201

Potentiative action of alpha- and beta-adrenergic receptor stimulation in inducing lordosis behavior. Fernández-Guasti A, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):613-7

Serotonin antagonist pirenperone inhibits sexual behavior in the male rat: attenuation by quipazine. Mendelson SD, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):565-71

Suppression of male copulatory behavior by delta 9-THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415-20

SHARED PARANOID DISORDER

A relapsing folie à trois. Fernando FP, et al. **Br J Psychiatry** 1985 Mar; 146:315-6

SLEEP

Effects of doxylamine and acetaminophen on postoperative sleep. Smith GM, et al. **Clin Pharmacol Ther** 1985 May;37(5):549-57

Beta 1 and beta 2 adrenergic receptors: their role in the regulation of paradoxical sleep in the rat. Lanfumey L, et al. **Electroencephalogr Clin Neurophysiol** 1985 Jun;60(6):558-67

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

Effects of exhaustive submaximal exercise on cardiovascular function during sleep. Bunnell DE, et al. **J Appl Physiol** 1985 Jun; 58(6):1909-13

Auto-tolerance to the endogenous opioids and sleep. Gillman MA, et al. **Med Hypotheses** 1985 Apr;16(4):393-5

Effects of acute and chronic treatment with amitryptyline on the sleep-wake activity of rats. Obál F Jr, et al. **Neuropharmacology** 1985 Mar;24(3):223-9

p-Chloroamphetamine: effect on sleep and respiration in the rat. DeMesquita S. **Pharmacol Biochem Behav** 1985 May;22(5):889-91

Involvement of the serotonergic system in the prolongation of pentobarbital sleeping time produced by prostaglandin D2. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar; 22(3):365-70

SLEEP DEPRIVATION

Can lithium carbonate prolong the antidepressant effect of sleep deprivation? [letter] Baxter LR Jr. **Arch Gen Psychiatry** 1985 Jun; 42(6):635

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

[Sleep deprivation as a method of treating endogenous depression] Vovin RIa, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):560-5 (Eng. Abstr.) **(Rus)**

SLEEP, REM

Internight variability of REM latency in major depression: implications for the use of REM latency as a biological correlate. Ansseau M, et al. **Biol Psychiatry** 1985 May;20(5):489-505

Cholinomimetic drug RS 86, REM sleep, and depression [letter] Berger M, et al. **Lancet** 1985 Jun 15;1(8442):1385-6

Paradoxical sleep deprivation and the immobility response in the rat: effects of desipramine and phentolamine. van Luijtelaar EL, et al. **Sleep** 1985;8(1):49-55

SLEEP STAGES

Prenatal exposure to diazepam results in enduring reductions in brain receptors and deep slow wave sleep. Livezey GT, et al. **Brain Res** 1985 May 20;334(2):361-5

Relationship between sleep efficiency and urinary excretion of catecholamines in bed-rested humans. Nishihara K, et al. **Sleep** 1985; 8(2):110-7

SOCIAL ADJUSTMENT

Treatment characteristics of psychiatric programs that correlate with patient community adjustment. Collins JF, et al. **J Clin Psychol** 1985 May;41(3):299-308

[Social integration of long-term paraphrenic patients with low-dose depot neuroleptic medication] Lesch OM, et al. **Psychiatr Prax** 1985 Mar; 12(2):63-8 (Eng. Abstr.) **(Ger)**

SODIUM

Human platelet alpha 2-adrenergic receptors: effect of Na+ on interaction with the adenylate cyclase system and on epinephrine-stimulated platelet secretion. Limbird LE, et al. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:235-42

Studies on role of calmodulin in Ca2+ regulation of rabbit ileal Na and Cl transport. Donowitz M, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 1):G726-40

Central effects of angiotensin II and dopamine in sodium-depleted sheep. Huang BS, et al. **Am J Physiol** 1985 May;248(5 Pt 2):R541-8

Mineralocorticoid regulation of apical cell membrane Na+ and K+ transport of the cortical collecting duct. Sansom SC, et al. **Am J Physiol** 1985 Jun;248(6 Pt 2):F858-68

A novel technique for assessing the sources of dietary sodium. Sanchez-Castillo CP, et al. **Ann Clin Res** 1984;16 Suppl 43:44-8

Inhibition of Na+/Ca2+ exchange in pituitary plasma membrane vesicles by analogues of amiloride. Kaczorowski GJ, et al. **Biochemistry** 1985 Mar 12;24(6):1394-403

Coupling of a loop diuretic-sensitive Na+ influx with the net loop diuretic-sensitive K+ efflux in mouse NIH 3T3 cells. Panet R, et al. **Biochim Biophys Acta** 1985 Jun 27;816(2):278-82

The effect of the intracellular sodium level on the activity of amino acid transport systems L and A in SV40 3T3 cells. Petronini PG, et al. **Biochim Biophys Acta** 1985 May 28;815(3):361-8

Characterization of sodium-dependent, high-affinity serotonin uptake in rat spinal cord synaptosomes. Stauderman KA, et al. **Brain Res** 1985 Mar 18;330(1):11-20

Study of the interrelationship between dopaminergic activity and potassium ion. Matsuda S, et al. **Clin Exp Hypertens [A]** 1984; 6(12):2249-61

The influence of the membrane sodium pump activity on the ability of human peripheral blood lymphocytes to form early rosettes with SRBC. Witkowski J. **Immunology** 1985 Jun;55(2):339-45

Localization of potassium and sodium fluxes in the rat lens. Reszelbach R, et al. **Invest Ophthalmol Vis Sci** 1985 Jul;26(7):945-52

Evidence for tyrosyl residues at the Na+ site on the intestinal Na+/glucose cotransporter. Peerce BE, et al. **J Biol Chem** 1985 May 25;260(10):6026-31

Na+ (Li+)-proline cotransport in Escherichia coli. Chen CC, et al. **J Membr Biol** 1985;84(2):157-64

Sodium-dependent modulation of the renal Na-K-ATPase: influence of mineralocorticoids on the cortical collecting duct. O'Neil RG, et al. **J Membr Biol** 1985;85(2):169-79

Influence of lead ions on cation permeability in human red cell ghosts. Simons TJ. **J Membr Biol** 1985;84(1):61-71

GABAergic inhibition of hypertonic saline-induced vasopressin-dependent hypertension. Brennan TJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):663-71

Effects of angiotensin or carbachol on sodium intake and excretion in adrenalectomized or deoxycorticosterone-treated rats. Fitzsimons JT, et al. **J Physiol (Lond)** 1985 Feb;359:447-58

Cation activation of the pig kidney sodium pump: transmembrane allosteric effects of sodium. Karlish SJ, et al. **J Physiol (Lond)** 1985 Feb;359:119-49

Inhibition of sodium transport in frog skin and iodination of tyrosine in vitro by a peptide of renal origin. Fregly MJ, et al. **Klin Wochenschr** 1985;63 Suppl 3:102-6

The relation of sodium transport to blood pressure in the adrenalectomized rat. Friedman SM. **Klin Wochenschr** 1985;63 Suppl 3:55-8

Modulation of erythrocyte Na transport pathway(s) by excess Na intake. Dagher G, et al. **Life Sci** 1985 Jul 22;37(3):243-53

Intracellular Ca indicator Quin-2 inhibits Ca2+ inflow via Na/Ca exchange in squid axon. Allen TJ, et al. **Nature** 1985 Jun 27-Jul 3; 315(6022):755-6

The effect of phenylalanine on intracellular pH and sodium activity in proximal convoluted tubule cells of the frog kidney. Messner G, et al. **Pflugers Arch** 1985 May;404(2):145-9

Behaviour of chemically modified sodium channels in frog nerve supports a three-state model of inactivation. Schmidtmayer J. **Pflugers Arch** 1985 May;404(1):21-8

Effect of a low sodium medium, ouabain and noradrenaline on relaxation of the myocardium of the perfused rabbit heart. Fišer B, et al. **Physiol Bohemoslov** 1985;34(1):77-84

Effect of dialysate sodium on the dopamine, adrenaline and noradrenaline concentration in haemodialysis patients. Ksiażek A, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985;21:225-9

Study of the ionic basis of visual transduction in vertebrate retinal rods. Yau KW, et al. **Prog Clin Biol Res** 1985;176:21-31 (36 ref.)

[Possible participation of slow Na+--Ca++ channels in realizing cholinergic effects on the cardiac pacemaker] Sukhova GS, et al. **Fiziol Zh SSSR** 1985 Apr;71(4):506-9 (Eng. Abstr.) **(Rus)**

SOMATOSTATIN

Somatostatin inhibition of cyclic AMP accumulation and adrenocorticotropin release from mouse anterior pituitary tumor cells: mode of action and self-regulation. Reisine TD. **Adv Cyclic Nucleotide Protein Phosphorylation Res** 1985;19:169-77

Cholecystokinin potently releases somatostatin from canine fundic mucosal cells in short-term culture. Soll AH, et al. **Am J Physiol** 1985 May;248(5 Pt 1):G569-73

The somatostatin-28 convertase of rat brain cortex generates both somatostatin-14 and somatostatin-28. Gluschankof P, et al. **Biochem Biophys Res Commun** 1985 May 16;128(3):1051-7

Effect of somatostatin on the proliferation of mouse spleen lymphocytes in vitro. Pawlikowski M, et al. **Biochem Biophys Res Commun** 1985 May 31;129(1):52-5

Difference in dose-response curves for glucose-induced insulin and somatostatin release in rat pancreas. Dettori-Gera C, et al. **Biochim Biophys Acta** 1985 May 8;839(3):281-6

The biological activity of duck 'big' somatostatin on chicken adipose tissue. Di Scala-Guenot D, et al. **Biochim Biophys Acta** 1985 May 30; 845(2):261-4

Immunocytochemical localization of somatostatin and cholecystokinin in the cat visual cortex. Demeulemeester H, et al. **Brain Res** 1985 Apr 22;332(2):361-4

Immunocytochemical localization of somatostatin-28 in the rat hypothalamus. Guy J, et al. **Brain Res** 1985 Mar 25;330(2):283-9

Thyroid hormones reversibly suppress somatostatin secretion and immunoreactivity in cultured neocortical cells. Peterfreund RA, et al. **Brain Res** 1985 Mar 4;328(2):259-70

The effects of neurotensin, vasoactive intestinal polypeptide and other neuropeptides on the secretion of somatostatin from cerebral cortical cells. Robbins RJ, et al. **Brain Res** 1985 Apr 15;332(1):161-4

Vasoactive intestinal peptide and PHI stimulate somatostatin release from rat cerebral cortical and diencephalic cells in dispersed cell culture. Tapia-Arancibia L, et al. **Brain Res** 1985 Jun 10;336(1):67-72

Comparison of somatostatin-28 and somatostatin-14 clearance by the perfused rat liver. Seno M, et al. **Can J Physiol Pharmacol** 1985 Jan; 63(1):62-7

Tissue-specific posttranslational processing of pre-prosomatostatin encoded by a metallothionein-somatostatin fusion gene in transgenic mice. Low MJ, et al. **Cell** 1985 May;41(1):211-9

Localization of somatostatin-, bombesin-, and serotonin-like immunoreactivity in the lung of the fetal rhesus monkey. Dayer AM, et al. **Cell Tissue Res** 1985;239(3):621-5

Somatostatin-14 modulates postprandial glucose levels and release of gastrointestinal and pancreatic hormones. O'Shaughnessy DJ, et al. **Digestion** 1985;31(4):234-42

Characterization of tissue and releasable molecular forms of somatostatin-28[1-12]-like immunoreactivity in rat median eminence. Charpenet G, et al. **Endocrinology** 1985 May;116(5):1863-8

Somatostatin-14 and somatostatin-28 pretreatment down-regulate somatostatin-14 receptors and have biphasic effects on forskolin-stimulated cyclic adenosine, 3',5'-monophosphate synthesis and adrenocorticotropin secretion in mouse anterior pituitary tumor cells. Heisler S, et al. **Endocrinology** 1985 Jul;117(1):217-25

Forskolin, an activator of adenylate cyclase, stimulates pancreatic insulin, glucagon, and somatostatin release in the dog: studies in vitro. Hermansen K. **Endocrinology** 1985 Jun;116(6):2251-8

Somatostatin secretion from the isolated perfused dog ileum. Hermansen K. **Endocrinology** 1985 Jul;117(1):287-91

Cysteamine induces a loss of tissue somatostatin-28 when measured as somatostatin-28(15-28)-like immunoreactivity but not when assessed as somatostatin-28(1-14)-like immunoreactivity: evidence for the importance of the disulfide bond for cysteamine action. Patel YC, et al. **Endocrinology** 1985 May;116(5):1699-702

Mouse hypothalamic somatostatin release: roles of calcium and calmodulin. Richardson S, et al. **Endocrinology** 1985 Jul; 117(1):369-75

Hepatic metabolism of somatostatin-14 and somatostatin-28: immunochemical characterization of the metabolic fragments and comparison of cleavage sites. Ruggere MD, et al. **Endocrinology** 1985 Jul;117(1):88-96

Antiserum to rat growth hormone (GH)-releasing factor suppresses but does not abolish antisomatostatin-induced GH release in the rat. Thomas CR, et al. **Endocrinology** 1985 Jun;116(6):2174-8

Immunoreactive and biologically active somatostatin in human and sheep milk. Werner H, et al. **Eur J Biochem** 1985 Apr 15;148(2):353-7

Pituitary growth hormone and hypothalamic somatostatin in young female rats versus old constant estrous female rats. Forman LJ, et al. **Experientia** 1985 May 15;41(5):653-4

Effect of long acting somatostatin-analogue, SMS 201 995, on gut hormone secretion in normal subjects. Kraenzlin ME, et al. **Experientia** 1985 Jun 15;41(6):738-40

Neurobiological actions of cysteamine. Brown M, et al. **Fed Proc** 1985 Jun;44(9):2556-60

Regulatory peptides (glucagon, somatostatin, substance P, and VIP) in the brain and gastrointestinal tract of Ambystoma mexicanum. Conlon JM, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):150-8

Is somatostatin a humoral regulator of the endocrine pancreas and gastric acid secretion in man? Loud FB, et al. **Gut** 1985 May;26(5):445-9

Differential changes in calcitonin, somatostatin and gastrin/cholecystokinin-like immunoreactivities in rat thyroid parafollicular cells during ontogeny. Larsson LI. **Histochemistry** 1985; 82(2):121-30

Different effects of prostaglandin E1, E2 and D2 on pancreatic somatostatin release. Nishi S, et al. **Horm Metab Res** 1984 Dec; 16 Suppl 1:114-8

Effect of long and short photoperiod and/or pinealectomy on immunoreactive somatostatin in the Syrian hamster. Webb SM, et al. **Horm Metab Res** 1985 Feb;17(2):107-8

Z-DNA in the rat somatostatin gene. Hayes TE, et al. **J Biol Chem** 1985 Jul 5;260(13):8145-56

In situ hybridization of putative somatostatin mRNA within hypothalamus of the rat using synthetic oligonucleotide probes. Arentzen R, et al. **J Cell Biochem** 1985;27(4):415-22

A unique control mechanism in the regulation of insulin secretion. Secretagogue-induced somatostatin receptor recruitment. Draznin B, et al. **J Clin Invest** 1985 May;75(5):1510-6

Effects of cysteamine and antibody to somatostatin on islet cell function in vitro. Evidence that intracellular somatostatin deficiency augments insulin and glucagon secretion. Patel YC, et al. **J Clin Invest** 1985 Apr; 75(4):1249-55

Multiple forms of somatostatin-like immunoreactivity in the hypothalamus and amygdala of the rat: selective localization of somatostatin-28 in the median eminence. Pierotti AR, et al. **J Endocrinol** 1985 Jun; 105(3):383-9

Modulation of lymphocyte function by sensory neuropeptides. Payan DG, et al. **J Immunol** 1985 Aug;135(2 Suppl):783s-786s

Modulation by monoamines of somatostatin-sensitive adenylate cyclase on neuronal and glial cells from the mouse brain in primary cultures. Chneiweiss H, et al. **J Neurochem** 1985 Jun;44(6):1825-31

Localization of somatostatin receptors in secretion vesicles in anterior pituitary cells and pancreatic islets. Draznin B, et al. **J Recept Res** 1985; 5(1):83-103

Effect of a cyclic hexapeptide analog (L363,586) of somatostatin on the function of pancreas grafts in dogs. Liu T, et al. **J Surg Res** 1985 Jul; 39(1):39-45

Somatostatin: hormonal and therapeutic roles [editorial] **Lancet** 1985 Jul 13;2(8446):77-8

Different effects of three kinds of somatostatin (15-28, 1-14, 1-28) on rabbit's platelet aggregation. Fuse I, et al. **Life Sci** 1985 May 27; 36(21):2047-52

Somatostatin antagonist analogue stimulates growth in rats. Spencer GS, et al. **Life Sci** 1985 Jul 8;37(1):27-30

Effect of a selective octapeptide analogue of somatostatin on renal water excretion in the dog. Mountokalakis T, et al. **Metabolism** 1985 May; 34(5):408-9

Somatostatin release from the median eminence of unanesthetized rats: lack of correlation with pharmacologically suppressed growth hormone secretion. Fukata J, et al. **Neuroendocrinology** 1985 Mar; 40(3):193-200

The binding of somatostatin to rat synaptosomal membranes: effects of detergent solubilisation and of bacitracin. Weightman DR, et al. **Neuropeptides** 1985 Mar;6(1):83-92

Rat brain membranes possess two high-affinity binding sites for [3H]somatostatin. Weightman DR, et al. **Neurosci Lett** 1985 Apr 9; 55(2):161-6

Long-term suspension culture of isolated hypothalamic nuclei of the rat: morphological differentiation and release of substances influencing corticotropin and growth hormone secretion. Gyévai A, et al. **Neuroscience** 1985 Feb;14(2):519-33

The somatostatin systems of the guinea-pig brainstem. Taber-Pierce E, et al. **Neuroscience** 1985 May;15(1):215-35

Immunohistochemical studies of substance P, cholecystokinin-octapeptide and somatostatin in dorsal root ganglia of the rat. Tuchscherer MM, et al. **Neuroscience** 1985 Feb;14(2):593-605

Effects of MET-ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):139-48

Somatostatin analogs: correlation of receptor affinity with inhibition of cyclic AMP formation in pancreatic acinar cells. Taparel D, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):109-14

Human pancreatic polypeptide and somatostatin in chronic renal failure. Lugari R, et al. **Proc Eur Dial Transplant Assoc Eur Ren Assoc** 1985; 21:614-7

Cerebrospinal fluid cholecystokinin, bombesin and somatostatin in schizophrenia and normals. Gerner RH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(1):73-82

Effects of carbamazepine on cerebrospinal fluid somatostatin. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1985;85(2):210-3

Evidence against prostaglandin-mediation of somatostatin-inhibition of gastric secretions. Albinus M, et al. **Regul Pept** 1985 Mar; 10(2-3):259-66

Somatostatin and GABA correlate with cervical autonomic nerve activity. Tonoue T, et al. **Regul Pept** 1985 Apr;10(4):299-307

Effects of somatostatin-14 and somatostatin-28 on plasma hormonal and gastric secretory responses to cephalic and gastrointestinal stimulation in man. Konturek SJ, et al. **Scand J Gastroenterol** 1985 Jan; 20(1):31-8

Effect of somatostatin on bethanechol-stimulated gastric pepsin secretion in gastric fistula dogs. Ladegaard L, et al. **Scand J Gastroenterol** 1985 Jan;20(1):87-91

Effects of substance P and somatostatin on taurocholate-stabilized and CCK- or secretin-induced choleresis in the anesthetized dog. Magnusson I, et al. **Scand J Gastroenterol** 1984 Nov;19(8):1007-14

The microvasculature of the small-intestinal mucosa of the rat: quantification of hemodynamic effects of topically applied cimetidine, ranitidine, somatostatin, and vasopressin. Neff M, et al. **Scand J Gastroenterol [Suppl]** 1985;112:6-11

High plasma levels of immunoreactive somatostatin in transgenic mice expressing a metallothionein-somatostatin fusion gene. Low MJ, et al. **Trans Assoc Am Physicians** 1984;97:205-9

[Somastostatin in domestic fowl] Baldissera FG, et al. **Riv Biol** 1985 Spring;78(1):123-8 (Eng. Abstr.) **(Ita)**

[Effect of somatostatin on the neurosecretory cells of the hypothalamic paraventricular nucleus and argentaffin cells of the antral part of the rat stomach] Kotel'nikova VI, et al. **Fiziol Zh SSSR** 1985 Feb; 71(2):206-12 (Eng. Abstr.) **(Rus)**

SOMATOTROPIN RELEASING HORMONE

Human pancreatic tumor GH-releasing factor. Thorner MO, et al. **Acta Neurochir (Wien)** 1985;75(1-4):72-80

Growth hormone releasing factor (GRF) and dopamine coexist in hypothalamic arcuate neurons. Meister B, et al. **Acta Physiol Scand** 1985 May;124(1):133-6

Physiological studies with somatocrinin, a growth hormone-releasing factor. Wehrenberg WB, et al. **Annu Rev Pharmacol Toxicol** 1985; 25:463-83 (98 ref.)

The effects of testosterone and estrogen on the pituitary growth hormone response to growth hormone-releasing factor. Wehrenberg WB, et al. **Biol Reprod** 1985 Mar;32(2):369-75

Plasma growth hormone secretion during constant growth hormone-releasing factor infusion. Takano K, et al. **Endocrinol Jpn** 1984 Dec;31(6):681-5

Pituitary response of growth hormone release in administration of hpGRF-44 to pregnant rats. Uchida N, et al. **Endocrinol Jpn** 1984 Dec; 31(6):831-5

Effects of intraventricular growth hormone-releasing factor on growth hormone release: further evidence for ultrashort loop feedback. Lumpkin MD, et al. **Endocrinology** 1985 May;116(5):2070-4

Dose-response characteristics of various peptides with growth hormone-releasing activity in the unanesthetized male rat. McCormick GF, et al. **Endocrinology** 1985 Jul;117(1):97-105

Antiserum to rat growth hormone (GH)-releasing factor suppresses but does not abolish antisomatostatin-induced GH release in the rat. Thomas CR, et al. **Endocrinology** 1985 Jun;116(6):2174-8

Interaction of growth hormone-releasing factor (GRF) and 14 GRF analogs with vasoactive intestinal peptide (VIP) receptors of rat pancreas. Discovery of (N-Ac-Tyr1,D-Phe2)-GRF(1-29)-NH2 as a VIP antagonist. Waelbroeck M, et al. **Endocrinology** 1985 Jun; 116(6):2643-9

Interaction between human pancreatic growth hormone releasing factor (hpGRF) and thyrotropin releasing hormone (TRH) on growth hormone secretion in domestic fowl. Harvey S, et al. **Horm Metab Res** 1985 Feb;17(2):113-4

Augmentation by propranolol of growth hormone-releasing hormone-(1-44)-NH2-induced growth hormone release in normal short and normal children. Chihara K, et al. **J Clin Endocrinol Metab** 1985 Aug;61(2):229-33

Growth hormone responses to continuous infusions of growth hormone-releasing hormone. Gelato MC, et al. **J Clin Endocrinol Metab** 1985 Aug;61(2):223-8

Effect of different growth hormone-releasing factors on the concentrations of growth hormone, insulin and metabolites in the plasma of sheep maintained in positive and negative energy balance. Hart IC, et al. **J Endocrinol** 1985 Apr;105(1):113-9

Effect of intravenous bovine growth hormone or human pancreatic growth hormone-releasing factor on milk production and plasma hormones and metabolites in sheep. Hart IC, et al. **J Endocrinol** 1985 May;105(2):189-96

GnRH pulse frequency determines LH pulse amplitude by altering the amount of releasable LH in the pituitary glands of ewes. Clarke IJ, et al. **J Reprod Fertil** 1985 Mar;73(2):425-31

Changes in pulsatile LH secretion and the positive and negative feedback actions of oestradiol after administration of a GnRH agonist in the ovariectomized ewe. Fitzgerald BP, et al. **J Reprod Fertil** 1985 Mar; 73(2):433-40

Radioimmunoassay for human growth hormone-releasing factor (hGRF 1-40): comparison of plasma immunoreactive GRF after intravenous and subcutaneous administration to rats. Rafferty B, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):19-25

Expression of human growth hormone-releasing factor in transgenic mice results in increased somatic growth. Hammer RE, et al. **Nature** 1985 May 30-Jun 5;315(6018):413-6

Modification of basal and GRF-stimulated cyclic AMP levels and growth hormone release by phospholipid metabolic enzyme inhibitors. Cronin MJ, et al. **Neuroendocrinology** 1985 Apr;40(4):332-8

Long-term suspension culture of isolated hypothalamic nuclei of the rat: morphological differentiation and release of substances influencing corticotropin and growth hormone secretion. Gyévai A, et al. **Neuroscience** 1985 Feb;14(2):519-33

Growth hormone releasing hormone and growth hormone: genetic studies in familial growth hormone deficiency. Rogol AD, et al. **Pediatr Res** 1985 May;19(5):489-92

Levels of human and rat hypothalamic growth hormone-releasing factor as determined by specific radioimmunoassay systems. Audhya T, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):2970-4

SPATIAL BEHAVIOR

Place preference conditioning with methylphenidate and nomifensine. Martin-Iverson MT, et al. **Brain Res** 1985 Apr 15;332(1):59-67

STARTLE REACTION

Central noradrenergic involvement in yohimbine excitation of acoustic startle: effects of DSP4 and 6-OHDA. Kehne JH, et al. **Brain Res** 1985 Mar 18;330(1):31-41

Antagonism of apomorphine-enhanced startle by alpha 1-adrenergic antagonists. Davis M, et al. **Eur J Pharmacol** 1985 Feb 5; 108(3):233-41

STEREOTYPED BEHAVIOR

Effect of duration of haloperidol treatment on DA receptor supersensitization in aging C57BL/6J mice. Randall PK, et al. **Brain Res** 1985 Apr 29;333(1):85-95

Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. Molloy AG, et al. **Eur J Pharmacol** 1985 Feb 5;108(3):305-8

Opposite effects of sulpiride and metoclopramide on amphetamine-induced stereotypy. Robertson A, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):81-9

Unexpected potentiation by discriminant benzamide derivatives of stereotyped behaviours elicited by dopamine agonists in mice. Vasse M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Apr; 329(2):108-16

Effect of gestational and neonatal styrene exposure on dopamine receptors. Zaidi NF, et al. **Neurobehav Toxicol Teratol** 1985 Jan-Feb;7(1):23-8

Effect of chronic haloperidol and quinacrine coadministration on striatal HVA levels and stereotypic behaviors in response to apomorphine in the rat. Deutsch SI, et al. **Neurochem Res** 1985 Apr;10(4):491-8

Antistereotypic effects of cholecystokinin octapeptide (CCK-8), ceruletide and related peptides on apomorphine-induced gnawing in sensitized mice. Zetler G. **Neuropharmacology** 1985 Mar;24(3):251-9

The morphogenesis of stereotyped behavior induced by the dopamine receptor agonist apomorphine in the laboratory rat. Szechtman H, et al. **Neuroscience** 1985 Mar;14(3):783-98

Serotonin and schizophrenia: correlations between serotonergic activity and schizophrenic motor behavior. King R, et al. **Psychiatry Res** 1985 Mar;14(3):235-40

Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY 171555 in 6-hydroxydopamine-lesioned rats. Arnt J, et al. **Psychopharmacology (Berlin)** 1985;85(3):346-52

Effects of apomorphine and haloperidol on 'spontaneous' stereotyped licking behaviour in the Cebus monkey. Korsgaard S, et al. **Psychopharmacology (Berlin)** 1985;85(2):240-3

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204-9

Differential effects of dopamine D-1 and D-2 agonists and antagonists in 6-hydroxydopamine-lesioned rats. Arnt J. **Psychopharmacology [Suppl]** 1985;2:60-1

Intermittent treatment with droperidol, a short-acting neuroleptic, increases behavioral dopamine receptor sensitivity. Belmaker RH, et al. **Psychopharmacology [Suppl]** 1985;2:194-9

Induction and reversal of dopamine dyskinesia in rat, cat, and monkey. Lloyd KG, et al. **Psychopharmacology [Suppl]** 1985;2:200-10

[TRH and its analog (DN-1417). Effects on central dopaminergic system-dependent behaviors in rats and mice] Miyamoto M, et al. **Nippon Yakurigaku Zasshi** 1985 Mar;85(3):129-41 (Eng. Abstr.) **(Jpn)**

[Continuous suppression of methamphetamine-induced supersensitivity by chronic haloperidol administration] Kashihara K, et al. **Seishin Shinkeigaku Zasshi** 1984;86(11):928-32 **(Jpn)**

STRESS, PSYCHOLOGICAL

Interaction of chemical and psychogenic stress: biochemical response to repeated 'conditioned fear' and chronic carbon disulphide poisoning. Beneš V, et al. **Act Nerv Super (Praha)** 1985 Mar;27(1):23-5

Effects of psychological stress on male reproduction: a review. McGrady AV. **Arch Androl** 1984;13(1):1-7

Enhancement of some 5-HT-dependent behavioural responses following repeated immobilization in rats. Kennett GA, et al. **Brain Res** 1985 Mar 25;330(2):253-63

Platelet activation and secretion associated with emotional stress. Levine SP, et al. **Circulation** 1985 Jun;71(6):1129-34

Exercise and stress reduction. Rosch PJ. **Compr Ther** 1985 Apr; 11(4):10-5

Stress and immunomodulation: the role of depression and neuroendocrine function. Stein M, et al. **J Immunol** 1985 Aug; 135(2 Suppl):827s-833s

Reduction of the cyclic adenosine 3',5'-monophosphate response to catecholamines in rat brain slices after repeated restraint stress. Stone EA, et al. **J Pharmacol Exp Ther** 1985 May;233(2):382-8

Methionine-enkephalin inhibits stress-induced increases in noradrenaline turnover in brain regions of rats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Jan;37(1):117-9

Psychic distress and the immune response. Tecoma ES, et al. **Life Sci** 1985 May 13;36(19):1799-812 (58 ref.)

Effects of emotional stress on the immune system. Miller NE. **Pavlov J Biol Sci** 1985 Apr-Jun;20(2):47-52

Brain amines and effects of chlordiazepoxide on motor activity in response to stress. Freeman GB, et al. **Pharmacol Biochem Behav** 1985 May; 22(5):665-70

Habituation to repeated stress is stressor specific. Kant GJ, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):631-4

A psychophysiological field study of stress at Three Mile Island. Gatchel RJ, et al. **Psychophysiology** 1985 Mar;22(2):175-81

[Spatial reorganization of the organelles of catecholamine-synthesizing group A1 neurons during emotional stress] Zhigadlo BA, et al. **Arkh Anat Gistol Embriol** 1985 Feb;88(2):11-6 (Eng. Abstr.) **(Rus)**

[The state of brain mitochondrial membranes in stress and its correction with drugs] Kresiun VI. **Biofizika** 1985 Mar-Apr;30(2):306-8 (Eng. Abstr.) **(Rus)**

[Changes in the substance P content of the blood and hypothalamus during experimental emotional stress] Iumatov EA, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):397-9 (Eng. Abstr.) **(Rus)**

[Changes in the opioid peptide content of the adrenals of rats during immobilization stress] Val'dman AV, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):404-6 (Eng. Abstr.) **(Rus)**

[Effect of phenazepam on the peripheral catecholaminergic systems in immobilization stress] Malikova LA, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):23-7 (Eng. Abstr.) **(Rus)**

[Changes in blood monoamine and 11-hydroxycorticosteroid levels in rats under the action of stress] Ugarova OP. **Fiziol Zh** 1985 Mar-Apr; 31(2):224-7 **(Rus)**

[The hemato-encephalic barrier in emotional stress] Belova TI, et al. **Usp Fiziol Nauk** 1985 Apr-Jun;16(2):61-76 (105 ref.) **(Rus)**

[Effect of an alimentary factor on the activity of the sympathetic-adrenal system in workers performing stressful work] Khotimchenko SA, et al. **Vopr Pitan** 1985 Mar-Apr;(2):36-9 **(Rus)**

SUBSTANCE P

Central action of substance P: possible role in reward. Stäubli U, et al. **Behav Neural Biol** 1985 Jan;43(1):100-8

The metabolism of neuropeptides. Endopeptidase-24.11 in human synaptic membrane preparations hydrolyses substance P. Matsas R, et al. **Biochem J** 1985 Jun 1;228(2):487-92

The role of substance P as a neurotransmitter in the reflexes of slow time courses in the neonatal rat spinal cord. Akagi H, et al. **Br J Pharmacol** 1985 Mar;84(3):663-73

The effect of a conditioning lesion on the regeneration rate of peripheral nerve axons containing substance P. Bisby MA, et al. **Brain Res** 1985 Jun 17;336(2):201-6

Substance P depolarizes nerve terminals in an autonomic ganglion. Dryer SE, et al. **Brain Res** 1985 Jun 10;336(1):190-4

Attenuation of the reflex pressor response to muscular contraction by a substance P antagonist. Kaufman MP, et al. **Brain Res** 1985 Apr 29; 333(1):182-4

Synaptic interaction between catecholaminergic neurons and substance P-immunoreactive axons in the caudal part of the nucleus of the solitary tract of the rat: demonstration by the electron microscopic mirror technique. Kubota Y, et al. **Brain Res** 1985 Apr 29;333(1):188-92

Coexistence of calcitonin gene-related peptide and substance P-like peptide in single cells of the trigeminal ganglion of the rat: immunohistochemical analysis. Lee Y, et al. **Brain Res** 1985 Mar 18; 330(1):194-6

Substance P mechanisms of the spinal cord related to vasomotor tone in the spontaneously hypertensive rat. Takano Y, et al. **Brain Res** 1985 May 13;334(1):105-16

Reduction of [3H]substance P binding in the intermediolateral cell column after sympathectomy. Takano Y, et al. **Brain Res** 1985 Apr 29; 333(1):193-6

Sciatic nerve transection produces death of dorsal root ganglion cells and reversible loss of substance P in spinal cord. Tessler A, et al. **Brain Res** 1985 Apr 22;332(2):209-18

The acute and chronic effects of capsaicin on slow excitatory transmission in rat dorsal horn. Urbán L, et al. **Brain Res** 1985 Mar 25; 330(2):390-6

Release of substance P from peripheral nerve terminals following electrical stimulation of the sciatic nerve. White DM, et al. **Brain Res** 1985 Jun 10;336(1):27-31

A comparison of the effects of serotonin, substance P and thyrotropin-releasing hormone on excitability of rat spinal motoneurons in vivo. White SR. **Brain Res** 1985 May 27;335(1):63-70

Ontogeny of substance P-containing fibers in the taste buds and the surrounding epithelium. I. Light microscopic analysis. Yamasaki H, et al. **Brain Res** 1985 Feb;350(1-2):301-5

A presynaptic site of action of substance P and vasoactive intestinal polypeptide on myenteric neurons. Yau WM, et al. **Brain Res** 1985 Mar 25;330(2):382-5

Vascular actions of VIP, substance P and neurotensin on the isolated perfused human fetal placenta. de Moura RS, et al. **Contrib Gynecol Obstet** 1985;13:174-5

Trials of serotonin, substance P and alpha 2-adrenergic receptor effects on the equine large colon. Sellers AF, et al. **Cornell Vet** 1985 Apr; 75(2):319-23

Sympathectomy enhances the substance P-mediated breakdown of the blood-aqueous barrier in response to infrared irradiation of the rabbit iris. Bynke G, et al. **Experientia** 1985 Apr 15;41(4):488-9

Substance P-like immunoreactivity in the frog dorsal root ganglia. Kemali M, et al. **Experientia** 1985 Apr 15;41(4):481-2

Regulatory peptides (glucagon, somatostatin, substance P, and VIP) in the brain and gastrointestinal tract of Ambystoma mexicanum. Conlon JM, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):150-8

Vasoactive effects of substance P on isolated rabbit pulmonary artery. Tanaka DT, et al. **J Appl Physiol** 1985 Apr;58(4):1291-7

The role of substance P in arterial chemoreflex control of ventilation. Gallagher PJ, et al. **J Auton Nerv Syst** 1985 Feb-Mar; 12(2-3):195-210

Spinal cord substance P mediates bicuculline-induced activation of cardiovascular responses from the ventral medulla. Keeler JR, et al. **J Auton Nerv Syst** 1985 May;13(1):19-33

Origin of small primary afferent substance P-immunoreactive nerve fibers in the guinea-pig heart. Urban L, et al. **J Auton Nerv Syst** 1985 Apr; 12(4):321-31

Effect of substance P and other tachykinins on arterial pressure in guinea-pigs. Hancock JC, et al. **J Auton Pharmacol** 1985 Mar; 5(1):25-30

Modulation of lymphocyte function by sensory neuropeptides. Payan DG, et al. **J Immunol** 1985 Aug;135(2 Suppl):783s-786s

Substance P in human plasma is degraded by dipeptidyl peptidase IV, not by cholinesterase. Nausch I, et al. **J Neurochem** 1985 May; 44(5):1354-7

Autoradiographic localization and characterization of spinal cord substance P binding sites: high densities in sensory, autonomic, phrenic, and Onuf's motor nuclei. Charlton CG, et al. **J Neurosci** 1985 Jun; 5(6):1653-61

Cardiovascular effects of spinal cord substance P: studies with a stable receptor agonist. Keeler JR, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):755-60

Blockade of slow excitatory post-synaptic potential by substance P antagonists in guinea-pig sympathetic ganglia. Konishi S, et al. **J Physiol (Lond)** 1985 Apr;361:115-30

Substance P raises neuronal membrane excitability by reducing inward rectification. Stanfield PR, et al. **Nature** 1985 Jun 6-12; 315(6019):498-501

Substance P enteric neurons mediate non-cholinergic transmission to the circular muscle of the guinea-pig intestine. Costa M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):446-53

Substance P action on phosphoinositides in guinea-pig intestinal muscle: a possible transduction mechanism? Holzer P, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Mar;329(1):50-5

Substance P, enkephalins, somatostatin, cholecystokinin, oxytocin, and vasopressin in human spinal cord. Schoenen J, et al. **Neurology** 1985 Jun;35(6):881-90

Immunocytochemical localization of glutamic acid decarboxylase and substance P in the lateral cervical nucleus: a light and electron microscopic study in the cat. Blomqvist A, et al. **Neurosci Lett** 1985 May 14;56(2):229-33

Effects of substance P antagonists on the atropine-sensitive and atropine-resistant responses of guinea-pig ileum to substance P. Chahl LA. **Neurosci Lett** 1985 Mar 22;55(1):35-40

Binding sites for [3H]substance P on neurons of cultured rat spinal cord and brain stem: an autoradiographic study. Hösli E, et al. **Neurosci Lett** 1985 May 14;56(2):199-203

Opiate and histamine H1 receptors are present on some substance P-containing dorsal root ganglion cells. Ninkovic M, et al. **Neurosci Lett** 1985 Jan 7;53(1):133-7

Substance P concentrations in human cerebrospinal fluid vary inversely with age. Tam PK, et al. **Neurosci Lett** 1985 Mar 15;54(2-3):327-32

The comparative distribution of enkephalin, dynorphin and substance P in the human globus pallidus and basal forebrain. Haber SN, et al. **Neuroscience** 1985 Apr;14(4):1011-24

Effects of glutamate, substance P and eledoisin-related peptide on solitary tract neurones involved in respiration and respiratory reflexes. Henry JL, et al. **Neuroscience** 1985 Mar;14(3):863-73

Comparison of substance P and enkephalin distribution in rat brain: an overview using radioimmunocytochemistry. McLean S, et al. **Neuroscience** 1985 Mar;14(3):837-52

Immunohistochemical studies of substance P, cholecystokinin-octapeptide and somatostatin in dorsal root ganglia of the rat. Tuchscherer MM, et al. **Neuroscience** 1985 Feb;14(2):593-605

Effects of MET-ENK, substance P and SRIF on the behavior of Hemichromis bimaculatus. Christ H. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):139-48

Cardiovascular interactions between methionine-enkephalin and substance P in the conscious dog. Sander GE, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):133-7

Sympathetic neuron density differentially regulates transmitter phenotypic expression in culture. Adler JE, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4296-300

Identification of substance P precursor forms in human brain tissue. Nyberg F, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(11):3921-4

The effects of vagal nerve stimulation on endoluminal release of serotonin and substance P into the feline small intestine. Grønstad KO, et al. **Scand J Gastroenterol** 1985 Mar;20(2):163-9

Effects of substance P and somatostatin on taurocholate-stabilized and CCK- or secretin-induced choleresis in the anesthetized dog. Magnusson I, et al. **Scand J Gastroenterol** 1984 Nov;19(8):1007-14

Immunohistochemical demonstration of nociceptors in the ligamentous structures of the lumbar spine. Korkala O, et al. **Spine** 1985 Mar; 10(2):156-7

[Recent advances in research on substance P and related neuropeptides] Kanazawa I. **No To Hattatsu** 1985 Mar;17(2):94-102 (17 ref.) **(Jpn)**

[Changes in the substance P content of the blood and hypothalamus during experimental emotional stress] Iumatov EA, et al. **Biull Eksp Biol Med** 1985 Apr;99(4):397-9 (Eng. Abstr.) **(Rus)**

SUBSTANCE USE DISORDERS

[Attempted suicide with barbiturate after glue sniffing] Sami HO, et al. **Orv Hetil** 1985 Mar 31;126(13):781-3 (Eng. Abstr.) **(Hun)**

SUCKING BEHAVIOR

Plasma prolactin in the rat during suckling without prior separation from pups. Mattheij JA, et al. **Acta Endocrinol (Copenh)** 1985 Apr; 108(4):468-74

Control of suckling and feeding by methysergide in weaning albino rats: a determination of Y-maze preferences. Stoloff ML, et al. **Dev Psychobiol** 1985 May;18(3):273-85

SYMPATHOMIMETICS

In vitro studies on the pharmacological properties of diacetolol, the major metabolite of acebutolol in man. Borchard U, et al. **Arch Int Pharmacodyn Ther** 1985 Jan;273(1):4-17

Adrenergic ligand binding in human serum. Sager G, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2812-5

Comparison of postnatal changes in alpha 1-adrenoceptor binding and adrenergic stimulation of phosphoinositide hydrolysis in rat cerebral cortex. Schoepp DD, et al. **Biochem Pharmacol** 1985 Aug 1; 34(15):2705-11

The effect of glucagon and adrenergic agonists on intracellular pH of isolated rat hepatocytes. Deutsch CJ, et al. **J Biol Chem** 1985 Jun 10; 260(11):6808-10

Effects of beta-adrenoceptor antagonist administration on beta 2-adrenoceptor density in human lymphocytes. The role of the 'intrinsic sympathomimetic activity'. Brodde OE, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Feb;328(4):417-22

[Heptaminol adenosine phosphate and the premenstrual syndrome] Anglade JP. **Rev Fr Gynecol Obstet** 1985 Mar;80(4):245-7 (Eng. Abstr.) **(Fre)**

SYNAPTIC RECEPTORS

Effects of long-term drug treatments on the sensitivity of presynaptic receptors regulating neurotransmitter release. Raiteri M, et al. **Ann Ist Super Sanita** 1984;20(1):57-64

Corticosterone modulation of neurotransmitter receptors in rat hippocampus: a quantitative autoradiographic study. Biegon A, et al. **Brain Res** 1985 Apr 22;332(2):309-14

The ontogenetic development of neurotensin-like immunoreactivity and neurotensin receptors in the cat striatum. Goedert M, et al. **Brain Res** 1985 May;352(1):127-31

Age-related changes in 5HT uptake and [3H]imipramine binding sites in rat cerebral cortex. Brunello N, et al. **Eur J Pharmacol** 1985 Apr 16;110(3):393-4

Possible relationship between antimanic effect and activity of zotepine to 5HT1 receptor. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):473-80

Ibotenic acid analogues. Synthesis, molecular flexibility, and in vitro activity of agonists and antagonists at central glutamic acid receptors. Lauridsen J, et al. **J Med Chem** 1985 May;28(5):668-72

High- and low-affinity binding components for [3H]imipramine in rat cerebral cortex. Conway PG, et al. **J Neurochem** 1985 Jul; 45(1):206-9

5-Methoxytryptoline, a competitive endocoid acting at [3H]imipramine recognition sites in human platelets. Segonzac A, et al. **J Neurochem** 1985 Jul;45(1):249-56

Pharmacological characterization of postsynaptic receptors for excitatory amino acids in Purkinje cell dendrites in the guinea pig cerebellum. Kimura H, et al. **J Pharmacobiodyn** 1985 Feb;8(2):119-27

Cardiovascular effects of spinal cord substance P: studies with a stable receptor agonist. Keeler JR, et al. **J Pharmacol Exp Ther** 1985 Jun; 233(3):755-60

Effects of calcium hopantenate on neurotransmitter receptors in the rat brain. Ogawa N, et al. **Jpn J Pharmacol** 1985 Jan;37(1):45-50

Modulation of receptor sensitivity and action potentials by transmitters in vertebrate neurones. Koketsu K. **Jpn J Physiol** 1984;34(6):945-60 (59 ref.)

3H-Imipramine binding sites in platelets of hospitalized psychiatric patients. Gentsch C, et al. **Psychiatry Res** 1985 Mar;14(3):177-87

[Antenatal effect of imipramine on the ontogeny of the imipramine receptors in the cerebral cortex of rats] Pirogova MV, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):35-8 (Eng. Abstr.) **(Rus)**

TERRITORIALITY

Short-term changes in plasma levels of hormones during establishment and defense of a breeding territory in male song sparrows, Melospiza melodia. Wingfield JC. **Horm Behav** 1985 Jun;19(2):174-87

TESTOSTERONE

Neuro-endocrine effects of isotheoline. Zhelyazkov D, et al. **Acta Physiol Pharmacol Bulg** 1984;10(4):53-8

Long-term, pulsatile, low dose, subcutaneous luteinizing hormone-releasing hormone administration in men with idiopathic oligozoospermia. Failure of therapeutic and hormonal response. Fauser BC, et al. **Andrologia** 1985 Mar-Apr;17(2):143-9

Regulation of infant and developing rat testicular gonadotropin and prolactin receptors and steroidogenesis by treatments with human chorionic gonadotropin, gonadotropin-releasing hormone analogs, bromocriptine, prolactin, and estrogen. Huhtaniemi IT, et al. **Biol Reprod** 1985 May;32(4):721-32

The effects of testosterone and estrogen on the pituitary growth hormone response to growth hormone-releasing factor. Wehrenberg WB, et al. **Biol Reprod** 1985 Mar;32(2):369-75

Effects of steroid hormones on the neuropil of the hypothalamic paraventricular nucleus of male chickens. Panzica GC, et al. **Cell Tissue Res** 1985;240(1):169-74

The influence of testosterone in the brain of the male rat on levels of serotonin (5-HT) and hydroxyindole-acetic acid (5-HIAA). Martinez-Conde E, et al. **Comp Biochem Physiol [C]** 1985; 80(2):411-4

The role of calcium/phospholipid-dependent protein kinase in Leydig cell steroidogenesis. Lin T. **Endocrinology** 1985 Jul;117(1):119-26

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

FSH and LH response to testosterone and gonadotropin-releasing hormone in aging male rats. Sartin JL, et al. **Exp Aging Res** 1984 Winter; 10(4):183-7

Seasonal variations in plasma luteinizing hormone and testosterone levels in the European badger Meles meles L. Audy MC, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):445-53

Seasonal changes in plasma testosterone, thyroxine, and cortisol levels in wild rabbits (Oryctolagus cuniculus algirus) of Zembra island. Ben Saad M, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):383-8

Annual and diurnal cycles in plasma testosterone and thyroxine in the male green sea turtle Chelonia mydas. Licht P, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):335-44

Effect of temperature and darkness on testosterone concentration in the testes of intact frogs (Rana esculenta) treated with gonadotrophin-releasing hormone analog (HOE 766). Pierantoni R, et al. **Gen Comp Endocrinol** 1985 Apr;58(1):128-30

Short-term changes in plasma levels of hormones during establishment and defense of a breeding territory in male song sparrows, Melospiza melodia. Wingfield JC. **Horm Behav** 1985 Jun;19(2):174-87

Hyperprolactinaemia and testosterone production. Observations in 2 men on long-term dialysis. Stegmayr B, et al. **Horm Res** 1985; 21(4):224-8

Possible role of prolactin in the inhibitory effect of testosterone on the hypothalamic-pituitary-testicular axis in the rat. Tresguerres JA, et al. **J Endocrinol** 1985 Jun;105(3):423-7

Newborn and immature rat testes contain gonadotropin-releasing hormone (GnRH) receptors, and their testosterone production is stimulated by a GnRH agonist in vitro. Huhtaniemi IT, et al. **Mol Cell Endocrinol** 1985 Apr;40(1):41-4

Influence of perinatal androgen on the sexually dimorphic distribution of tyrosine hydroxylase-immunoreactive cells and fibers in the anteroventral periventricular nucleus of the rat. Simerly RB, et al. **Neuroendocrinology** 1985 Jun;40(6):501-10

Suppression of male copulatory behavior by delta 9-THC is not dependent on changes in plasma testosterone or hypothalamic dopamine or serotonin content. Shrenker P, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):415-20

Neonatal phenobarbital imprinting of hepatic microsomal enzymes in adult rats: modulation by neonatal testosterone presence. Bagley DM, et al. **Toxicol Appl Pharmacol** 1985 Jun 30;79(2):227-35

THIORIDAZINE

Effects of thioridazine and fluphenazine on the pituitary, thyroid and adrenal functions in patients with paranoid schizophrenia. Horodnicki JM, et al. **Psychiatr Pol** 1984 May-Jun;18(3):205-11

Lateral ventricular enlargement and clinical response in schizophrenia. Smith RC, et al. **Psychiatry Res** 1985 Mar;14(3):241-53

A computer-supported method for analyzing behavioral observations: studies with stereotypy. Lewis MH, et al. **Psychopharmacology (Berlin)** 1985;85(2):204-9

THIOTHIXENE

Acute thiothixene overdose. Kemal M, et al. **J Anal Toxicol** 1985 Mar-Apr;9(2):94-5

Treatment-resistant catatonic stupor and combined lithium-neuroleptic therapy: a case report. Climo LH. **J Clin Psychopharmacol** 1985 Jun; 5(3):166-70

THYROID HORMONES

Thyroid hormones reversibly suppress somatostatin secretion and immunoreactivity in cultured neocortical cells. Peterfreund RA, et al. **Brain Res** 1985 Mar 4;328(2):259-70

Modulatory effect of thyroid hormones on uptake of phosphate and other solutes across luminal brush border membrane of kidney cortex. Yusufi AN, et al. **Endocrinology** 1985 Jun;116(6):2438-49

3,5,3'-Triiodothyronine receptors and thyroxine 5'-monodeiodinating activity in thyroid hormone-insensitive amphibia. Galton VA. **Gen Comp Endocrinol** 1985 Mar;57(3):465-71

Relationship of the menstrual cycle and thyroid hormones to whole-body protein turnover in women. Garrel DR, et al. **Hum Nutr Clin Nutr** 1985 Jan;39(1):29-37

Changes in cardiac function following administration of thyroid hormones in thyroidectomised rats: assessment using the isolated working rat heart preparation. Brooks I, et al. **J Cardiovasc Pharmacol** 1985 Mar-Apr; 7(2):290-6

Routine measurement of thyroid hormones and FSH in infertility not worthwhile [letter] Conway DI, et al. **Lancet** 1985 Apr 27; 1(8435):977-8

Correlation between thyroid function and nephron loss. Giordano C, et al. **Life Support Syst** 1985 Jan-Mar;3(1):41-3

Thyroid gland volume and serum concentrations of thyroid hormones in chronic renal failure. Hegedüs L, et al. **Nephron** 1985;40(2):171-4

[Effect of preventive administration of lithium carbonate on serum concentrations of various pituitary and peripheral hormones in patients with endogenous depression] Horodnicki JM, et al. **Psychiatr Pol** 1984 Jul-Aug;18(4):319-25 (Eng. Abstr.) **(Pol)**

[Hormones of the thyroid gland and pancreas in lethally irradiated rats] Ahlersová E, et al. **Bratisl Lek Listy** 1985 Apr;83(4):433-9 (Eng. Abstr.) **(Slo)**

[The thyroid and amiodarone (I). Changes in peripheral thyroid hormones caused by prolonged treatment with amiodarone] Gómez JM, et al. **Med Clin (Barc)** 1985 Mar 16;84(10):381-3 (Eng. Abstr.) **(Spa)**

THYROTROPIN

Serum concentrations of thyroxine, 3,5,3'-triiodothyronine, thyrotropin, and prolactin in dogs before and after thyrotropin-releasing hormone administration. Kaufman J, et al. **Am J Vet Res** 1985 Feb; 46(2):486-92

Sensitive immunoradiometric assay (IRMA) for serum thyrotropin may be insufficient to make the thyrotropin-releasing-factor test unnecessary [letter] Rodríquez-Espinosa J, et al. **Clin Chem** 1985 Jun; 31(6):1081-2

Intranasal thyrotrophin releasing hormone is a potent stimulus for TSH release in man (comparison with intravenous and oral TRH). Staub JJ, et al. **Clin Endocrinol (Oxf)** 1985 Apr;22(4):567-72

Functional specificity of gonadotropin and thyrotropin in Fundulus heteroclitus. Brown CL, et al. **Gen Comp Endocrinol** 1985 May; 58(2):252-8

Administration of low doses of TSH result in a rapid increase in the metabolic rate of young lambs. Lynch MA, et al. **Horm Metab Res** 1985 Mar;17(3):136-40

Thyroxine binding and TSH in recurrent depressive episodes. Tollefson G, et al. **J Clin Psychiatry** 1985 Jul;46(7):267-72

Hypothalamo-pituitary regulation of thyrotrophin secretion in chronically catheterized Brattleboro rats. Wolf BA, et al. **J Endocrinol** 1985 May; 105(2):277-83

Photoperiodic regulation of thyroid responsiveness to TSH in Fundulus heteroclitus. Grau EG, et al. **J Exp Zool** 1985 May;234(2):199-205

Effects of TSH on iodination in rat thyroid follicles studied by autoradiography. Ofverholm T, et al. **Mol Cell Endocrinol** 1985 Apr; 40(1):1-7

Acute effect of triiodothyronine on the dynamics of thyrotropin release from superfused anterior pituitary cells. Shiota K, et al. **Mol Cell Endocrinol** 1985 Jun;41(1):79-84

Oxytocin attenuates TRH-induced TSH release from rat pituitary cells. Frawley LS, et al. **Neuroendocrinology** 1985 Mar;40(3):201-4

Role of the sympathetic nervous system in the control of thyroid compensatory growth of normal and hypophysectomized rats. Romeo HE, et al. **Neuroendocrinology** 1985 Apr;40(4):309-15

THYROXINE

Plasma growth hormone and thyroxine levels in the chronically catheterised pig foetus and the effect of thyrotrophin releasing hormone. Macdonald AA, et al. **Acta Endocrinol (Copenh)** 1985 May; 109(1):126-9

Effect of thyroxine on hepatic glucose-6-phosphatase activity and glycogen content of toad (Bufo melanostictus) and Lata fish (Ophicephalus punctatus) at different stages of life. Paul AK, et al. **Acta Physiol Hung** 1985;65(3):233-8

Effect of propylthiouracil dose on serum thyroxine, growth, and weaning in young rats. Blake HH, et al. **Am J Physiol** 1985 May; 248(5 Pt 2):R524-30

Transport of thyroxine bound to human prealbumin into rat liver. Pardridge WM, et al. **Am J Physiol** 1985 May;248(5 Pt 1):G545-50

Serum concentrations of thyroxine, 3,5,3'-triiodothyronine, thyrotropin, and prolactin in dogs before and after thyrotropin-releasing hormone administration. Kaufman J, et al. **Am J Vet Res** 1995 Feb; 46(2):486-92

Effects of D- and L-thyroxine on the glucocorticoid binding capacity of adult rat liver. Naito K, et al. **Biochem Biophys Res Commun** 1985 Jun 14;129(2):447-52

Regulation of NAD- and NADP-linked isocitrate dehydrogenase by thyroxine in the brain and liver of female rats of various ages. Yadav RN. **Biochem Med** 1985 Jun;33(3):312-9

In vitro synthesis of thyroxine in a low molecular weight polypeptide fragment from human thyroglobulin. Lejeune PJ, et al. **Biochimie** 1985 Feb;67(2):199-203

Least squares calculation of the standard curve for the EMIT manual thyroxin assay [letter] Johnson D Jr, et al. **Clin Chem** 1985 Jul; 31(7):1247

Differences between measurements of free thyroxin in serum from siliconized and nonsiliconized tubes are influenced by analyte concentration [letter] Ordóñez-Llanos J, et al. **Clin Chem** 1985 Jul; 31(7):1249-50

The production and characterisation of a monoclonal antibody to thyroxine. Mpoko CN, et al. **Clin Chim Acta** 1985 Mar 15; 146(2-3):215-22

The effect of in vivo glucose administration on human erythrocyte Ca2+-ATPase activity and on enzyme responsiveness in vitro to thyroid hormone and calmodulin. Davis FB, et al. **Diabetes** 1985 Jul; 34(7):639-46

Seasonal changes in plasma testosterone, thyroxine, and cortisol levels in wild rabbits (Oryctolagus cuniculus algirus) of Zembra island. Ben Saad M, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):383-8

3,5,3'-Triiodothyronine receptors and thyroxine 5'-monodeiodinating activity in thyroid hormone-insensitive amphibia. Galton VA. **Gen Comp Endocrinol** 1985 Mar;57(3):465-71

Thyroid hormone binding in serum of 15 vertebrate species: isolation of thyroxine-binding globulin and prealbumin analogs. Larsson M, et al. **Gen Comp Endocrinol** 1985 Jun;58(3):360-75

Annual and diurnal cycles in plasma testosterone and thyroxine in the male green sea turtle Chelonia mydas. Licht P, et al. **Gen Comp Endocrinol** 1985 Mar;57(3):335-44

Thyroxine binding and TSH in recurrent depressive episodes. Tollefson G, et al. **J Clin Psychiatry** 1985 Jul;46(7):267-72

Immunocytochemistry of luteinizing hormone-releasing hormone during spontaneous and thyroxine-induced metamorphosis of bullfrogs. Whalen R, et al. **J Exp Zool** 1985 Apr;234(1):131-44

Effect of breast-feeding vs formula-feeding on circulating thyroxine levels in premature infants. Oberkotter LV, et al. **J Pediatr** 1985 May; 106(5):822-5

Chronic thyroxine treatment of rats down-regulates the noradrenergic cyclic AMP generating system in cerebral cortex. Schmidt BH, et al. **J Pharmacol Exp Ther** 1985 May;233(2):466-72

Lead poisoning and euthyroid hyperthyroxinaemia [letter] Tiwari I, et al. **Lancet** 1985 Jun 29;1(8444):1508-9

Photoperiodic and light spectral conditions which inhibit circulating concentrations of thyroxine in the male hamster. Vaughan MK, et al. **Life Sci** 1985 Jun 10;36(23):2183-8

The effects of acute and chronic treatment with triiodothyronine and thyroxine on the hypothalamic and telencephalic catecholamine nerve terminal systems of the hypophysectomized male rat. Chronic treatment modulates catecholamine utilization in discrete catecholamine nerve terminal systems. Andersson K, et al. **Neuroendocrinology** 1985 May; 40(5):398-408

Role of thyroxine in the postnatal development of rat hepatic tryptophan oxygenase and ornithine aminotransferase. Vandewater LJ, et al. **Proc Soc Exp Biol Med** 1985 May;179(1):83-9

[Automated recording of precision profiles for the radioimmunological determination of T4 using a pocket calculator of the HP-41 CV type] Ditu M, et al. **Ann Endocrinol (Paris)** 1984;45(6):393-6 (Eng. Abstr.) **(Fre)**

[Lugol's solution and thyroid gland activity in cattle. Determination of the total thyroxine in blood plasma as a method for evaluating thyroid gland activity] Braun U, et al. **Tierarztl Prax** 1985;Suppl 1:33-40 (Eng. Abstr.) **(Ger)**

[Evaluation of free thyroxine radioimmunoassays for assessing thyroid function in hypoproteinemia] Matsumura K, et al. **Kaku Igaku** 1985 Apr;22(4):511-20 (Eng. Abstr.) **(Jpn)**

[Effect of the administration of thyroxine and estradiol on the morphology of the anterior lobe of the pituitary gland] Szczurek Z, et al. **Patol Pol** 1984 Oct-Dec;35(4):499-507 (Eng. Abstr.) **(Pol)**

TIME PERCEPTION

Arginine vasopressin inoculates against age-related changes in temporal memory. Meck WH, et al. **Ann NY Acad Sci** 1985;444:453-6

Cannabis, atropine, and temporal information processing. Hicks RE, et al. **Neuropsychobiology** 1984;12(4):229-37

TRANQUILIZING AGENTS

1st Czechoslovak Conference on Biological Psychiatry. Karlovy Vary (Karlsbad), September 1983. Abstracts. **Act Nerv Super (Praha)** 1985 Mar;27(1):60-72

Sex differences in the use of alcohol and tranquilizers: testing a role convergence hypothesis. Bell R, et al. **Am J Drug Alcohol Abuse** 1984; 10(4):551-61

Chlordiazepoxide toxicity in Limbitrol overdose [letter] Goethe JW, et al. **Am J Psychiatry** 1985 Jun;142(6):774

Some neurochemical effects of a new antianxiety agent centazolone. Laxmi CV, et al. **Indian J Exp Biol** 1984 Dec;22(12):649-52

Determination of cyclobenzaprine in plasma and urine using capillary gas chromatography with nitrogen-selective detection. Constanzer ML, et al. **J Chromatogr** 1985 May 3;339(2):414-8

Serotonin antagonist pirenperone inhibits sexual behavior in the male rat: attenuation by quipazine. Mendelson SD, et al. **Pharmacol Biochem Behav** 1985 Apr;22(4):565-71

[Practical advice concerning the immobilization of wild and zoo animals] Wiesner H, et al. **Tierarztl Prax** 1985;13(1):113-27 (Eng. Abstr.) **(Ger)**

TRANQUILIZING AGENTS, MAJOR

Clinical characteristics of hospitalized psychotic patients who refuse antipsychotic drug therapy. Zito JM, et al. **Am J Psychiatry** 1985 Jul; 142(7):822-6

Prolonged pharmacologic activity of neuroleptics [letter] Campbell A, et al. **Arch Gen Psychiatry** 1985 Jun;42(6):637

Selection of neuroleptic dosage [letter] Teicher MH, et al. **Arch Gen Psychiatry** 1985 Jun;42(6):636-7

Schizophrenia with good and poor outcome. I: Early clinical features, response to neuroleptics and signs of organic dysfunction. Kolakowska T, et al. **Br J Psychiatry** 1985 Mar;146:229-39

Platelet monoamine-oxidase activity in schizophrenia. Relation to genetic load of the illness and treatment with antipsychotic drugs. Kemali D, et al. **Encephale** 1985 Jan-Feb;11(1):31-4

Increased hepatic and reduced prostatic prolactin (PRL) binding in iron deficiency and during neuroleptic treatment: correlation with changes in serum PRL and testosterone. Barkey RJ, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):193-200

Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Creese I, et al. **Eur J Pharmacol** 1985 Feb 12; 109(1):127-8

Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Gessa GL, et al. **Eur J Pharmacol** 1985 Feb 26;109(2):269-74

Repeated treatment with imipramine decreased the number of [3H]piflutixol binding sites in the rat striatum. Klimek V, et al. **Eur J Pharmacol** 1985 Feb 12;109(1):131-2

Possible relationship between antimanic effect and activity of zotepine to 5HT1 receptor. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1984; 38(4):473-80

Pharmacokinetics and initial distribution of a new neuroleptic agent picobenzide (M-14012-4). Calvo MV, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 May;23(5):233-7

Stimulants and neuroleptics in hyperactive children [letter] Gualtieri CT, et al. **J Am Acad Child Psychiatry** 1985 May;24(3):363-4

Neuroleptic bioequivalency: tablet versus concentrate. Fann WE, et al. **J Clin Pharmacol** 1985 May-Jun;25(4):305-6

Drugs and the quality of life: the patient's point of view. Diamond R.

J Clin Psychiatry 1985 May;46(5 Pt 2):29-35

Compliance issues in outpatient treatment. Kane JM. **J Clin Psychopharmacol** 1985 Jun;5(3 Suppl):22S-27S

Focal neuroleptization: an approach to optimal dosing for initial and continuing therapy. Tupin JP. **J Clin Psychopharmacol** 1985 Jun; 5(3 Suppl):15S-21S

Synthesis and neuroleptic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles. Strupczewski JT, et al. **J Med Chem** 1985 Jun;28(6):761-9

Problems in classification of schizophrenics as neuroleptic responders and nonresponders. Csernansky JG, et al. **J Nerv Ment Dis** 1985 Jun; 173(6):325-31 (93 ref.)

Inactivation of D1 and D2 dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vivo: selective protection by neuroleptics. Meller E, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):656-62

Mental health dilemmas. Parts of a whole. Lacey R. **Nurs Times** 1985 May 1-7;81(18):27-8

Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. Gramling SE, et al. **Pharmacol Biochem Behav** 1985 Apr; 22(4):541-5

One-year outcome of schizophrenic patients--the interaction of chronicity and neuroleptic treatment. Gaebel W, et al. **Pharmacopsychiatry** 1985 May;18(3):235-9

1,2-Anellated 1,4-benzodiazepine derivatives--a new class of antipsychotics. Ruhland M, et al. **Pharmacopsychiatry** 1985 Jan; 18(1):174-7

Amphetamine response and relapse risk after depot neuroleptic discontinuation. Angrist B, et al. **Psychopharmacology (Berlin)** 1985; 85(3):277-83

Chronic neuroleptic treatment and mesolimbic dopamine denervation induce behavioural supersensitivity to opiates. Stinus L, et al. **Psychopharmacology (Berlin)** 1985;85(3):323-8

Pharmacological differentiation of dopamine D-1 and D-2 antagonists after single and repeated administration. Christensen AV, et al. **Psychopharmacology [Suppl]** 1985;2:182-90

Receptor-binding profiles of neuroleptics. Hyttel J, et al. **Psychopharmacology [Suppl]** 1985;2:9-18

Akinesia, tardive dysmentia, and frontal lobe disorder in schizophrenia. Goldberg E. **Schizophr Bull** 1985;11(2):255-63

Tardive dysmentia : further comments. Jones BD. **Schizophr Bull** 1985; 11(2):187-9

Acutely psychotic patients: a treatment approach. Wagemaker H, et al. **South Med J** 1985 Jul;78(7):833-7

[Benzonitrile and structural analogs. Action of para-aminobenzonitrile on the central nervous system] Cheav SL, et al. **Ann Pharm Fr** 1984; 42(4):367-78 (Eng. Abstr.) **(Fre)**

[Adsorption of cationic amphiphilic drugs to antacids and adsorbents. 3. Adsorption of tricyclic antidepressive agents and neuroleptics in relation to their colloid chemical properties] Thomas K, et al. **Pharm Acta Helv** 1985;60(2):39-47 (Eng. Abstr.) **(Ger)**

[The effect of psychopharmacologic agents on the passive transport of Ca2+ induced by vanadate in human erythrocytes] Pogády J, et al. **Bratisl Lek Listy** 1985 Apr;83(4):345-52 (Eng. Abstr.) **(Slo)**

TRANQUILIZING AGENTS, MINOR

The relationship between buspirone bioavailability and dose in healthy subjects. Gammans RE, et al. **Biopharm Drug Dispos** 1985 Apr-Jun; 6(2):139-45

Rapid gas chromatographic assay for monitoring valnoctamide in plasma. Bialer M, et al. **J Chromatogr** 1985 Feb 8;337(2):408-11

1-Azacycloalkyl-1,4-benzodiazepin-2-ones with antianxiety-antidepressant actions. Sugasawa T, et al. **J Med Chem** 1985 Jun;28(6):699-707

Effects of acute and chronic treatment on the pro- and anti-convulsant actions of CL 218, 872, PK 8165 and PK 9084, putative ligands for the benzodiazepine receptor. File SE, et al. **J Pharm Pharmacol** 1985 Apr;37(4):252-6

Animal models for the study of anti-anxiety agents: a review. Treit D. **Neurosci Biobehav Rev** 1985 Summer;9(2):203-22

Evidence that tolerance develops to the anxiolytic effect of diazepam in rats. Treit D. **Pharmacol Biochem Behav** 1985 Mar;22(3):383-7

The sedative effects of CL 218,872, like those of chlordiazepoxide, are reversed by benzodiazepine antagonists. File SE, et al. **Psychopharmacology (Berlin)** 1985;85(3):295-300

A comparison between chlordiazepoxide and CL 218,872--a synthetic nonbenzodiazepine ligand for benzodiazepine receptors on spontaneous locomotor activity in rats. McElroy JF, et al. **Psychopharmacology (Berlin)** 1985;85(2):224-6

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: punished barpressing. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;85(2):244-51

Anxiolytic drugs and the acquisition of conditioned fear in mice. Sanger DJ, et al. **Psychopharmacology (Berlin)** 1985;85(3):284-8

[Thiophene as a structural element in physiologically active substances. 15. Thiophene analogs of an anxiolytic acting 1,2,4-triazolo[4,3-b]pyridazine] Binder D, et al. **Arch Pharm (Weinheim)** 1985 Mar;318(3):243-9 (Eng. Abstr.) **(Ger)**

[Anxiolytic action of sodium valproate (possible role of gamma-aminobutyric acid in affective disorders)] Raevskii KS, et al. **Zh Nevropatol Psikhiatr** 1985;85(4):574-9 (Eng. Abstr.) **(Rus)**

TRANYLCYPROMINE

Lack of pharmacokinetic interaction of carbamazepine with tranylcypromine [letter] Joffe RT, et al. **Arch Gen Psychiatry** 1985 Jul; 42(7):738

Platelet monoamine oxidase inhibition by deprenyl and tranylcypromine: implications for clinical use. Simpson GM, et al. **Biol Psychiatry** 1985 Jun;20(6):684-7

TRIFLUOPERAZINE

Sites of interaction of calmodulin with trifluoperazine and glucagon. Steiner RF, et al. **Arch Biochem Biophys** 1985 Jul;240(1):297-311

Behavioral interaction of adenosine and trifluoperazine in mice. DeLong RE, et al. **Neurosci Lett** 1985 Jan 7;53(1):101-7

Evidence that a Ca2+ chelator and a calmodulin blocker interfere with the structure of inter-Sertoli junctions. Franchi E, et al. **Tissue Cell** 1985;17(1):13-25

The effect of trifluoperazine (Stellazine) on Hymenolepis diminuta in vitro. Brandford White CJ, et al. **Z Parasitenkd** 1985;71(3):365-72

TRYPTAMINES

Increased protective effect of cystamine and mexamine against radiation after activation of the haemopoiesis by dextran sulphate in mice. Vacek A, et al. **Acta Radiol [Oncol]** 1985 Mar-Apr;24(2):193-8

In vitro pigment formation from tryptamine. Role of indole-3-acetaldehyde. Das PK, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2663-7

Tryptamine-induced vasoconstrictor responses in rat caudal arteries are mediated predominantly via 5-hydroxytryptamine receptors. Bradley PB, et al. **Br J Pharmacol** 1985 Apr;84(4):919-25

Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Shenker A, et al. **Eur J Pharmacol** 1985 Mar 12; 109(3):427-9

Indoleamine-sensitive adenylate cyclase in rabbit retina: characterization and distribution. Blazynski C, et al. **J Neurochem** 1985 Aug; 45(2):440-7

Tryptamine concentrations in areas of 5-hydroxytryptamine terminal innervation after electrolytic lesions of midbrain raphe nuclei. Juorio AV, et al. **J Neurochem** 1985 Aug;45(2):422-6

5-Hydroxytryptamine receptor in isolated rabbit aorta: characterization with tryptamine analogs. Clancy BM, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):761-9

Membrane responses and changes in cAMP levels in Aplysia sensory neurons produced by serotonin, tryptamine, FMRFamide and small cardioactive peptideB (SCPB). Ocorr KA, et al. **Neurosci Lett** 1985 Apr 9;55(2):113-8

TRYPTOPHAN

Plasma tryptophan, age and depression. Phipps DA, et al. **Age Ageing** 1985 Mar;14(2):71-5

An amino-terminal tryptophan derivative which is refractory to Edman degradation. Mahoney WC. **Anal Biochem** 1985 Jun;147(2):331-5

Spectrophotometric estimation of protein concentration in the presence of tryptophan modified by 2-hydroxy-5-nitrobenzyl bromide. Malin EL, et al. **Anal Biochem** 1985 Feb 1;144(2):356-61

Identification of peptides containing tryptophan, tyrosine, and phenylalanine using photodiode-array spectrophotometry. Yang CY, et al. **Anal Biochem** 1985 Feb 15;145(1):67-72

Energy transfer from tryptophan residues to pyridoxal 5'-phosphate at the active site of ribulose-1,5-bisphosphate carboxylase/oxygenase. Verma NC, et al. **Biochem Biophys Res Commun** 1985 May 31; 129(1):256-61

Effect of tryptophan metabolites on the activities of rat liver pyridoxal kinase and pyridoxamine 5-phosphate oxidase in vitro. Takeuchi F, et al. **Biochem J** 1985 Apr 15;227(2):537-44

Analysis and identification of aromatic signals in the proton magnetic resonance spectrum of the kringle 4 fragment from human plasminogen. De Marco A, et al. **Biochemistry** 1985 Jan 29;24(3):748-53

Protein structural changes accompanying formation of enzymatic transition states: tryptophan environment in ground-state and transition-state analogue complexes of adenosine deaminase. Kurz LC, et al. **Biochemistry** 1985 Mar 12;24(6):1342-6

In vitro characterization of hybrid promoters and altered tryptophan operon promoters. Russell DR, et al. **Biochemistry** 1985 Mar 12; 24(6):1410-7

Effect of tryptophan derivatives on the phase properties of bilayers. Jain

MK, et al. **Biochim Biophys Acta** 1985 Jun 11;816(1):153-62

Abilities of some tryptophan and phenylalanine derivatives to inhibit gastric acid secretion. Magous R, et al. **Biochim Biophys Acta** 1985 May 30;845(2):158-62

A controlled clinical trial of L-tryptophan in acute mania. Chouinard G, et al. **Biol Psychiatry** 1985 May;20(5):546-57

Effect of alkylation of tryptophan residues on the enzymatic and pharmacological properties of snake venom phospholipase A2. Condrea E, et al. **Can J Physiol Pharmacol** 1985 Apr;63(4):331-9

Tryptophan content of serum albumin. Kaldy MS, et al. **Comp Biochem Physiol [B]** 1985;80(4):743-5

The microbial metabolism of tryptophan in rats fed a diet containing 7.5% saccharin in a two-generation protocol. Sims J, et al. **Food Chem Toxicol** 1985 Apr-May;23(4-5):437-44

Nucleotide sequence of the Bacillus subtilis tryptophan operon. Henner DJ, et al. **Gene** 1985;34(2-3):169-77

Nutritive value of D-tryptophan for the growing pig. Arentson BE, et al. **J Anim Sci** 1985 Feb;60(2):474-9

Xanthurenic acid 8-O-beta-D-glucoside, a novel tryptophan metabolite in eye-color mutants of Drosophila melanogaster. Ferre J, et al. **J Biol Chem** 1985 Jun 25;260(12):7509-14

Analysis of the requirements for transcription pausing in the tryptophan operon. Fisher RF, et al. **J Mol Biol** 1985 Apr 5;182(3):397-409

Clues from Xanthomonas campestris about the evolution of aromatic biosynthesis and its regulation. Whitaker RJ, et al. **J Mol Evol** 1984-85; 21(2):139-49

The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3-4):175-81

Variables influencing the effect of a meal on brain tryptophan. Sarna GS, et al. **J Neurochem** 1985 May;44(5):1575-80

Lowering of plasma free tryptophan in normal and portacaval shunt dogs. Miyai M, et al. **J Surg Res** 1985 Jul;39(1):8-15

Ontogenetic studies on tryptophan transport into plasma membrane vesicles derived from rat brain synaptosomes: effect of thyroid hormones. Herrero E, et al. **Neurochem Res** 1985 May;10(5):579-89

The effects produced by prostaglandin D2 on serotonin turnover and release and tryptophan uptake. Hollingsworth EB, et al. **Pharmacol Biochem Behav** 1985 Mar;22(3):371-5

UGA is read as tryptophan in Mycoplasma capricolum. Yamao F, et al. **Proc Natl Acad Sci USA** 1985 Apr;82(8):2306-9

Fluorescence properties of insulin analogs with tryptophan substitutions. Wang ZZ. **Sci Sin [B]** 1985 Mar;28(3):264-72

TRYPTOPHAN HYDROXYLASE

Effect of clonidine on the activity of tryptophan hydroxylase from rat brainstem following in vivo or in vitro treatment. Weekley LB, et al. **Biochem Pharmacol** 1985 May 1;34(9):1549-57

Tryptophan 5-hydroxylase. Rapid purification from whole rat brain and production of a specific antiserum. Cash CD, et al. **Eur J Biochem** 1985 Jun 3;149(2):239-45

Regulation of 3-indoleacetic acid production in Pseudomonas syringae pv. savastanoi. Purification and properties of tryptophan 2-monooxygenase. Hutcheson SW, et al. **J Biol Chem** 1985 May 25; 260(10):6281-7

TYROSINE

Identification of peptides containing tryptophan, tyrosine, and phenylalanine using photodiode-array spectrophotometry. Yang CY, et al. **Anal Biochem** 1985 Feb 15;145(1):67-72

L-Phenylalanine and L-tyrosine catabolism by selected Streptomyces species. Pometto AL 3d, et al. **Appl Environ Microbiol** 1985 Mar; 49(3):727-9

Chemiluminescence in L-tyrosine-H2O2-horseradish peroxidase system: possible formation of tyrosine cation radical. Ushijima Y, et al. **Biochem Biophys Res Commun** 1985 Apr 30;128(2):936-41

Analysis and identification of aromatic signals in the proton magnetic resonance spectrum of the kringle 4 fragment from human plasminogen. De Marco A, et al. **Biochemistry** 1985 Jan 29;24(3):748-53

Formation of radiation-induced cross-links between thymine and tyrosine: possible model for cross-linking of DNA and proteins by ionizing radiation. Simic MG, et al. **Biochemistry** 1985 Jan 1;24(1):233-6

Enzymatic and nonenzymatic dehydration reactions of L-arogenate. Zamir LO, et al. **Biochemistry** 1985 Mar 26;24(7):1607-12

Elastase-cathepsin G inhibitors eglin b and eglin c differ by a single Tyr----His substitution. A micro-method for the identification of amino-acid substitution. Chang JY, et al. **Biol Chem Hoppe Seyler** 1985 Mar;366(3):281-6

Properties of the aminotyrosine derivatives of calmodulin. Steiner RF, et al. **Biopolymers** 1985 Mar;24(3):547-63

Inhibition of tyrosine hydroxylation in tissue slices of the rat striatum by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Hirata Y, et al. **Brain Res** 1985 Jun 24;337(1):193-6

Blood-brain barrier permeability to leucine-enkephalin, D-alanine2-D-leucine5-enkephalin and their N-terminal amino acid (tyrosine). Zlokovic BV, et al. **Brain Res** 1985 Jun 10;336(1):125-32

Hapten-specific T-cell response to azobenzenearsonate-N-acetyl-L-tyrosine in the Lewis rat. IV. Rat dendritic cells present soluble and insoluble azobenzenearsonate conjugates to T cells. Amsden A, et al. **Cell Immunol** 1985 Jul; 93(2):447-58

Bone cell phosphotyrosine phosphatase: characterization and regulation by calcitropic hormones. Puzas JE, et al. **Endocrinology** 1985 Jun; 116(6):2463-8

Tyrosine-311 of a beta chain is the essential residue specifically modified by 4-chloro-7-nitrobenzofurazan in bovine heart mitochondrial ATPase. Sutton R, et al. **Eur J Biochem** 1985 May 2;148(3):551-4

Clostridium pasteurianum glutamine synthetase mechanism. Evidence for active site tyrosine residues. Krishnan IS, et al. **FEBS Lett** 1985 Jun 17;185(2):267-71

Species variation in the tyrosine sulfation of mammalian gastrins. Andersen BN. **Gen Comp Endocrinol** 1985 Apr;58(1):44-50

Biosynthesis of chlortetracycline: Part I--oxidative metabolism of L-tyrosine by Streptomyces aureofaciens and its relation to the biosynthesis of chlortetracycline. Maiadkar NK. **Hindustan Antibiot Bull** 1984 Aug-Nov;26(3-4):81-95

Structural studies of mitochondrial coupling factor 1 using tyrosine fluorescence. Fernandez-Belda F, et al. **Int J Biochem** 1985; 17(2):223-8

Tyrosine sulfation of yolk proteins 1, 2, and 3 in Drosophila melanogaster. Baeuerle PA, et al. **J Biol Chem** 1985 May 25;260(10):6434-9

pH-induced hysteretic transitions of ovoperoxidase. Deits T, et al. **J Biol Chem** 1985 Jul 5;260(13):7882-8

The interaction of slow-release immunoadjuvants with selected antigens measured in vitro. Penney C, et al. **J Biol Stand** 1985 Jan; 13(1):43-52

Clues from Xanthomonas campestris about the evolution of aromatic biosynthesis and its regulation. Whitaker RJ, et al. **J Mol Evol** 1984-85; 21(2):139-49

The effect of acute lithium administration on brain monoamine synthesis and the precursor amino acids tyrosine and tryptophan in brain and plasma in rats. Berggren U. **J Neural Transm** 1985;61(3-4):175-81

Inhibition of sodium transport in frog skin and iodination of tyrosine in vitro by a peptide of renal origin. Fregly MJ, et al. **Klin Wochenschr** 1985;63 Suppl 3:102-6

N-acetyl-L-tyrosine as a tyrosine source during total parenteral nutrition in adult rats. Im HA, et al. **Pediatr Res** 1985 Jun;19(6):514-8

TYROSINE AMINOTRANSFERASE

Deletions near the albino locus on chromosome 7 of the mouse affect the level of tyrosine aminotransferase mRNA. Schmid W, et al. **Proc Natl Acad Sci USA** 1985 May;82(9):2866-9

TYROSINE HYDROXYLASE

Catecholamine microfluorometry of nigral perikarya and tyrosine hydroxylase assay in some telencephalic structures of rats exposed to different behavioral situations. Divac I, et al. **Acta Neurobiol Exp (Warsz)** 1984;44(6):262-72

Decrease in tyrosine hydroxylase synthesis in cultured adrenal medulla by N6-methyladenosine. Burke WJ, et al. **Biochem Pharmacol** 1985 Aug 1;34(15):2621-7

Effects of alpha-difluoromethylornithine on polyamine biosynthesis and tyrosine hydroxylase induction in the adrenal gland of the rat subjected to stress or apomorphine. Ekker M, et al. **Biochem Pharmacol** 1985 Apr 15;34(8):1315-20

Evidence for the involvement of Ca2+-calmodulin and cyclic AMP in the regulation of the tyrosine hydroxylase system in rat striatal tissue slices. Hirata Y, et al. **Biochem Pharmacol** 1985 Aug 1; 34(15):2637-43

Immunohistochemical evidence for phenylethanolamine-N-methyltransferase-positive/tyrosine hydroxylase-negative neurones in the retina and the posterior hypothalamus of the rat. Foster GA, et al. **Brain Res** 1985 Mar 18; 330(1):183-8

Synaptic interaction between catecholaminergic neurons and substance P-immunoreactive axons in the caudal part of the nucleus of the solitary tract of the rat: demonstration by the electron microscopic mirror technique. Kubota Y, et al. **Brain Res** 1985 Apr 29;333(1):188-92

Intrinsic tyrosine hydroxylase (TH) immunoreactive axons synapse with TH immunopositive neurons in the rat arcuate nucleus. Leranth C, et al. **Brain Res** 1985 Apr 8;331(2):371-5

The distribution of monoaminergic cells and fibers in a periventricular preoptic nucleus involved in the control of gonadotropin release: immunohistochemical evidence for a dopaminergic sexual dimorphism. Simerly RB, et al. **Brain Res** 1985 Mar 18;330(1):55-64

A comparative study of tyrosine 3-monooxygenase from rat adrenal and brainstem. Okuno S, et al. **J Biochem (Tokyo)** 1985 Jan;97(1):265-73

Purification and characterization of rat striatal tyrosine hydroxylase. Comparison of the activation by cyclic AMP-dependent phosphorylation and by other effectors. Richtand NM, et al.

J Biol Chem 1985 Jul 15;260(14):8465-73

Characteristics of tyrosine hydroxylase activation by K+-induced depolarization and/or forskolin in rat striatal slices. el Mestikawy S, et al. **J Neurochem** 1985 Jul;45(1):173-84

Appearance of the noradrenergic markers tyrosine hydroxylase and neuropeptide Y in cholinergic nerves of the iris following sympathectomy. Björklund H, et al. **J Neurosci** 1985 Jun; 5(6):1633-40

A combined autoradiographic and immunocytochemical study of 3H-corticosterone target neurons and catecholamine neurons in rat and mouse lower brain stem. Duncan GE, et al. **Neuroendocrinology** 1985 Mar;40(3):262-71

Influence of perinatal androgen on the sexually dimorphic distribution of tyrosine hydroxylase-immunoreactive cells and fibers in the anteroventral periventricular nucleus of the rat. Simerly RB, et al. **Neuroendocrinology** 1985 Jun;40(6):501-10

Differential effects of transection of the spinal cord and splanchnic nerve on adrenal tyrosine hydroxylase and catecholamines. Gagner JP, et al. **Neuroscience** 1985 Mar;14(3):907-20

Morphological evidence for a dopaminergic terminal field in the hippocampal formation of young and adult rat. Verney C, et al. **Neuroscience** 1985 Apr;14(4):1039-52

Distribution of CRF- and tyrosine hydroxylase-immunoreactive neurons in the brainstem of the domestic fowl (Gallus domesticus). Knigge KM, et al. **Peptides (Fayetteville)** 1985 Jan-Feb;6(1):97-101

Sympathetic neuron density differentially regulates transmitter phenotypic expression in culture. Adler JE, et al. **Proc Natl Acad Sci USA** 1985 Jun;82(12):4296-300

[Comparative effect of the psychostimulants sidnocarb and fenamin on the tyrosine hydroxylase activity of the brain synaptosomes in rats] Ganiev MM, et al. **Farmakol Toksikol** 1985 Mar-Apr;48(2):27-32 (Eng. Abstr.) **(Rus)**

VANILMANDELIC ACID

Liquid-chromatographic determination of vanillylmandelic acid in urine. Anderson GM, et al. **Clin Chem** 1985 Jun;31(6):819-21

VASOPRESSINS

Leukotriene D4 reduces pressor responses to sympathetic stimulation, angiotensin, and vasopressin. Bayorh MA, et al. **Adv Prostaglandin Thromboxane Leukotriene Res** 1985;13:51-4

Alpha 2-adrenoceptor antagonism of vasopressin-induced changes in sodium excretion. Smyth DD, et al. **Am J Physiol** 1985 Jun; 248(6 Pt 2):F767-72

Stimulation of prostacyclin production in isolated rat adipocytes by angiotensin II, vasopressin, and bradykinin: evidence for two separate mechanisms of prostaglandin synthesis. Axelrod L, et al. **Endocrinology** 1985 Jun;116(6):2548-53

Foot shock stress-induced release of vasopressin in adenohypophysectomized and hypophysectomized rats. Knepel W, et al. **Endocrinology** 1985 Jul;117(1):292-9

Evidence for the formation of inositol 4-monophosphate in stimulated human platelets. Siess W. **FEBS Lett** 1985 Jun 3;185(1):151-6

The contribution of vasopressin and angiotensin to the maintenance of blood pressure after autonomic blockade. Hiwatari M, et al. **Hypertension** 1985 Jul-Aug;7(4):547-53

GABAergic inhibition of hypertonic saline-induced vasopressin-dependent hypertension. Brennan TJ, et al. **J Pharmacol Exp Ther** 1985 Jun;233(3):663-71

Hormonal control of renal potassium excretion. Field MJ, et al. **Kidney Int** 1985 Feb;27(2):379-87 (86 ref.)

Co-localization of corticotropin releasing factor and vasopressin mRNA in neurones after adrenalectomy. Wolfson B, et al. **Nature** 1985 May 2-8;315(6014):59-61

Senescent change in tissue weight and immunoreactive beta-endorphin, enkephalin, and vasopressin in eight regions of C57BL/6J mouse brain and pituitary. Rogers J, et al. **Neurobiol Aging** 1985 Spring;6(1):1-9

The compartmentalized hypothalamo-neurohypophysial system: evidence for a neurohypophysial action of acetylcholine on vasopressin release. Gregg CM. **Neuroendocrinology** 1985 May;40(5):423-9

Substance P, enkephalins, somatostatin, cholecystokinin, oxytocin, and vasopressin in human spinal cord. Schoenen J, et al. **Neurology** 1985 Jun;35(6):881-90

The microvasculature of the small-intestinal mucosa of the rat: quantification of hemodynamic effects of topically applied cimetidine, ranitidine, somatostatin, and vasopressin. Neff M, et al. **Scand J Gastroenterol [Suppl]** 1985;112:6-11

[Effects of diltiazem on plasma ACTH, beta-ELI and ADH levels during surgery] Kono K, et al. **Masui** 1985 Jan;34(1):18-24 (Eng. Abstr.) **(Jpn)**

VIOLENCE

The limit of violence: psychotropic drugs, law and ethics. Tamm JM. **Med Law** 1985;4(2):155-66

Behavioural and endocrine reactions in boys scoring high on Sennton neurotic scale viewing an exciting and partly violent movie and the importance of social support. Arnetz BB, et al. **Soc Sci Med** 1985; 20(7):731-6

WAKEFULNESS

Effects of acute and chronic treatment with amitryptyline on the sleep-wake activity of rats. Obál F Jr, et al. **Neuropharmacology** 1985 Mar;24(3):223-9

ZIMELIDINE

High incidence of multisystemic reactions to zimeldine. Langlois R, et al. **Eur J Clin Pharmacol** 1985;28(1):67-71

The *Psychopharmacology Bulletin* is available on subscription from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Subscription price $19.00 per year for the United States. All other countries add $4.75 for postage. This price was in effect at time of printing. Prices are subject to change. Please make check or money order payable to the Superintendent of Documents. An annual subscription for four quarterly issues begins with the next issue following receipt of the order. Single copies and back issues may also be ordered from the Superintendent of Documents. The expiration date is printed on the top line of the address label. Change of address and complaints about non-receipt of issues should be sent to the Superintendent of Documents, and should include the old address, perferably a mailing label, as well as the new address.

ORDER FORM Mail To: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

Enclosed is $________ ☐ check,
(U.S. Currency Only)
☐ money order, or charge to my
Deposit Account No.
☐☐☐☐☐☐☐–☐

Order No. ______________

VISA®

master charge

Credit Card Orders Only

Total charges $________ Fill in the boxes below

Credit Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiration Date Month/Year ☐☐☐☐

Please enter my subscription to **PSYCHOPHARMACOLOGY BULLETIN**
[PSBU]
☐ $19.00 domestic, ☐ $23.75 foreign

Name—First, Last

Street address

Company name or additional address line

City **State** **ZIP Code**

(or Country)

PLEASE PRINT OR TYPE

For Office Use Only.

	Quantity	Charges
Enclosed		
To be mailed		
Subscriptions		
Postage		
Foreign handling		
MMOB		
OPNR		
UPNS		
Discount		
Refund		

**DEPARTMENT OF
HEALTH & HUMAN SERVICES**

Public Health Service
Alcohol, Drug Abuse, and Mental
Health Administration
Rockville MD 20857

Official Business
Penalty for Private Use $300

SPECIAL FOURTH CLASS MAIL
POSTAGE AND FEES PAID
PHS/ADAMHA
PERMIT NO. G-283

DHHS Publication No. (ADM) 86-173
Printed 1986

22/2

PSYCHOPHARMACOLOGY BULLETIN

NATIONAL INSTITUTE OF MENTAL

LD [illegible] C
NEWARK PUBLIC LIBRARY
U.S. DOCUMENTS

Special Features:

Strategies for Analyzing Side Effect Data
Long-Term Use of Benzodiazepines

1986
Vol. 22, No. 2

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

HE20.8109:

Editor-in-Chief:

Nina R. Schooler, Ph.D.
NIMH, Rockville, Md.

Special Features Editor:

Allen Raskin, Ph.D.
Lafayette Clinic, Wayne State University
Detroit, Mich.

Acting Managing Editor:

David Haddock
NIMH, Rockville, Md.

Associate Editors:

Jonathan O. Cole, M.D.
McLean Hospital, Belmont, Mass.

Seymour Fisher, Ph.D.
University of Texas Medical Center
Galveston, Texas

Arnold J. Friedhoff, M.D.
New York University School of Medicine

Gerald L. Klerman, M.D.
Cornell University Medical Center, New York

David J. Kupfer, M.D.
Western Psychiatric Institute & Clinic
University of Pittsburgh School of Medicine

Judith L. Rapoport, M.D.
NIMH, Bethesda, Md.

Donald S. Robinson, M.D.
Bristol-Myers Pharmaceuticals
Wallingford, Conn.

The *Psychopharmacology Bulletin* is prepared by the Division of Clinical Research of the National Institute of Mental Health. Its purpose is to facilitate the dissemination and exchange of information among the national and international scientific community. This emphasis is on rapid, informal reporting of work which has not appeared in the more formal literature. In accordance with new policy set forth by our Associate Editors, we are no longer accepting unsolicited papers for publication in the *Bulletin.*

All material published in the *Psychopharmacology Bulletin* is in the public domain unless otherwise noted. Publication in the *Bulletin* therefore does not preclude publication elsewhere.

Vol. 22, No. 2

PSYCHOPHARMACOLOGY BULLETIN

1986

NEWARK PUBLIC LIBRARY
AUG 1 8 1986
U. S. GOVT. PUBS.
DEPOSITORY 326

Table of Contents

339 **In the Pipeline**—*George M. Simpson*

Strategies for Analyzing Side Effect Data from SAFTEE—

343 SAFTEE: A Technique for the Systematic Assessment of Side Effects in Clinical Trials—*Jerome Levine and Nina R. Schooler*

382 Interrater Agreement and Intraclass Reliability Measures of SAFTEE in Psychopharmacologic Clinical Trials—*Alan F. Jacobson, Burton J. Goldstein, Roberto A. Dominguez, and Richard M. Steinbook*

389 Side Effect Assessment With SAFTEE: Pilot Study of the Instrument—*Judith Godwin Rabkin and Jeffrey S. Markowitz*

397 Reliability and Validity of SAFTEE: Preliminary Analyses—*William Guy, William H. Wilson, Beth Brooking, Gregory Manov, and Olaf Fjetland*

402 Side Effects Data Analysis—*Philip W. Lavori*

Issues in the Long-Term Use of Benzodiazepines Workshop—

405 Introduction—*Karl Rickels and Allen Raskin*

407 Low-Dose Dependence in Chronic Benzodiazepine Users: A Preliminary Report on 119 Patients—*Karl Rickels, W. George Case, Edward E. Schweizer, Charlotte Swenson, and Reita B. Fridman*

416 Long-Term Administration of Benzodiazepines: Pharmacokinetic versus Pharmacodynamic Tolerance—*David J. Greenblatt and Richard I. Shader*

424 The Behavioral Effects of Benzodiazepines Following Long-Term Use—*Irwin Lucki and Karl Rickels*

434 A Survey of Diazepam Patients—*David Haskell, Jonathan O. Cole, Susan Schniebolk, and Bernard Lieberman*

439 Physiological and Performance Responses to Diazepam: Two Types of Effects—*Rudolf Hoehn-Saric and Daniel R. McLeod*

Report of the NIMH-NIH Consensus Development Conference on Electroconvulsive Therapy—

445 Introduction—*Jack Blaine and Susan M. Clark*

Statement of the Consensus Development Panel

Abstracts of Presentations to the Panel and Conference—

455 The Use of Somatic Treatments for Psychiatric Illnesses—*Gerald L. Klerman*

457 Convulsive Therapy: How It Evolved—*Max Fink*

459 ECT: The Historical, Social, and Professional Sources of the Controversy—*David J. Rothman*

463 Utilization of ECT in U.S. Psychiatric Facilities, 1975 to 1980—*James W. Thompson*

465 Efficacy in Depression: Controlled Trials—*Sydney Brandon*

468 Efficacy in Depression: ECT Versus Antidepressants—*Jan Fawcett and William Scheftner*

469 Efficacy of ECT in Schizophrenia, Mania, and Other Disorders—*Joyce G. Small*

472 ECT: Possible Mechanisms of Action—*Bernard Lerer*

475 Systemic Effects of ECT—*Trevor R.P. Price*

476 Neuropathology and Cognitive Dysfunction from ECT—*Peter R. Breggin*

479 Quantitative Neuropathology in Electrically Induced Generalized Convulsions—*Agnete M. Dam*

482 Acute Cognitive Side Effects of ECT—*Harold A. Sackeim*

484 The Question of Long-Term Effects—*Larry R. Squire*

487 Patients' Attitudes Toward ECT—*Christopher Freeman*

490 Legal Parameters of Informed Consent for ECT Administered to Mentally Disabled Persons—*John Parry*

494 Data on Informed Consent for ECT—*Loren H. Roth*

495 Clinical Strategies in Choice and Timing of ECT—*Richard Abrams*

497 General Technique of ECT—*Ferris N. Pitts, Jr.*

499 Electrical Dosage, Stimulus Parameters, and Electrode Placement—*Richard D. Weiner*

Articles—

503 Major Depression and Panic Disorder: Diagnostic and Neurobiological Relationships—*Dennis S. Charney, George R. Heninger, Lawrence H. Price, and Alan Breier*

512 The Role of the Locus Coeruleus—Limbic Noradrenergic Transmission in the Action of Antidepressant Drugs—*Wojciech Kostowski, Adam Plaznik, and Wojciech Danysz*

523 Eating Disorders: A Bibliography—*Natalie Reatig*

532 Attention Deficit Disorders: A Bibliography—*Natalie Reatig*

543 Psychobiological Markers for Schizophrenia: State of the Art and Future Perspectives—*Joseph Zubin* (Corrected and reprinted from Vol. 21, No. 3, 1985 of the *Bulletin*)

B1 Psychopharmacology—A Recurring Bibliography—

In the Pipeline—

George M. Simpson, M.D.

In the Pipeline is a regular feature of the *Psychopharmacology Bulletin*. The major thrust is on new drugs that are "in the pipeline" but have not obtained final approval from the Food and Drug Administration for marketing and sale in the United States. Dr. George Simpson, who is responsible for this issue's column, alternates with Dr. Barry Blackwell.

Dr. George M. Simpson is a clinical psychiatrist who studied at Liverpool University and Rockland State Hospital (now the Nathan Kline Institute). His current research interests include the diagnosis and treatment of schizophrenia, evaluation and treatment of depression, side effects of neuroleptics, and tardive dyskinesia. Dr. Simpson currently chairs the APA Task Force on Sudden Death. His current academic position is Professor of Psychiatry and Pharmacology and Director of Clinical Psychopharmacology in the Department of Psychiatry at the Medical College of Pennsylvania.

New Drugs

It is a sad commentary that there are *no* new antipsychotic drugs. Lenperone, sulpiride, and penfluridol did not make it to the market. Clozapine is still undergoing trials but more of that at a later date. Pimozide did make it as an orphan drug for the treatment of Tourette's syndrome. Several new potential antipsychotic agents have run into difficulties early in clinical trials and certainly none appear likely to be on the market for several years.

This leaves a new/old drug to talk about—haloperidol decanoate (HD), a long-acting antipsychotic agent which, as with the prototypical fluphenazine decanoate (FD), is a conventional antipsychotic agent esterified with a long-chain fatty acid which is then suspended in sesame oil. In animals, both measurable and pharmacologically active concentrations of haloperidol were detected up to 2 months after a single injection. There is very little potential to produce tissue irritation. Because of the relative ease of measuring haloperidol compared to fluphenazine, much more is known about the pharmacokinetics of this agent. This preparation is released slowly in the tissues. In animals and in humans, studies have shown that HD has a long half-life and can be given at 1-month intervals for the maintenance of schizophrenic patients. There is no evidence of early dose dumping, although further work may be necessary to establish that there is no very early release of haloperidol into the bloodstream. Peak concentrations took place just over 6 days after the initial injection and steady-state is reached by the third monthly visit (Deberdt et al., 1980). A followup of 181 chronically treated patients confirmed that steady-state was reached by the time of the third injection. In the 67 subjects who completed 2 years' follow-up, plasma levels after this time remained remarkably constant (Reyntjiens et al., 1982). Much information on this product can be found in a special publication of *Therapeutics Today* (Pakes, 1982) and in a review article by Marr and Batchelor (1982) which evaluates the results of studies of over 700 patients treated with HD for up to 2 years.

The New Drug Application (NDA) was submitted in December 1981 and contained information on approximately 200 patients who received HD. Since that time, some additional information has been obtained, and the Advisory Committee met in September 1983 concerning HD. Information is now available on some 400 subjects. Efficacy is based on six clinical trials. Several hundred additional subjects in other countries have received HD but these are not included in the NDA.

In one study, patients were converted from oral haloperidol to HD; the ratio of maintenance to oral haloperidol was 10-15:1 (5 to 50 mg orally; 75 to 500 mg HD). Bloods were drawn pre-dose and at 3, 8, 24, and 48 hours afterwards and then 7, 14, 21, and 28 days after. In all patients, haloperidol was present at all timepoints. The authors calculated that only 5.5 to 7.2% of the area under the curve for the month of the study occurred on Day 1. From this, they claim the preparation clearly did not "dump" (Deberdt et al., 1980).

The steady-state peak and average plasma haloperidol concentrations from the decanoate were lower than those from the oral dosing, as was the steady-state minimal plasma concentrations. Patients were treated at monthly intervals by injection and showed similar findings, i.e., the steady-state peak minimum and mean concentrations were significantly lower for the decanoate as compared to the oral dosing. The fluctuation between peak minimal haloperidol plasma concentrations was smaller during the decanoate treatment, and the amount of haloperidol ingested over a 28-day period was lower for the decanoate than the oral.

A double-blind parallel group study compared the decanoate to placebo in patients stabilized on oral haloperidol, half of whom were switched to placebo or to HD. The parenteral injections could be supplemented with open oral haloperidol. Sixteen patients were randomly assigned to each treatment group. All 16 decanoate patients completed 16 weeks on active medication compared to 4 placebo patients. Supplemental oral haloperidol was required for 6 HD patients and by 14 in a placebo group. Various measures on the Brief Psychiatric Rating Scale and the Nurse's Observation Scale for Inpatient Evaluation confirmed the efficacy of HD in this study (Zissis et al., 1982). Other studies consist of comparisons to FD or open clinical trials. These studies showed a side-effect profile similar to haloperidol and relatively similar to FD and, given the design of the study, some support for efficacy. HD was well tolerated by geriatric psychotic patients (Viukari et al., 1982). Several other studies are in progress.

From the data in the literature and from the pharmacology of the preparation, the following can be concluded: 1) HD in sesame oil appears to behave much the same way as haloperidol given orally and in a similar fashion to FD compared to fluphenazine HCl; 2) HD has a long half-life and can be given in injections once a month; 3) steady state is achieved by 3 months, i.e., after two monthly injections; 4) haloperidol is less affected by the absorptional metabolism effect (first-pass) than is fluphenazine; and 5) maintenance requirements would appear to range from 50 to 500 mg/monthly injection. Up to 900 mg has been given in a single dose but much lower amounts appear adequate, e.g., 100 to 250 mg.

HD is already available in 28 countries in the world including Canada, Sweden, Norway, France, Germany, Belgium, and the Netherlands. The approval of HD in the U.S. would provide a needed extension of antipsychotic therapy for the treatment of schizophrenia. Most countries have five, six, or seven long-acting agents available. The existence of only one in the U.S. limits the availability of proven and logical maintenance treatments for schizophrenia. While HD may have no unique qualities, it has the virtue of adding a proven drug by a new and convenient route of administration. Given that it is a combination of two substances with a 20-year history in pharmacotherapy, the problem of protecting human subjects from toxicity or serious side effects does not appear to exist.

HD is not a new drug. It is a new delivery system for an old drug using old techniques. Like all such preparations, there is a problem with a starting dose but this, at the very least, would be equal to, if not less than the situation currently presented by FD.

Since this article was prepared, the FDA has approved HD for use in the United States. In one of a series of articles on long-acting antipsychotics published in the *Journal of Clinical Psychopharmacology* (Feb. 1986), Nair et al. (1986) compared HD and oral haloperidol in 20 chronic schizophrenic patients. Patients were stabilized on oral haloperidol and then converted to long-acting. The two drugs showed comparable efficacy and safety. Plasma levels were lower during the HD treatment than the oral and were remarkably reproducible over two consecutive months. The authors confirmed that there was no dose dumping. They suggest initiating therapy with a low initial dose based on the patient's symptomatology and previous medication history with dosage adjustment as necessary rather than attempting fixed oral to intramuscular ratios.

References

Deberdt, R., Elens, P., Berghmans, W., et al. Intramuscular haloperidol decanoate for neuroleptic maintenance therapy: Efficacy, dosage schedule, and plasma levels. *Acta Psychiatr. Scand.*, 62:356–363, 1980.

Marr, W., and Batchelor, D. Haloperidol decanoate: Major progress with antipsychotic therapy. *Clin. Res. Rev.*, 2:61–79, 1982.

Nair, N.P.V., Suranyi-Cadotte, B., Schwartz, G., et al. A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety and dosage equivalence. *J. Clinical Psychopharmacology*, 6:30S–37S, 1986.

Pakes, G.E. Haloperidol decanoate: Comparisons with orally administered haloperidol. *Ther. Today*, 2:83–91, 1982.

Reyntjiens, A.J.M., Heykants, J.J.P., Woestenborghs, R.J.H., et al. Pharmacokinetics of haloperidol decanoate: A 2-year followup. *Int. Pharmacopsychiatr.*, 17:238–246, 1982.

Viukari, M., Salo, H., Lamminsivu, U., et al. Tolerance and serum levels of haloperidol during parenteral and oral haloperidol treatment in geriatric patients. *Acta Psychiatr. Scand.*, 65:301–308, 1982.

Zissis, N.P., Psaras, M., and Lyketsos, G. Haloperidol decanoate, a new long-acting antipsychotic, in chronic schizophrenics: Double-blind comparison with placebo. *Curr. Ther. Res.*, 31:650–655, 1982.

Strategies for Analyzing Side Effect Data from SAFTEE

A Workshop Held Fall 1985 in Rockville, Maryland

The five papers which make up the contents of this section of the Bulletin include a basic description of SAFTEE (Systematic Assessment for Treatment Emergent Events), three papers describing research results using the instrument, and one paper describing statistical methods useful in analyzing side effect data. These papers and the discussion of them formed the core of the NIMH-sponsored workshop. Their publication represents an effort to share the results of this workshop with the scientific community.

JEROME LEVINE, M.D.
NINA R. SCHOOLER, PH.D.

SAFTEE: A Technique for the Systematic Assessment of Side Effects in Clinical Trials

Jerome Levine, M.D.,[1] and Nina R. Schooler, Ph.D.[2]

Introduction

Progress in developing methods for the clinical assessment of pharmacologic treatments does not proceed at an even pace. Over time, even the emphasis on what domain of treatment assessment is important changes. For example, in the area of psychopharmacology, the development of rating scales to assess psychopathology and hence efficacy has received continued attention. More recently, the development of criteria for more standardized diagnosis of mental disorders has also been an area of increased activity.

In general, little attention has been given to side effect assessment in clinical trials. Considering safety assessment more broadly, research has focused on adverse drug reaction detection in an epidemiologic postmarketing surveillance context. These studies generally seek to detect the rare but serious (often life-threatening) adverse drug reactions (ADR's) and are usually not designed to develop information on the more common but less severe side effects. Thus, the development of a relatively complete side effect profile for a given pharmacologic treatment usually occurs in the context of clinical trials primarily designed for efficacy assessment. In the area of psychopharmacology, no single scale has achieved as widespread acceptance and utilization for side-effect assessment as have, for example, the Hamilton Rating Scale for Depression and the Brief Psychiatric Rating Scale for efficacy assessment. Perhaps the Treatment Emergent Symptom Scale (TESS) and the Dosage Record and Treatment Emergent Symptoms Scale (DOTES) of the National Institute of Mental Health (NIMH) Early Clinical Drug Evaluation Unit/New Clinical Drug Evaluation Unit (ECDEU/NCDEU) assessment system have been the

---

[1] University of Maryland Department of Psychiatry (MPRC), Baltimore, MD 21228. (Formerly Chief, Pharmacologic and Somatics Treatments Research Branch, NIMH.)

[2] Schizophrenia Research Branch, NIMH, Rockville, MD 20858. (Formerly Assistant Chief, Pharmacologic and Somatic Treatments Research Branch, NIMH.)

most widely used (ECDEU Assessment Manual, 1972).

In an effort to improve the precision with which side effects are assessed during clinical trials, the authors conducted a review and logical analysis of the methods and instruments that were being used circa 1980. On the basis of that analysis, a number of problems or deficiencies were identified in the way that side effects were being detected or ascertained—and a strategy or technique for dealing with them was developed. It was concluded that immediate progress could be made if an instrument which embodied these strategies could be used in clinical trials. During the following 3 years, an instrument named SAFTEE (Systematic Assessment for Treatment Emergent Events) was designed. It is the purpose of this paper to briefly describe the rationale for the approaches and techniques built into SAFTEE, to describe the two versions of the instrument that are available, and to mention work currently under way with the instrument.

SAFTEE Concepts and Approaches to Side-Effect Assessment

Standardized Inquiry Procedure

Our review of available side-effect reporting instruments revealed that there was no standardized inquiry (ascertainment) procedure associated with most of them. Even with instruments that included a list of adverse events (like DOTES), there were no instructions as to how the presence of events should be determined. Therefore, some raters could routinely ask about each event while others might only inquire in the most general way and yet fill out the detailed list of events (generally with a succession of negatives). In use of most instruments, it is not possible to know if all raters in a given clinical trial have used the instrument in the same way.

It is not known whether the use of a detailed and more specific inquiry technique or a less detailed, more general inquiry technique leads to a more valid detection of side effects. The argument in favor of global inquiry procedures is that "significant" adverse effects will be reported and that inclusion of more detailed questions simply leads patients to report unimportant occurrences which add "noise" rather than information. The case for a more detailed inquiry is that patients may not report events that could turn out to be important unless they are reminded in some way. It is clear that *not* using a standardized inquiry procedure (whether global or detailed) leads to increased and unnecessary reporting variability and a less valid assessment technique.

Because both global and specific inquiry procedures had their strong advocates and because no compelling empirical data were available to make a rational choice, two versions of SAFTEE (both employing standardized inquiry procedures), SAFTEE-GI (General Inquiry) and SAFTEE-SI (Specific Inquiry), were developed. SAFTEE-GI uses only a standardized general inquiry (i.e., have you had any physical or health problems? etc.), while the SAFTEE-SI uses the general inquiry followed by a specific inquiry. This latter inquiry takes its format and organization from the widely used physician's review of (bodily) systems and is not merely an alphabetical list of all possible symptoms. Each inquiry item serves as a stimulus to the patient to report any adverse health event associated with that body system (e.g., have you had any problems with your eyes or vision, things like swelling or irritation, blurring, etc.?).

In both the SAFTEE-GI and SI forms, the standardized inquiry questions are presented along the left margin of the page in the precise form they are to be asked of the patient.

Event Reporting

Using the SAFTEE technique, *all* reports of adverse health events elicited in response to the standardized inquiry procedure are recorded *regardless* of whether they are suspected to be drug related or not. The goal of this strategy is to reduce the under-reporting of unanticipated events compared to "known or expected" events. By removing the responsibility from the rater (or the patient) to decide whether or not to report an event based on its assumed drug relatedness, we also remove another source of rater variance. The requirement of an *a priori* suspicion that the event is drug related characterizes some spontaneous reporting systems where the emphasis is on detecting only serious events. In the more controlled setting of clinical trials, event reporting should lead to a less biased and more reliable estimate of side effects because determination of the relationship of a particular event to a drug can be made on the basis of differences between groups in the trial rather than rater judgments in individual cases.

Preferred Event Terms

Although side-effect assessment scales which use a specific inquiry approach include lists of symptoms, most scales using a general or nonstandardized inquiry approach may only leave a blank space where the rater labels or describes the event being reported. Sometimes this is done using "the patient's own words"; at other times, it is the clinician's symptom description or even diagnosis of the reported event that is recorded. Since there are many synonyms for describing the same symptom, and since patients' descriptions of the same event vary widely, some type of categorization or coding must be done if events are to be counted and presented and not merely listed. Usually this "post-coding" is done weeks, months, or years after the original data were collected by individuals who have never seen the patient. This is another source of variability and unreliability in capturing valid data. In an attempt to address this problem, SAFTEE uses a list of some 76 preferred-event terms which are organized into two lists, one alphabetical and the other by body system. Raters are asked to use these terms preferentially to record the reported event if they are appropriate, rather than their own term or the patient's words. If there is no appropriate preferred term, then an "idiosyncratic write-in" is used. Syndromes and diagnoses are not used to describe events but provision is made elsewhere on the form for recording diagnoses and syndromes (e.g., respiratory infection) and relating them to the reported events.

Comprehensive Event Information

For many scales, once an event is elicited and its presence recorded, little if any additional information about the event is captured. In order to be able to interpret the significance of the event, the SAFTEE approach requires collection of information about the onset, duration, pattern, severity, judgment of attribution of cause, and action taken by the clinician in response to the event. Regardless of how the report of the event was elicited (spontaneously reported by the patient, SI or GI inquiry), these data about the event need to be captured. SAFTEE provides two aids to facilitate the collection of this information. First, precoded responses to each category of information (e.g., severity—minimal, mild, moderate, severe, and very severe) are available to be checked; and second, a series of suggested probe questions (e.g., how bad is it? does it bother you a lot?) for each category of information is provided above the column where the information is recorded. Obtaining this information at the time the event is reported is essential, as followup is frequently difficult and information that is recalled may be less reliable.

Time Interval

Specifying a specific time interval about which to inquire is easily, but not frequently, done. Unless this is done, patients frequently report events that occurred well in the past. Asking, "have you had any headaches?" rather than "have you had any headaches during the past week?" can elicit very different responses. This is especially important at the start of a trial when a baseline rate of adverse health events for a specific period (like a week) and not a lifetime history of the event is needed against which to evaluate events that occur during the trial. It is also important to ask about a uniform reporting interval throughout the course of a trial. Thus, SAFTEE requires the researcher to establish a specific interval of inquiry for a trial and adhere to that interval throughout the trial. Depending on the nature of the trial, this may be designed to provide full coverage of the trial (e.g., weekly for 5 weeks) or may sample times during the trial (e.g., 1 week pretreatment and 1 week after 5 weeks of treatment).

The SAFTEE Instruments and Associated Documentation

As described above, there are two versions of the SAFTEE form, GI and SI. Both are reproduced (in reduced size) along with a brief set of instructions called SAFTEE TIPS at the end of this paper. The length of these forms and their format may appear formidable. This is, in part, because the forms provide space to record information about each event. In reality, usually only a small number of events are reported and the SAFTEE-SI interview and recording of events takes about 20 minutes with psychiatric patients.

In addition to the event information, the first page of SAFTEE collects identifying information about the patient and rater and some information about how the instrument is being used (i.e., baseline or followup assessment). SAFTEE also provides space for "study specific" inquiries to be written in and space for responses to be recorded. A reporting capability for capturing laboratory and physical examination data associated with adverse health events is also included and a form for recording medication dosage. Neither of these latter two formats is required to be used in order to use the GI or SI inquiries, and space is provided on the face page of the form to indicate whether or not they will be used.

A comprehensive manual describing the use of the scale has also been prepared and has been deposited with the National Technical Information Service (NTIS) where copies can be requested. While data from the SAFTEE form may be processed in any way the investigator usually handles data, a microcomputer-based data entry system has been developed with support of a Small Business Innovation Research (SBIR) grant (Clyde, 1986).

Ongoing Activities

Following the development of SAFTEE, the NIMH sent out a request for applications seeking investigators who would conduct studies establishing the reliability, validity, and characteristics of use of the instrument. Three grant awards were made and early results from these studies were presented at a workshop held at NIMH in the Fall, 1985. Summaries of this work are presented in the three papers following this one. Several pharmaceutical firms and other clinical investigators have requested copies of the instrument and have either used it as designed or have created modified versions using some or all of the principles underlying the instrument. Further workshops and reports on the instrument at scientific meetings should be expected, and the first author is interested in the continued development of the preferred terms coding concept.

Conclusion

In conclusion, we believe that a more valid method for collecting side-effect data is available with the publication of SAFTEE. Experience with the instruments and the results from ongoing studies should lead to modifications, especially in format. However, we believe that the principles underlying the instrument will endure and that they should be used as a kind of guideline when judging the quality of side-effect instruments used in clinical trials.

References

Clyde, Dean J. SAFTEE: Data System for side effect assessment scale. *Psychopharmacol. Bull.*, 22:287, 1986.

National Technical Information Service, Department of Commerce, Washington, D.C.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION
NATIONAL INSTITUTE OF MENTAL HEALTH

Systematic Assessment for Treatment Emergent Events (SAFTEE-GI)

SAFTEE is designed to collect information on adverse health events occurring during a specified time period of a clinical trial. The SAFTEE-GI form consists of seven components:

- the identifying information on this page;
- Event Terms on pages 2 and 3;
- the examination procedures, printed on the extreme left hand side of pages 4 through 7 and consisting of Opening Remarks, General Inquiry, Closing Inquiry, and Study Specific Events;
- spaces for recording information obtained in the examination, printed next to the examination procedures on pages 4 through 7;
- concluding information printed following the examination procedures on page 4;
- the Laboratory/Physical Findings Record on page 8; and
- the Dosage Record on page 9.

A fuller set of instructions called SAFTEE TIPS is available describing use of this rating system. Briefly, to use the SAFTEE-GI rating system first fill out the identifying information on this page of the booklet. Then go to page 4 and administer the examination beginning with the Opening Remarks (printed on the top left hand side of the page) and continuing with General Inquiry and Closing Inquiry. If an adverse event is detected in the examination, information on that event should be recorded on the form. Suggested queries for eliciting the relevant data are given above each category used to rate the event.

After completing the examination, enter concluding information based upon the examination. This includes the examiner's judgment of patient reliability, any formal diagnoses that can be made, whether an FDA form 1639 is to be filled out, and — if the patient is to be terminated from the trial — the reasons for termination. Dosage information and additional information regarding laboratory and physical findings may be entered at this time or subsequently. The rater should refer to SAFTEE TIPS for complete instructions concerning use of the rating system.

Study ________ **Pat.** ____ **Form** ____

Per. ____ **Rater** ___ **Card** ___ **ASSIGN:** ______

Identifying Information

Patient Initials	Age	Sex	Date of Assessment
__ __ __	__ __	__	__ __ __ __ __ __

Rater ID ____________________________

Assessment is (select one):
☐ Initial ☐ Other baseline ☐ Follow-up ☐ Final

Assessment is (select one):
☐ Scheduled ☐ Unscheduled

Assessment interval (i.e. period of time for which events are inquired about):
☐ One week or ______ days

Is the SAFTEE Laboratory/Physical Findings Record to be used with this examination?
☐ Yes ☐ No

Is the SAFTEE Dosage Record to be used with this examination?
☐ Yes ☐ No

Prepared by SysteMetrics, Inc. (Christy Moynihan, Ph.D.) for the National Institute of Mental Health, ADAMHA, DHHS. Additional information and copies may be obtained by contacting Jerome Levine, M.D. or Nina Schooler, Ph.D. at the Pharmacologic and Somatic Treatments Research Branch, NIMH, 5600 Fishers Lane, Room 10-C-06, Rockville, Maryland, 20857, TEL. (301) 443-3524.

ADM 9-81 (4/83)

EVENT TERMS

Presented below are the preferred terms for naming events reported during the examination. The examiner should use these terms — rather than synonymous or related terms — whenever possible. Alternate terms should be used only when no listed term adequately describes the reported event.

The preferred terms are listed both alphabetically and by body system. To record a reported event first check the alphabetical list to see if it is present. If not, the appropriate body system list should be examined to ascertain whether there is a preferred term available which is applicable to the event. If there is no term which describes the event, write in a term which most precisely describes it.

When using either a preferred or other term the examiner may further describe or elaborate by writing in the Comments column. For events marked by an asterisk or by instructions that additional specification is needed, further description should be provided in the Comments column.

ALPHABETICAL LIST OF PREFERRED TERMS

accidental injury*
akathisia
akinesia
anxiety
appetite decrease
appetite increase
attempted suicide
blurred vision
breast pain/swelling
change in color (urine)
chest pain
concentration difficulty
confusion
constipation
coughing
cramps
decreased libido
dental problems*
depression
diarrhea
difficulty falling asleep
difficulty swallowing
difficulty urinating
discharge (nipples)
dizziness/faintness
drowsiness
dry mouth
dyskinesia* (specify where)
dystonia* (specify where)
ear ache
early morning awakening
edema* (specify where)
eye irritation
fever
flatulence
genital discomfort*
gum problems*
hair problems*
headache*
hypersalivation
increased frequency (urination)
increased libido
increased thirst
intercurrent illness*
interrupted sleep
irregular heartbeat
irritability
loss of consciousness*
medical or surgical procedure*
memory problems
menstrual irregularity*
mouth ulcer
muscle/bone/joint pain*
nasal congestion
nausea
over-arousal*
painful urination
perceptual problems
poor hearing
premenstrual tension
rapid heartbeat
rigidity (muscle)
sexual dysfunction
shortness of breath
skin irritation*
sore throat
sore tongue*
stomach/abdominal discomfort*
stool discoloration
taste abnormality*
tinnitus
tiredness/fatigue
tremor
vomiting
weight gain
weight loss
wheezing

LIST OF PREFERRED TERMS BY BODY SYSTEM

HEAD
headache*
dizziness/faintness
loss of consciousness*

EYES
eye irritation
blurred vision

EARS
ear ache
poor hearing
tinnitus

MOUTH
mouth ulcer
dry mouth
hypersalivation
sore tongue*
gum problems*
dental problems*

NOSE/THROAT
nasal congestion
sore throat
difficulty swallowing

CHEST
chest pain
shortness of breath
wheezing
coughing
breast pain/swelling
discharge (nipples)

CARDIOVASCULAR
rapid heartbeat
irregular heartbeat

GASTROINTESTINAL
stomach/abdominal discomfort*
nausea
vomiting
diarrhea
constipation
flatulence
stool discoloration
appetite increase
appetite decrease
weight gain
weight loss
taste abnormality*
increased thirst

GENITOURINARY
painful urination
difficulty urinating
increased frequency (urination)
change in color (urine)
menstrual irregularity*
cramps
premenstrual tension
genital discomfort*
increased libido
decreased libido
sexual dysfunction

MUSCULOSKELETAL
muscle/bone/joint pain*
edema* (specify where)
akinesia
dyskinesia* (specify where)
dystonia* (specify where)
akathisia
rigidity (muscle)
tremor

SKIN
skin irritation*
hair problems*

PSYCHOLOGICAL
tiredness/fatigue
over-arousal*
difficulty falling asleep
early morning awakening
interrupted sleep
drowsiness
confusion
concentration difficulty
memory problems
perceptual problems
depression
anxiety
irritability

OTHER
accidental injury*
attempted suicide
fever
intercurrent illness*
medical or surgical procedure*

BEGIN SAFTEE EXAMINATION Patient ID ___|___|___ MM ___ DD ___ YY ___	To help determine appropriate event category WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ___ OR ___? DO YOU HAVE TROUBLE ___?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THINGS (e.g. eating, sleeping)? HOW HARD IS IT TO (move, stand, stay awake, etc)? If possible, observe impairment
OPENING REMARKS WE'VE BEEN TALKING ABOUT (name condition being treated). NOW I'D LIKE TO ASK YOU SOME MORE GENERAL QUESTIONS ABOUT YOUR HEALTH. I WANT TO FIND OUT HOW YOU'VE BEEN FEELING IN THE LAST WEEK (or other assessment interval as specified on the first page of the form).	**EVENT** If event elicited, complete information as requested. (If event previously elicited in General Inquiry, check Prev. Rec. below.) * = For event marked with *, record further description in Comments/Descriptor area Lines to record additional events on page 6	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM:DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
GENERAL INQUIRY A. HAVE YOU HAD ANY PHYSICAL OR HEALTH PROBLEMS DURING THE PAST WEEK (or specified assessment interval)? HAVE YOU NOTICED ANY CHANGES IN YOUR PHYSICAL APPEARANCE DURING THE PAST WEEK (or specified assessment interval)? HAVE YOU CUT DOWN ON THE THINGS YOU USUALLY DO BECAUSE OF NOT FEELING WELL PHYSICALLY DURING THE PAST WEEK (or specified assessment interval)? Check if no events elicited ☐	Write in events elicited. If appropriate, use preferred terms listed on pages 2 and 3			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
	1. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	7. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	8. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	9. ______	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
IF REQUIRED BY PROTOCOL, GO TO STUDY SPECIFIC EVENTS (NEXT PAGE) OR CONTINUE WITH THE EXAMINATION BELOW.							
CLOSING INQUIRY B. Observe the patient's appearance and behavior for such problems as skin irritation, weight gain or loss, drowsiness, restlessness, trouble breathing, tremor, rigidity, and other abnormal movements. If the patient fails to mention a problem which has been observed during the examination or which has been reported by staff or family, say: I NOTICE ___ HAS THAT BEEN BOTHERING YOU? Follow up on any problems reported in a previous session that have not been covered in the examination: LAST TIME ___ WAS BOTHERING YOU. ARE YOU STILL HAVING TROUBLE WITH THAT? If no, check assessed & absent. Close with (except omit at initial exam): LASTLY, HAS YOUR MEDICINE CAUSED YOU ANY PROBLEMS DURING THE PAST WEEK (or specified assessment interval) Check if no events elicited ☐	Write in events elicited. If appropriate, use preferred terms listed on pages 2 and 3 assessed & absent			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
	1. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	7. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	8. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	9. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	10. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	11. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	12. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	13. ______ ☐	__ __:__ __	_ _ _	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

DURING THE EXAMINATION, PATIENT WAS:
- ☐ Nonverbal
- ☐ Verbal: low reliability
- ☐ Verbal: moderate reliability
- ☐ Verbal: high reliability

IS AN FDA 1639 TO BE FILED?
- ☐ Don't know
- ☐ No
- ☐ Yes

Adverse drug experience (event or diagnosis to be reported) ______

IF FINAL ASSESSMENT, REASON FOR TERMINATION IS:
- ☐ Not final assessment
- ☐ Patient dropped from study
- ☐ Patient withdrew from study
- ☐ Patient died
- ☐ Other (specify)

DIAGNOSES: Record any diagnoses that can be made on the basis of events reported during the examination.

Diag. 1: ______

Diag. 2: ______

Diag. 3: ______

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient

Patient ID ___|___|___

MM DD YY ___|___|___

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
II = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested

Additional space for comments on page 11

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	________	_ _ _ _ _ _ _

For each diagnosis, write in previously recorded associated events. (Record event letter and number.)

EVENT TERM	EVENT TERM	EVENT TERM	
__ __ ____________	__ __ ____________	__ __ ____________	_ _ _ _ _ _ _
__ __ ____________	__ __ ____________	__ __ ____________	_ _ _ _ _ _ _
__ __ ____________	__ __ ____________	__ __ ____________	_ _ _ _ _ _ _

STUDY SPECIFIC EVENTS

	To help determine appropriate event category WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ____ OR ____ ? DO YOU HAVE TROUBLE ____ ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THINGS (e.g. eating, sleeping)? HOW HARD IS IT TO (move, stand, stay awake, etc)? If possible observe impairment
	EVENT If event elicited, complete information as requested	**DATE OF ONSET** 00:00 – started prior to beginning of this assessment interval MM DD	**DURATION IN DAYS** (only within current assessment interval) 000 – less than one day	**PATTERN** IS – Isolated IN – Intermittent CO – Continuous	**CURRENT STATUS** CO – Continuing R – Recovered w/o sequelae RS – Recovered w/ sequelae I – Indeterminate	**SEVERITY** MN – Minimal MI – Mild MO – Moderate S – Severe VS – Very Severe	**FUNCTIONAL IMPAIRMENT** MN – Minimal MI – Mild MO – Moderate S – Severe VS – Very Severe
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
Z. (Enter script for Study Specific Events)	1. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	7. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	8. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	9. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
	10. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	11. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	12. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	13. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	14. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	15. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	16. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RETURN TO PREVIOUS PAGE FOR CLOSING INQUIRY	17. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	18. ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

WRITE-IN SPACE FOR ADDITIONAL EVENTS

For each write-in: Record query letter, use next number in sequence, and specify						
			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
— — ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
— — ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
— — ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
— — ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
— — ____	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

Continuation form needed?
Check, if yes: ☐

Patient ID ___|___|___

MM DD YY ___|___|___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE?
(Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN?
(De/Rechallenge not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient

STUDY SPECIFIC WRITE-IN

POSSIBLE CONTRIBUTORY FACTORS Check as many as apply CD = Current disorder (being treated) II = Intercurrent illness OD = Other disorder (prior) PH = Prior history of event PD = Protocol drug DI = Other drug/drug interaction O = Other (specify) OR N = None Apparent	**RELATIONSHIP OF DRUG TO EVENT** Check as many as apply D = Dose response DR = Dechallenge/rechallenge TO = Timing of onset S = Seen in other patients in this trial K = Known drug effect L = Laboratory data O = Other (specify) OR NA = Not applicable (PD or DI not checked in Contributory Factors column)	**ACTION TAKEN** (by clinician) N = None IS = Increased Surveillance C = Contra-active RX CH = Change dose CC = Contra-active RX plus change dose SU = Suspend RX DC = Discontinue RX O = Other (specify) X = Don t know	**COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION** Use to provide further characterization of event especially where requested Additional space for comments on page 18	**CODE** (do not write in this space)
CD II OD PH PD DI O or N	D DR TO S K L O or NA	N IS C CH CC SU DC O X		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
CD II OD PH PD DI O or N	D DR TO S K L O or NA	N IS C CH CC SU DC O X		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _

CD II OD PH PD DI O or N	D DR TO S K L O or NA	N IS C CH CC SU DC O X		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐	____	_ _ _ _ _ _ _

Patient ID __|__|__

MM DD YY __|__|__

LABORATORY/PHYSICAL FINDINGS RECORD To be used (1) to record Lab/Physical findings (normal or abnormal) associated with elicited events or (2) to record abnormal Lab/Physical findings not associated with an event. Use page 19 for comments or to specify where requested. SPECIFY TEST BELOW Check if no lab/physical findings are reported ☐	**ASSOCIATION TO EVENT** N = No associated event OR If associated, enter event letter and number. N or event	**DATE OF TEST** MM DD	**RESULTS** Record value or score using both number and units.	**CLINICAL ABNORMALITY** Y = Yes N = No X = Uncertain	**POSSIBLE CONTRIBUTORY FACTORS** Enter as many as apply. CD = Current disorder (being treated) II = Intercurrent illness OD = Other disorder (prior) PH = Prior history of abnormal test PD = Protocol drug DI = Other drug/drug interaction O = Other (specify) OR N = None Apparent	**ACTION TAKEN BY CLINICIAN** Enter as many as apply. N = None R = Repeat test IS = Increased surveillance C = Contra-active Rx CH = Change dose SU = Suspend Rx DC = Discontinue Rx O = Other (specify) OR X = Don't know	**CODE** (do not write in this space)
LAB-HEMATOLOGIC	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
LAB-LIVER FUNCTION	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
LAB-KIDNEY	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
LAB-OTHER	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
RADIOLOGIC	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
ELECTRO-PHYSIOLOGIC (e.g. EKG,EEG)	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
PHYSICAL FINDINGS (e.g. weight, B.P.)	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
OTHER (Specify)	N			Y N X	CD II OD PH PD DI O or N	N R IS C CH SU DC O or X	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	

Continuation form needed?
Check, if yes: ☐

Patient ID ___|___|___

MM DD YY ___|___|___

DOSAGE RECORD Record DOSAGE PRESCRIBED AT LAST ASSESSMENT, all INTERIM CHANGES IN DOSAGE OR DOSAGE SCHEDULE, and DOSAGE PRESCRIBED FOR NEXT ASSESSMENT PERIOD. Include both protocol drugs and concomitant medications. Use page 19 for comments or to specify where requested. Check if no drugs prescribed ☐	**DRUG NAME OR CODE** For protocol drug, use PD. (If more than one, use PD1, PD2 etc.) For any other drugs, write in name or code.	**DATE** Enter date drug prescribed. MM DD	**TOTAL DAILY DOSE** **QUANTITY** If discontinued, enter 0000.	**UNITS** Mg. = Milligrams Ml. = Milliliters Caps = Capsules Tabs = Tablets 0 = Other (Specify)	**ROUTE OF ADMINISTRATION** PO = Oral IM = Intramuscular IV = Intravenous 0 = Other (Specify)	**DOSAGE SCHEDULE** hs = hour of sleep only qd = once per day bid = twice per day tid = three times per day qid = four times per day prn = as requested 0 = Other (specify)	**PROPORTION** EQ = Equal Proportions UN = Unequal Proportions NA = Not Applicable	**REASON FOR DOSAGE CHANGE** N = No change OR I = Initiated CP = Changed according to protocol CI = Changed due to ineffectiveness CT = Changed due to toxicity DC = Discontinued/Suspended DR = Drug reinstated following suspension 0 = Other (specify)
				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
DOSAGE PRESCRIBED AT LAST ASSESSMENT: Enter required information for all drugs prescribed at last assessment.				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
INTERIM CHANGES IN DOSAGE OR DOSAGE SCHEDULE: Enter required information for any drug initiated or discontinued since the last assessment or for any other changes in dosage or dosage schedule. Enter information only when there is a change in a previous prescription.				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
DOSAGE PRESCRIBED FOR NEXT ASSESSMENT PERIOD: Enter required information for all drugs prescribed at this time for the next assessment period.				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐
				☐☐☐☐☐	☐☐☐☐	☐☐☐☐☐☐☐	☐☐☐	☐ ☐☐☐☐☐☐☐

Continuation form needed?
Check, if yes: ☐

Patient ID ____|____|____

MM ____ DD ____ YY ____

ADDITIONAL SPACE FOR COMMENTS

(IF REFERRING TO A SPECIFIC EVENT REPORTED ON THE PREVIOUS PAGES, RECORD EVENT NAME, LETTER AND NUMBER)

SPACE FOR COMMENTS FOR LAB AND DOSAGE RECORDS (if used)

(SPECIFY LAB TEST, PHYSICAL FINDING, OR DRUG REPORTED ON PREVIOUS PAGES)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION
NATIONAL INSTITUTE OF MENTAL HEALTH

Systematic Assessment for Treatment Emergent Events (SAFTEE-SI)

SAFTEE is designed to collect information on adverse health events occurring during a specified time period of a clinical trial. The SAFTEE-SI form consists of six components:

- the identifying information on this page;
- the examination procedures, printed on the extreme left hand side of pages 2 through 15 and consisting of Opening Remarks, General Inquiry, Systematic Inquiry, Closing Inquiry, and Study Specific Events;
- spaces for recording information obtained in the examination, printed next to the examination procedures on pages 2 through 15;
- concluding information printed following the examination procedures on page 12;
- the Laboratory/Physical Findings Record on page 16, and
- the Dosage Record on page 17.

A fuller set of instructions called SAFTEE TIPS is available describing use of this rating system. Briefly, to use the SAFTEE-SI rating system first fill out the identifying information on this page of the booklet. Then go to page 2 and administer the examination beginning with the Opening Remarks (printed on the top left hand side of the page) and continuing with General Inquiry, Systematic Inquiry, and Closing Inquiry. If an adverse event is detected in the examination, information on that event should be recorded on the form. Suggested queries for eliciting the relevant data are given above each category used to rate the event.

After completing the examination, enter concluding information based upon the examination. This includes the examiner's judgment of patient reliability, any formal diagnoses that can be made, whether an FDA form 1639 is to be filled out, and — if the patient is to be terminated from the trial — the reasons for termination. Dosage information and additional information regarding laboratory and physical findings may be entered at this time or subsequently. The rater should refer to SAFTEE TIPS for complete instructions concerning use of the rating system.

Study ________ Pat. ___ Form ___

Per. ___ Rater __ Card __ ASSIGN: _____

Identifying Information

Patient Initials Age Sex Date of Assessment

Rater ID

Assessment is (select one):
☐ Initial ☐ Other baseline ☐ Follow-up ☐ Final

Assessment is (select one):
☐ Scheduled ☐ Unscheduled

Assessment interval (i.e. period of time for which events are inquired about):
☐ One week or days

Is the SAFTEE Laboratory/Physical Findings Record to be used with this examination?
☐ Yes ☐ No

Is the SAFTEE Dosage Record to be used with this examination?
☐ Yes ☐ No

Prepared by SysteMetrics, Inc. (Christy Moynihan, Ph.D.) for the National Institute of Mental Health, ADAMHA, DHHS. Additional information and copies may be obtained by contacting Jerome Levine, M.D. or Nina Schooler, Ph.D. at the Pharmacologic and Somatic Treatments Research Branch, NIMH, 5600 Fishers Lane, Room 10-C-06, Rockville, Maryland, 20857, TEL. (301) 443-3524.

ADM 9-82 (4/83)

BEGIN SAFTEE EXAMINATION	To help determine appropriate event category: WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ____ OR ____ ? DO YOU HAVE TROUBLE ____ ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THINGS (e.g. eating, sleeping)? HOW HARD IS IT TO (move, stand, stay awake, etc)? If possible observe impairment
OPENING REMARKS WE'VE BEEN TALKING ABOUT (name condition being treated). NOW I'D LIKE TO ASK YOU SOME MORE GENERAL QUESTIONS ABOUT YOUR HEALTH. I WANT TO FIND OUT HOW YOU'VE BEEN FEELING IN THE LAST WEEK (or other assessment interval as specified on the first page of the form).	**EVENT** If event elicited, complete information as requested * = For event marked with *, record further description in Comments/Descriptor area Lines to record additional events on page 14	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM:DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
GENERAL INQUIRY	Write in events elicited. If appropriate, use same event names as in Systematic Inquiry			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
A. HAVE YOU HAD ANY PHYSICAL OR HEALTH PROBLEMS DURING THE PAST WEEK (or specified assessment interval)? HAVE YOU NOTICED ANY CHANGES IN YOUR PHYSICAL APPEARANCE DURING THE PAST WEEK (or specified assessment interval)? HAVE YOU CUT DOWN ON THE THINGS YOU USUALLY DO BECAUSE OF NOT FEELING WELL PHYSICALLY DURING THE PAST WEEK (or specified assessment interval)? Check if no events elicited ☐	1. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	7. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	8. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	9. ________	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
SYSTEMATIC INQUIRY NOW I'D LIKE TO ASK YOU SOME MORE SPECIFIC QUESTIONS ABOUT YOUR HEALTH DURING THE PAST WEEK (or specified assessment interval)? Note RQ?: If an event is elicited by any query, record information, and then repeat query as follows: ANY OTHER PROBLEMS WITH YOUR ____, LIKE (continue with unadministered items).	**EVENT** If event elicited, complete information as requested. (If event previously elicited in General Inquiry, check Prev. Rec. below.) * = For event marked with *, record further description in Comments/Descriptor area If event previously recorded only check PREV REC box. Prev. Rec. ☑	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM:DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
B. HAVE YOU HAD ANY PROBLEMS WITH YOUR HEAD; THINGS LIKE HEADACHES, DIZZINESS, FAINTING, BLACKOUTS, OR SEIZURES? RQ? Check if no events elicited ☐	1. headache* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. dizziness/faintness ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. loss of consciousness* ☐ other (specify)	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
C. HAVE YOU NOTICED ANY PROBLEMS WITH YOUR EYES OR VISION; THINGS LIKE SWELLING OR IRRITATION, BLURRING, DOUBLE VISION, POOR VISION, OR LIGHT BOTHERING YOU? RQ? Check if no events elicited ☐	1. eye irritation ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. blurred vision ☐ other (specify)	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

Patient ID ___ | ___ | ___

MM DD YY ___ | ___ | ___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient

HEAD

EYES

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
II = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested

Additional space for comments on page 18

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
II = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested

Additional space for comments on page 18

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _

Patient ID ____|____|____

MM DD YY ____|____|____

	To help determine appropriate event category: WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ____ OR ____ ? DO YOU HAVE TROUBLE ____ ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THINGS (e.g. eating, sleeping)? HOW HARD IS IT TO (move, stand, stay awake, etc)? If possible observe impairment.
Note RQ?: If an event is elicited by any query, record information, and then repeat query as follows: ANY OTHER PROBLEMS WITH YOUR ____ , LIKE (continue with unadministered items).	**EVENT** If event elicited, complete information as requested. (If event previously elicited in General Inquiry, check Prev. Rec. below.) * = For event marked with *, record further description in Comments/Descriptor area Lines to record additional events on page 14	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM:DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
	Prev. Rec. ☑			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
D. HAVE YOU HAD ANY TROUBLE WITH YOUR EARS OR HEARING; THINGS LIKE PAIN OR DISCHARGE, TROUBLE HEARING, RINGING IN YOUR EARS?	1. ear ache ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. poor hearing ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. tinnitus ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	other (specify) 4. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	5. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
E. HAVE YOU HAD ANY PROBLEMS WITH YOUR MOUTH, LIPS, OR TEETH; THINGS LIKE SORES IN YOUR MOUTH, SWOLLEN OR SORE TONGUE, DRY MOUTH OR TOO MUCH SALIVA, BLEEDING GUMS, OR DENTAL PROBLEMS?	1. mouth ulcer ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. dry mouth ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. hypersalivation ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. sore tongue* ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. gum problems* ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. dental problems* ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	other (specify) 7. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	8. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
F. HAVE YOU HAD ANY PROBLEMS WITH YOUR NOSE OR THROAT; LIKE NOSEBLEEDS, STUFFY NOSE, SORE THROAT, LARYNGITIS, OR DIFFICULTY SWALLOWING?	1. nasal congestion ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. sore throat ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. difficulty swallowing ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 4. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
G. HAVE YOU HAD ANY TROUBLE WITH YOUR CHEST; SUCH AS CHEST PAINS, SHORTNESS OF BREATH, WHEEZING, OR COUGHING?	1. chest pain ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. shortness of breath ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. wheezing ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. coughing ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 5. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
H. *For men:* ANY OTHER PROBLEMS WITH YOUR CHEST, SUCH AS SWELLING OR DISCHARGE FROM THE NIPPLES? *For women:* HAVE YOU HAD ANY PROBLEMS WITH YOUR BREASTS, SUCH AS PAINS OR SWELLING OR DISCHARGE?	1. breast pain/swelling ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. discharge ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	other (specify) 3. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	5. ____ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

Patient ID ___|___|___

MM DD YY ___|___|___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event:
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient

EARS

MOUTH

NOSE/THROAT

CHEST

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
II = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested

Additional space for comments on page 18.

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		

Patient ID ___|___|___

MM DD YY ___|___|___

	To help determine appropriate event category: WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ____ OR ____ ? DO YOU HAVE TROUBLE ____ ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THING (e.g. eating, sleeping) HOW HARD IS IT TO (move, stand, stay awake, etc)? If possib observe impairment.
Note RQ?: If an event is elicited by any query, record information, and then repeat query as follows: ANY OTHER PROBLEMS WITH YOUR ________, LIKE (continue with unadministered items).	**EVENT** If event elicited, complete information as requested. (If event previously elicited in General Inquiry, check Prev. Rec. below.) * = For event marked with *, record further description in Comments/Descriptor area Lines to record additional events on page 14	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM:DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
	Prev. Rec. ☑			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
I. HAVE YOU HAD ANY TROUBLE WITH YOUR HEART; SUCH AS IT BEATING TOO FAST, POUNDING, OR SKIPPING?	1. rapid heart beat ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. irregular heart beat ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	other (specify) 3. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	4. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
J. HAVE YOU HAD ANY PROBLEMS WITH YOUR STOMACH; ANY ACHES OR PAINS, CRAMPS, HEARTBURN, NAUSEA, OR VOMITING?	1. stomach/abdominal discomfort* ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. nausea ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. vomiting ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 4. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
K. HAVE YOU NOTICED ANY CHANGES IN YOUR BOWEL MOVEMENTS; THINGS LIKE DIARRHEA, CONSTIPATION, GAS, CHANGES IN COLOR, OR PROBLEMS WITH HEMORRHOIDS OR PAINFUL BOWEL MOVEMENTS?	1. diarrhea ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. constipation ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. flatulence ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. stool discoloration ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 5. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
L. HOW HAS YOUR APPETITE BEEN; HAVE YOU NOTICED ANY RAPID WEIGHT GAIN OR LOSS, HAS FOOD TASTED DIFFERENT OR HAVE YOU HAD A BAD TASTE IN YOUR MOUTH; HAVE YOU BEEN THIRSTY?	1. appetite increase ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. appetite decrease ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. weight gain ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. weight loss ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. taste abnormality* ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. increased thirst ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 7. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	8. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
M. HAVE YOU HAD ANY PROBLEMS URINATING, THINGS LIKE PAIN, BURNING, DIFFICULTY STARTING TO URINATE, DECREASE IN THE FORCE OF YOUR URINARY STREAM, NEEDING TO URINATE MORE OFTEN, CHANGE IN THE COLOR OF YOUR URINE?	1. painful urination ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. difficulty urinating ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. increased frequency ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. change in color ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 5. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ____________ ☐	__ __ : __ __	__ __ __	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

Patient ID ___ \| ___ \| ___   MM ___ DD ___ YY ___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event:
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient.

CV
GI
GU

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
II = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		— — — — — — —

Patient ID ___|___|___

MM DD YY ___|___|___

	To help determine appropriate event category: WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ____ OR ____ ? DO YOU HAVE TROUBLE ____ ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THI (e.g. eating, sleepi HOW HARD IS IT T (move, stand, stay awake, etc)? If poss observe impairment.
Note RQ?: If an event is elicited by any query, record information, and then repeat query as follows: ANY OTHER PROBLEMS WITH YOUR ______ . LIKE (continue with unadministered items).	**EVENT** If event elicited, complete information as requested. (If event previously elicited in General Inquiry, check Prev. Rec. below.) * = For event marked with *, record further description in Comments/Descriptor area Lines to record additional events on page 14.	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM:DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
N. *For females:* HAVE YOU HAD ANY PROBLEMS WITH YOUR PERIOD; SUCH AS IRREGULARITY, CRAMPS, HEAVY BLEEDING, SPOTTING, PREMENSTRUAL TENSION, HOT FLASHES?	Prev. Rec. ☑			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
	1. menstrual irregularity* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. cramps ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. premenstrual tension ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 4. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
O. HAVE YOU HAD ANY PROBLEMS WITH YOUR GENITALS (PRIVATES) OR SEXUAL FUNCTIONING; ANY PAIN, SWELLING, OR DISCHARGE, ANY CHANGE IN YOUR INTEREST IN SEX, OR ANY PROBLEMS WITH SEX?				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
	1. genital discomfort* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. increased libido ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. decreased libido ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. sexual dysfunction* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	other (specify) 5. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
P. HAVE YOU HAD ANY PROBLEMS WITH YOUR MUSCLES, BONES, OR JOINTS; SUCH AS ACHES OR PAINS, SWELLING IN YOUR ARMS AND LEGS, TINGLING OR NUMBNESS IN YOUR HANDS OR FEET?				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
	1. muscle/bone/joint pain* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. edema* (specify location) ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	other (specify) 3. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	4. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
Q. HAVE YOU HAD ANY TROUBLE WITH WALKING OR MOVING; THINGS LIKE BEING UNSTEADY ON YOUR FEET, TROUBLE STARTING TO MOVE, CONTROLLING UNWANTED MOVEMENTS, FEELING RESTLESS OR LIKE YOU CAN'T STAY STILL, SHAKING, OR FEELING STIFF OR RIGID?				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
	1. akinesia ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. dyskinesia* (specify where) ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. dystonia* (specify where) ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. akathisia ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. rigidity ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	6. tremor ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	other (specify) 7. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	8. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
R. HAVE YOU HAD ANY PROBLEMS WITH YOUR SKIN, HAIR, OR SCALP; THINGS LIKE RASHES, ITCHING, IRRITATION, BRUISING, YOUR SKIN BEING MORE SENSITIVE TO THE SUN, OR SWEATING A LOT?				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
	1. skin irritation* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. hair problems* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	other (specify) 3. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RQ? Check if no events elicited ☐	4. ______ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

Patient ID ___|___|___

MM DD YY ___|___|___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event:
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient

GU (contd)

MUSCULO-SKELETAL

SKIN

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
I I = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested

Additional space for comments on page 18.

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X	COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION	CODE
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		

Patient ID

MM DD YY

	To help determine appropriate event category: WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ____ OR ____ ? DO YOU HAVE TROUBLE ____ ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING TH (e.g. eating, sle HOW HARD IS IT T (move, stand, stay awake, etc)? If po observe impairme
Note RQ?: If an event is elicited by any query, record information, and then repeat query as follows: ANY OTHER PROBLEMS WITH YOUR ________ , LIKE (continue with unadministered items).	**EVENT** If event elicited, complete information as requested. (If event previously elicited in General Inquiry, check Prev. Rec. below.) * = For event marked with *, record further description in Comments/Descriptor area Lines to record additional events on page 14.	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM:DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Sever
	Prev. Rec. ☑			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
S. HAVE YOU HAD ANY FEVER OR CHILLS?	1. fever ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	other (specify) 2. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
RQ? Check if no events elicited ☐	3. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
T. HOW ENERGETIC HAVE YOU BEEN; HAVE YOU FELT TIRED OR FATIGUED, OR HAVE YOU HAD TOO MUCH ENERGY, LIKE BEING EXCITED, OVERACTIVE, OR ELATED?	1. tiredness/fatigue ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	2. over-arousal* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	other (specify) 3. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
RQ? Check if no events elicited ☐	4. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
U. HAVE YOU HAD ANY PROBLEMS WITH YOUR SLEEP; ANY PROBLEMS FALLING ASLEEP, STAYING ASLEEP, WAKING UP TOO EARLY, SLEEPING TOO MUCH, OR FEELING DROWSY DURING THE DAY?	1. difficulty falling sleep ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	2. early morning awakening ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	3. interrupted sleep ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	4. drowsiness ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	other (specify) 5. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
RQ? Check if no events elicited ☐	6. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
V. HAVE YOU HAD ANY TROUBLE THINKING, CONCENTRATING, REMEMBERING THINGS, ANYTHING LIKE THAT?	1. confusion ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	2. concentration ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	3. memory ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	4. perceptual ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	other (specify) 5. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
RQ? Check if no events elicited ☐	6. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S
W. HAVE YOU HAD ANY PROBLEMS WITH YOUR MOOD OR SPIRITS: SUCH AS FEELING DOWN AND BLUE, DEPRESSED, ANXIOUS, OR IRRITABLE?	1. depression ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	2. anxiety ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	3. irritability ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
	other (specify) 4. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐
RQ? Check if no events elicited ☐	5. ________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐

Patient ID ___|___|___

MM DD YY ___|___|___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event:
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient.

FEVER
SLEEP
THINKING
MOOD

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
II = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested.

Additional space for comments on page 18.

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		

Patient ID

MM DD YY

Note RQ?: If an event is elicited by any query, record information, and then repeat query as follows: ANY OTHER PROBLEMS WITH YOUR ________ , LIKE (continue with unadministered items).

X. DURING THE LAST WEEK (or specified assessment interval) HAVE YOU HAD ANY UNPLEASANT OR BAD EXPERIENCES; THINGS LIKE FALLING, ACCIDENTS, EMERGENCIES, SUDDEN ILLNESS THAT MADE YOU GO TO THE DOCTOR OR HOSPITAL, OR TO THE DRUGSTORE FOR MEDICINE?

RQ? Check if no events elicited ☐

To help determine appropriate event category: WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE ____ OR ____ ? DO YOU HAVE TROUBLE ____ ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK (or specified interval?)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THINGS (e.g. eating, sleeping)? HOW HARD IS IT TO (move, stand, stay awake, etc)? If possible, observe impairment.
EVENT If event elicited, complete information as requested. (If event previously elicited in General Inquiry, check Prev. Rec. below.) * = For event marked with *, record further description in Comments/Descriptor area Lines to record additional events on page 14.	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
Prev. Rec. ☑			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
1. accidental injury* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
2. attempted suicide ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
3. intercurrent illness* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
4. medical or surgical procedure* ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
other (specify) 5. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
6. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

IF REQUIRED BY PROTOCOL, GO TO STUDY SPECIFIC EVENTS (NEXT PAGE) OR CONTINUE WITH THE EXAMINATION BELOW.

CLOSING INQUIRY

Y. Observe the patient's appearance and behavior for such problems as skin irritation, weight gain or loss, drowsiness, restlessness, trouble breathing, tremor, rigidity, and other abnormal movements. If the patient fails to mention a problem which has been observed during the examination or which has been reported by staff or family, say: I NOTICE ____ . HAS THAT BEEN BOTHERING YOU?

Follow up on any problems reported in a previous session that have not been covered in the examination: LAST TIME ____ WAS BOTHERING YOU. ARE YOU STILL HAVING TROUBLE WITH THAT? If no, check assessed & absent.

Close with (except omit at initial exam): LASTLY, HAS YOUR MEDICINE CAUSED YOU ANY PROBLEMS DURING THE PAST WEEK (or specified assessment interval)

Check if no events elicited ☐

Write in events elicited: If appropriate, use same event names as in Systematic Inquiry — assessed & absent						
			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
1. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
2. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
3. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
4. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
5. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
6. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
7. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
8. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
9. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
10. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
11. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
12. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
13. ____________ ☐	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

DURING THE EXAMINATION, PATIENT WAS:
- ☐ Nonverbal
- ☐ Verbal, low reliability
- ☐ Verbal, moderate reliability
- ☐ Verbal, high reliability

IS AN FDA 1639 TO BE FILED?
- ☐ Don't know
- ☐ No
- ☐ Yes

Adverse drug experience (event or diagnosis to be reported)

IF FINAL ASSESSMENT, REASON FOR TERMINATION IS:
- ☐ Not final assessment
- ☐ Patient dropped from study
- ☐ Patient withdrew from study
- ☐ Patient died
- ☐ Other (specify)

DIAGNOSES: Record any diagnoses that can be made on the basis of events reported during the examination.

Diag. 1: ____________

Diag. 2: ____________

Diag. 3: ____________

Patient ID ___|___|___

MM DD YY ___|___|___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?

For Relationship of Drug to Event:
HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response)
HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation)
DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset)

Relationship may be inferred by examiner if not reported by patient

OTHER CLOSING INQUIRY DIAGNOSES

POSSIBLE CONTRIBUTORY FACTORS

Check as many as apply

CD = Current disorder (being treated)
II = Intercurrent illness
OD = Other disorder (prior)
PH = Prior history of event
PD = Protocol drug
DI = Other drug/drug interaction
O = Other (specify)
OR
N = None Apparent

RELATIONSHIP OF DRUG TO EVENT

Check as many as apply

D = Dose response
DR = Dechallenge/rechallenge
TO = Timing of onset
S = Seen in other patients in this trial
K = Known drug effect
L = Laboratory data
O = Other (specify)
OR
NA = Not applicable (PD or DI not checked in Contributory Factors column)

ACTION TAKEN (by clinician)

N = None
IS = Increased Surveillance
C = Contra-active RX
CH = Change dose
CC = Contra-active RX plus change dose
SU = Suspend RX
DC = Discontinue RX
O = Other (specify)
X = Don't know

COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION

*Use to provide further characterization of event, especially where requested

Additional space for comments on page 18

CODE

(do not write in this space)

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _

CD	II	OD	PH	PD	DI	O	or	N	D	DR	TO	S	K	L	O	or	NA	N	IS	C	CH	CC	SU	DC	O	X		
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _
☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		_ _ _ _ _ _ _

For each diagnosis, write in previously recorded associated events. (Record event letter and number.)

		EVENT TERM			EVENT TERM			EVENT TERM	
__	__	______	__	__	______	__	__	______	_ _ _ _ _ _ _
__	__	______	__	__	______	__	__	______	_ _ _ _ _ _ _
__	__	______	__	__	______	__	__	______	_ _ _ _ _ _ _

Patient ID ___|___|___

MM DD YY ___|___|___

STUDY SPECIFIC EVENTS

	To help determine appropriate event category: WHAT KIND OF TROUBLE? CAN YOU TELL ME MORE ABOUT IT? WHERE IS IT? CAN YOU POINT TO IT? IS IT MORE LIKE OR ? DO YOU HAVE TROUBLE ?	WHEN DID THIS BEGIN? HAS IT HAPPENED IN THE PAST WEEK? (or specified interval)	HOW LONG DID IT LAST? (only during past week or specified interval)	DID IT HAPPEN MORE THAN ONCE? DID YOU HAVE IT ALL OF THE TIME? PART OF THE TIME?	IS IT A PROBLEM NOW?	HOW BAD IS IT? DOES IT BOTHER YOU A LOT?	DOES IT KEEP YOU FROM DOING THINGS (e.g. eating, sleeping)? HOW HARD IS IT TO (move, stand, stay awake, etc)? If possible, observe impairment.
	EVENT If event elicited, complete information as requested.	**DATE OF ONSET** 00:00 = started prior to beginning of this assessment interval MM DD	**DURATION IN DAYS** (only within current assessment interval) 000 = less than one day	**PATTERN** IS = Isolated IN = Intermittent CO = Continuous	**CURRENT STATUS** CO = Continuing R = Recovered w/o sequelae RS = Recovered w/ sequelae I = Indeterminate	**SEVERITY** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe	**FUNCTIONAL IMPAIRMENT** MN = Minimal MI = Mild MO = Moderate S = Severe VS = Very Severe
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
Z. (Enter script for Study Specific Events)	1. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	2. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	3. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	4. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	5. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	6. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	7. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	8. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	9. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
				IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
	10. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	11. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	12. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	13. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	14. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	15. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	16. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
RETURN TO PREVIOUS PAGE FOR CLOSING INQUIRY	17. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	18. ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
WRITE-IN SPACE FOR ADDITIONAL EVENTS	For each write-in: Record query letter, use next number in sequence, and specify.			IS IN CO	CO R RS I	MN MI MO S VS	MN MI MO S VS
	— — ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	— — ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	— — ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	— — ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
	— — ______	— — : — —	— — —	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

Continuation form needed?
Check, if yes: ☐

Patient ID ___|___|___

MM DD YY ___|___|___

IS IT A PROBLEM NOW? IS THIS UNUSUAL FOR YOU? IS THIS SOMETHING YOU'VE ALWAYS HAD? HAS IT CHANGED/GOTTEN WORSE RECENTLY? CAN YOU THINK OF ANYTHING ELSE THAT MIGHT HAVE CAUSED IT?	For Relationship of Drug to Event HAS THERE BEEN ANY CHANGE SINCE WE INCREASED/DECREASED YOUR DOSAGE? (Dose response) HAS THERE BEEN A CHANGE SINCE YOU STOPPED THE DRUG/STARTED IT AGAIN? (De/Rechallenge, not for drug initiation) DOES IT USUALLY HAPPEN RIGHT AFTER YOU TAKE YOUR MEDICINE? (Timing of onset) Relationship may be inferred by examiner if not reported by patient

STUDY SPECIFIC WRITE-IN

POSSIBLE CONTRIBUTORY FACTORS Check as many as apply CD = Current disorder (being treated) II = Intercurrent illness OD = Other disorder (prior) PH = Prior history of event PD = Protocol drug DI = Other drug/drug interaction O = Other (specify) OR N = None Apparent	**RELATIONSHIP OF DRUG TO EVENT** Check as many as apply D = Dose response DR = Dechallenge/rechallenge TO = Timing of onset S = Seen in other patients in this trial K = Known drug effect L = Laboratory data O = Other (specify) OR NA = Not applicable (PD or DI not checked in Contributory Factors column)	**ACTION TAKEN** (by clinician) N = None IS = Increased Surveillance C = Contra-active RX CH = Change dose CC = Contra-active RX plus change dose SU = Suspend RX DC = Discontinue RX O = Other (specify) X = Don't know	**COMMENTS, DESCRIPTORS & ADDITIONAL SPECIFICATION** Use to provide further characterization of event especially where requested Additional space for comments on page 18	**CODE** (do not write in this space)
CD II OD PH PD DI O or N	D DR TO S K L O or NA	N IS C CH CC SU DC O X		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
CD II OD PH PD DI O or N	D DR TO S K L O or NA	N IS C CH CC SU DC O X		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		

CD II OD PH PD DI O or N	D DR TO S K L O or NA	N IS C CH CC SU DC O X		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		
☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐☐		

Patient ID

MM DD YY

LABORATORY/PHYSICAL FINDINGS RECORD To be used (1) to record Lab/Physical findings (normal or abnormal) associated with elicited events or (2) to record abnormal Lab/Physical findings not associated with an event. Use page 19 for comments or to specify where requested. SPECIFY TEST BELOW — Check if no lab/physical findings are reported ☐	**ASSOCIATION TO EVENT** N = No associated event OR If associated, enter event letter and number. N or event	**DATE OF TEST** MM:DD	**RESULTS** Record value or score using both number and units.	**CLINICAL ABNORMALITY** Y = Yes N = No X = Uncertain	**POSSIBLE CONTRIBUTORY FACTORS** Enter as many as apply CD = Current disorder (being treated) II = Intercurrent illness OD = Other disorder (prior) PH = Prior history of abnormal test PD = Protocol drug DI = Other drug/drug interaction O = Other (specify) OR N = None Apparent	**ACTION TAKEN BY CLINICIAN** Enter as many as apply N = None R = Repeat test IS = Increased surveillance C = Contra-active Rx CH = Change dose SU = Suspend Rx DC = Discontinue Rx O = Other (specify) OR X = Don't know	**CODE** (do not write in this space)
LAB-HEMATOLOGIC	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
LAB-LIVER FUNCTION	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
LAB-KIDNEY	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
LAB-OTHER	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
RADIOLOGIC	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
ELECTRO-PHYSIOLOGIC (e.g. EKG,EEG)	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
PHYSICAL FINDINGS (e.g. weight, B.P.)	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
OTHER (Specify)	N ☐ or	– – : – –		Y N X ☐☐☐	CD II OD PH PD DI O or N ☐☐☐☐☐☐☐ ☐	N R IS C CH SU DC O or X ☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	
	☐ or	– – : – –		☐☐☐	☐☐☐☐☐☐☐ ☐	☐☐☐☐☐☐☐☐ ☐	

Continuation form needed?
Check, if yes: ☐

Patient ID ___|___|___

MM ___ DD ___ YY ___

DOSAGE RECORD Record DOSAGE PRESCRIBED AT LAST ASSESSMENT, all INTERIM CHANGES IN DOSAGE OR DOSAGE SCHEDULE, and DOSAGE PRESCRIBED FOR NEXT ASSESSMENT PERIOD. Include both protocol drugs and concomitant medications. Use page 19 for comments or to specify where requested. Check if no drugs prescribed ☐	**DRUG NAME OR CODE** For protocol drug, use PD. (If more than one, use PD1, PD2 etc.) For any other drugs, write in name or code.	**DATE** Enter date drug prescribed. MM DD	**TOTAL DAILY DOSE** **QUANTITY** If discontinued, enter 0000.	**UNITS** Mg. = Milligrams Ml. = Milliliters Caps = Capsules Tabs = Tablets 0 = Other (Specify)	**ROUTE OF ADMINISTRATION** PO = Oral IM = Intramuscular IV = Intravenous 0 = Other (Specify)	**DOSAGE SCHEDULE** hs = hour of sleep only qd = once per day bid = twice per day tid = three times per day qid = four times per day prn = as requested 0 = Other (specify)	**PROPORTION** EQ = Equal Proportions UN = Unequal Proportions NA = Not Applicable	**REASON FOR DOSAGE CHANGE** N = No change OR I = Initiated CP = Changed according to protocol CI = Changed due to ineffectiveness CT = Changed due to toxicity DC = Discontinued/Suspended DR = Drug reinstated following suspension 0 = Other (specify)
DOSAGE PRESCRIBED AT LAST ASSESSMENT: Enter required information for all drugs prescribed at last assessment.				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
INTERIM CHANGES IN DOSAGE OR DOSAGE SCHEDULE: Enter required information for any drug initiated or discontinued since the last assessment or for any other changes in dosage or dosage schedule. Enter information only when there is a change in a previous prescription.				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
DOSAGE PRESCRIBED FOR NEXT ASSESSMENT PERIOD: Enter required information for all drugs prescribed at this time for the next assessment period.				Mg Ml Caps Tabs 0	PO IM IV 0	hs qd bid tid qid prn 0	EQ UN NA	N or I CP CI CT DC DR 0
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
				☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Continuation form needed?
Check, if yes: ☐

Patient ID ___|___|___

MM ___ DD ___ YY ___

ADDITIONAL SPACE FOR COMMENTS

(IF REFERRING TO A SPECIFIC EVENT REPORTED ON THE PREVIOUS PAGES, RECORD EVENT NAME, LETTER AND NUMBER)

SPACE FOR COMMENTS FOR LAB AND DOSAGE RECORDS (if used)

(SPECIFY LAB TEST, PHYSICAL FINDING, OR DRUG REPORTED ON PREVIOUS PAGES)

SAFTEE TIPS

SAFTEE (Systematic Assessment For Treatment Emergent Events) is designed to collect information on adverse health events occurring during a clinical trial. It is administered periodically to record adverse events occurring during a specified period prior to the assessment. There are two versions of SAFTEE: Form-GI (General Inquiry) and Form-SI (Systematic Inquiry). Form-GI provides for standardized general inquiry about health-related events while Form-SI provides both a general inquiry and an inquiry based on review of body systems. The two forms ask for identical information regarding any adverse event that is detected. SAFTEE Tips provides guidance on the use of both forms and is most useful when a copy of SAFTEE is at hand for easy reference.

The SAFTEE rating system consists of eight components:

- The instructions and identifying information on the front page of the booklet;
- A list of preferred event terms presented both alphabetically and by body system (SAFTEE-GI only);
- The examination procedures, printed on the extreme left hand side of pages 2 through 15 of Form-SI and pages 4 through 7 of Form-GI. These consist of Opening Remarks, General Inquiry, Closing Inquiry, and Study Specific Events. SAFTEE-SI also includes Systematic Inquiry which is administered immediately following General Inquiry;
- Spaces for recording information obtained in the examination printed next to the examination procedures;
- The Laboratory/Physical Findings Record on page 16 of SAFTEE-SI and page 8 of SAFTEE-GI;
- The Dosage Record on page 17 of SAFTEE-SI and page 9 of SAFTEE-GI;
- Space for additional comments on pages 18 and 19 of SAFTEE-SI and pages 10 and 11 of SAFTEE-GI.

To use the SAFTEE rating system the examiner first fills out the identifying information on the front page of the booklet, and then administers the examination beginning with the Opening Remarks (printed on the top left hand side of the page) and continuing with General Inquiry, Systematic Inquiry (SAFTEE-SI only), and Closing Inquiry. If an adverse event is detected, information on that event is recorded on the form. The categories of information for describing the event include date of onset, duration in days, pattern, current status, severity, functional impairment, possible contributory factors, relationship of drug to event, and action taken by the clinician.

After completing the examination, the examiner enters concluding information based upon the examination. This includes the examiner's judgment of patient reliability, any formal diagnoses that can be made, whether an FDA Drug Experience Report (form 1639) is to be filled out, and – if the patient is to be terminated from the trial – the reasons for termination. Dosage information and additional information regarding laboratory and physical findings may be entered at this time or subsequently, at the convenience of the examiner.

The various components of the rating system will be discussed more fully below:

A. IDENTIFYING INFORMATION

The first page of the SAFTEE booklet is used to record identifying information about the assessment. The shaded box uses categories established by the Pharmacologic and Somatic Treatments Research Branch of NIMH, but may be adapted to meet the requirements of any institution. Additional identifying information includes the patient's initials, age, sex, the date of the assessment, and the rater's identification.

The first page also asks for the following information describing the assessment itself: (1) whether the assessment is an initial one, other baseline, follow-up or final; (2) whether the assessment is scheduled or unscheduled and (3) what assessment interval is being used. Follow-up assessments are all assessments, scheduled or unscheduled, other than initial, baseline, or final assessments. The assessment interval is the period of time that events are to be inquired about. Only events occurring within this period are to be inquired about and recorded during the assessment. This interval may be a week or some other period specified by protocol. Whatever period is selected should also be used for the initial assessment. That is, at the initial assessment, the examiner should inquire only about those events occurring in the previous week, or other specified assessment interval. The SAFTEE rating system should **not** be used to take a life-time history at the initial assessment. If, for example, the patient has had a problem in the past, but has not experienced any adverse events in the prior assessment interval, then that event should **not** be recorded.

Also included on the first page are items asking whether or not the SAFTEE Laboratory/Physical Findings Record and Dosage Record are to be used in conjunction with the examination.

Prepared by SysteMetrics, Inc. (Christy Moynihan, Ph.D.) for the National Institute of Mental Health, ADAMHA, DHHS. Additional information and copies may be obtained by contacting Jerome Levine, M.D. or Nina Schooler, Ph.D. at the Pharmacologic and Somatic Treatments Research Branch, NIMH, 5600 Fishers Lane, Room 10-C-06, Rockville, Maryland 20857. TEL. (301) 443-3524.

March, 1983

B. EXAMINATION PROCEDURES

The SAFTEE examination procedures are printed in the left hand side of each page with the queries to be spoken by the examiner highlighted in capital letters. To administer the SAFTEE–GI examination, the rater should first read the Opening Remarks, then proceed with General Inquiry, Study Specific Events (if any), and Closing Inquiry. To administer the SAFTEE–SI examination, the rater should read the Opening Remarks, and then proceed with General Inquiry, Systematic Inquiry, Study Specific Events (if any), and Closing Inquiry.

General Inquiry is made up of three queries concerned with general health status. **Systematic Inquiry** follows with 24 queries concerning more specific health problems, organized by body system. **Closing Inquiry** provides additional queries and procedures necessary for completing the examination in a thorough manner.

Problems observed by the examiner, but not reported by the patient during General or Systematic Inquiry, are covered during Closing Inquiry. The same is true for problems reported by third parties or for problems noted at a previous assessment. To avoid biasing the responses obtained from the patient during General and Systematic Inquiry such events should be assessed only during Closing Inquiry. The Closing Inquiry section is, thus, the only section in which the examiner may report events which were specifically asked about and found to be absent.

In administering the General, Systematic and Closing Inquiry sections, the examiner should ask each query of the patient, allowing sufficient time for a response. When administering Systematic Inquiry, the patient may respond positively to an event that is part of a query. For example, when asked "HAVE YOU HAD ANY TROUBLES WITH YOUR CHEST, SUCH AS SHORTNESS OF BREATH, WHEEZING OR COUGHING?", the patient may say he is short of breath. The examiner should then proceed to record necessary information about that event. The notation "RQ?" (repeat query) below each query is a prompt to remind the examiner to re-administer the query to insure that the patient has had an opportunity to respond to the other items on the list. In the above example, "HAVE YOU HAD ANY **OTHER** PROBLEMS WITH YOUR CHEST, SUCH AS WHEEZING OR COUGHING?"

If, as determined by protocol, there are additional events to be assessed in the evaluation that are not covered in Systematic Inquiry, these may be added in the section titled "Study Specific Events." This section, located on pages 14 and 15 of SAFTEE–SI and pages 6 and 7 of SAFTEE–GI is administered immediately after Systematic Inquiry (or General Inquiry for SAFTEE–GI) and before Closing Inquiry. A set of queries or instructions for eliciting information on the occurrence of such events should be entered in the left hand column of the page.

Throughout the examination, the examiner should ask the patient only about events occurring in the previous assessment interval (*i.e.*, either the past week or other interval as specified by the protocol). A phrase reminding the patient of the interval being inquired about is incorporated into many of the queries. The examiner should reiterate this phrase as necessary to focus the patient on the appropriate time period.

C. COMPLETION OF THE RECORDING FORM

If an adverse event is elicited during the examination, then information on that event should be recorded on the form. If an event is elicited during General Inquiry, it should be recorded in the General Inquiry section of the booklet. The same procedure should be used for Closing Inquiry. In writing in the event, the examiner should use the most definitive term available. When administering Form–SI, the same event names printed in the Systematic Inquiry portion of the examination should be used whenever appropriate for events elicited during General Inquiry. When administering Form–GI, the examiner should refer to pages 2 and 3 for preferred event terms. These are listed both alphabetically and by body system, following the sequence used in the Systematic Inquiry portion of Form–SI.

If an event is reported during Systematic Inquiry, the examiner should determine whether it can be described by any of the terms listed next to the query on the recording form. If the event is not listed on the form, the examiner should write in the event in the space provided next to the query. For any of the event names listed in Systematic Inquiry, additional descriptors may be written in the Comments section to enable the event to be defined and coded more precisely. Additional information is requested particularly for those events followed by an asterisk (*). For example, *headache** may be further described as *tension, frontal, sinus, etc.*

If the number of events elicited to any query exceeds the number of write-in spaces provided, additional write-in space is available on page 18 of SAFTEE–SI and page 10 of SAFTEE–GI. To indicate the event to which reference is being made, use the query letter (*e.g.*, A for General Inquiry, B for "Head" under Systematic Inquiry, etc.) and the next number in sequence in a given section. Thus the first additional write-in obtained for General Inquiry would be labeled A 10, that for "Head" under Systematic Inquiry would be B 6 and so forth.

If an event is elicited under General Inquiry and again under Systematic Inquiry, it should **not** be recorded twice. If any event has been elicited and recorded previously, this should be indicated by checking the box labeled "PREV REC".

SAFTEE provides for the recording of the following items of information on every elicited event. In order to obtain information from the patient to complete these items, suggested queries for eliciting the relevant data are printed above each column heading on the form.

- **DATE OF ONSET** should be used to record the month and day that the event first occurred. If, however, the first occurrence of the event was prior to the beginning of the assessment interval, 00/00 should be recorded. For example, if the assessment interval is one week, and the event first occurred two weeks previously, the date of onset should be entered as 00/00. This is true even for the initial assessment. If the patient currently reports an event with a prior history dating back three years and the assessment interval is one week, 00/00 should be recorded.
- The **DURATION** of the event is recorded in days. Events that last less than one day should be recorded as 000. The duration is equal to the maximum period of time over which the event has extended, even if the event has occurred intermittently over that period. For example, if the patient had a headache six days prior to the assessment, another three days prior, and another two days prior, the duration of the event is five days – that is, the period of time over which headaches occurred ranged from six days to two days prior to the assessment for a total of five days. The next category, PATTERN, will be used to indicate that the event occurred intermittently over that period. As with date of onset, only the duration *within* the previous assessment interval should be recorded. If an event has lasted continuously for one month, but the assessment interval is seven days, the duration should be recorded as seven days. The recording of 00/00 under DATE OF ONSET will indicate that the event first began prior to the seven day assessment interval.
- **PATTERN** is used to indicate whether the event occurred continuously over its period of duration, intermittently or was isolated. Isolated refers to events that occur only once for a short period during the assessment interval.
- **CURRENT STATUS** is used to indicate whether the problem is ongoing or whether the patient has recovered either with or without sequelae.
- **SEVERITY** is concerned with the intensity of the event and can be assessed through observation and/or through patient report of subjective distress.
- **FUNCTIONAL IMPAIRMENT** is concerned with the degree of interference from the event with the general activities of daily living or with specific activities that might be susceptible to disruption by the event (*e.g.*, the effect of tremor on fine motor activity). This factor may be assessed both through observation (if possible) and through the patient's verbal report.
- **CONTRIBUTORY FACTORS** is used to indicate those factors the examiner hypothesizes to be possible causes of the adverse event. The examiner may indicate more than one such factor and does not have to be certain of any to enter it on the form. The following factors are listed on the form. "Current disorder" is used to indicate that the event is consistent with the symptomatology of the disorder the patient is being treated for. "Intercurrent illness" indicates the event is caused by some transitory disorder recently arisen (*e.g.*, flu, hangover). "Other disorder (prior)" indicates the event is consistent with a pre-existing chronic condition (*e.g.*, heart disorder). "Prior history" indicates that the event, though atypical in the population, is common or usual for the patient (*e.g.*, headache, rash). "Protocol drug" is used when there is reason to believe the event is related to the treatment drug. Effects of concomitant medications or interactions among drugs (protocol or others) should not be placed in this category but may be indicated by the option, "Other drug/drug interaction." "Other factors" may include such events as protocol violations and should be specified in the Comments section.
- **RELATIONSHIP OF DRUG TO EVENT** is used if the examiner suspects that the event may be drug-related (either an effect of the protocol drug, of concomitant medications, or drug interaction). This category provides the opportunity to indicate the reasons for suspecting a drug-related effect. (If no such effect is suspected, check "Not Applicable.") "Dose response" indicates that the intensity of the event is related to the dosage level. "Dechallenge/Rechallenge" is used if the drug has been stopped and/or restarted with a concomitant improvement/exacerbation of the problem. "Timing of onset" is used if the onset of the event has some regular relationship to drug administration (*e.g.*, it always occurs one hour after taking the drug). Other reasons for suspecting a drug relationship are that it is consistently "Seen in other patients in this trial," that it is a "Known drug effect," or that it is supported by "Laboratory data." Any other reason should be specified in the Comments section.
- **ACTION TAKEN** refers to the clinician's response to a particular event. If a patient has experienced ten adverse events in the assessment interval, one of which causes the clinician to lower the dosage of the protocol drug, then "Change dose" should be used for that event only and not for all ten events.
- The space for **COMMENTS, DESCRIPTORS, AND ADDITIONAL SPECIFICATION** is used to write in additional text describing the event, particularly where called for. Additional space for comments is provided (page 18 in Form–SI, page 10 in Form–GI). If this space is used to refer to a specific event, the query letter and event number should be recorded as well.

D. CONCLUDING INFORMATION

Following the Closing Inquiry, the examiner should indicate the patient's reliability in the space provided at the bottom of that page. Further information to be provided includes whether an FDA Drug Experience Report (form 1639) is to be filed, the reason for termination if the assessment is the patient's final one and any formal diagnoses (*e.g.*, upper respiratory infection, tardive dyskinesia) that can be made on the basis of events elicited in the examination. These latter three items may be completed by someone other than the examiner.

E. LABORATORY/PHYSICAL FINDINGS RECORD

The SAFTEE Laboratory/Physical Findings Record is **not** intended to provide a complete laboratory record for a clinical trial but to supplement information on adverse events gained from the verbal examination. Its primary use is to record lab/physical findings relevant to an event elicited during the examination whether these findings are clinically normal *or* abnormal. In addition, *abnormal* lab/physical findings can be recorded whether or not associated with an elicited event.

First enter the name of any test or finding for which results are to be reported. Following this, indicate whether or not the test is associated with an event (*i.e.*, whether the lab/physical finding provides supplementary information on one of the events recorded previously). If so, the letter and number of the event should be indicated in the space provided. If not, the box labeled "No associated event" should be checked. Write in the date of the test or finding, the observed value, and whether or not the value appears clinically abnormal. "Possible contributory factors" is used to indicate factors believed to be possible causes of a clinically abnormal value and "Action taken" refers to the clinician's response to an observed laboratory or physical finding. These are completed in the same manner described previously. Space for comments or additional specification as requested is provided on page 19 (Form–SI) or page 11 (Form–GI).

F. DOSAGE RECORD

The SAFTEE Dosage Record, when used at each assessment, will provide a complete dosage record for both protocol drugs and concomitant medications. At each assessment, record both (1) the drugs and dosage previously prescribed (DOSAGE PRESCRIBED AT THE LAST ASSESSMENT) and (2) the drugs and dosage prescribed for the coming assessment interval (DOSAGE PRESCRIBED FOR NEXT ASSESSMENT PERIOD). Record any *changes* or additional medications used in an intervening period (since last assessment) in the space titled, "INTERIM CHANGES IN DOSAGE OR DOSAGE SCHEDULE." Only indicate in this section *changes* since the last assessment. The form should not be used as a day-at-a-time medication record.

When referring to a protocol drug, the examiner need only enter PD (or PD1, PD2, etc. if more than one protocol drug is being used). For non-protocol drugs write in the name of the drug. DATE refers to the month and day the drug was prescribed. TOTAL DAILY DOSE should be entered rather than the dosage taken at any one time. Indicated next are the ROUTE OF ADMINISTRATION, DOSAGE SCHEDULE, and PROPORTION in which the drug is taken. REASON FOR DOSAGE CHANGE indicates whether or not the dosage has been changed and, if so, the reasons for change (*e.g.*, "changed according to protocol", changed due to toxicity).

At the initial assessment, drugs and dosage the patient received (if any) during the specified assessment interval should be recorded under DOSAGE PRESCRIBED AT THE LAST ASSESSMENT. If a drug is being prescribed for the first time this is recorded in the DOSAGE PRESCRIBED FOR NEXT ASSESSMENT PERIOD section. At the next assessment (new SAFTEE form) this same information is recorded in the DOSAGE PRESCRIBED AT LAST ASSESSMENT section. If the dosage and/or dosage schedule were changed during this time, however, this should be entered on a new line (INTERIM CHANGES IN DOSAGE OR DOSAGE SCHEDULE) and the date of the change indicated. If the drug is to be continued into the next assessment interval then the relevant information must be recorded in the DOSAGE PRESCRIBED FOR NEXT ASSESSMENT PERIOD. If the drug is *not* to be continued this is indicated by entering the drug name or code, the date, 0000 for total daily dose, and the Reason for Dosage Change.

* * * * * * * * * * * * * * *

Use of SAFTEE provides a comprehensive examination of adverse health events during a specific period of a clinical trial. Information which the examiner feels is important and which has not been recorded should be reported using the space for comments on pages 18-19 (Form–SI) or pages 10-11 (Form–GI). If additional space is needed for the Study Specific Events page, or the Laboratory and Physical Findings or Dosage Record pages, check the appropriate box at the bottom of the respective page and use a new SAFTEE form. Fill out the IDENTIFYING INFORMATION (identical to the parent form) and write "CONTINUATION" in the shaded box.

Interrater Agreement and Intraclass Reliability Measures of SAFTEE in Psychopharmacologic Clinical Trials[1]

Alan F. Jacobson, Ph.D.,[2] Burton J. Goldstein, M.D.,[2] Roberto A. Dominguez, M.D.,[2] Richard M. Steinbook, M.D.[2]

The measurement of the adverse consequences of drug treatment has received little methodologic consideration in clinical trials of psychotropic drugs (Karch et al., 1976, 1977; Michaux, 1961). Improvement in the sensitivity, reliability, and validity of the measurement of adverse drug reactions would provide greater protection for patients from toxic compounds, provide comparison data on the side effects of psychotropic drugs to facilitate their clinical use, and improve the quality of clinical trials across multicenter settings. It is difficult to justify the delay in further development and standardization of the methodology for the assessment of adverse reactions (Petrie & Levine, 1978).

Currently, a number of factors contribute to problems in the detection of adverse reactions in clinical trials. There is much variability in the actual methodology used to collect side-effect data. Direct inquiry of the patient with regard to adverse reactions is the usual way of studying such events. Two different methodologies have evolved for eliciting this information from patients. The "unstructured" or "open-ended" method is designed to allow the patient to spontaneously report any side effects that have occurred, as opposed to the "structured" method in which a formalized list of possible side reactions is presented, to which the patient may respond positively or negatively. An advantage of the unstructured method is that it does not suggest side reactions to the subjects. On the other hand, an advantage of the structured method is that it may elicit side effects which patients might fail to spontaneously report. A number of researchers have verified that the structured method elicits more symptoms from subjects than the unstructured method (Avery et al., 1967; Downing et al., 1970; Harlow, 1972). While some investigators have questioned the validity of these "additional" adverse events detected by the structured method (Avery et al., 1967; Harlow, 1972), others have found that even in neurotic patients, the structured method was more likely to measure mild symptoms that might be overlooked in the unstructured assessment, or omitted as not drug related (Downing et al., 1970). In addition, the structured method has been reported to better discriminate active drug from placebo with regard to the occurrence and severity of adverse reactions (Rickels et al., 1970).

The elicitation of mild complaints during placebo washout periods or pretreatment evaluations presents the problem of distinguishing these events from the actual occurrence of autonomic, anticholinergic, or central nervous system adverse reactions during active drug treatment. Guy (1976) has suggested the elimination of such symptoms present during pretreatment and the rating of only newly occurring adverse events after the introduction of active drug.

An additional problem in the measurement of adverse reactions in psychopharmacology is that many symptoms of psychiatric illnesses are similar to the possible adverse reactions of the related pharmacotherapy. An attempt must be made during pretreatment evaluations to screen for symptoms related to the illness to avoid confounding them with side effects when active drug is introduced (Busfield et al., 1962).

The most common method for the detection of adverse drug reactions involves the use of side-effect checklists. However, the content of such checklists is undoubtedly biased (Tiplady et al., 1983), and many checklists are plagued by the poor definition of

---

[1] This research was supported by NIMH Grant #MG-38751.

[2] Department of Psychiatry University of Miami-School of Medicine, Miami, FL 33101.

Reprint requests to: Alan F. Jacobson, Ph.D.; Department of Psychiatry (D4-12); University of Miami-School of Medicine; P.O. Box 016960; Miami, FL 33101.

The authors gratefully acknowledge the assistance of Linda Knowles, R.N., Judith Lopez, R.N., Ms. Annie Baker, and Ms. Gayle Williams in conducting this research.

terms and severity ratings, widely varying symptom lists, and difficult and confusing recording formats (Petrie et al., 1978). In clinical trials, the adverse reactions to the reference drugs are usually known and therefore included in the side-effect checklist. In addition, most studies include "standard" drug-related symptoms in their checklists. Although this "standard" list encompasses a wide range of symptoms, there are practical limitations which may hamper the detection of adverse reactions of new drugs which were not previously anticipated (Simpson et al., 1980). Skegg and Doll (1977), in light of these limitations, have proposed that all clinically significant medical events occurring during a clinical trial be recorded whether or not any relationship with the trial drug is suspected. The resulting degree of association with a given drug could then be determined statistically after all data had been collected.

Systematic Assessment for Treatment Emergent Events (SAFTEE) is a newly developed system designed to obtain information on the occurrence of adverse health events in clinical trials of psychotropic drugs. The development of SAFTEE was sponsored by the National Institute of Mental Health (NIMH). SAFTEE provides a standardized examination procedure to be used in identifying the occurrence of adverse health events. There are two versions of SAFTEE: Form-GI (General Inquiry) and Form-SI (Systematic Inquiry). The GI version provides a standardized general inquiry about health-related events while the SI version provides both a general inquiry and a systematic inquiry based on a review of 23 body systems. The two versions of SAFTEE ask for identical information regarding any adverse event that is detected.

The present study provides some preliminary scientific data about the reliability and validity of the GI and SI versions of SAFTEE. In addition, the GI and SI versions were compared according to the frequency with which adverse health events were detected. The use of a uniform recording procedure in both GI and SI versions made it possible to compare event patterns observed under GI conditions with those elicited through SI conditions. Because the SI version contains a GI section as well as the SI section, it is possible to compare how many more events are elicited through subsequent systematic inquiry of the 23 body systems, compared to the number of events initially detected with the open-ended general inquiry procedure.

Method

Subjects: Adverse health event assessments using SAFTEE (either GI, SI, or both) were added to the standard assessment procedures of nine ongoing clinical trials. These studies included four inpatient studies being conducted at the University of Miami/Jackson Memorial Medical Center. Also included were five outpatient studies being done at our Symptomatic Volunteer Research Program (Brauzer et al., 1973; Goldstein et. al., 1970). The four inpatient studies consisted of either schizophrenic patients or those patients with major depressive episode with psychotic features hospitalized on our Inpatient Research Units. The five Symptomatic Volunteer studies consisted of outpatients suffering from moderate or greater severity levels of anxiety, depression, or insomnia. The various medications used in the nine studies consisted of reference and investigational neuroleptics, antidepressants, anxiolytics, and hypnotics.

Procedures: The study objectives were twofold: 1) to determine the interrater reliability of each of the two levels of SAFTEE, GI and SI; and 2) to compare the GI version with the SI version of SAFTEE in their ability to elicit the presence of adverse health events.

In order to collect data on the interrater reliability of each of the two versions of SAFTEE (SI and GI) in a clinical trial setting, two raters were used with both present at the same evaluation and both completing the same version of SAFTEE. The patients' assigned rater, either the psychiatrist or research nurse, conducted the standard interview for assessment of efficacy and standard side-effect information. The non-assigned rater, either the psychiatrist or research nurse, then joined the assigned rater for a joint rating on either the GI or SI form of SAFTEE. Although the raters were not assigned to the patients on a truly random basis, it is not expected that this was a source of systematic bias. Rater-assignment was determined on the basis of rater availability at the time a given patient was ready for assessment.

The methodology used to compare the two levels of elicitation (GI and SI) in their ability to detect the presence of adverse health events consisted of the following: patients were randomly assigned, within specific studies to one of two assessment conditions: a) the project psychiatrist administered the standard efficacy assessments followed by GI; subsequently, the research nurse independently administered SI; or b) the study research nurse administered the standard efficacy assessments followed by GI; subsequently, the psychiatrist independently administered SI. This methodology provided data determining if the subsequent administration of SI following GI elicited more events than originally obtained.

Data Analysis: Interrater reliability data were analyzed to determine whether raters assessing patients in the same evaluation period agree on the occurrence of adverse health events using the statistic kappa (Cohen, 1960; Fleiss, 1973). In addition, the interrater reliability on ratings of the duration of event, the severity of event, and the functional impairment caused by the event were compared using the intraclass correlation coefficient.

Results

A total of 652 SAFTEE assessments were made on a total of 134 patients during their scheduled weekly evaluations as specified by the individual study protocols. Of these SAFTEE assessments, 288 consisted of the GI version, while 364 consisted of the SI version. Dual conjoint ratings to determine the interrater reliability of each version of SAFTEE were made on a total of 74 patients. The SI-SI doctor-nurse paired evaluations were made on a sample of 46 patients and resulted in 86 pairs of evaluations (representing 172 SI booklets). There were 53 pairs of GI-GI doctor-nurse evaluations from a sample of 28 patients (totaling 106 GI booklets). The independent GI-SI assessments by doctor-nurse and nurse-doctor pairs resulted in 139 GI-SI paired ratings done on a total of 60 patients. Table 1 presents the results of the interrater reliability analysis for each of the above three groups of patients (GI-GI, SI-SI, and GI-SI).

TABLE 1. Overall Interrater Agreement and Reliability Coefficients Among the Different Versions of SAFTEE Across Three Patient Samples.

	GI-GI	SI-SI	GI-SI	Totals
Number of Patients in Sample	28	46	60	134
Number of Paired Ratings	53	86	139	278
Number of Different Adverse Event Categories Detected	21	66	37	124
Overall Mean Kappa Coefficients of Agreement	.95	.88	.40	
Number of Kappas Averaged for Means	21	66	37	
Mean Intraclass Reliability Coefficients on Duration	.26	−.60	.37	
Mean Intraclass Reliability Coefficients on Severity	.21	.40	.37	
Mean Intraclass Reliability Coefficients on Functional Impairment	.30	.13	−.06	
Number of Intraclass Reliability Coefficients Averaged for Means	11	46	23	

Reliability is expressed using the kappa statistic which indexes chance-connected agreement between the two raters on whether a specific adverse health event was detected as being present or absent. The kappas in Table 1 represent the mean of all kappas for each of the events detected in that sample. In addition, Table 1 contains the mean intraclass correlation coefficient representing the average intraclass reliability between the raters on the duration, severity, and functional impairment of each of the adverse events detected.

The results indicate that, although the paired conjoint GI-GI rating groups had the smallest number of events (21) detected within that particular sample of patients, it had the best overall level of interrater agreement (kappa = .95). The paired conjoint SI-SI rating group also showed a high level of interrater reliability (kappa = .88) on an overall average of the 66 events detected. As might be expected the independent (two separate individual assessments) GI-SI interrater reliability was low (kappa = .40) averaged over the 37 events detected by either the GI rater, the SI rater, or by both raters. Interrater agreement on the duration of the event resulted in

TABLE 2. Kappa Coefficients of Agreement and Intraclass Reliability Coefficients for the Adverse Health Event: Drowsiness.

Interrater Agreement			Conjoint Ratings								Independent Ratings			
			GI-GI (Pat. *N*=28)				SI-SI (Pat. *N*=46)				GI-SI (Pat. *N*=60)			
			2nd Rater				2nd Rater				2nd Rater(GI)			
			No	Yes	Kappa	*P*	No	Yes	Kappa	*P*	No	Yes	Kappa	*P*
Drowsiness detected	1st Rater	No	46	0			81	2			117	5		
		Yes	0	7	1.00	.001***	0	3	.74	.001***	9	8	.48	.001***
Number of pairs with event detected by both raters			*N*=7				*N*=3				*N*=8			

Interrater Reliability Variable	Mean	Intraclass Correlation	*P*	Mean	Intraclass Correlation	*P*	Mean	Intraclass Correlation	*P*
Duration	4.8	.99	.001***	6.5	.00	N.S.	6.8	.97	.001***
Severity	2.6	.91	.001***	2.8	.00	N.S.	2.4	.36	.077
Impairment	2.6	.92	.001***	2.2	−.67	N.S.	1.8	.21	.142

***P<.001.

the highest mean intraclass correlations for each of the three samples as compared to severity ad impairment. The SI-SI raters had the highest level of agreement on duration and severity compared to the other two samples.

A better appreciation of these results will be obtained by looking at the results of interrater reliability within each of the three patient samples on the following sample of adverse events: Drowsiness (Table 2); Muscle/Bone/Joint Pain (Table 3); and Skin Irritation (Table 4). The kappa coefficients of agreement (on the presence vs the absence) for each adverse health event are statistically significant for each of the three patient samples. There is always better agreement when both of the raters were present for the same interview using the same version of SAFTEE (the conjoint ratings) as opposed to the inde-

TABLE 3. Kappa Coefficients of Agreement and Intraclass Reliability Coefficients for the Adverse Health Event: Muscle/Bone/Joint Pain.

Interrater Agreement			Conjoint Ratings								Independent Ratings			
			GI-GI (Pat. *N*=28)				SI-SI (Pat. *N*=46)				GI-SI (Pat. *N*=60)			
			2nd Rater				2nd Rater				2nd Rater (GI)			
			No	Yes	Kappa	*P*	No	Yes	Kappa	*P*	No	Yes	Kappa	*P*
Muscle/bone/joint pain detected	1st Rater	No	44	0			73	2			93	2		
		Yes	0	9	1.00	.001***	1	13	.85	.001***	31	13	.33	.001***
Number of pairs with event detected by both raters			*N*=9				*N*=10				*N*=13			

Interrater Reliability Variable	Mean	Intraclass Correlation	*P*	Mean	Intraclass Correlation	*P*	Mean	Intraclass Correlation	*P*
Duration	6.3	.21	.135	4.7	.74	.002**	7.5	.92	.001***
Severity	2.4	.75	.002**	2.4	.56	.015*	2.6	.37	.044*
Impairment	2.0	.70	.005**	2.0	.82	.001***	2.1	.25	.094

*P<.05. **P<.01. ***P<.001.

TABLE 4. Kappa Coefficients of Agreement and Intraclass Reliability Coefficients for the Adverse Health Event: Skin Irritation.

Interrater Agreement			Conjoint Ratings								Independent Ratings			
			GI-GI (Pat. $N=28$)				SI-SI (Pat. $N=46$)				GI-SI (Pat. $N=60$)			
			2nd Rater				2nd Rater				2nd Rater (GI)			
			No	Yes	Kappa	*P*	No	Yes	Kappa	*P*	No	Yes	Kappa	*P*
Skin irritation detected	1st Rater	No	49	0			77	0			129	1		
		Yes	0	4	1.00	.001***	1	8	.93	.001***	5	4	.55	.001***
Number of pairs with event detected by both raters			$N=4$				$N=8$				$N=4$			

Interrater Reliability									
Variable	Mean	Intraclass Correlation	*P*	Mean	Intraclass Correlation	*P*	Mean	Intraclass Correlation	*P*
Duration	5.5	.95	.001***	5.5	.87	.001***	5.5	.42	1.00
Severity	1.5	.60	.053	1.6	.82	.001***	2.3	.57	.060
Impairment	1.1	.00	N.S.	1.5	.64	.012*	1.5	.14	.191

*P<.05. ***P<.001.

pendent ratings when each rater conducted their own separate interview (on the same day) with each of the two raters using a different version of SAFTEE (one rater using GI followed by the second rater using SI).

On the adverse event drowsiness (Table 2), the GI-GI conjoint ratings had the highest intraclass reliability coefficients (all greater than 0.90) of the three patient groups on the varibles of duration of event (days), severity of event (1 = minimal, 5 = very severe), and functional impairment caused by the event (1 = minimal, 5 = very severe). The SI-SI conjoint ratings failed to demonstrate interrater agreement on the duration, severity, and impairment of drowsiness. However, the number of rater-pairs in which both raters detected drowsiness, on which these results are based, is only three. On the other hand, when we use the data from all 86 rater-pairs in the kappa coefficients of agreement on the presence of drowsiness in the SI-SI group, we find good agreement with kappa = .74 ($p<.001$). The GI-SI group demonstrated very high intraclass reliability on the duration of drowsiness (kappa = .97, $p<.001$), but relatively little agreement on severity and impairment.

On the event of muscle/bone/joint pain presented in Table 3, high kappa coefficients of agreement are found in the conjoint rating samples GI-GI and SI-SI. Much less agreement is found in the GI-SI sample, with the SI ratings detecting the presence of this event on 31 assessments, but the GI ratings only detecting the presence of this event on 13 of these 31 assessments (as well as picking up on two cases not detected in the SI assessments). Intraclass reliability on the duration of muscle/bone/joint pain was good in the SI-SI patient sample, and very good in the GI-SI sample, while the GI-GI sample did not fare very well. The conjoint rating samples (GI-GI and SI-SI) had better intraclass reliability on the variables of severity and impairment than did the independent rating group, GI-SI.

Table 4 demonstrates that interrater agreement on the presence of skin irritation was very good in the conjoint ratings groups while only fair in the GI-SI independent ratings group. The SI-SI group had the best overall interrater reliability coefficients on the event of skin irritation.

The top half of Table 5 summarizes some of the comparative statistics on the two versions of SAFTEE, GI and SI. The number of assessments includes paired ratings (multiple assessments) on the same patient for the same time period, and also represents an overlap of patients between the two versions (the GI-SI group used the same 60 patients for both the GI and SI assessments). However, these fac-

TABLE 5. Comparative Data on the GI and SI Versions of SAFTEE ($N = 134$).

SAFTEE Version	Number of Assessments	Number of Adverse Events Detected	Mean Number of Events Per Assessment	Number of Patients (Groups Overlap)
GI	288	361	1.25	88
SI	364	2150	5.91	106
Total	652	2511		194

SI Version	Number of Adverse Events Detected	Mean Number of Adverse Events Per Assessment	Mean Severity	Mean Impairment
General Inquiry Section of SI	279	.77	2.45	1.98
Systematic Inquiry Section of SI	1871	5.14	2.21	1.72
Total	2150	5.91		

tors probably do not distort the GI:SI ratio of events with regard to the average number of events per assessment. The overall results suggest that SI yields an average of six events per assessment compared to one event per assessment using GI.

This finding is further supported by the data on the bottom half of Table 5. These data are based on the 2,150 events detected using SI reported in the top half of the table. As mentioned previously, the SI version contains the GI version followed by the systematic inquiry section. Therefore, the number of additional events detected by the use of SI (the SI part of SI) compared to the initial use of only GI can be estimated. These results indicate that, on the average assessment, the SI version will detect an additional five events to the one event detected by GI.

Discussion

These preliminary findings demonstrate a high degree of interrater agreement on the presence of adverse health events for both the GI and SI versions of SAFTEE. Agreement is best achieved when both raters are present for the same interview and are using the same version of SAFTEE (conjoint ratings). The overall interrater reliability coefficients (on duration, severity, and functional impairment), averaged across all of the adverse events detected within the individual patient groups, are not very impressive. However, examination of some of the individual events (Tables 2 to 4) indicates much variability, with some events yielding high levels of reliability, while other events have low interrater reliability on these variables. Future research should focus on the nature of this variability and methodologies for reducing it.

Another important finding of this study is that, of the 2,511 adverse events detected, the events could be categorized to fit into no more than 90 different event categories. Of these 90 event categories (i.e., event names), three times as many kinds of events were detected in the SI-SI patient sample as in the GI-GI patient sample. Although these samples are of different sizes and from different drug studies, the results suggest that the SI version definitely elicits the presence of a greater variety of adverse health event categories (as well as six times as many events) than does the GI version. This replicates previous findings that a structured method elicits more symptoms than an unstructured general method of inquiry (Avery et al., 1967; Downing et al., 1970; Harlow, 1972).

These results also suggest that the events volunteered during the GI portion of SI have a higher mean severity and impairment than events elicited during the SI portion of SI. It may be speculated that the more severe the event is perceived to be by the patient, the greater the probability of its being detected by GI when compared to SI.

References

Avery, C.W., Ibelle, B.P., Allison, B., and Mandel, N. Systematic errors in the evaluation of side effects. *Am. J. Psychiatry*, 123:875–878, 1967.

Brauzer, B., and Goldstein, B.J. Symptomatic volunteers: Another patient dimension for clinical trials. *J. Clin. Pharmacol.*, 13:89–98, 1973.

Busfield, B.L., Schneller, P., and Capra, D. Depressive symptoms or side effect? A comparative study of symptoms during pretreatment and treatment periods of patients on three antidepressant medications. *J. Nerv. Ment. Dis.*, 134:339, 1962.

Cohen, J.A. Coefficient of agreement for nominal scales. *Educ. Psychol. Meas.*, 20:37–46, 1960.

Downing, R.W., Rickels, K., and Meyers, F. Side reactions in neurotics. I. A comparison of two methods of assessment. *J. Clin. Pharm. New Drugs*, 10:289–297, 1970.

Fleiss, J.B. *Statistical Methods for Rates and Proportions.* New York: John Wiley & Sons, 1973.

Goldstein, B.J., and Weiner, D.M. Comparative evaluation of benzoctamine and diazepam in treatment of anxiety. *J. Clin. Pharmacol.*, 10:194–198, 1970.

Guy, W. *ECDEU Assessment Manual for Psychopharmacology.* Revised 1976. DHEW Publication No. 76-338. National Institute of Mental Health, Rockville, Md., 1976.

Harlow, B.J. Monitoring of adverse reactions by a pharmaceutical company before marketing. In: *Adverse Drug Reactions.* Baltimore: Williams & Wilkins, 1972.

Karch, F.E., and Lasagna, L. Toward the operational definition of adverse drug reactions. *Clin. Pharmacol. Ther.*, 21:247–254, 1977.

Karch, F.E., Smith, C.L., Kerzner, B., et al. Adverse drug reactions: A matter of opinion. *Clin. Pharmacol. Ther.*, 19:489–492, 1976.

Michaux, W.W. Side effects, resistance, and dosage deviations in psychiatric outpatients treated with tranquilizers. *J. Nerv. Ment. Dis.*, 133:203, 1961.

Petrie, W.M., and Levine, J. The assessment of adverse drug reactions in clinical trials. *Int. Pharmacopsychiatry*, 13:209–216, 1978.

Rickels, K., and Downing, R.W. Side reactions in neurotics. II. Can patients judge which symptoms are caused by their medication? *J. Clin. Pharm. New Drugs*, 10:298–305, 1970.

Simpson, R.J., Tiplady, B., and Skegg, D.C.G. Event recording in a clinical trial of a new medication. *Br. Med. J.*, 280-1133–1134, 1980.

Skegg, D.C.G., and Doll, R. The case for recording events in clinical trials. *Br. Med. J.*, 277:1523–1524, 1977.

Tiplady, B., Elton, R.A., and Loudon, J.B. Coding and analysis of spontaneously reported symptoms in clinical trials. *Psychopharmacol. Bull.*, 19(1):30–32, 1983.

Side Effect Assessment With SAFTEE: Pilot Study of the Instrument

Judith Godwin Rabkin, Ph.D.,[1] and
Jeffrey S. Markowitz, M.P.H.[1]

Introduction

It is widely acknowledged that methods for assessing side effects in clinical trials are far less sophisticated than those currently available for assessing efficacy (Assenzo & Shu, 1982; Petrie & Levine, 1978). Guy has observed that "the rating of adverse reactions has remained on a psychometrically primitive level" (1982). Although an estimated 25,000 studies of psychotropic drugs have been conducted to date (American Psychiatric Association Commission on Psychotherapies, 1982), and standard ratings of drug efficacy and clinical status have been employed routinely in drug trials for years, there are no established side-effect scales. In their absence, identification of side effects remains somewhat arbitrary (Larch & Lasagna, 1977).

Progress has been impeded for several reasons. These include difficulties in side-effect definition, different opinions about measurement strategies, and variations in the dimensions measured.

Problems of definition, and even terminology, abound. It is difficult to establish consensus on what constitutes a side effect in terms of both frequency and magnitude of the behavior in question. Both reliability of patient report and agreement between raters are uneven. Further, it is not always clear whether changes that are reliably observed are the direct consequences of drug administration, whether they are unrelated but occur concomitantly, or whether they are a consequence of the disorder for which the drug is being given (Guy, 1979). These problems are particularly challenging with antidepressants and anxiolytics, since many of their most common side effects (e.g., insomnia, tremor, sweating, drowsiness, dry mouth) are also symptoms of untreated depression and anxiety. As such, they may be present before treatment or appear subsequently without being drug related.

An associated problem is knowing what changes to look for and what to regard as drug related. For example, it is only recently that the possibility of a relation between monoamine oxidase inhibitors and development of carpal tunnel syndrome has been proposed (Harrison et al., 1983). Symptoms of carpal tunnel syndrome include sensory loss, parasthesias, or weakness of hand grip. Earlier studies did not identify such symptoms as potentially drug related.

In addition to the task of defining what constitutes a side effect, a major unresolved methodological issue concerns methods of data collection. Two approaches have dominated assessment. One is the open-ended or general approach in which the patient is asked a broad question about how he or she has felt within a recent specified time frame. The patient then spontaneously reports symptoms. The second approach is the structured, specific checklist method in which the patient is asked directly about a prepared list of symptoms thought to be drug related.

The major advantage of the general inquiry is the absence of suggestion. It is assumed that symptoms volunteered by the patient in this manner are true reports. It also may be argued that if something isn't sufficiently troublesome to the patient to warrant his reporting it when asked about how he is feeling, then it is not a "significant" event in terms of his clinical management, although this remains to be demonstrated. The major disadvantages of this method concern underreporting due to several possible sources. The patient may fail to link a symptom with the drug and not mention it at all. He may fail to recognize a symptom as such or conceal it out of discomfort or embarrassment, especially in the area of sexual dysfunction.

The specific form of inquiry circumvents these problems by presenting to the patient those symptoms considered by the investigator to be drug relevant. Its major potential

---

[1] New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons, Department of Psychiatry, 722 West 168th Street, New York, NY 10032.

sources of error are inadequate selection of items to inquire about, and the risk of overreporting stemming from patient suggestibility and variations in response sets. Even if present, symptoms thus elicited may be trivial in terms of clinical management.

Some work has been conducted to compare side effects using the two different formats. However, the available evidence is inconsistent regarding causes of the observed differences in number of events elicited by the two approaches. Downing et al. (1970) compared incidence of side effects using open-ended and structured methods in sequence, administered after 4 weeks of treatment with antidepressants, anxiolytics, or placebo medication. They found significantly more side effects with the structured method for active drug patients but not placebo patients. They attributed this "excess," reported with the structured method, to "true" but mild side effects that patients had overlooked or failed to relate to their medication in the general inquiry format. A different interpretation to the greater number of side effects elicited with a checklist compared to a general inquiry was given by Avery et al. (1967). In their opinion, the "excess" was probably due to "noise" or error variance rather than accurate reporting of genuine side effects.

Available Instruments

Until now, most investigators have compiled their own lists of side effects presumed to be associated with the drug being studied. Some are self-report scales filled out by patients at each visit or by the treating clinician. In studies of investigational drugs, the sponsoring pharmaceutical company often provides a checklist.

The Dosage Record and Treatment Emergent Symptoms Scale (DOTES), developed by the National Institute of Mental Health's (NIMH) Early Clinical Drug Evaluation Unit (ECDEU) program is probably the most widely used of the instruments designed to cover a broad range of potential side effects. It is a 41-item scale which includes 33 symptoms in addition to information about drug dose, laboratory data, a global presence, intensity, relationship to drug, and physician action taken. Although a scale is provided for each rating, and precoded forms have been worked out for detailed responses, the symptoms themselves are not clearly defined, and raters find administration of the scale cumbersome (Guy, 1982). Petrie and Levine (1978) note that the "chief difficulties of the DOTES are the several undefined or nonparallel items, the confusion and awkwardness most raters experience with the scale, and the difficulty in data analysis." These criticisms apply to the other side-effect checklists also in use. In addition, many include widely variable listings which combine signs, symptoms, and syndromes. Certainly, the available evidence regarding problems with extant instruments justifies development of a new measurement strategy as represented by the Systematic Assessment for Treatment Emergent Events (SAFTEE) (Levine & Schooler, this issue).

The overall goal of our research is improvement of methods for assessment of adverse consequences of psychotropic drugs in the context of clinical trials. Using SAFTEE, the instrument developed under the auspices of NIMH, we set out to compare the General Inquiry (GI) (short) and Systematic Inquiry (SI) (long) forms of SAFTEE in order to determine whether clinically useful information is generated by the long form beyond that obtained with the short form.

Method

Sample

This sample includes the first 83 patients in the SAFTEE study. They were receiving outpatient treatment in special research clinics for anxiety disorders ($N = 15$), bulimia ($N = 19$), or depressive disorder ($N = 49$ including 11 adolescents). Patients with anxiety disorders were not currently depressed, but half of the bulimia patients had concurrent diagnoses of depression, so that nearly three quarters of this sample were depressed at the time of baseline assessment.

Occasions

SAFTEE interviews were conducted at two different times for each patient: pretreatment baseline, and after 4 weeks in placebo-controlled clinical trials or open trials of investigational drugs.

Medications

In this sample, the following medications were administered: imipramine ($N = 15$), phenelzine ($N = 16$), placebo ($N = 13$), alprazolam ($N = 12$), nortriptyline ($N = 9$), an investigational antidepressant ($N = 11$) and miscellaneous other ($N = 7$). By the time of their second SAFTEE interview, patients were receiving doses of 200 mg of imipramine (or equivalent) in standardized protocols.

Interviewers

Interviewers were trained by the senior author in both group and individual meetings. After observing a SAFTEE interview and scoring a practice audiotape, each rater recorded two or three interviews which were then reviewed by the senior author, with corrections fed back to the rater.

In this study, patients were administered SAFTEEs by the same interviewer on both occasions. Most were conducted by the treating psychiatrist; in a minority of instances they were done by research nurses.

Data Analyses

In this preliminary report, the GI and the SI forms of SAFTEE are compared in terms of number and type of events elicited on both study occasions. Relationships between the various event ratings were analyzed. Comparisons are made for events reported by patients taking double-blind placebo and those on selected active medications. Larger samples and more extensive analyses will be reported at a future date.

Results

I. Descriptive Characteristics

Number of Events Reported

On the average, 1 or 2 events per person were reported on the GI on either occasion, and 8 to 10 events were reported on the SI. Over time, the number of GI events increased slightly and the number of SI events declined ($t = 2.51$ and $p = .01$, $t = 3.68$ and $p < .01$, respectively). In general, depressed patients reported more events than other patients. This is at least partly due to the presence on the SI of at least 14 events about energy, sleep, concentration, and mood which are common depressive symptoms.

On the GI, 45 (60%) patients reported no events at all at baseline and 39 (47%) reported none at week 4. In contrast, only two patients on the SI failed to report events at either baseline or week 4.

Frequencies of Individual Events

General Inquiry. At Time 1, 38 patients reported a total of 72 events in 28 different categories. At Time 2, 43 patients reported a total of 115 events. The only events reported by more than 5 patients were headache, fatigue, dizziness, and muscle pain, as shown in Table 1.

Systematic Inquiry. At Time 1, 81 patients reported a total of 747 events, and at Time 2, 80 patients reported 600 events. The events reported by at least 25% of respondents are shown in Table 1. They include indices of generalized distress, specific symptoms of depression, and, at Time 2, common drug side effects.

TABLE 1. Most Frequently Reported Events by Form and Occasion, for 83 Patients.

	General Inquiry[1]			Systematic Inquiry[2]	
	Time 1	Time 2		Time 1	Time 2
Event	*N*	*N*	Event	*N*	*N*
Headache	16	11	Headache	25	19
Fatigue	8	7	Fatigue	43	37
Dizziness	6	12	Drowsiness	27	--
Muscle pain	--	14	Initial insomnia	30	--
			Middle insomnia	29	21
			Terminal insomnia	20	--
			Poor concentration	40	29
			Poor memory	32	--
			Depression	65	53
			Anxiety	42	33
			Irritability	33	29
			Dry mouth	--	30
			Constipation	--	19
			Decreased libido	--	18

[1] Events reported by at least 5 patients.

[2] Events reported by at least 20% of sample.

Treatment Group by Event Categories (Body Systems). We analyzed events in terms of the 23 categories enumerated in the SI, by treatment condition [placebo, phenelzine, imipramine (IMI), alprazolam, and an experimental antidepressant or "EA"]. In the GI, only one category showed significant differences: problems with urination were reported by only two patients, both on phenelzine. Muscle pain tended to be more commonly associated ($p = .09$) with patients taking phenelzine (13 out of 16) and the experimental drug (7/11).

In the SI, problems with urination again varied by treatment. About half the patients taking IMI or the EA reported problems with urination; those on phenelzine did not, having done so earlier in the GI. Other differences were found with blurred vision (lower incidence on placebo, highest incidence on phenelzine and IMI), problems with stomach (highest rate in placebo group), and a higher rate of IMI patients reporting skin problems compared to other treatment groups.

Overall, these differences are far from dramatic, and considering the number of comparisons made, some may be due to chance. Nevertheless, the results generally are consistent with the side effects known to be associated with these marketed drugs.

II. Psychometric Analyses

SAFTEE is designed so that each event reported to have occurred is scored in 10 areas, some of which themselves have non-mutually exclusive ratings. In order to identify relationships between the event parameters elicited in the column queries, we compared each parameter with others. Given our relatively small data set, these findings must be considered preliminary. The unit of analysis is the event. In the following analyses, events from Time 1 and Time 2 are combined to enlarge the sample size.

Pattern

The pattern of an event is scored as either isolated (lasting less than a day), intermittent, or continuous. These scores are determined by the possible range of occurrence, not by their literal manifestation. For example, early morning awakening can occur only once a day, but if it occurs every morning from day of onset, it is scored as continuous.

The frequencies for the three patterns were unequal. Nine percent of the 1,814 events in this data set were classified as isolated, 35% as intermittent, and 56% as continuous.

Duration and pattern are significantly correlated, with a mean correlation coefficient of 0.58 (range of .32 to .66) across forms (GI and SI) and occasions. Severity and functional impairment both are related to pattern in that isolated and intermittent events are, as a rule, more often rated mild while continuous events more often are rated severe, both in terms of distress and functional impairment.

Pattern and status are overlapping measures. Isolated events were rated recovered, intermittent events were rated as indeterminate, and continuous events were rated as continuing. Nearly 90% of all reported events fit this description.

No clear relationships emerged for pattern and possible contributory factors. Both apparent symptoms (rated by interviewer as part of current disorder) and side effects (rated by interviewer as due to protocol drug) came in all patterns. Neither was there a correspondence between pattern and physician action taken except for the category of "drug discontinued." Nearly 80% of events leading to drug discontinuation were classified as continuous.

Current Status

This score refers to presence of a reported event at time of interview. Seventy-three percent were described as continuing, 17% as "recovered without sequelae," 1% as "recovered with sequelae," and 9% as "indeterminate."

Subjective severity was loosely related to current status. About 60% of events scored as "recovered" or "indeterminate" were classified as minimal or mild, while 13% were rated severe or very severe. Continuing events, in contrast, were more often rated severe or very severe (22%). The same relationship is seen with functional impairment but it is more clearcut: 80% of events described as causing severe or very severe functional impairment were classified as continuous.

Current status was not systematically related to possible contributory factors. However, 75% of events leading to drug discontinuation were classified as "continuing." Overall, continuing events were seen as more distressing and disruptive than other categories of status.

Severity

On a 5-point scale ranging from minimal to very severe, 35% were rated as moderate, 46% as minimal or mild, and 20% as severe or very severe. As noted above, events rated as severe in subjective distress were more often continuous in pattern and continuing in current status.

The correlations between subjective severity and functional impairment ranged from .52 to .67 depending on form (GI or SI) and occasion (Time 1 or Time 2). The lowest *r* was on the GI at Time 1, and the highest on the SI at Time 2. All are statistically significant. At best, however, knowledge of severity accounts for only 45% of the variance of functional impairment scores, so that both measures contribute unique information.

Upon inspection of the cross-tabulations of ratings of severity and functional *impairment*, we found that in most cases of discrepancy, "severity" is rated as more severe than impairment. That is, subjective distress may occur in the absence of significant impairment, but the converse is seldom reported. Exceptions to this pattern tended to include symptoms of mania such as "excited" and "overtalkative" which didn't upset the patient very much but were seen by the rater as severely impairing function.

Possible contributory factors were not systematically related to severity of distress; both apparent symptoms and side effects were rated throughout the range of severity.

Functional Impairment

Of the 1,814 events, 44% were rated as causing minimal impairment, 18% = mild, 24% = moderate, 11% = severe, and 3% = very severe. While more events rated severe or very severe were reported on the SI than GI (50 vs. 3), the percent with such scores was higher on the GI (21% vs. 13% on SI). The distributions are shown on Table 2.

TABLE 2. Frequency Distributions of Event—Functional Impairment Scores by Inquiry and Occasion.

		General Inquiry		Systematic Inquiry	
Value		Time 1	Time 2	Time 1	Time 2
(1)	Minimal	37	46	386	336
(2)	Mild	16	30	150	130
(3)	Moderate	28	40	216	158
(4)	Severe	15	34	85	63
(5)	Very Severe	0	3	30	20
	Mean Severity	2.2	2.5	2.1	2.0
	S.D.	1.1	1.2	1.2	1.1
	Number Events	96	153	867	707

Another way to examine the severe ratings of functional impairment is to see on which form they appear. Of the 250 events rated as causing severe or very severe functional impairment, 79% appeared on the SI. One hundred thirty, presumably illness symptoms, were reported at Time 1, and 120, presumably including side effects, were reported at Time 2.

Among the 23 events scored as causing very severe impairment at Time 2, only 3 were recorded on the GI. All three were reported by the same patient, who became hypomanic and whose medication was discontinued. The other 20 events were recorded on the SI and represented side effects or symptoms reported by a total of 8 patients. In none of these cases was medication discontinued.

The overall impression is that ratings of functional impairment contribute meaningful information over and above that provided by ratings of the severity of distress. Our pilot data show that events causing extreme functional impairment do not only appear in the GI portion of the SAFTEE interview; indeed, most were reported in the SI.

Possible Contributory Factors

Eight different scoring options are provided in this category, most of which are not mutually exclusive. In this report, we focus on only three categories: current disorder (i.e., symptoms), intercurrent illness (unrelated illness occurring during past week), and protocol drug (i.e., side effect). Table 3 shows their distribution.

TABLE 3. Possible Contributory Factors: Percent Present by Category, Form, and Occasion.

	General Inquiry		Systematic Inquiry	
	Time 1	Time 2	Time 1	Time 2
Current Disorder	16	16	53	36
Intercurrent Illness	18	17	5	8
Protocol Drug	0	43	0	28

Symptoms of the psychiatric disorder for which the patient seeks treatment are not often reported on the GI. This is reasonable in view of the GI Opening Remarks: "We've been talking about (condition being treated). Now I'd like to ask some more general questions about your health: 'have you had any physical or health problems during the past week?'" Given this framework, it is not surprising that in the GI, in contrast to the SI, patients emphasize intercurrent illnesses and say relatively little about psychiatric symptoms.

Less than half of all events reported at Time 2 were identified by the raters as possible side effects (attributable to protocol drug). A larger percent of events reported in the GI than SI were scored as side effects; this difference is statistically significant (43% vs. 27%, $\chi^2_{\text{corr.}} = 4.95$, $p = .026$, 1 df). In general, in the raters' opinions, the majority of events elicited by either SAFTEE method are not true side effects.

Relationship of Drug to Event

The response categories of "dose-response," "dechallenge/rechallenge," "laboratory data," and "other" were scarcely if ever used. Most events identified as attributable to protocol drug were said to be "known side effects" or "seen in other patients in study." These two categories were significantly correlated with protocol drug scores ($r = +0.71$ and $+0.67$, respectively).

Physician Action Taken

We had hoped to use scores in this category as dependent variables to which we could relate evaluations of severity, impairment, and other event parameters. It turned out, however, that for 90% of all events reported, no action was taken at all. When we look at events reported at Time 2, after patients were on active or placebo medication for 4 weeks, no action was taken for 80% of all events then recorded. Since only 31% of events recorded at Time 2 were judged to be side effects by the raters, this is not as surprising as it might otherwise seem.

Comparing the GI and SI with respect to action taken, we first compared percent of events reported on each form where *any* action was taken. On the GI, some action occurred for 31% of events, compared to 17% of events on the SI ($\chi^2_{\text{corr.}} = 4.63$, 1 df, $p = .03$)

We examined ratings of duration, severity, and functional impairment in terms of their correlation with the *action taken* variable, which was dichotomized into two scores: *no* action vs. *any* action. The point-biserial correlation coefficients for these three parameters with Action Taken were 0.25, 0.27, and 0.40, respectively, for events reported on the GI. That is, each parameter was significantly ($p < .01$) related to some action being taken. The relationships of these predictors to action taken for events on the SI were much weaker: 0.05, 0.10, and 0.05, respectively, and only for the severity variable ($r = 0.10$) was the correlation statistically significant ($p = .01$). Overall, then, severity, duration, and impairment associated with events reported on the GI were much better predictors of action taken than they were for events reported on the SI.

Altogether, only 28 events led to drug discontinuation at Time 2. They were recorded for only 6 patients, of whom 1 had 12 such events. Two of the 6 patients stopped taking medication on their own initiative, while doctors made the decision for the others.

The majority of events leading to drug discontinuation were reported on the GI (18 vs. 10). They constituted 12% of all GI Time 2 events, compared to 1% of SI Time 2 events.

Four of the patients reported events leading to drug discontinuation on the GI, while two brought up these events only in the SI. The patient with a clear toxic reaction, who reported 12 events, did so on the GI, as did others with major side effects. Of the two who mentioned them only in the SI, one had severe fatigue. The other had four events which cumulatively rather than singly led to drug discontinuation, since each separately was rated as no more than moderately severe or causing mild or moderate impairment.

III. Validity Studies

A crucial validity test of any side-effect measure is its ability to elicit the particular "treatment emergent events" known to characterize standard drugs, in comparison to each other and to placebo. Illness symptoms, on the other hand, are expected to appear with equivalent frequency across medication conditions, at least before clinical improvement. With disorders such as depression and anxiety, however, a number of events may be either symptoms or drug-related side effects, such as dry mouth and rapid heart beat which may accompany anxiety, and loss of appetite and fatigue, which often occur with depression. When our data set is complete, we will apply a method to distinguish between events present at baseline which are absent after treatment (presumably treatment-responsive symptoms), and those absent or mild at baseline that appear with greater severity after treatment (presumably side effects).

At this time and with our pilot data, we simply looked at events appearing at Time 2 which almost certainly are either side effects of antidepressant medication, or illness symptoms not believed to be exacerbated by the medications used. We compared their relative incidence in patients receiving active drug and placebo.

As shown in Table 4, only 1 of 52 events presumed to be a side effect was experienced by a placebo-treated patient. Events included in these analyses were difficulty urinating, dizziness, sweating, blurred vision, and dry mouth. In contrast, presumed symptoms (i.e., anxiety or depression) were distributed relatively evenly among all treatment conditions, including placebo.

Collapsing, first across active drugs (imipramine, phenelzine, and alprazolam), and then across presumed side effects and presumed symptoms, we obtain a highly significant ($\chi^2_{\text{corr.}} = 13.3$; $p<.001$) 2×2 interaction effect. That is, events associated with drug treatment are more likely to be presumed side effects than presumed symptoms.

TABLE 4. Events—Time 2 (GI+SI Forms).

	Drug Condition			
Presumed Side Effects	*PBO*	*IMI*	*PZ*	*ALP*
Difficulty urinating	0	4	2	0
Dizziness	1	4	1	1
Sweating	0	6	1	0
Blurred vision	0	5	5	1
Dry mouth	0	10	9	2
Presumed Symptoms				
Anxiety	9	6	4	6
Depression	10	9	11	10

Abbreviations:
PBO = placebo
IMI = imipramine
PZ = phenelzine
ALP = alprazolam

Comment

Our pilot data show internal consistency between related parameters, and preliminary evidence of validity in the SAFTEE's capacity to distinguish correctly between symptoms and side effects. While we cannot draw major conclusions from this small data set, it appears that nonredundant and clinically meaningful information is elicited in the SI, beyond that spontaneously reported by patients in the GI.

The total number of events reported at baseline was 819 and a significant number of these same events were reported by the same subjects at endpoint. Events reported at both baseline and endpoint can be viewed as treatment nonresponsive events or persistent symptoms. These events should not be viewed as treatment emergent. The high prevalence of symptoms reported at baseline underscores the importance of controlling for these events in side-effect assessment studies. Similarly, the high prevalence of baseline symptoms will have to be taken into account when examining the relative utility of the GI and SI.

The validity of a measure is limited by its reliability. In fact, instrument reliability is generally considered to be a precondition for validity (Nunnally, 1978). Consequently reliability studies of our SAFTEE data set are required in order to adequately assess the psychometric properties of SAFTEE. Such studies are presently underway and the results of these tests will be reported at a later date.

References

APA Commission on Psychotherapies; *Psychotherapy Research: Methodological and Efficacy Issues*. Washington, D.C.: American Psychiatric Association, 1982.

Assenzo, J., and Shu, V. Use of statistics in the analysis of side effect data from clinical trials of psychoactive drugs. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:543–550, 1982.

Avery, C., Ibelle, B., Allison, B., et al. Systematic errors in the evaluation of side effects. *Am. J. Psychiatry*, 123:875–878, 1967.

Downing, R.W., Rickels, K., and Meyers, F. Side reactions in neurotics: I. A comparison of two methods of assessment. *J. Clin. Pharmacol.: New Drugs*, 10:289–297, 1970.

Guy, W. Documentation of early phase II trials. In: Levine, J. (ed.), *Coordinating Clinical Trials in Psychopharmacology*. Washington, D.C.: U.S. Government Printing Office, 1979, pp. 15–42.

Guy, W. Patient assessment in clinical trials. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6:601–606, 1982.

Harrison, W., Stewart, J., Lovelace, R., and Quitkin, F. Case report of carpal tunnel syndrome associated with tranylcypromine. *Am. J. Psychiatry*, 140:1229–1230, 1983.

Karch, F., and Lasagna, L. Toward the operational identification of adverse drug reactions. *Clin. Pharmacol. Ther.*, 21:247–254, 1977.

Levine, J., and Schooler, N.R. Strategies for analyzing side effect data from SAFTEE workshop—Background and development. *Psychopharmacol. Bull.*, 22(2):343–346, 1986.

Nunnally, J.C. *Psychometric Theory*, 2nd ed. New York: McGraw Hill Book Company, 1978.

Petrie, W., and Levine, J. The assessment of adverse drug reactions in clinical trials. *Inter. Pharmacopsychiatry*, 13:209–216, 1978.

Reliability and Validity of SAFTEE: Preliminary Analyses[1]

William Guy, Ph.D.,[2] William H. Wilson, Ph.D.,[2] Beth Brooking, R.N., M.S.N.,[2] Gregory Manov, M.D.,[2] and Olaf Fjetland[2]

The Systematic Assessment for Treatment Emergent Events (SAFTEE) has been designed to collect detailed information by two methods of elicitation: a general inquiry and a systematic review of bodily systems. Its most innovative feature is a structured inquiry in which specific questions are asked of each event in an ordered manner. Given this format, it was felt that SAFTEE would be uniquely suited for use by paraprofessionals (RN's, LPN's etc.) as well as by physicians. The specific aim of the project, therefore, was to obtain estimates of reliability among a multi-discipline cohort of raters through the use of video-taped interviews and through the employment of multiple ratings of SAFTEE during the course of clinical trials. An estimate of validity will be obtained by comparing SAFTEE with a comparable standard assessment instrument as well as a determination of whether analyses of its data would produce different adverse event profiles for different patient populations and/or different drug treatments.

Method

Data for the psychometric analyses of SAFTEE have been acquired from two sources: direct interviews of clinical trial participants by multiple raters, and ratings of videotape interviews by multiple raters.

In the clinical trial setting, SAFTEE has been employed as part of the assessment procedures. Fifty patients were examined and rated by four raters with all interviews occurring within a 48-hour period. Two nurses, alternating as interviewers, completed both SAFTEE General and Systematic Inquiries. A psychiatrist independently completed the General Inquiry, while a psychologist completed the comparison assessment instrument, the AMDP Somatic Signs (AMDP-SS).

The AMDP-SS is an integral part of the assessment battery developed by the European Association for Methodology and Documentation in Psychiatry. The scale consists of 44 symptoms each rated on a 5-point scale of severity (Figure 1). Anchor points for each symptom have been provided and a semi-structured inquiry procedure is used for the elicitation of events. The scale has been in use for over a decade and a substantial number of validity and reliability studies have been published (Guy & Ban, 1982).

For the videotape segment of the project, 20 patients were interviewed by a registered nurse using both the General and Systematic Inquiry procedures. From this group, 10 videotapes were selected for viewing by a rater cohort of 30—consisting of nurses (RN's and LPN's), psychiatric residents, psychiatrists, and psychologists. An additional tape was produced for training purposes. This tape was viewed section by section. The rating of each SAFTEE variable was discussed. Differences in ratings were resolved or, at least, arbitrated. Following the training session, raters viewed and rated the first of the 10 videotapes without interruption. A review and discussion of this interview was then conducted, but no changes in rating were permitted. The raters then proceeded to rate each of remaining tapes on two separate occasions in order to obtain estimates of test-retest reliability. Thus, a data base consisting of 10 videotapes rated twice by 30 raters representing several professional disciplines are obtained.

Results

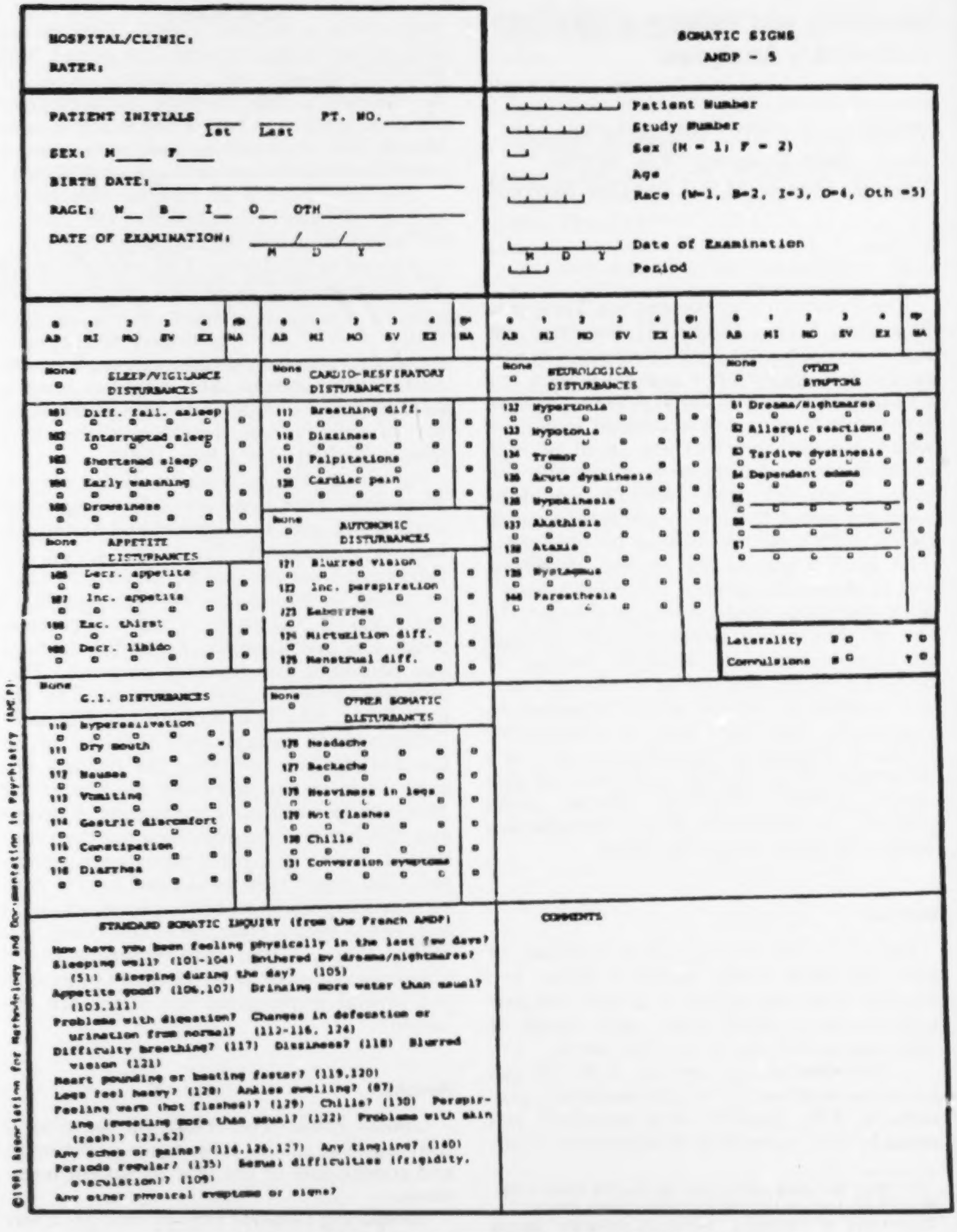
Clinical Trials. The results on the clinical trial segment of the project are preliminary and consist only of the first 25 patient interviews.

Comparing General Inquiry ratings, it was found that the psychiatrist rated 44% of the

---

[1] This study was supported in part by USPHS Grant 1-R01-MH3876-02. from the National Institute of Mental Health.

[2] Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN 37232.



HOSPITAL/CLINIC:
RATER:

SOMATIC SIGNS
AMDP - 5

PATIENT INITIALS ___ ___ (1st Last) PT. NO.________
SEX: M____ F____
BIRTH DATE:________________________
RACE: W__ B__ I__ O__ OTH____________
DATE OF EXAMINATION: ___/___/___ (M D Y)

Patient Number
Study Number
Sex (M = 1; F = 2)
Age
Race (W=1, B=2, I=3, O=4, Oth =5)
Date of Examination (M D Y)
Period

None ○ SLEEP/VIGILANCE DISTURBANCES

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
101 Diff. fall. asleep	○	○	○	○	○	○
102 Interrupted sleep	○	○	○	○	○	○
103 Shortened sleep	○	○	○	○	○	○
104 Early wakening	○	○	○	○	○	○
105 Drowsiness	○	○	○	○	○	○

None ○ APPETITE DISTURBANCES

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
106 Decr. appetite	○	○	○	○	○	○
107 Inc. appetite	○	○	○	○	○	○
108 Exc. thirst	○	○	○	○	○	○
109 Decr. libido	○	○	○	○	○	○

None G.I. DISTURBANCES

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
110 Hypersalivation	○	○	○	○	○	○
111 Dry mouth	○	○	○	○	○	○
112 Nausea	○	○	○	○	○	○
113 Vomiting	○	○	○	○	○	○
114 Gastric discomfort	○	○	○	○	○	○
115 Constipation	○	○	○	○	○	○
116 Diarrhea	○	○	○	○	○	○

None ○ CARDIO-RESPIRATORY DISTURBANCES

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
117 Breathing diff.	○	○	○	○	○	○
118 Dizziness	○	○	○	○	○	○
119 Palpitations	○	○	○	○	○	○
120 Cardiac pain	○	○	○	○	○	○

None ○ AUTONOMIC DISTURBANCES

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
121 Blurred vision	○	○	○	○	○	○
122 Inc. perspiration	○	○	○	○	○	○
123 Seborrhea	○	○	○	○	○	○
124 Micturition diff.	○	○	○	○	○	○
125 Menstrual diff.	○	○	○	○	○	○

None ○ OTHER SOMATIC DISTURBANCES

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
126 Headache	○	○	○	○	○	○
127 Backache	○	○	○	○	○	○
128 Heaviness in legs	○	○	○	○	○	○
129 Hot flashes	○	○	○	○	○	○
130 Chills	○	○	○	○	○	○
131 Conversion symptoms	○	○	○	○	○	○

None ○ NEUROLOGICAL DISTURBANCES

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
132 Hypertonia	○	○	○	○	○	○
133 Hypotonia	○	○	○	○	○	○
134 Tremor	○	○	○	○	○	○
135 Acute dyskinesia	○	○	○	○	○	○
136 Hypokinesia	○	○	○	○	○	○
137 Akathisia	○	○	○	○	○	○
138 Ataxia	○	○	○	○	○	○
139 Nystagmus	○	○	○	○	○	○
140 Paresthesia	○	○	○	○	○	○

None ○ OTHER SYMPTOMS

	0 AB	1 MI	2 MO	3 SV	4 EX	99 NA
81 Dreams/Nightmares	○	○	○	○	○	○
82 Allergic reactions	○	○	○	○	○	○
83 Tardive dyskinesia	○	○	○	○	○	○
84 Dependent edema	○	○	○	○	○	○
85 ________	○	○	○	○	○	○
86 ________	○	○	○	○	○	○
87 ________	○	○	○	○	○	○

Laterality N ○ Y ○
Convulsions N ○ Y ○

STANDARD SOMATIC INQUIRY (from the French AMDP)

How have you been feeling physically in the last few days?
Sleeping well? (101-104) Bothered by dreams/nightmares? (51) Sleeping during the day? (105)
Appetite good? (106,107) Drinking more water than usual? (103,111)
Problems with digestion? Changes in defecation or urination from normal? (112-116, 124)
Difficulty breathing? (117) Dizziness? (118) Blurred vision (121)
Heart pounding or beating faster? (119,120)
Legs feel heavy? (128) Ankles swelling? (87)
Feeling warm (hot flashes)? (129) Chills? (130) Perspiring (sweating more than usual? (122) Problems with skin (rash)? (23,62)
Any aches or pains? (114,126,127) Any tingling? (140)
Periods regular? (135) Sexual difficulties (frigidity, ejaculation)? (109)
Any other physical symptoms or signs?

COMMENTS

©1981 Association for Methodology and Documentation in Psychiatry (AMDP)

FIGURE 1. AMDP Somatic Signs (sample data collection form).

interviews as asymptomatic in contrast to 32% so rated by the nurses. The two nurses were in agreement in 7 of their 8 asymptomatic ratings, while the psychiatrist was in agreement with the nurses in 7 of his 11 asymptomatic ratings. Overall, the mean number of symptoms cited by the nurses was 1.34—slightly higher than the psychiatrist's mean of 1.14. When asymptomatic interviews are excluded, the mean number of symptoms cited per interview rose to 2.40 for the nurses and 2.00 for the psychiatrist. The percent of symptoms upon which all three raters were in agreement was 89.4%. An interclass correlation of .735 was obtained on the ratings of severity of symptomatology. The mean severity rating of the psychiatrist (2.55) was higher than that obtained by the nurses (2.03) since the psychiatrist made much greater use of the rating point "moderate" than did the nurses. There was a total of 13 symptoms cited on General Inquiry—the most frequent being fatigue, headache, decreased appetite, and difficulty falling asleep. Since most of the patients in this data set were depressed, these citations could be considered psychopathological symptoms as well as adverse events. In summary, the advantages of the General Inquiry are its brevity, its "nonsuggestiveness," and its format which is similar to the technique usually employed by clinicians in their routine evaluations. The major disadvantage is the possibility of not eliciting symptoms which may be present.

No asymptomatic records were obtained on the Systematic Inquiry of either nurse. The mean number of symptoms/interview on their combined Systematic Inquiry was 6.6 with a range of 3 to 19 symptoms. The mean number of symptoms/interview of the combined General and Systematic Inquiries was approximately eight—a figure which corresponds to that obtained by other research units involved in the SAFTEE project.

The percent of agreement on the presence or absence of symptoms between the two nurses was 84.5%. The interclass correlation for the rating of severity was .791. Almost all severity ratings were either "Minimal" or "Mild"—the mean rating for both nurses being 1.21. Thirty-three individual symptoms were cited by the two nurses, i.e., approximately 45% of all of the symptoms printed on the SAFTEE form. The most frequently cited symptoms (dry mouth, depression, memory difficulties, urinary difficulties, constipation, anxiousness, restlessness) again contain a number of symptoms (20%) which could be considered "psychopathological" as well as adverse events.

Table 1 presents the intercorrelation among several of the Systematic Inquiry variables. Duration correlates positively with Pattern, Severity, and Functional Impairment. It would seem that the longer a symptom persists, the higher the degree of severity/impairment associated with it. Pattern is similarly—and not unexpectedly—positively correlated with Severity and Functional Impairment. Severity and Functional Impairment obtained the highest intercorrelation (.88) reflecting, perhaps, a tendency on the part of raters to judge these variables together, i.e., as a unit.

In the interviews using the AMDP-SS, there were also no asymptomatic records. The mean number of symptoms/interview was 4.71 with a range of 2 to 13 symptoms. This mean is substantially lower than that obtained with the SAFTEE. Since the AMDP-SS was designed to be used routinely in conjunction with a psychopathological symptom scale, the authors omitted those symptoms which they considered "psychopathological," e.g., depression, anxiety, etc.. Since some 20% of the symptoms cited on the SAFTEE-Specific Inquiry could be considered "psychopathological," the percent of agreement between the psychologist rating the AMDP-SS and the two nurses rating SAFTEE was only 77.4%. Excluding this type of symptom, however, raises the percent of agreement to almost 90%. The interclass correlation for severity was .805. The mean severity rating for AMDP-SS was 1.59 compared to the nurses' mean rating of 1.21—reflecting the greater

TABLE 1. Intercorrelations Among SAFTEE—S1 Variables.

Item	1	2	3	4	5
1. Duration	-	.69	.20	.51	.51
2. Pattern	-	-	.20	.61	.58
3. Current Status	-	-	-	.21	.21
4. Severity	-	-	-	-	.88
5. Functional Impairment	-	-	-	-	-

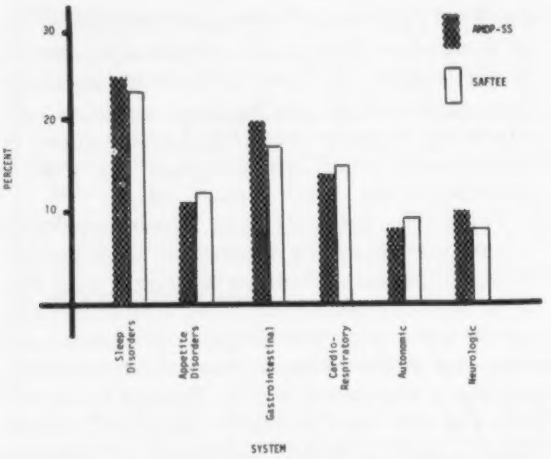


FIGURE 2. Distribution of AMDP-SS and SAFTEE symptoms among body systems.

use of "Moderate" by the psychologist. The total number of symptoms cited on the AMDP-SS was 27—a figure which constitutes 57% of all the symptoms printed on the form. The most frequently cited symptoms correspond well to those obtained on SAFTEE (dry mouth, micturition difficulties, constipation, restlessness). Two write-in symptoms (fatigue, memory/concentration) were also among those frequently cited and correspond in frequency to those obtained on SAFTEE. Although the two scales do not match precisely in their classification of symptoms, it was possible to compare the distribution of symptoms by bodily systems and that comparison is shown in Figure 2. The profiles obtained are commensurate with the depressed population sampled and suggest that the scales may have potential for differentiating drug effects within specific populations.

Videotape Interviews. The results presented here consist only of data from 12 raters (6 RN's, 6 LPN's) obtained from viewing of the first four videotapes.

Agreement among RN's and LPN's was determined separately for the ratings of Presence/Absence of symptoms and for the severity of symptom. The statistical methods employed are those described by Bartko et al. (1980). For the ratings of Presence/Absence, separate Kappa coefficients were determined for each patient by employing a Rater-by-Symptoms matrix and an overall Kappa was determined across all patients. Presented in Table 2 are the results for individual patients and overall Kappas for RN's and LPN's determined for both the initial and second rating sessions. The overall ratings for the RN's were slightly lower than for the LPN's at both rating sessions. However, analysis revealed that all four overall Kappas were statistically significant. The significance was determined by the relationship: $z = \text{Kappa}/\sigma$. One advantage of calculating individual Kappas is that they revealed interpatient differences in rating difficulty. Patient #2 proved to be the most difficult patient to rate for both the RN's and LPN's, and reliability of the ratings did not improve on the second rating of this patient.

The level of agreement was also ascertained for the ratings of severity of symptoms at the initial rating period. These results are presented in Table 3. These data indicate a substantially lower level of agreement than found for the presence of symptoms. This was the case for both RN's and LPN's.

Finally, to compare the RN's with the LPN's in their judgment of the presence of symptoms, all symptoms for all patients were rescored as present or absent if the majority of raters were in agreement, e.g., if 80% of the RN's (or LPN's) rated a symptom as present, it was so scored. This was done for both RN's and LPN's. A Kappa was then determined and was found to be .855, reflecting

TABLE 2. Kappa (κ) Reliability Coefficients Determined for Rating of Presence/Absence of Symptoms.

RN's					
Initial Rating Patient	1		2	3	4
κ	.601		.127	.598	.625
Overall κ		.488			
Second Rating Patient	1		2	3	4
κ	.360		.070	.555	1.00
Overall κ		.496			
LPN's					
Initial Rating Patient	1		2	3	4
κ	.657		.268	.666	1.0
Overall κ		.648			
Second Rating Patient	1		2	3	4
κ	.430		.229	.690	1.0
Overall κ		.587			

TABLE 3. Kappa (κ) Reliability Coefficients Determined for Ratings of Severity of Symptoms.

RN's					
Initial Rating Patient	1		2	3	4
κ	.165		.219	.326	.134
Overall κ		.211			
LPN's					
Patient	1		2	3	4
κ	.205		.092	.330	.284
Overall κ		.228			

highly significant agreement between RN's and LPN's as to the presence of symptoms.

Discussion

While agreement between the psychiatrist and the nurses on the General Inquiry conducted during the clinical trials was substantial on both the presence and severity of symptoms, it seems clear that this method of elicitation produces a minimum of data. The data, however, have the virtue of being relatively spontaneous in comparison to the more probing inquiry of the Systematic Inquiry. The kinds of symptoms reported on the General Inquiry tend to be those which could be construed as "psychopathological" as well as "adverse." It is of interest to note that the first question of the inquiry procedure of the AMDP-SS (How have you been feeling in the last few days?) has the quality of a "general inquiry" in that it elicits symptoms of a similar nature.

Agreement on both the presence and severity of symptoms between the nurses on the Systematic Inquiry was substantial. Compared to the psychiatrist and psychologist, the nurses tended to rate symptoms more conservatively, i.e., at a lower level of severity. Recognizing the exclusion of "psychopathological symptoms" on the AMDP-SS, the agreement obtained between the two scales for both presence and severity of symptoms reflects a high degree of equivalence. It is clear, however, that the amount of information obtained on any given symptom is much greater with SAFTEE. While the amount of time necessary to complete both sections of SAFTEE is greater than that required to complete the AMDP-SS, the time differential does not appear too burdensome or unprofitable. Both scales appear to have potential in differentiating different populations and treatments through symptom profiles.

Compared to the raters involved in the clinical trial segment of the project, the raters of the videotapes can be considered neophytes. As a consequence, they showed an initial apprehension at the length of the SAFTEE form. With experience, the raters became accustomed to the sequence of questions and the initial apprehension was dissipated. Rating from videotapes, however, engendered difficulties not evident in the clinical trial segment. Clarification of ambiguous patient responses proved to be the major problem for these raters. It was initially difficult to pinpoint the duration of a symptom, and a special "standard" for the timing of duration had to be developed to alleviate this problem. From the data analyses, the agreement levels for the rating of severity reflect a greater degree of difficulty than that seen for the rating of presence/absence. This may also be due, in part, to the ambiguity in patient responses. It should be kept in mind, however, that the present data are based on the first four patient interviews. Levels of agreement for severity may well improve when the total data base is analyzed.

In summary, preliminary analyses suggest that nurses (RN's and LPN's) can complete SAFTEE in a valid and reliable manner when compared with other professional disciplines. Training of raters through the use of videotapes is feasible, although some problems are evident. Taking into consideration their different contents and orientations, SAFTEE and AMDP-SS exhibited a high degree of equivalence.

References

Bartko, J., Strauss, J., and Carpenter, W. Selecting techniques for evaluating the reliability of psychiatric data: A report from the international pilot study of schizophrenia. In: Bartko, J., and Bulbinat, W. (eds.), *Multivariate Statistical Methodologies Used in the Pilot Study of Schizophrenia*. DHHS Publ. No. (ADM) 80-630, 1980.

Guy, W., and Ban, T.A. *The AMDP System: A Manual for Assessment and Documentation in Psychopathology*. Heidelberg: Springer Verlag, 1982.

Side Effects Data Analysis

Philip W. Lavori, Ph.D.[1]

Introduction

The analytic demands of side-effects data are considerable and many difficult features that may arise individually in other data analysis contexts arise in concert in side-effects data. The typical side-effects dataset is highly multivariate (there are many types of events, from headache to dyskinesia), sparse (most side effects will have low expected incidence), of complex datatype (there is often a severity or impairment rating and a duration or pattern of occurrence attached to each notation of a side effect), longitudinal (each patients' may have several assessments), censored (patients leave study at varying times), and incomplete (assessments may be missing at times). These are formidable challenges one by one; together they seem overwhelming! Threading a path through this thicket requires close cooperation and communication between statistician and clinical researcher; what follows is a rough guide to the terrain. It is limited to the role of an agenda for the discussion between clinical investigator and statistician, rather than a manual of techniques.

Sparse Multivariate Data—Lump or Split?

Individual side effects such as toxic confusional state may be rare; others such as headache may be more common in a particular experiment. An event that occurs with very low frequency may be clinically crucial or irrelevant but it is not statistically informative by itself. Only by combining rare events into less rare groups of events can the statistician make inferential calculations (such as comparison of active drug and placebo or dose-response). Thus, besides enumeration and archiving, there is little to be done with individual rare events, unless samples are truly enormous.

Grouping of events may be based on different criteria. For example, all events that lead to discontinuation of treatment have something in common that may be a useful focus of analysis. Some events are thought to be manifestations of an underlying physical process (such as anti-cholinergic or extrapyramidal signs). These may be combined into complexes of events for further analyses. Assuming the clinical utility of these groupings, and the statistical necessity of a reasonably high rate of occurrence, we propose some techniques for analyzing data. For example, suppose the goal is to determine the difference between drug and placebo in the rate of some event or complex of events. If the time from start of study treatment to the event or to the end of study is available, the methods of survival analysis may apply. These will provide estimates of the probability that the event will occur by each time of study, for each treatment group. Models of covariate influence on the hazard can be constructed, so that the effects of age, sex, initial "side effect" status, fixed dose effects, and other factors can be assessed. With the time-dependent proportional hazards model the dose-response can be investigated even when the dose varies across time for a patient. Of course, just as in efficacy analyses, the usual requirements of independent censoring must be met, or the analysis will not be valid. Given this, the methods take account of varying time-on-followup.

This approach could be repeated for several groups of events and for several criteria for grouping (e.g., by body system, by severity). Some individual events may be frequent enough, and interesting enough by themselves to warrant separate analysis. Perhaps the discomfort that many investigators feel about "lumping" events of different kinds may be relieved by the possibility that one kind of "lumping" may complement the other so that, in sum, no information is lost.

If the event does not cause termination but persists for a while and then resolves, the "clock" can be restarted, and the analysis repeated for the length of time to second occurrence. This may be useful if the event occurs at irregular intervals over time, since it makes use of the "second wave" of information. If the *duration* of the event itself is of interest, then that can be analyzed as well.

---

[1] Massachusetts General Hospital, Boston, MA 02114.

Fancier methods, such as renewal processes and embedded Markov chains (in which both the times between events and the probability of occurrence of events are modeled), might be applied to studies whose length, size, and cost justify the considerable investment in analysis that these "high-tech" methods require.

It is clear that longitudinal data add information about the individual response to a drug. If the side effects are random, rare events, then greater length of follow-up will give better estimates of rates of occurrence. Patterns of occurrence (related to drug dose, for example) may be more informative than single-occasion reports. The efficient, valid use of such longitudinal data requires expertise in a statistical specialty which at this writing is at the front lines of research, with many exciting developments in theory and practice. Such an unsettled state is both rewarding and difficult, and the clinical investigator will not find many "off-the-shelf" solutions to the problems that come up. Methods that do not explicitly take into account the longitudinal quality of the data (multiple, ordered measures on each individual) will often produce biased results, and will be inefficient as well.

Analyzing Sparse Patterns

If there are 50 types of events, and each may or may not occur, there are 2^{50}, or about 10^{15} (1,000,000,000,000,000) possible cells in the full cross-tabulation at each time. Even with only 10 compound events there are more than 1,000 cells. Thus, even a very large study will leave most of the cells empty, and a more typical sample will be nearly lost in the cross-tabulation. In practice, it is likely that a few cells will contain most of the patients at an assessment; these cells may be known in advance, or discovered by exploration. If this is the case, it may be fruitful to find the one-dimensional set of exhaustive, exclusive alternatives and write them down as a single classification variable. These classifications can then be analyzed across time by methods of categorical data analysis (such as mover-stayer models or Markov models). Many of these models can be viewed as special instances of log-linear analysis, for which good software is readily available. If there are no such small "subspaces" of the full cross-classification, then there is not likely to be much information at that level of aggregation of events.

Interval Level Measurements of Events

If the clinician can make use of a scalar measure (such as severity or impairment) then the event will have a "degree" rather than just a "presence." This opens the possibility of discriminating between drug and placebo by the level of (multivariate) events. Although classical discriminant function methods could be applied, the typical characterization of the event level data (highly skewed toward zero) recommends logistic regression as a robust alternative. For longitudinal continuous (multivariate) data, methods such as structural equations modeling and the two-stage repeated measures models proposed by Laird and Ware (1982) might find use. The sparseness problem must be solved first, by aggregation. These methods (especially the Laird-Ware methods) are equipped to deal with the "ragged right margin" of most longitudinal datasets (i.e., different numbers of follow-up assessments among patients), and internal (time varying within individual) factors, such as dose or clinical response.

Can the Data Tell the Investigator How to Aggregate?

At the level of dichotomous (presence/absence) event data, there must be some preparation and "pre-shrinking" of the dataset by the judicious use of clinical insight, before any multivariate latent variable, discriminant function, factor analysis, cluster analysis, or other automatic method can be relied on. If the events are aggregated to the extent that the clinician finds comfortable, then the methods of log-linear analysis may provide an approach to obtaining more stable estimates of rates of occurrence than the raw observed proportion of occurrence. The basic idea is to fit a low-dimensional log linear model (all two-factor terms, perhaps) which can then be used to form expected cell proportions. These may have better stability than the raw rates. This is explored in the Bishop-Feinberg-Holland (1975) text on multivariate contingency table methods.

References

Bishop, Y.M.M., Feinberg, S.E., and Holland, P.W. (eds.) *Discrete Multivariate Analysis: Theory and Practice.* Cambridge, Mass.: MIT Press, 1975.

Laird, N.M., and Ware, J.H. Random-effects models for longitudinal data. *Biometrics*, 38:963–974, 1982.

Issues in the Long-Term Use of Benzodiazepines Workshop—

Introduction

Karl Rickels and Allen Raskin,
Workshop Co-Chairs

The Pharmacologic and Somatic Treatments Research Branch (PSTRB) of the National Institute of Mental Health (NIMH) sponsored a two-day workshop, September 16–17, 1985, in Washington, D.C., on "Issues in the Long-Term Use of Benzodiazepines." The articles that follow are expanded versions of five of the nine papers presented at that workshop.

There has been considerable interest and concern of late about the negative effects of chronic use of benzodiazepines, especially benzodiazepines with long half-lives such as diazepam (Valium). These concerns center around the psychological addicting potential of these drugs and the anxiety and other negative effects associated with their withdrawal after long-term use. Less well known or understood are the beneficial effects that accrue to some patients who do well on these drugs and poorly when the drugs are withdrawn or when they are shifted to other classes of psychotropic drugs. Recent studies also indicate that withdrawal effects can be minimized by a better understanding of the symptoms associated with withdrawal and appropriate drug management such as gradual rather than abrupt discontinuation. Work is also in progress on some of the newer benzodiazepines with short half-lives to determine if these compounds are less addicting and cause fewer problems when withdrawn than benzodiazepines with long half-lives. Adaptation effects or tolerance to these drugs occurs over time and we now know that their pharmacologic properties following acute administration do not accurately mirror their pharmacologic effects with chronic administration. Recent electrophysiological studies have also demonstrated that long-term exposure to benzodiazepines attenuates their ability to enhance postsynaptic GABAnergic transmission. These basic findings support clinical and behavioral evidence that tolerance does develop to the pharmacologic actions of benzodiazepines with chronic use. The aim of the two-day workshop was to explore these and related issues in an informal atmosphere in which participants would have ample opportunity to raise questions and comment on the findings and observations of the other participants. Specific topics covered and speakers are noted below:

Topic:	Prevalence, Patterns, and Relative Risks of Benzodiazepine Usage: A Cross-National Appraisal
Speaker:	Mitchell B. Balter Public Health Research Center
Topic:	Patients Who Profit from Maintenance Benzodiazepine Treatment
Speaker:	Karl Rickels University of Pennsylvania Medical School
Topic:	The Occasional Long-Term Use of Benzodiazepines
Speaker:	Jonathan O. Cole McLean Hospital
Topic:	Behavioral Effects of Acute and Chronic Use of Benzodiazepines
Speaker:	Rudolf Hoehn-Saric Johns Hopkins University School of Medicine

Topic: Behavioral Effects of Benzodiazepines: Another View
Speaker: Irwin Lucki
University of Pennsylvania Medical School

Topic: The Pharmacology of Benzodiazepines: Acute vs. Chronic Administration
Speaker: David J. Greenblatt
Tufts-New England Medical Center

Topic: Alprazolam Withdrawal Experience with Cross-National Study
Speaker: Russell Noyes
University of Iowa School of Medicine

Topic: Benzodiazepines Compared on Their Potential for Self-Administration
Speaker: Roland Griffiths
Johns Hopkins University School of Medicine

Topic: Acute and Chronic Effects of Benzodiazepine Use on Receptors
Speaker: Dorothy W. Gallagher
Yale University School of Medicine

Low-Dose Dependence in Chronic Benzodiazepine Users: A Preliminary Report on 119 Patients[1]

Karl Rickels, M.D.,[2] W. George Case, M.D.,[2] Edward E. Schweizer, M.D.,[2] Charlotte Swenson, Ph.D.,[2] and Reita B. Fridman, B.S.[2]

Introduction

It has been estimated by Mellinger and Balter (1981) that 1.6% of the adult American population have been using minor tranquilizers, primarily benzodiazepines (BZ) for 1 year or longer. While this figure may overestimate consistent daily BZ use, since many patients may self-medicate on an irregular basis, even a reduced estimate would still represent a large number of patients being treated chronically with BZs.

These data have to be understood in light of survey findings that anxiety is the most frequent psychiatric diagnosis made in America. A recently conducted National Institute of Mental Health (NIMH) catchment area household survey (Shapiro et al., 1984), which involved almost 10,000 persons, estimated that 8.3% of the adult U.S. population suffered from anxiety disorders during the past 6 months. The two next highest diagnostic categories were alcohol and drug abuse (6.4%) and depression (6.0%). Interestingly, however, only 23% of those patients suffering from anxiety actually received treatment. These data are in agreement with those obtained in the 1979 National Household Survey conducted by Balter and associates (Mellinger & Balter, 1981; Uhlenhuth et al., 1983) who found the following psychiatric illness prevalences for the past year: agoraphobic panic disorder 1.2%, other phobic disorders 2.3%, generalized anxiety disorder 6.4%, and depressive disorders 5.1%. This household survey again observed that only a relatively small percentage of those patients suffering from psychic distress and, given a DSM-III diagnosis as derived from the Hopkins Symptom Checklist criteria, actually were treated for anxiety (Uhlenhuth et al., 1983).

In the pharmacological treatment of anxiety, benzodiazepines have been found to be the only medications to produce consistently and significantly more relief of anxiety than placebo (Greenblatt et al., 1983; Lader & Petursson, 1983; Rickels, 1978). In fact, it has been clearly shown that clinical improvement obtained with short-term, acute BZ therapy could be maintained on placebo or no drug condition for at least several weeks, and frequently for longer periods of time, in 50% of even chronically anxious patients (Rickels, 1985; Rickels et al., 1983). In the same chronically anxious population, Rickels et al. (1986) observed an anxiety recurrence rate of 65% within a 12-month follow-up period. Despite this high relapse rate, the evidence in the literature for the necessity and effectiveness of chronic BZ therapy is much less well established than is the evidence for acute BZ therapy (Rickels et al., 1985a). Recently, however, two controlled double-blind studies demonstrated that over a 6-month treatment period patients suffering from chronic anxiety did not develop tolerance to the anxiolytic effect of their benzodiazepines (Rickels et al., 1985a,b). In addition, Lucki et al. (1985), giving an acute BZ dose to chronic BZ users, observed tolerance to its sedative but not to its anxiolytic effect.

The clinical evidence thus seems to indicate that besides producing clinically significant short-term effects, BZ's may retain their anxiolytic efficacy during more chronic use. Long-term treatment may be required for selected patients with severe generalized anxiety, as well as patients with panic disorder (Ballenger et al., 1985; Sheehan et al., 1984), or those suffering from non-psychiatric medical disorders (Hollister et al., 1981).

The risk of developing low-dose physical dependence during chronic, long-term BZ therapy has been clearly demonstrated (Petursson & Lader, 1981; Rickels et al., 1983, 1984; Schoepf, 1983; Tyrer et al., 1981; Winokur et al., 1980). More recently, some evidence, albeit sketchy and of uncertain clinical significance, has been presented suggesting the transient occurrence of mild rebound anxiety upon abrupt BZ discontinuation in at least some patients treated with BZ's for only 4 to 6 weeks (Fountain et al., 1984; Murphy et al., 1984; Power et al., 1985). The results of Power et al. have been questioned by Oswald (1985) on methodological grounds. The report of Murphy et al. also raises questions because of the seemingly paradoxical observation of rebound anxiety after 6 weeks of diazepam therapy, but not after 12 weeks. The data reported by Fountain et al. may represent both recrudescence of original symptoms as well as rebound anxiety, as endpoint results do not allow a clear separation between the two. Rickels et al. (in preparation) observed similar results in a 4-week double-blind trial of alprazolam, clorazepate, and placebo in anxious patients. A 4-week double-blind treatment phase was followed by a fifth week period in which patients received 50% of their medication for 3 days and no medication for 4 days. While 50% of patients maintained their improvement during that period, 50% experienced either some rebound anxiety or return of original symptoms (Table 1). Symptom increase was larger for patients having been treated with the intermediate half-life BZ alprazolam than for patients on the long half-life BZ clorazepate ($p<.10$; two-tailed). Only further extensive research can tell whether or not these findings can be replicated and what clinical significance can be attached to them. Nevertheless, it appears possible that in selected patients rebound anxiety, and not merely return of symptoms, may occur after short-term BZ therapy and that such rebound conceivably could lead to unnecessary chronic BZ use in at least some patients.

---

[1] This research is being supported by USPHS grant MH-08957. All data analyses were carried out by Mrs. J. Vlahovich and Mr. Eric Mak, members of the computer group of the Psychopharmacology Research and Treatment Unit.

[2] Psychopharmacology Research and Treatment Unit, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104.

TABLE 1. Change (HAM-A Total) From Week 4 to One Week Follow-up ($N=110$).

Treatment	Week 4 Score		Change	
Alprazolam	7.82	=	+4.74--	$p<.10$ (Neuman-Keuls)
Clorazepate	8.62	=	+2.40--	
Placebo	13.00	=	−1.74	

F (ANACOVA) = 7.62, df 2.106, $p<.001$

In summary, anxiety disorders constitute a fairly prevalent group of diagnoses for which acute BZ treatment is enormously effective, but for which chronic BZ treatment may be required more often than not. In addition, there is emerging evidence that symptoms of physical dependence and withdrawal upon BZ discontinuation may develop not only for patients treated chronically or at moderate-to-high daily doses, but also perhaps in patients treated either at lower doses or more acutely. In light of this, a better understanding of the clinical implications of chronic BZ use is of some public health concern.

We therefore undertook to study the natural history of chronic BZ use in a general population, and to examine the phenomena of dependence and withdrawal in an abrupt BZ discontinuation protocol. This report describes the first 119 patients who were long-term, regular BZ users and who entered the BZ discontinuation program. It also presents some results obtained during abrupt BZ discontinuation of 38 chronic BZ patients consecutively assigned to abrupt withdrawal; and finally, it gives a follow-up on 62 patients in terms of their medication history after BZ discontinuation.

BZs, in this report, have been divided into: a) long half-life BZ's (i.e., diazepam and clorazepate); b) short half-life BZ's (i.e., lorazepam and alprazolam); and c) "other" BZ's. Since no significant within-group differences were found on a variety of intake and outcome variables, long half-life BZ's were analyzed together as were short half-life BZ's.

Patients were diagnosed by a psychiatrist using a semi-structured interview and also by a Ph.D. psychologist using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L). Discrepancies were resolved in discussions which followed these interviews, and the arbitrary decision was made to assign the SADS-L diagnosis of "intermittent depression with generalized anxiety disorder" to the anxiety group. The panic group includes patients suffering from panic disorder with and without agoraphobia.

TABLE 2. Description of Population ($N = 119$).

Parameter	Long Half-Life (Diazepam, Clorazepate) ($N=52$)	Short Half-Life (Lorazepam, Alprazolam) ($N=51$)	Other BZ's ($N=16$)	Total ($N=119$)
Sex:				
Male	23	20	7	50
Female	29	31	9	69
Marital Status:				
Married	12	9	0	21
Widowed/Divorced	27	30	13	70
Single	13	12	3	28
Education:				
<High School	1	2	0	3
High School	24	25	9	58
>High School	27	24	7	58
Age:				
<40	22	21	3	46
<50	15	8	5	28
<60	10	9	3	22
>60	5	13	5	23

The depression group includes 1 dysthymic and 16 major depressive disorders, and the "other" diagnostic group includes 1 schizophrenic, 2 cyclothymic, 2 polyphobic, and 3 drug/alcohol-dependent patients.

Patients were evaluated twice, 3 weeks apart, during which time their benzodiazepines were provided in the same daily dose but in capsules to allow double-blind placebo substitution during the withdrawal phase, and also to assess whether patients had been taking their BZ's regularly. During abrupt withdrawal, BZ plasma levels (not reported on here) were determined daily during the first week, and weekly thereafter. The first interview lasted about 4 hours and the second interview about 2 hours. A variety of rating scales were administered. Written informed consent was obtained.

Long-Term Benzodiazepine Users

Table 2 gives demographic data for 119 chronic BZ users and indicates that the population consists of slightly more females than males (58%), is primarily widowed or divorced, has a relatively high educational level, and a mean age of >40 years. Table 3 gives duration of BZ therapy as well as the daily BZ dose taken at intake. The population certainly represents a chronic user group with 68% taking BZ's longer than 5 years, 45% longer than 10 years, and 32% longer than 15 years. In fact, 2 patients had been treated with meprobamate prior to the introduction of BZ's. A higher percentage of long half-life than short half-life BZ patients were treated for periods of over 10 years. This observation may well be a function of the fact that short half-life BZ's were introduced much later into medicine than long half-life ones. Yet other explanations may also have to be considered since quite a few patients had been switched by their physicians from one BZ to another during the many years of treatment. Also interesting is the fact that the daily BZ dose is for most patients at the slightly lower end of the therapeutic range. Similar findings were reported by Petursson and Lader (1981) and Tyrer et al. (1981).

Table 4 presents the main symptoms for which patients sought help originally from their physician; while anxiety symptoms clearly predominate, panic symptoms, depressive symptoms, and insomnia were also frequently named. Table 5 gives the psychiatric diagnosis the patient received when entering the program (present diagnosis) and the diagnosis received when initiating BZ therapy

TABLE 3. Length of Benzodiazepine Treatment and Mean Daily Dosage.

Years	Diaz. ($N=40$)	Cloraz. ($N=12$)	Long Half-Life ($N=52$)	Loraz. ($N=38$)	Alpraz. ($N=15$)	Short Half-Life ($N=51$)	Other BZ's ($N=16$)	Total ($N=119$)
<3	2	3	5	7	6	13	2	20
3-5	5	1	6	8	2	10	2	18
>5-10	12	3	15	11	1	12	0	27
>10-15	7	3	10	4	2	6	0	16
>15	14	2	16	6	4	10	12	38
Dosage (mg/d)								
Mean	15.2	18.2		3.9	2.7			
Range	5-60	7.5-60		1-10	1-7			

X^2 (3 drug groups by ≤10 years and >10 years) = 10.85, df 2, $p<.01$

TABLE 4. Main Symptoms Necessitating Original Benzodiazepine Therapy ($N = 119$).

Symptom	Long Half-Life (Diazepam, Clorazepate) ($N = 52$)	Short Half-Life (Lorazepam, Alprazolam) ($N = 51$)	Other BZ's ($N = 16$)	Total
Anxiety	31	26	6	63
Panic	7	9	2	18
Insomnia	6	2	6	14
Depression	8	14	2	24

TABLE 6. Mean Scores of MMPI Clinical Scales for Several Diagnostic Groups.

MMPI Scale	Anxiety ($N = 39$)	Panic ($N = 24$)	Depression ($N = 14$)	Phobic ($N = 3$)	Other ($N = 6$)	None ($N = 8$)	F	p
HS	68	78	74	61	70	63	2.67	.03
D	80	82	93	67	82	68	3.26	.01
HY	70	75	77	68	74	65	1.89	.10
PD	67	69	78	72	73	63	1.74	.ns
PA	64	64	71	56	68	58	2.42	.05
PT	71	73	85	66	77	66	3.18	.01
SC	77	75	81	66	79	60	2.32	.05
MA	56	60	55	57	62	58	0.59	.ns
SI	61	62	69	62	64	52	2.97	.02

Abbreviations:
HS = Hypochondriasis
D = Depression
HY = Conversion Hysteria
PD = Psychopathic Deviate
PA = Paranoia
PT = Psychasthenia
SC = Schizophrenia
MA = Hypomania
SI = Social Introversion

(past diagnosis). Forty-four percent of the patients suffered at intake from anxiety, primarily generalized anxiety disorder (GAD), 27% from panic disorder (PD), 15% from depression, 6% from other diagnoses, and only 8% had no psychiatric illness. It should be added here that if the SADS diagnosed patients of "intermittent depression plus GAD" had been assigned to the depression group, the depression group would have been increased by 15%.

We reported earlier (Rickels et al., 1984) on Minnesota Multiphasic Personality Inventory (MMPI) clinical scale scores for 28 chronic BZ patients. We now report on a total of 94 patients (Table 6). The present data support the earlier results of a rather chronically ill population, but now presents additional data which indicate that depressed patients have the highest and patients with no psychiatric diagnosis the lowest MMPI scale scores. Similar results were attained for the Hamilton Anxiety Scale total score recorded at intake (Figure 1). Clearly, patients not receiving a psychiatric diagnosis have normal Hamilton scores, while patients suffering from depression or "other" diagnoses were given higher Hamilton scores than patients diagnosed as GAD or PD.

TABLE 5. Present and Past Psychiatric Diagnosis and Benzodiazepine Therapy ($N = 119$).

	Long Half-Life (Diazepam, Clorazepate) ($N = 52$)	Short Half-Life (Lorazepam, Alprazolam) ($N = 51$)	Other BZ's ($N = 16$)	Total
Present Diagnosis				
None	4	2	4	10
Anxiety*	26	23	3	52
Panic	13	14	5	32
Depression	4	10	3	17
Other	5	2	1	8
Past Diagnosis				
None	2	0	5	7
Anxiety*	28	17	3	48
Panic	14	19	4	37
Depression	6	14	2	22
Other	2	1	2	5

*SADS diagnosis of intermittent depression + GAD is included in anxiety.

Turning to recreational drug use, we originally observed such use in 50% of our first 31 patients (Rickels et al., 1984). This figure has now decreased to 33%. Drugs primarily taken were marijuana, but to some extent also Quaalude, "downers," amphetamines, LSD, and cocaine. When questioning patients about prior attempts to discontinue their BZ intake, 43 patients stated that they never tried to do so, 3 patients that they previously had no problem stopping medications, and

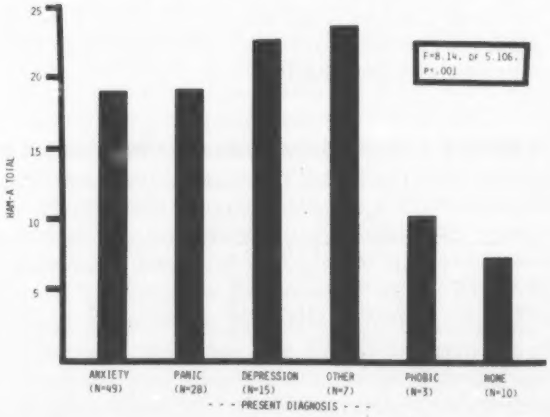


FIGURE 1. Hamilton Anxiety Scale total score at intake and present diagnosis ($N = 112$).

TABLE 7. Psychiatric Diagnosis and Satisfaction With Maintenance Therapy.

	Satisfaction Present Diagnosis		Satisfaction Past Diagnosis	
Psychiatric Diagnosis	Yes	No	Yes	No
None	10	0	5	2
Anxiety	44	8	42	6
Panic	23	9	31	6
Depression	6	11	8	14
Other	4	4	1	4

X^2 (anxiety + panic vs. depression + other diagnoses).
a) present diagnosis: $X^2 = 12.83$, df 1, $p < .001$.
b) past diagnosis: $X^2 = 26.24$, df 1, $p < .001$

73 patients that they had tried to stop their BZ intake but were unable to do so because of symptom return.

At the time of study enrollment, most patients claimed that they experienced some benefit from their BZ, this despite the presence of relatively high psychopathology scores at intake. It is of interest, however, that patients with depression or "other" diagnoses (Table 7) reported significantly (*p*<.001) less satisfaction with their chronic BZ therapy than patients diagnosed as suffering from GAD or PD.

Disposition made at the initial visit is given in Table 8. Only 10 patients were not accepted into the program, the reason being that the research team felt that those patients would be best off staying on their low dose BZ intake.

Abrupt Benzodiazepine Discontinuation

During abrupt withdrawal, patients were seen daily for 5 days (Monday through Friday) and again on the eighth day, the next Monday. Patients were withdrawn under double-blind conditions, including a control patient group which continued with their BZ intake while believing to be in abrupt withdrawal. This withdrawal phase started after the initial 3 weeks of patient evaluation described earlier. The psychiatrist was available to the patient on a 24-hour basis and the patient was given a set of emergency BZ medication. If withdrawal symptoms were too disturbing to the patient or were considered to be of a potentially serious nature by the psychiatrist, the patient was instructed to take his/her emergency medication which was carried by the patient at all times. At the next visit, usually within 24 hours, the patient was placed back on his original BZ regimen and scheduled for slow withdrawal.

TABLE 8. Disposition at Study Intake of 119 Long-Term BZ Users Who Applied Consecutively to a Benzodiazepine Discontinuation Program.

Disposition	Diaz.	Cloraz.	Loraz.	Alpraz.	Other*	Total
Not accepted	4	0	1	3	2	10
Abrupt withdrawal	23	12	18	6	6	65
Slow withdrawal	9	0	14	6	8	37
Abrupt withdrawal outside study protocol	4	0	3	0	0	7
Total	40	12	36	15	16	119

*Other: 5 oxazepam, 2 triazolam, 1 temazepam, 3 flurazepam, 2 chlordiazepoxide, 2 halazepam, 1 prazepam.

Table 9 gives numbers of patients experiencing definite, questionable, or no withdrawal. This withdrawal judgment was based on several patient, physician, and predetermined study criteria, including increase of original symptoms and appearance of new symptoms (Rickels et al., 1983; Schoepf, 1983; Winokur et al., 1980). For both long and short half-life BZ's the incidence of withdrawal was high and of identical percentage. Eighty-two percent of patients having been abruptly discontinued experienced withdrawal. Thus no difference between short and long half-life BZ's could be demonstrated in this measure of withdrawal.

However, when analyzing severity of withdrawal symptoms, the patient's withdrawal experience clearly differed as a function of BZ half-life. Short half-life BZ's produced significantly more severe symptomatology than long half-life BZ's during the first week of BZ discontinuation, being consistently significant at days 2 and 3. This observation is graphically presented in Figures 2 and 3 for the total

TABLE 9. Number of Patients Experiencing Withdrawal After Abrupt Benzodiazepine Discontinuation (*N* = 38).

Withdrawal	Long Half-Life		Short Half-Life	
Yes	17	82%	12	81%
Questionable	1		1	
No	4		3	
N	22		16	

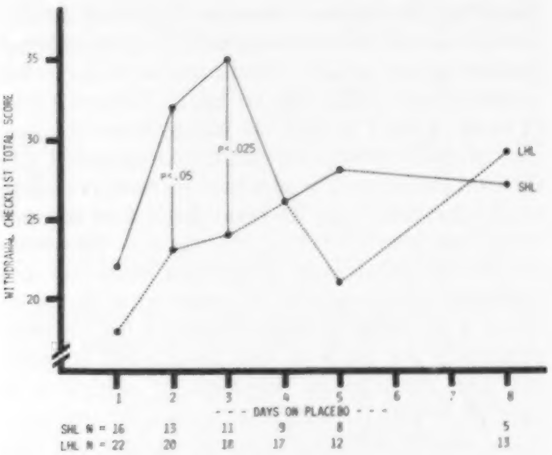


FIGURE 2. A comparison of long half-life (LHL) and short half-life (SHL) benzodiazepine daily scores adjusted for pre-withdrawal score (analysis of covariance); Withdrawal Checklist total score.

score of the Physician Benzodiazepine Withdrawal Checklist. This is a 39-item checklist that rates frequently observed withdrawal symptoms on a 4-point scale and provides seven cluster scores in addition to a total score. Figure 2 includes only those patients available at a given visit and Figure 3 presents endpoint data, i.e., the last available score for dropped patients was carried forward. As can be seen, rather similar curves were obtained. The observed differences in withdrawal intensity between short and long half-life BZ's was contributed to by differences in the mood, somatic, central nervous system (CNS), sleep, gastrointestinal, and adrenergic symptom clusters of the checklist. Figure 2 also indicates a rather striking, yet nonsignificant observation of higher dropout rates to occur in patients on short than on long half-life BZ's (69% vs. 35%).

Figure 4 presents similar results using the Hamilton Anxiety Scale total score as dependent variable. Results for the 6 control patients, who under double-blind conditions maintained their BZ intake during abrupt withdrawal, are also included in Figures 3 and 4. These scores did not change at all and no pseudo-withdrawal was observed in these patients. It should be added here that when these patients were later shifted into BZ withdrawal, 5 experienced definite and 1 probable withdrawal.

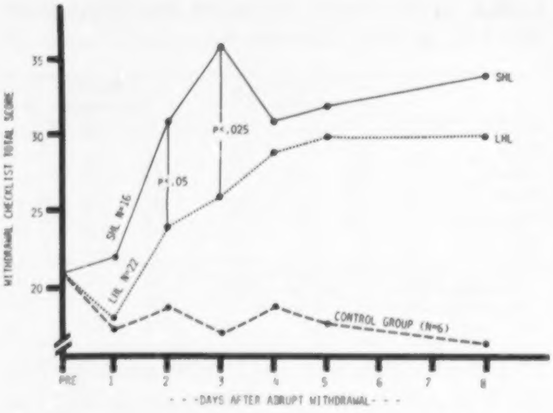


FIGURE 3. A comparison of long half-life (LHL) and short half-life (SHL) benzodiazepine and medication controls daily scores adjusted for pre-withdrawal score (*p* values based on Newman-Keuls statistics; analysis of covariance); Withdrawal Checklist total score (endpoint analysis). At day 2 only SHL, from day 3 on, SHL and LHL benzodiazepines differed significantly from controls.

Thus, the data on abrupt withdrawal clearly support the hypothesis that short half-life BZ's produce more severe withdrawal effects than long half-life BZ's, at least during the first week of treatment, but the data do not support the hypothesis that incidence of withdrawal experiences would also be higher for patients on short than on long half-life BZ's.

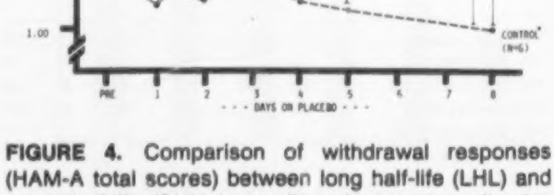


FIGURE 4. Comparison of withdrawal responses (HAM-A total scores) between long half-life (LHL) and short half-life (SHL) benzodiazepines and medication controls (*p* values based on Newman-Keuls statistics; analysis of covariance).

TABLE 10. A Follow-up of 62 Patients Having Gone Through Benzodiazepine Withdrawal.

Diagnosis at Intake	Treatment			
	BZ	BZ+TCA	TCA	None
GAD	18*			6
PD	4	2	3	
PD+Depression		4		
Depression (major and minor)			14	
Tinnitus	1			
Benign essential tremor (plus propranolol)	1			
No current diagnosis				9
Total	24 (39%)	6 (10%)	17 (27%)	15 (24%)

*Includes 8 patients on as-needed medication. Almost all others are on lower daily dosages than at intake.

Medication Intake in the Post-Benzodiazepine Withdrawal Period

Table 10 summarizes therapy provided to 62 patients who went through our BZ discontinuation program. Most interestingly, none of the patients without a current psychiatric diagnosis were on medication. Supporting the chronic illness nature of most of our patients, 37% received antidepressant medication for either PD or depression, and 39% were still taking a BZ. The majority of GAD patients, however, were taking their BZ either as needed or at a lower daily dosage than at study intake.

These results point toward the importance of correct diagnosis and appropriate treatment. Simply discontinuing BZ's, while appropriate for patients without emotional symptoms and without a psychiatric diagnosis, seems inappropriate for many other patients, unless one replaces their BZ's with either antidepressant medication or psychotherapeutic nondrug interventions. But even then, some patients may have to be maintained, for some time at least, on a BZ regimen.

Comments

This population of chronic BZ users represents a rather educated group of patients with a higher than expected percentage of divorced and widowed patients (60%). The clinical significance of these demographic features is uncertain. The patients studied had been taking BZ's for many years, most of them in doses at the lower end of the therapeutic range. Diagnostically, the patient population under study was heterogeneous, with the preponderance falling in the "anxious-depressed" spectrum. About 50% of patients initiated BZ treatment for other than GAD symptoms. In fact, only 44% of patients were given a present GAD diagnosis. A PD diagnosis was given to 27%, a depression diagnosis to 14%, "other" diagnoses to 7%, and "no diagnosis" to 8% of the patients.

Most patients had highly abnormal MMPI and Hamilton Anxiety Scale scores. These ranged from normal scores for patients not afforded a psychiatric diagnosis, to rather high scores for patients given other diagnoses, notably depression. Similarly, satisfaction with BZ treatment was experienced significantly less for those patients given nonanxiety diagnoses such as depression. The high percentage of patients given a psychiatric diagnosis in our sample is quite in contrast to the 12 patients reported by Ashton (1984), 10 of whom supposedly had no psychiatric illness, despite high symptom scores at baseline. This is also in contrast to Tyrer et al. (1981, 1983), who stated that most of their patients had "no reason" for taking their BZ's.

While most of our patients had a diagnosis that justified psychopharmacologic treatment, BZ therapy was often not the treatment of choice. Some agoraphobic and most depressed patients would have been perhaps better treated with antidepressant medications. In fact, successful BZ discontinuation in subsequent phases of our program often hinged on patients receiving appropriate treatment.

The fairly high initial psychopathology scores observed by us at intake have also been reported by others (Ashton, 1984; Lader & Petursson, 1983; Laughren et al., 1982). Several explanations may be offered: 1) Some long-term benzodiazepine users may be partially treatment resistant, at least to treatment with benzodiazepines. This speculation is supported by the abnormal MMPI profiles observed, and by the many non-GAD diagnoses given. 2) Other patients may be responsive to benzodiazepine therapy, but have been undertreated (Laughren et al., 1982). This may particularly be true for some PD and GAD patients and is supported by the relatively low daily dosage taken by many of these patients. 3) Some patients may be living constantly in a state of mild to moderate withdrawal having, out of fear of developing dependence, reduced their BZ intake to the lowest possible level which still affords them some anxiety relief (Ashton, 1984).

Turning to abrupt withdrawal results, we observed that 82% of long-term BZ patients experienced withdrawal. This percentage, while rather high, is similar to the ones reported by Petursson and Lader (1981) and Ashton (1984), but lower than the ones reported by Tyrer et al. (1981, 1983) and by Marks (1983). Patient pre-selection, and chronicity of illness as well as of treatment, probably contributed to these results. While the percentage of patients experiencing withdrawal was similar for short and long half-life BZ's, intensity of the withdrawal experience was clearly more marked in the short half-life group. Tyrer et al. (1981) and Marks (1983) made similar observations. These differences were consistently significant during days 2 and 3 of withdrawal, thus supporting the occasional but not necessarily regular (Zipursky et al., 1985) use of long half-life benzodiazepines when withdrawing patients on short half-life BZ's.

Summary

The results presented describe a rather chronically anxious and depressed population of 119 long-term BZ users, with more than 90% having been given a psychiatric diagnosis. While for many patients BZ therapy appeared appropriate, for many others it was not, and other treatments, whether psychotherapeutic or psychopharmacologic, would appear to have been more appropriate. Most patients, besides suffering from anxiety and/or depression, also showed evidence of chronic psychiatric problems, and almost all were in need of a great deal of support and assurance. In fact, one hard-earned lesson is that long-term BZ users are in need of much more intensive psychiatric and social support than other anxious or depressed patients. A follow-up of 62 patients, 6 to 12 months after study participation, indicated that 24% of them were without medication, 37% had been treated with antidepressants, and 39% were still taking BZ's, frequently on an as-needed or low daily dosage.

It was of interest to note that the subset of 10 patients without a psychiatric diagnosis had normal Hamilton Anxiety scores prior to discontinuation. In addition, while most of them experienced some withdrawal symptoms, the intensity was milder, and all were able to successfully withdraw. None of the 10 were in need of psychiatric medication after BZ discontinuation. This raises the intriguing possibility that the intensity of BZ withdrawal may be only partly a function of the chemistry of declining blood levels. Instead, the intensity of the BZ withdrawal syndrome may be partly a function of degree of psychopathology and other premorbid personality variables. This parallels the experience of Nelson et al. (1984) who found antidepressant side effects to be more correlated with premorbid psychopathology than actual antidepressant blood levels.

Abrupt BZ discontinuation produced withdrawal symptoms in 82% of patients regardless of the type of BZ which they had been taking. Severity of withdrawal, however, was clearly related to benzodiazepine half-life, with short half-life BZ's producing a more severe withdrawal reaction during the first week of placebo substitution than long half-life BZ's. There was also a suggestion that the severity of withdrawal might be partly dependent on nonpharmacologic variables such as premorbid psychopathology.

The results in general support the recommendation made earlier by this research group (Rickels, 1985a) that chronically anxious patients in need of BZ therapy should be treated only for short periods of time, their diagnosis should be frequently reassessed and, if found to be still in need of chronic BZ therapy, this should be offered on an intermittent rather than continuous basis. Emerging research suggests that optimum BZ therapy consists of just such judicious, circumspect, and critically monitored use of BZ's in terms of target symptoms and diagnoses. The very safety and effectiveness of BZ's have perhaps slowed the realization of these therapeutic goals.

References

Ashton, H. Benzodiazepine withdrawal: an unfinished story. *Br. Med. J.*, 288:1135–1140, 1984.

Ballenger, J.C., Burrows, G.D., Noyes, R., et al. Alprazolam treatment of agoraphobia/panic disorder. Presented at the 138th Annual Meeting of the American Psychiatric Association, Dallas, May, 1985.

Fontaine, R., Chouinard, G., and Annable, L. Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. *Am. J. Psychiatry*, 141:848–852, 1984.

Greenblatt, D.J., Shader, R.I., and Abernethy, D.R. Current status of benzodiazepines (Parts one and two). *N. Engl. J. Med.* 309:354–358 and 410–416, 1983.

Hollister, L.E., Conley, F.K., Britt, R.H., and Shuer, L. Long-term use of diazepam. *JAMA*, 246:1568–1570, 1981.

Lader, M., and Petursson, H. Rational use of anxiolytic/sedative drugs. *Drugs*, 25:514–528, 1983a.

Lader, M., and Petursson, H. Long-term effects of benzodiazepines. *Neuropharmacology*, 22(4):527–533, 1983b.

Laughren, T.P., Battey, Y.W., and Greenblatt, D.J. Chronic diazepam treatment in psychiatric outpatients. *J. Clin. Psychiatry*, 43:461–462, 1982.

Lucki, I., Rickels, K., and Geller, A.M. Psychomotor performance following the long-term use of benzodiazepines. *Psychopharmacol. Bull.*, 21(1):93–96, 1985.

Marks, J. The benzodiazepines—For good or evil. *Neuropsychobiology*, 10:115–126, 1983.

Mellinger, G.D., and Balter, M.B. Prevalence and patterns of use of psychotherapeutic drugs: Results from a 1979 national survey of American adults. In: Tognoni, G., Bellantuono, C., and Lader, M. (eds.), *Epidemiologic Impact of Psychotropic Drugs*. Amsterdam: Elsevier North Holland, Inc., 1981, pp. 117–135.

Murphy, S.M., Owen, R.T., and Tyrer, P.J. Withdrawal symptoms after six weeks' treatment with diazepam. Letters to the Editor. *The Lancet*, December 15, 1984:1389.

Nelson, J.C., Jatlow, P.I., and Quinlan, D.M. Subjective complaints during desipramine treatment. *Arch. Gen. Psychiatry*, 41:55–59, 1984.

Oswald, I. Withdrawal symptoms and rebound anxiety after six week course of diazepam. Letters to the Editor. *Br. Med. J.*, 290:1827, 1985.

Petursson, H., and Lader, M.H. Withdrawal from long-term benzodiazepine treatment. *Br. Med. J.*, 283:643–645, 1981.

Power, K.G., Jerrom, D.W.A., Simpson, R.J., and Mitchell, M. Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety. *Br. Med. J.*, 290:1246–1248, 1985.

Rickels, K. Alprazolam in the management of anxiety. In: Lader, M.H., and Davies, H.C. (eds.), *Drug Treatment of Neurotic Disorders—Focus on Alprazolam*. Edinburgh: Churchill Livingstone, 1985, pp. 84–93.

Rickels, K. Use of antianxiety agents in anxious outpatients. *Psychopharmacology*, 58:1–17, 1978.

Rickels, K., Case, W.G., Downing, R.W., and Fridman, R. One year follow-up of anxious patients treated with diazepam. *J. Clin. Psychopharmacol.*, 6(1):32–36, 1986.

Rickels, K., Case, W.G., Downing, R.W., and Winokur, A. Indications and contraindications for chronic anxiolytic treatment: Is there tolerance to the anxiolytic effect? In: Kemali, D., and Racagni, G. (eds.), *Chronic Treatments in Neuropsychiatry*. New York: Raven Press, 1985, pp. 193–204.

Rickels, K., Case, W.G., Downing, R.W., and Winokur, A. Long-term diazepam therapy and clinical outcome. *JAMA*, 250:767–771, 1983.

Rickels, K., Case, W.G., Winokur, A., and Swenson, C. Long-term benzodiazepine therapy: benefits and risks. *Psychopharmacol. Bull.*, 20(4):608–615, 1984.

Rickels, K., Csanalosi, I., Chung, H., Case, W.G., and Schweizer, E. Buspirone, clorazepate and withdrawal. Presented at 1985 Annual Meeting of the American Psychiatric Association, held May 18–24, Dallas, Texas.

Schoepf, J. Withdrawal phenomena after long-term administration of benzodiazepines: A review of recent investigations. *Pharmacopsychiatria*, 16:1–8, 1983.

Shapiro, S., Skinner, E.A., Kessler, L.G., et al. Utilization of health and mental health services—Three epidemiologic catchment area sites. *Arch. Gen. Psychiatry*, 41:971–978, 1984.

Sheehan, D.V., Coleman, J.H., Greenblatt, D.J., et al. Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J. Clin. Psychopharmacol.*, 4(2):66–75, 1984.

Tyrer, P., Owen, R., and Dawling, S. Gradual withdrawal of diazepam after long-term therapy. *The Lancet*, June 25:1402–1406, 1983.

Tyrer, P., Rutherford, D., and Huggett, T. Benzodiazepine withdrawal symptoms and propranolol. *The Lancet*, March 7:520–522, 1981.

Uhlenhuth, E.H., Balter, M.B., Mellinger, G.D., et al. Symptom checklist syndromes in the general population. *Arch. Gen. Psychiatry*, 40:1167–1173, 1983.

Winokur, A., Rickels, K., Greenblatt, D.J., et al. Withdrawal reaction from long-term low-dosage administration of diazepam—A double-blind, placebo-controlled case study. *Arch. Gen. Psychiatry*, 37:101–105, 1980.

Zipursky, R.B., Baker, R.W., and Zimmer, B. Alprazolam withdrawal delirium unresponsive to diazepam: Case report. *J. Clin. Psychiatry*, 46(8):344–345, 1985.

Long-Term Administration of Benzodiazepines: Pharmacokinetic Versus Pharmacodynamic Tolerance

David J. Greenblatt, M.D.,[1] and Richard I. Shader, M.D.[1]

The chronic administration of benzodiazepines in clinical practice is of considerable importance in Western society. Most controlled clinical trials aimed at establishing and verifying the efficacy of benzodiazepine derivatives involve drug exposure for relatively short periods of time, usually 4 weeks or less. These studies consistently demonstrate a significant superiority of benzodiazepines over placebo (Greenblatt & Shader, 1974, 1978a; Greenblatt et al., 1983a; Rickels, 1978). Furthermore, side effects in short-term studies usually are manifestations of excessive central nervous system depression, which are reversible by appropriate clinical management such as dosage titration. Thus the risk-benefit ratio during short-term benzodiazepine treatment is reasonably favorable in anxious individuals without complicating medical disease.

Although this data is reassuring, many benzodiazepine users take these drugs for much longer periods of time, ranging from a few months to many years (Mellinger et al., 1984; Greenblatt et al., 1975). Long-term exposure raises the question of benzodiazepine dependence and tolerance, which are of less concern during short-term treatment (Rickels et al., 1984; Smith & Wesson, 1985; Owen & Tyrer, 1983; Lader, 1983). Because well-controlled prospective studies on benzodiazepine efficacy and toxicity become increasingly difficult to perform as the duration of exposure becomes longer, much less data is available on the relative risks and benefits of long-term benzodiazepine therapy in clinical practice (Rickels et al., 1983). Thus patients and physicians face a dilemma when they attempt to weight the probability of continued anxiolytic efficacy of benzodiazepines during chronic treatment against potential unfavorable effects of long-term exposure.

Mechanisms of Altered Benzodiazepine Effect During Long-Term Use

A change in the profile of clinical efficacy and/or toxicity of a benzodiazepine could occur from one or both of two possible mechanisms.

Altered Pharmacokinetics

Pharmacokinetic mechanisms involve a change in benzodiazepine clearance—either increased or decreased—because of chronic dosage. During multiple dose therapy with any given drug at a fixed daily dosing rate, the mean steady-state concentration (Css) in blood, serum, or plasma will depend on the two separate and independent factors of dosing rate and metabolic clearance, as follows:

$$\text{Css} = \frac{\text{Dosing rate}}{\text{Clearance}}$$

Dosing rate is given in units of mass divided by time (for example, mg/hr or mg/day), and is the rate at which the drug is being administered to the patient. Metabolic clearance has units of volume divided by time (such as ml/min or L/hr), and represents the capacity of that particular patient to remove that particular drug (Greenblatt & Koch-Weser, 1975; Greenblatt & Shader, 1985). Clearance can be conceptualized as the total volume of blood, serum, or plasma from which the substance is completely removed per unit time. The ratio of these two quantities yields Css, provided the drug has been administered for a sufficient period of time for the true steady-state to be attained.

Assuming a constant, fixed dosing rate of a benzodiazepine derivative over a long period of time (for example, diazepam, 15 mg/day),

---

[1] The Division of Clinical Pharmacology, Departments of Psychiatry and Medicine, Tufts University School of Medicine and New England Medical Center Hospital, Boston.

Supported in part by Grants MH-34223 and AG-00106 from the United States Public Health Service.

Address for correspondence: David J. Greenblatt, M.D., Division of Clinical Pharmacology, Box 1007, Tufts-New England Medical Center, 171 Harrison Avenue, Boston, MA 02111.

Css would rise or fall in inverse proportion to metabolic clearance. If clearance increased, Css would fall; conversely if clearance decreased, Css would rise. If clinical efficacy and/or toxicity is related to Css, then a change in metabolic clearance, causing a reciprocal change in Css, could lead to an alteration in the drug's clinical profile.

Altered drug clearance as a result of long-term administration is a well recognized pharmacokinetic phenomenon (Greenblatt & Koch-Weser, 1975; Greenblatt & Shader, 1985). For some drugs, continuous administration leads to a reduction in metabolic clearance. This can be attributed to self-inhibition by the drug itself of its own metabolic clearance, or to inhibition of parent drug clearance by one or more metabolic products. One example of this is the cardiac drug lidocaine, for which continuous intravenous infusion at a fixed rate leads to continued drug accumulation over time, consistent with reduced metabolic clearance with time (Ochs et al., 1980).

Conversely, some drugs stimulate their own clearance, as well as clearance of other agents, during continuous exposure. These drugs are sometimes termed "enzyme inducers," the prototype of which are the barbiturates, particularly phenobarbital (Breimer, 1974; Rhodes & Houston, 1983). During repeated dosage with barbiturates at a fixed dosing rate, for example, steady-state concentrations will fall over time due to enzyme induction and increased metabolic clearance. Other drugs known to have inducing properties include rifampin, carbamazepine, and glutethimide (Ochs et al., 1981; Robson et al., 1984). Enzyme induction is usually a relatively nonspecific process, and may lead to increased clearance of the drug being administered as well as other drugs biotransformed by hepatic drug metabolizing enzymes.

Pharmacodynamic Tolerance

Pharmacodynamic tolerance or adaptation describes the general phenomenon of altered clinical drug effect despite relatively constant drug concentrations in plasma and at the receptor site. Usually the term tolerance is used to describe a diminution of drug action in association with continued drug exposure. Although we will not review all of the evidence, it is well established that benzodiazepines may produce adaptation or tolerance to pharmacodynamic effects both after single doses and during continuous administration (File, 1985; Greenblatt & Shader, 1978b; Ryan & Boisse, 1983; Rosenberg & Chiu, 1985). It is commonly observed (*see* Figure 1) that acute sedative or performance-impairing effects of benzodiazepines following single doses will diminish or disappear far more rapidly than the plasma and/or brain concentrations will fall to zero (Greenblatt et al., 1979a; Smith et al., 1984). Nonspecific central depressant effects of benzodiazepines associated with chronic exposure to accumulating benzodiazepines such as diazepam may diminish in intensity as treatment proceeds, despite progressively increasing plasma and brain concentrations of active compounds (Greenblatt et al., 1981a, 1983a,b; Ochs et al., 1983; Salzman et al., 1983). The interpretation of acute and chronic tolerance to benzodiazepines is complicated, however, by the probability that the extent and time-course of tolerance to individual pharmacodynamic effects may differ within and between individuals for a given drug, as well as between drugs in a given individual (Aranko, 1985; Aranko et al., 1983, 1984; Ellinwood et al., 1983, 1985; File, 1985; Griffiths et al., 1985).

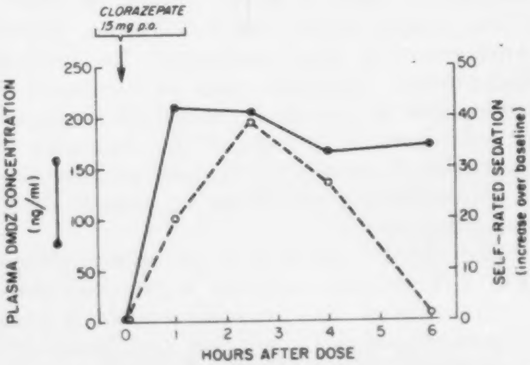


FIGURE 1. Self-rated sedative effects and plasma concentrations of desmethyldiazepam (DMDZ) were measured in healthy volunteers following a single 15-mg oral dose of clorazepate. Sedation ratings recover to baseline within 6 hours, whereas plasma DMDZ concentrations remain elevated. This is interpreted as evidence of acute adaptation or tolerance. *See* Greenblatt et al. (1979a).

Pharmacokinetic Consequences of Long-Term Benzodiazepine Treatment

Methodologic Options

The potential for benzodiazepine derivatives to induce or impair their own metabolism during chronic exposure can be evaluated by several methodologic approaches. The most direct approach involves assessment of the kinetics of a specific benzodiazepine in a given individual after a single dose, followed by comparison of these single-dose kinetic properties with those observed in the same individual during multiple-dose treatment (Abernethy et al., 1983; Greenblatt, 1979; Ochs et al., 1982). If benzodiazepine pharmacokinetics are independent of dosage, plasma concentration, and duration of exposure, then *predicted* steady-state concentrations based on single-dose kinetics should be highly consistent with those actually *observed* in the same individual during repeated administration (Greenblatt, 1979).

A second approach is to assess the pharmacokinetic properties of another agent, known to be susceptible to the influences of enzyme induction or inhibition, prior to chronic treatment in comparison with during (or just after) long-term benzodiazepine treatment. Antipyrine is the reference substrate most commonly used in such studies (Breimer, 1983; Vesell, 1979; Vesell & Penno, 1983). Antipyrine is biotransformed by hepatic microsomal oxidation, and its clearance is susceptible to change by metabolic inducers or inhibitors. A change in the clearance of antipyrine is usually interpreted as reflecting a corresponding alteration in hepatic drug-oxidizing capacity.

The third approach is an epidemiologic one, and involves assessment of steady-state concentrations of benzodiazepines during long-term usage in relation to identifiable sources of variance such as age, sex, body weight, dosage, duration of treatment, cigarette smoking, alcohol intake, and coadministration of other drugs. Appropriate statistical models can quantitate the relative contributions of each source of variance to the overall variability in steady-state plasma concentration (Greenblatt et al., 1977a).

These approaches each have benefits and limitations. The strongest data are obtained from comparative single- and multiple-dose pharmacokinetic studies, but these investigations generally are expensive and time consuming, and furthermore can only realistically assess benzodiazepine exposure for relatively short durations of time such as 1 to 4 weeks. Although this duration of exposure is considerably less than the true "long-term" treatment that is of medical and epidemiologic concern, data on the enzyme inducing or inhibiting properties of chronic benzodiazepine use are nonetheless meaningful, since the effects of chronic drug exposure on drug clearance, if they are to occur, usually are evident within the first few weeks of dosage. Furthermore, these well-controlled pharmacokinetic studies have high statistical power, because each individual subject serves as his or her own control. Much the same can be said for studies involving the influence of benzodiazepine exposure on the pharmacokinetics of a marker compound such as antipyrine. Epidemiologic studies, in contrast, have considerably less statistical power, inasmuch as "pre vs. post" assessments of pharmacokinetic properties within given individuals are not available. On the other hand, epidemiologic assessments are less expensive, can utilize much larger numbers of subjects or patients, and have the capacity to assess the effects of true long-term exposure on steady-state benzodiazepine concentrations under conditions of actual clinical use.

Pharmacokinetic Studies of Long-Term Benzodiazepine Exposure

Studies of single vs. multiple dose pharmacokinetics of benzodiazepine derivatives have assessed the following comparisons: a) benzodiazepine clearance following a single dose in comparison to clearance of the same drug in the same individual at steady-state during multiple dosage; b) mean steady-state concentrations during multiple dosage in comparison with those predicted based on a single-dose pharmacokinetic study; and c) the apparent elimination half-life of a benzodiazepine following a single dose in comparison with the apparent half-life of drug wash-

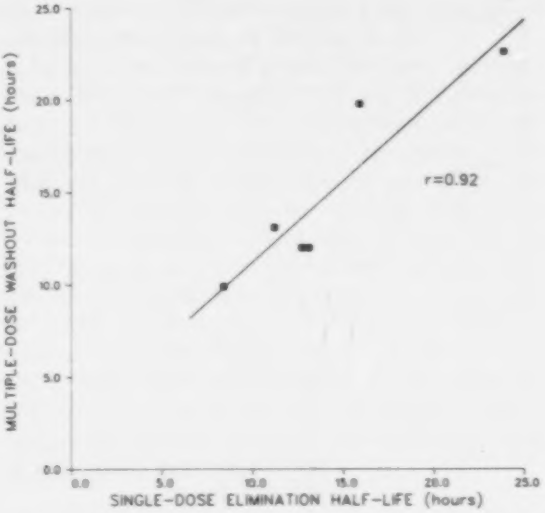


FIGURE 2. Relation between single-dose elimination half-life of lorazepam (x-axis) and the half-life of drug washout after termination of multiple-dose treatment (y-axis) in the same individuals. The two values were highly correlated. Reprinted from Greenblatt et al. (1979b), with permission.

out at the termination of multiple dose therapy.

In a study of 2 weeks of exposure to therapeutic dosage with lorazepam (3.0 mg daily) in six healthy volunteers (Greenblatt et al., 1979b), there was no significant difference between the single dose elimination half-life and the multiple dosage washout half-life (Figure 2). Likewise there was no significant difference between the observed and predicted degree of accumulation. In an earlier study, steady-state concentration of lorazepam and its glucuronide metabolite during chronic administration of doses as high as 10 mg per day were found to be highly correlated with daily dosage, and there was no evidence of an upward or downward change in steady-state concentration during long-term exposure for up to 20 weeks (Greenblatt et al., 1977b).

Pharmacokinetics of desalkylflurazepam, the final metabolite of flurazepam, were studied in a series of 18 volunteers following a single 15 mg dose of flurazepam, and during 2 weeks of multiple dosage with 15 mg of flurazepam daily (Greenblatt et al., 1981a). Desalkylflurazepam elimination half-life following a single dose was highly consistent with the half-life of drug washout following termination of dosage (Figures 3 and 4).

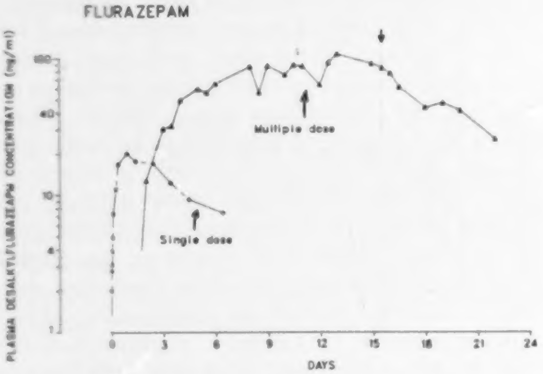


FIGURE 3. Plasma concentrations of desalkylflurazepam in a volunteer subject who ingested a single 15-mg dose of flurazepam on one occasion, following which plasma concentrations were measured over the next 7 days. After a suitable washout period, the subject ingested 15 mg nightly for 15 consecutive nights and discontinued therapy at the point indicated by the vertical dotted line under the arrow. Reprinted from Greenblatt et al. (1983b), with permission.

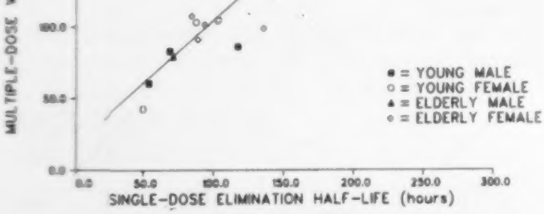


FIGURE 4. Comparison between elimination half-life of desalkylflurazepam following a single 15-mg dose of flurazepam (x-axis) versus the washout half-life after termination of multiple dosage (y-axis), as in Figure 2. The dotted line is the line of identity (y = x). The solid line was determined by linear regression analysis, and indicates a highly significant correlation. Reprinted from Greenblatt et al. (1983b), with permission.

The pharmacokinetics of the 1,5-benzodiazepine derivative clobazam were assessed following a single 20-mg dose, and again during and after 3 weeks of continuous dosage at 10 mg per day (Greenblatt et al., 1983c). There was a high degree of correlation between predicted steady-state concentrations based on the single-dose study and those actually observed during multiple dose therapy (Figure 5). Likewise single-dose clearance was highly correlated with multiple-dose clearance during a dosage interval at steady-state. After discontinuation of therapy, washout half-life was highly correlated with the half-life observed following single doses. In another study of 3 weeks of chronic exposure to clobazam, there was again no significant difference between single-dose clearance and multiple-dose clearance, and between single dose and washout half-life (Ochs et al., 1984a).

The kinetics of the triazolobenzodiazepine estazolam were evaluated during 3 weeks of chronic therapy in six healthy volunteers at daily dosages ranging from 2 mg/day to 6 mg/day (Allen et al., 1979). Steady-state concentration was found to be highly proportional to dosage, and there was no evidence of a change in steady-state concentration as a result of continued therapy (Figure 6).

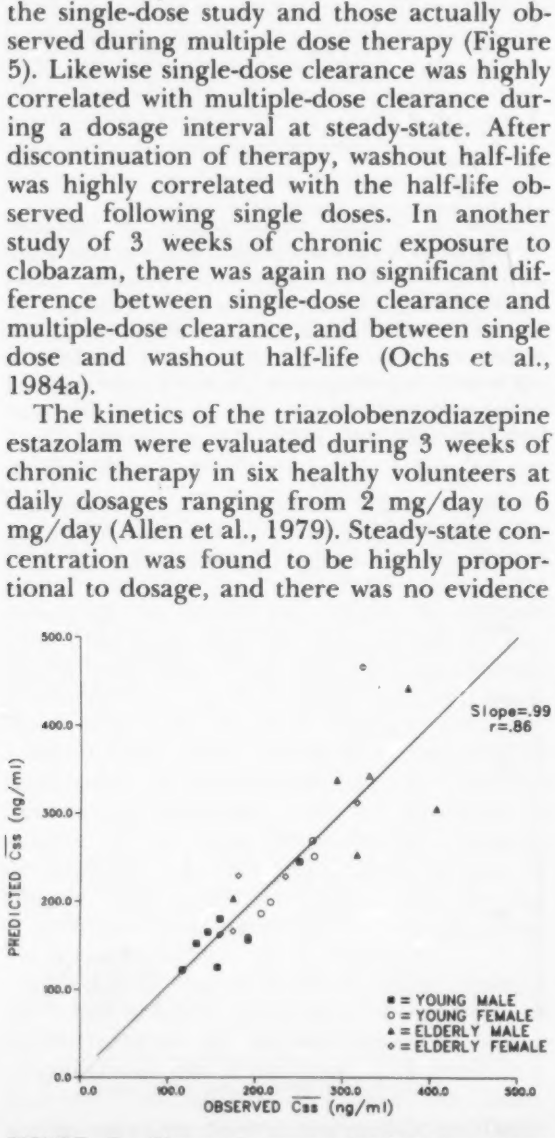


FIGURE 5. Observed mean steady-state plasma clobazam concentrations (Css) during a multiple-dose study (x-axis) compared with those predicted based on a single-dose study (y-axis). The two are highly correlated, with a regression slope nearly equal to unity. Reprinted from Greenblatt et al. (1983c), with permission.

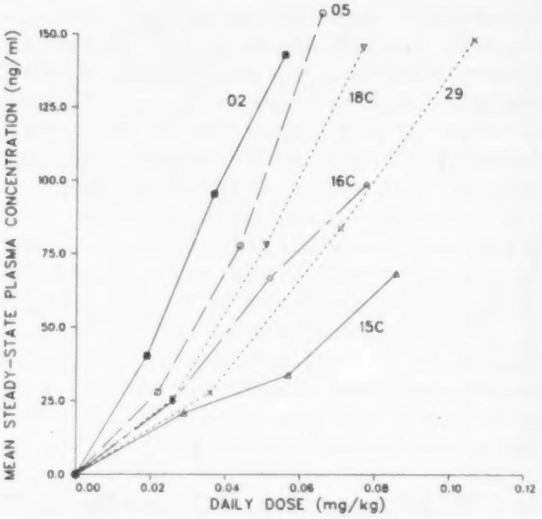


FIGURE 6. Relation between weight-corrected daily dose of estazolam (x-axis) and mean steady-state plasma concentration during multiple dosage (y-axis) among 6 subjects. In each case steady-state concentration is proportional to daily dose. Reprinted from Allen et al. (1979), with permission.

The pharmacokinetics of the triazolobenzodiazepine alprazolam were compared following a single 1.0 mg dose versus 6 days of multiple dosage (1.5 mg per day) in a series of 10 healthy volunteers. Kinetic variables were highly consistent between the single and multiple dose studies, including values of single dose vs. washout half-life (11.6 vs. 11.9 hr) as well as single-dose vs. steady-state clearance (1.00 vs. 1.07 ml/min/kg). Similar results were reported by Ciraulo et al. (in press), who found no significant differences in alprazolam kinetics following a single 1.0 mg dose in comparison with nine days of chronic dosage with up to 9 mg per day.

Ochs and associates (1984b) studied the kinetics of temazepam following a single 20 mg dose and again during 7 days of dosage with 20 mg daily. There was no significant difference between single-dose half-life and the washout half-life (means: 8.6 and 10.3 hours). Likewise there was no difference between observed and predicted accumulation ratios. Stevens et al. (1983) found no significant difference between the single-dose vs. washout half-life of loprazolam (means: 6.3 vs. 7.8 hr) when the kinetics of a single 2-mg dose were compared to 8 days of 2.0 mg daily.

In an unpublished study, we have assessed the kinetics of a single 5-10 mg intravenous dose of diazepam in comparison with the steady-state concentrations, clearance, and washout half-life values during and after two weeks of treatment with 5.0 mg daily in a series of healthy volunteers. There was a high degree of correlation between the single- and multiple-dose clearance (means: 0.37 vs. 0.39 ml/min/kg; $r=0.84$, $p<.001$), as well as between single-dose vs. washout half-life (means: 62.7 vs. 63.3 hr; $r=.93$, $p<.001$). Thus there is no evidence of enzyme induction or inhibition during 2 weeks of exposure to diazepam at this dosage.

Influence of Benzodiazepine Treatment on Antipyrine Kinetics

Several studies have assessed the effects of chronic benzodiazepine administration on the kinetics of a single dose of the marker compound antipyrine. Vesell and associates (1972) found that chronic administration of prazepam slightly impaired the clearance of antipyrine. In studies described above, antipyrine kinetics were similarly assessed prior to and again during, or immediately after, chronic treatment with lorazepam (Greenblatt et al., 1979b) or estazolam (Allen et al., 1979). Both of these studies indicated no significant influence of benzodiazepine treatment on antipyrine kinetics. Allen et al. (1984) found no influence of 6 days of treatment with bromazepam (18 mg per day) on the kinetics of a single dose of antipyrine. Abernethy and Greenblatt (1981) demonstrated that "loading" with high doses of clorazepate, leading to high steady-state concentrations of desmethyldiazepam, had no influence on the single dose pharmacokinetics of intravenous diazepam. This indicates no evidence for inhibition of diazepam metabolism despite the presence of high concentrations of the metabolic product desmethyldiazepam.

Epidemiologic Studies

Steady-state plasma concentrations of diazepam and its major metabolite, desmethyldiazepam, were assessed in an epidemiologic study of 110 anxious male patients who had received diazepam for periods of time ranging from one to 14 years (mean: 5.1 years). Daily dosage (mean: 19.9 mg per day) was the one factor that was significantly correlated with steady-state concentration (Greenblatt et al., 1981b). Duration of exposure, on the other hand, had no significant influence on steady-state concentrations of diazepam, desmethyldiazepam, or the ratio of diazepam to desmethyldiazepam.

Summary and Comment

Pharmacokinetic evidence from a number of sources is consistent, and indicates that multiple dosage treatment with benzodiazepine derivatives causes neither induction nor inhibition of benzodiazepine metabolism, nor does benzodiazepine treatment alter the kinetics of another metabolic indicator compound such as antipyrine. Furthermore, there is no evidence of a systematic change in plasma concentration as a result of chronic exposure. The scientific evidence strongly suggests that alterations in the profile of clinical efficacy and/or toxicity of benzodiazepines during long-term exposure are much more likely to be due to pharmacodynamic factors than to alterations in benzodiazepine pharmacokinetics.

Acknowledgments

We are grateful for the assistance and collaboration of Darrell R. Abernethy, Marcia K. Divoll, H.L. Friedman, Jerold S. Harmatz, and Hermann R. Ochs.

References

Abernethy, D.R., and Greenblatt, D.J. Effects of desmethyldiazepam on diazepam kinetics: A study of effects of a metabolite on parent drug disposition. *Clin. Pharmacol. Ther.*, 29:757–761, 1981.

Abernethy, D.R., Greenblatt, D.J., Divoll, M., et al. Prolonged accumulation of diazepam in obesity. *J. Clin. Pharmacol.*, 23:369–376, 1983.

Allen, J.G., Galloway, D.B., Ehsanullah, R.S.B., et al. The effect of bromazepam (Lexotan) administration on antipyrine pharmacokinetics in humans. *Xenobiotica*, 14:321–326, 1984.

Allen, M.D., Greenblatt, D.J., and Arnold, J.D. Single and multiple dose kinetics of estazolam, a triazolo benzodiazepine. *Psychopharmacology*, 66:267–274, 1979.

Aranko, K. Task-dependent development of cross-tolerance to psychomotor effects of lorazepam in man. *Acta Pharmacol. Toxicol.*, 56:373–381, 1985.

Aranko, K., Mattila, M.J., and Seppala, T. Development of tolerance and cross-tolerance to the psychomotor actions of lorazepam and diazepam in man. *Br. J. Clin. Pharmacol.*, 15:545–552, 1983.

Aranko, K., Mattila, M.J., Seppala, T., et al. The contribution of the active metabolites to the tolerance developing to diazepam in man: relationship to bioassayed serum benzodiazepine levels. *Med. Biol.*, 62:277–284, 1984.

Breimer, D.D. Interindividual variations in drug disposition: Clinical implications and methods of investigation. *Clin. Pharmacokinet.*, 8:371–377, 1983.

Breimer, D.D. *Pharmacokinetics of Hypnotic Drugs*. Nijmegen, Netherlands: Drukkerij-Uitgeverij Brakkenstein, 1974.

Ciraulo, D.A., Barnhill, J.G., Boxenbaum, H.G., et al. Pharmacokinetics and clinical effects of alprazolam in panic disorder patients following single and multiple oral doses. *J. Clin. Pharmacol.* (In press)

Ellinwood, E.H., Heatherly, D.G., Nikaido, A.M., et al. Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. *Psychopharmacology*, 86:392–399, 1985.

Ellinwood, E.H., Linnoila, M., Easler, M.E., et al. Profile of acute tolerance to three sedative anxiolytics. *Psychopharmacology*, 79:137–141, 1983.

File, S.E. Tolerance to the behavioral actions of benzodiazepines. *Neurosci. Biobehav. Rev.*, 9:113–121, 1985.

Greenblatt, D.J. Predicting steady state serum concentrations of drugs. *Ann. Rev. Pharmacol. Toxicol.*, 19:347–356, 1979.

Greenblatt, D.J., and Koch-Weser, J. Clinical pharmacokinetics. *N. Engl. J. Med.*, 293:702–705, 964–970, 1975.

Greenblatt, D.J., and Shader, R.I. *Benzodiazepines in Clinical Practice*. New York: Raven Press, 1974.

Greenblatt, D.J., and Shader, R.I. *Pharmacokinetics in Clinical Practice*. Philadelphia: W.B. Saunders, 1985.

Greenblatt, D.J., and Shader, R.I. Pharmacotherapy of anxiety with benzodiazepines and β-adrenergic blockers. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978a, pp. 1381–1389.

Greenblatt, D.J., Shader, R.I., and Abernethy, D.R. Current status of benzodiazepines. *N. Engl. J. Med.*, 309:354–358, and 410–416, 1983a.

Greenblatt, D.J., Shader, R.I., and Koch-Weser, J. Psychotropic drug use in the Boston area: a report from the Boston Collaborative Drug Surveillance Program. *Arch. Gen. Psychiatry*, 32:518–521, 1975.

Greenblatt, D.J., and Shader, R.I. Dependence, tolerance, and addiction to benzodiazepines: Clinical and pharmacokinetic considerations. *Drug Metab. Rev.*, 8:13–28, 1978b.

Greenblatt, D.J., Shader, R.I., Harmatz, J.S., et al. Self-rated sedation and plasma concentrations of desmethyldiazepam following single doses of clorazepate. *Psychopharmacology*, 66:289–290, 1979a.

Greenblatt, D.J., Divoll, M., Abernethy, D.R., et al. Benzodiazepine kinetics: implications for therapeutics and pharmacogeriatrics. *Drug Metab. Rev.*, 14:251–292, 1983b.

Greenblatt, D.J., Divoll, M., Harmatz, J.S., et al. Kinetics and clinical effects of flurazepam in young and elderly noninsomniacs. *Clin. Pharmacol. Ther.*, 30:475–486, 1981a.

Greenblatt, D.J., Harmatz, J.S., Stanski, D.R., et al. Factors influencing blood concentrations of chlordiazepoxide: A use of multiple regression analysis. *Psychopharmacology*, 54:277–282, 1977a.

Greenblatt, D.J., Allen, M.D., MacLaughlin, D.S., et al. Single- and multiple-dose kinetics of oral lorazepam in humans: The predictability of accumulation. *J. Pharmacokinet. Biopharm.*, 7:159–179, 1979b.

Greenblatt, D.J., Knowles, J.A., Comer, W.H., et al. Clinical pharmacokinetics of lorazepam. IV. Long-term oral administration. *J. Clin. Pharmacol.*, 17:495–500, 1977b.

Greenblatt, D.J., Divoll, M., Puri, S.K., et al. Reduced single-dose clearance of clobazam in elderly men predicts increased multiple-dose accumulation. *Clin. Pharmacokinet.*, 8:83–94, 1983c.

Greenblatt, D.J., Laughren, T.P., Allen, M.D., et al. Plasma diazepam and desmethyldiazepam concentrations during long-term diazepam therapy. *Br. J. Clin. Pharmacol.*, 11:35–40, 1981b.

Griffiths, R.R., Lamb, R.J., Ator, N.A., et al. Relative abuse liability of triazolam: Experimental assessment in animals and humans. *Neurosci. Biobehav. Rev.*, 9:133–151, 1985.

Lader, M. Dependence on benzodiazepines. *J. Clin. Psychiatry*, 44:121–127, 1983.

Mellinger, G.D., Balter, M.B., and Uhlenhuth, E.H. Prevalence and correlates of the long-term regular use of anxiolytics. *JAMA*, 251:375–379, 1984.

Ochs, H.R., Carstens, G., and Greenblatt, D.J. Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *N. Engl. J. Med.*, 303:373–377, 1980.

Ochs, H.R., Greenblatt, D.J., Roberts, G-M., et al.

Diazepam interaction with antituberculosis drugs. *Clin. Pharmacol. Ther.*, 29:671–678, 1981.

Ochs, H.R., Greenblatt, D.J., Eckardt, B., et al. Repeated diazepam dosing in cirrhotic patients: Cumulation and sedation. *Clin. Pharmacol. Ther.*, 33:471–476, 1983.

Ochs, H.R., Pabst, J., Greenblatt, D.J., et al. Digitoxin accumulation. *Br. J. Clin. Pharmacol.*, 14:225–229, 1982.

Ochs, H.R., Greenblatt, D.J., Lüttkenhorst, M., et al. Single and multiple dose kinetics of clobazam, and clinical effects during multiple dosage. *Eur. J. Clin. Pharmacol.*, 26:499–503, 1984a.

Ochs, H.R., Greenblatt, D.J., and Heuer, H. Is temazepam an accumulating hypnotic? *J. Clin. Pharmacol.*, 24:58–64, 1984b.

Owen, R.T. and Tyrer, P. Benzodiazepine dependence: A review of the evidence. *Drugs*, 25:385–398, 1983.

Rhodes, J.C., and Houston, J.B. Antipyrine metabolite kinetics in phenobarbital and β-naphthoflavone-induced rats. *Drug Metab. Disp.*, 11:131–136, 1983.

Rickels, K. Use of antianxiety agents in anxious outpatients. *Psychopharmacology*, 58:1–17, 1978.

Rickels, K., Case, G.W., Downing, R.W., et al. Long-term diazepam therapy and clinical outcome. *JAMA*, 250:767–771, 1983.

Rickels, K., Case, G.W., Winokur, A., et al. Long-term benzodiazepine therapy: Benefits and risks. *Psychopharmacol. Bull.*, 20(4):608–615, 1984.

Robson, R.A., Miners, J.O., Wing, L.M.H., et al. Theophylline-rifampicin interaction: non-selective induction of theophylline metabolic pathways. *Br. J. Clin. Pharmacol.*, 18:445–448, 1984.

Rosenberg, H.C., and Chiu, T.H. Time course for development of benzodiazepine tolerance and physical dependence. *Neurosci. Biobehav. Rev.*, 9:123–131, 1985.

Ryan, G.P., and Boisse, N.R. Experimental induction of benzodiazepine tolerance and physical dependence. *J. Pharmacol. Exp. Ther.*, 226:100–107, 1983.

Salzman, C., Shader, R.I., Greenblatt, D.J., et al. Long versus short half-life benzodiazepines in the elderly: Kinetics and clinical effects of diazepam and oxazepam. *Arch. Gen. Psychiatry*, 40:293–297, 1983.

Smith, D.E., and Wesson, D.R. (eds.). *The Benzodiazepines: Current Standards for Medical Practice*. Lancaster, U.K.: M.T.P. Press, 1985.

Smith, R.B., Gwilt, P.R., and Wright, C.E. Single- and multiple-dose pharmacokinetics of oral alprazolam in healthy smoking and nonsmoking men. *Clin. Pharmacy.*, 2:139–143, 1983.

Smith, R.B., Kroboth, P.D., Vanderlugt, J.T., et al. Pharmacokinetics and pharmacodynamics of alprazolam after oral and IV administration. *Psychopharmacology*, 84:452–456, 1984.

Stevens, L.A., Bevan, C.D., Salmon, J., et al. Single and repeated dose kinetics of the hypnotic agent loprazolam in healthy volunteers. *Eur. J. Clin. Pharmacol.*, 25:651–655, 1983.

Vesell, E.S. The antipyrine test in clinical pharmacology: Conceptions and misconceptions. *Clin. Pharmacol. Ther.*, 26:275–286, 1979.

Vesell, E.S., and Penno, M.B. Assessment of methods to identify sources of interindividual pharmacokinetic variations. *Clin. Pharmacokinet.*, 8:378–409, 1983.

Vesell, E.S., Passananti, G.T., Viau, J.-P., et al. Effects of chronic prazepam administration on drug metabolism in man and rat. *Pharmacology*, 7:197–206, 1972.

The Behavioral Effects of Benzodiazepines Following Long-Term Use

Irwin Lucki, Ph.D.,[1] and Karl Rickels, M.D.[1]

The benzodiazepines (BZs) are the most frequently used class of drugs in the treatment of anxiety disorders (Rickels, 1981). BZs are also widely used as sedative-hypnotics, muscle relaxants (for the control of seizures), and triazolo benzodiazepines like alprazolam may be effective antidepressant medications. The initial administration of BZs produces dose-related sedation and drowsiness in most subjects. This may be accompanied by impairment on a variety of behavioral tests used to measure psychomotor skills, visuomotor coordination, and cognitive functions (for review, *see* Vogel, 1979; Wittenborn, 1979; Kleinknecht and Donaldson, 1975). Since similar evidence of psychomotor impairment has been observed with anxious subjects at moderate doses of BZs (Linnoila et al., 1983; de Gier et al., 1981; Zimmerman-Tansella et al., 1978), patients should be appropriately cautioned that taking BZ medications may impair skills that are important for safe driving or for efficient functioning in the workplace. BZ medications will also potentiate the impairing effects of alcohol on driving performance so that this combination of drugs should be avoided (Chan, 1984). However, concern about behavioral impairment produced by the acute effects of BZs can be managed by physicians when therapy is initiated at drug doses with minimal sedating effects (Rickels, 1981).

BZ medications are most often taken repeatedly by patients for relatively short periods of time (e.g., weeks to months), but many individuals, particularly the elderly, may take them chronically for years (Mellinger and Balter, 1981). In general, most anxious subjects report that the subjective sedative effects of BZ medications diminish rapidly with repeated administration (Rickels et al., 1983). In fact, some patients may discontinue therapy if this effect does not occur rapidly enough. In addition, many of the performance-impairing effects of BZs have been shown to diminish after the repeated administration of BZs for just a few weeks (Aranko et al., 1983; Liljequist et al., 1979). Improvement of performance may be evident following just a single administration (File and Lister, 1983). Experience with the subjective effects of BZ medications appears to contribute to reducing the degree of behavioral disruption.

There have been recent reports that subjects that have taken BZ medications regularly for years demonstrate signs of generalized intellectual impairment (Hendler et al., 1980; Bergman et al., 1980). There have been few systematic studies of the behavioral effects of BZ medications in subjects that have taken them regularly for longer than a few weeks. Petursson et al. (1983) reported impaired performance by 22 long-term BZ users in the digit-symbol substitution test (DSST) and symbol copying test. The subjects' reduced level of performance persisted even as they discontinued taking their medication. Performance on tests of reaction time, tapping rate, or letter cancellation was not altered in the long-term BZ users. In a subsequent study, however, Lucki et al. (1985, 1986) reported that the DSST and symbol copying performance of 43 long-term BZ users did not differ from a matched group of drug-free anxious subjects. Although the chronic BZ users did not differ in tests of letter cancellation, free verbal recall, or in their subjective

---

[1] Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

Offprint requests to: Irwin Lucki, Ph.D., Psychopharmacology Research and Treatment Clinic, 133 South 36th St., Room 402, Philadelphia, PA 19104. The paper was presented at an NIMH workshop entitled: "Issues in the Long-Term Use of Benzodiazepines," held September 16–17, in Washington, D.C.

report of sedation, the chronic users did show a reduced critical flicker fusion (CFF) threshold and reported greater feelings of tranquilization than the drug-free anxious subjects.

An important factor involved in assessing the psychological performance of long-term BZ users is the time following the last dose of medication. Often, clinical studies have minimal control over this variable and must compare the behavior of subjects with widely different schedules of drug use. Most of the previous studies of chronic BZ users (except Lucki et al., 1985, 1986) did not report this variable. Although the behavioral effects produced acutely following the initial administration of BZs to normal volunteers have been studied frequently (Vogel, 1979; Wittenborn, 1979; Kleinknecht & Donaldson, 1975), only a single study has examined the acute effects of BZs in chronically medicated subjects. Lucki et al. (1985, 1986) reported that acute administration of therapeutically equivalent doses of BZs produced a reduction in CFF threshold, impaired delayed verbal recall, and increased the subjective report of tranquilization. There was no evidence that DSST, symbol copying, or letter cancellation performance was impaired acutely after BZ use nor was sedation reported acutely following BZ administration to chronic users. Thus, the acute behavioral effects of BZs may differ in long-term users of these medications from behavioral effects reported following their initial administration.

The present report is an update of our previous evaluation of the behavioral effects of BZ medications in long-term users (Lucki et al., 1986). First, the behavioral performance of 54 chronically medicated patients was compared with drug-free anxious subjects. The present data were collected from a larger number of subjects and include several behavioral tests that were not previously reported. Second, the acute effects of BZ medications were examined in 26 long-term users 60 to 90 minutes after their administration. Nine chronically medicated subjects served as controls by taking a placebo instead of their usual BZ medication. This allowed us to assess whether characteristics of the retesting situation or expectations of the subjects were involved in causing significant behavioral changes.

Method

Subjects

Chronic users of BZ medication ($N = 54$) were recruited from the BZ Discontinuation Program conducted by the Psychopharmacology Research and Treatment Clinic at the University of Pennsylvania. Each subject had taken BZ medications on a daily basis for at least one year. The subjects were 31 males and 23 females with an average age of 43.9 years (±1.6 years, 1 SEM; range = 26–70). Seventeen patients were taking diazepam (Valium, mean dose = 11.9 mg/day; range = 5–30 mg/day), 17 patients were taking lorazepam (Ativan, 4.1 mg/day; 1–12 mg/day), seven patients were receiving clorazepate dipotassium (Tranxene, 10.0 mg/day; 3.75–15 mg/day), and 10 subjects were taking alprazolam (Xanax, 3.4 mg/day; 0.75–9 mg/day). In nearly every case, the daily intake of BZ medications was within the range acceptable for therapeutic use. As a group, the 54 subjects had been taking their medications regularly for an average of 58 months (±6.4 months; 11–185 months). The duration of BZ use varied with the subject's medication: diazepam, 14 to 185 months; lorazepam, 15 to 120 months; chlorazepate, 11 to 84 months; and alprazolam, 14 to 23 months. Individual subjects were also included that were taking either chlordiazepoxide (Librium, 40 mg/day for 120 months), oxazepam (Serax, 10 mg/day for 36 months), or flurazepam (Dalmane, 30 mg/day for 108 months). A 5-ml sample of blood was taken at the initial interview and confirmed the presence of BZ medications or metabolites in plasma.

A group of control subjects was recruited from patients seeking treatment for anxiety-related disorders at the Clinic. This group of subjects was matched for sex, educational level, and age with the group of chronic BZ users. Each control subject was diagnosed with Generalized Anxiety Disorder (DSM-III criteria) after a psychiatric interview and scored greater than 18 on the Hamilton Anxiety Scale. All of the control subjects were drug free for at least 2 weeks prior to behavioral testing and none had been chronic users of BZ medications.

TABLE 1. Behavioral Tests Used to Evaluate the Psychological Skills of Chronic Users of Benzodiazepine Medications.

Behavior Test	Psychological Skills
Digit-symbol substitution test	Motor speed Information processing Visual scanning
Symbol copying	Motor speed
Choice Reaction Time:	
Recognition time	Visual scanning
Travel time	Motor speed
Tapping speed	Motor speed
Critical flicker fusion threshold	Visual perception CNS excitability
Memory tests:	
Immediate recall	Memory function
Delayed recall	Immediate memory
Memory decrement (%)	Consolidation
Digit span	Immediate memory
Mood Rating Scales:	
Mental sedation	Subjective feelings
Physical sedation	
Tranquilization	

Behavioral Tests

A battery of behavioral tests was administered at each session. The tests and psychological skills they examined are listed in Table 1. These behavioral tests, selected because they were previously reported to be sensitive to the effects of BZs in normal volunteers (Vogel, 1979; Wittenborn, 1979; Kleinknecht & Donaldson, 1975), are described below.

Digit-symbol substitution test (DSST). The DSST required subjects to record the appropriate symbol below the sample digits that were matched by a code appearing at the top of the form. The test was scored as the number of correct items completed in 90 seconds. Different forms and codes were used each time that the test was administered to prevent subjects from improving their performance by memorizing a single code. This test was similar to one of the subtests of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955). The DSST and the symbol copying test were readministered at the end of the first test session because subjects rapidly became familiar with the test procedures, and the score on the second administration was used.

Symbol copying test. The symbol copying test required subjects to draw symbols immediately below a sample and was scored as the number of items completed in 90 seconds. The same nine symbols that were used in the DSST were presented in random order on each test form.

Critical flicker fusion (CFF) threshold. The CFF threshold was used because it has been shown to be sensitive to a variety of psychoactive medication including BZs (Smith & Misiak, 1976), although its significance is not completely understood. The CFF was measured using a Leeds Psychomotor Tester apparatus. Subjects examined an illuminated display of four red light-emitting diodes (LEDs) placed approximately 1 meter from the subject at eye level. The subjects pressed an indicator button when they observed the display of flickering lights change to appear continuously illuminated (trials of ascending frequency) or when the continuously illuminated display changed to appear to flicker (trials of descending frequency). The score obtained was the combined average frequency (Hz) of five trials of ascending frequency and five trials of descending frequency.

Choice reaction time. Choice reaction time was also measured using the Leeds Psychomotor Tester apparatus. As soon as one of six red LEDs was illuminated, the subjects would move their finger from the starting position to press a metal button located in front of the LED. Two measures were obtained. Recognition time was measured as the time (msec) required to leave the starting position after illumination of the stimulus. Travel time was the time (msec) required for the subject to move from the starting position to touch the button in front of the illuminated red LED. A total of 75 trials was administered. The scores represent the average performance on the final 50 trials.

Tapping speed. Tapping speed was measured as the number of times that subjects could tap a metal stylus to a metal surface in 30 seconds.

Free recall of word lists. Verbal memory was measured after reading a list of 16 noncategorized nouns to subjects at a rate of 1 word/2 seconds. The subjects recorded as many of the words that they could recall immediately after the list of words was read, and then recorded as many words from the same list that they could remember 20 minutes later. Immediate and delayed recall were measured as the absolute number of words remembered after no delay and after a 20-minute delay, respectively. In addition, the memory decrement was measured as the percentage of words that were remembered immediately that could no longer be recalled 20 minutes later (1 − (delayed recall/immediate recall) × 100). Separate lists composed of nouns that were matched for their relative frequency of use in the English language were used for each presentation (Thorndike & Lorge, 1944; Paivio et al., 1968).

Digit span. Digit span was measured as described by Wechsler (1955). The score was the combined score for digits forward and backward.

Mood rating scales. The subjective report of mood states was measured using 100 mm lines that separated 12 pairs of items that described opposite feeling states, as described by Norris (1971). Scales of mental sedation (alert/drowsy, clear headed/fuzzy, quick witted/mentally slow, attentive/dreamy), physical sedation (strong/feeble, well coordinated/fuzzy, energetic/lazy, capable/incompetent), and tranquilization (calm/excited, contented/discontented, peaceful/agitated, relaxed/tense) were constructed by grouping the scores from four similar items. A larger score indicates a report of more intense feelings of mental sedation, physical sedation, or tranquilization.

Testing Procedure

The initial behavior evaluation of 54 chronic BZ users occurred during their first visit to the Psychopharmacology Research and Treatment Clinic. The subjects were told not to take their medication just prior to arrival at the Clinic, so that the behavior tests were conducted approximately 4 to 14 hours after their previous dose of medication. Thus, this evaluation might be regarded as representing the status of these patients as they ordinarily appear in their daily activities. The performance of the 54 chronically medicated subjects at this evaluation was compared with a group of drug-free anxious subjects.

Thirty-five of the chronic BZ users returned to the clinic approximately 3 weeks after their initial visit to assess the acute effect of their BZ medications. The subjects that participated in this lengthier test session were selected merely on the basis of their availability. Of this subset of subjects, 14 were taking diazepam, 12 lorazepam, 4 clorazepate, 4 alprazolam, and 1 chlordiazepoxide. They were instructed to eat only a light breakfast (juice and no caffeinated beverages) and to refrain from taking any medication immediately prior to their visit. Upon their arrival in the laboratory, the subjects were tested on the battery of behavioral tests. The subjects then took a fixed dose of their medication (most often their unit dose) and were retested on the behavior test battery starting 60 to 90 minutes later, or during the time of expected peak drug effect. The dose administered to these subjects was assigned according to their regular medication: 5 mg diazepam, 1 mg lorazepam, 7.5 mg clorazepate, 0.5 mg alprazolam, or 10 mg chlordiazepoxide. These are considered therapeutically equipotent doses. Performance following medication was compared with test scores measured immediately prior to taking the acute BZ dose. Under double blind conditions, nine of the subjects were given a placebo instead of their usual BZ medication.

Results

Initial Evaluation of Chronic BZ Users

The behavioral performance of the chronic users of BZs at their initial interview was compared with a matched group of anxious control subjects and is shown in Table 2. The performance of the chronic BZ users did not differ from the controls on the DSST, symbol copying, free verbal recall, and on the subjective report of mental and physical sedation. The chronically medicated subjects did show a significantly reduced CFF threshold and the degree of subjectively rated tranquilization was significantly greater in the BZ users than in control subjects. These results are similar to our previous report (Lucki et al., 1986).

The results of additional behavioral tests not previously reported are shown in Table

TABLE 2. Behavioral Performance of Chronic Users of Benzodiazepine Medications at Their Baseline Evaluation.

Behavior Test	Drug-Free Anxious Controls	*N*	Chronic BZ Users	*N*
Digit-symbol substitution test	62.6 ± 2.7	26	59.5 ± 1.5	52
Symbol copying	144.3 ± 5.1	26	138.9 ± 3.6	52
Critical flicker fusion threshold (Hz)	32.46 ± 0.52	24	31.18 ± 0.36*	52
Free Verbal Recall:				
Immediate recall	9.0 ± 0.6	22	8.0 ± 0.3	49
Delayed recall	7.0 ± 0.6		5.9 ± 0.3	
Memory decrement (%)	23.5 ± 3.9		27.0 ± 2.6	
Mood Rating Scales:				
Mental sedation	175.8 ± 15.9	22	140.1 ± 11.3	48
Physical sedation	150.8 ± 11.2		128.8 ± 11.5	
Tranquilization	186.4 ± 11.6		232.8 ± 14.3*	

All values represent the mean ± 1 SEM. (*) indicates that the value differs significantly from drug-free anxious controls according to Student's *t*-test for unrelated sample, $p < 0.05$.

3. The chronically medicated subjects did not perform differently than control subjects on tests of choice reaction time, tapping speed, or on digit span.

Acute Affects of BZs or Placebo in Chronic Drug Users

The results for the behavioral tests measured acutely following BZ intake in 26 chronic BZ users is shown in Table 4. The DSST showed a small but statistically significant elevation in scores after BZ intake. On other tests of motor performance, such as symbol copying, tapping speed, and choice reaction time, acute intake of BZs did not alter performance in the chronic users. The CFF threshold was significantly reduced by BZ intake in the chronic users.

Acute BZ administration produced interesting effects on the tests of memory function in the chronic users. Although immediate recall was unaltered, the recall of the word list after a 20-minute delay was reduced significantly shortly after drug intake. The percentage memory decrement indicates the amount of information recalled initially that was forgotten after 20 minutes. The memory decrement was correspondingly increased significantly by acute BZ administration. Similarly to immediate recall, digit span, a test of immediate memory, was unaffected by acute BZ administration.

The acute intake of BZ medication did not change the report of mental sedation but reduced significantly feelings of physical sedation. In addition, acute intake of BZs increased significantly the report of tranquilization.

TABLE 3. Performance of Chronic Benzodiazepine Users on Tests of Reaction Time, Tapping Speed, and Digit Span.

Behavior Test	Drug-Free Anxious Controls	*N*	Chronic BZ Users	*N*
Choice Reaction Time:				
Recognition time (msec)	484 ± 15	39	497 ± 16	43
Travel time (msec)	280 ± 11		286 ± 14	
Tapping speed	195 ± 4	39	203 ± 5	37
Digit span	12.9 ± 0.3	39	12.1 ± 0.4	45

All values represent the mean ± 1 SEM. No values for drug-free anxious controls differed significantly from the corresponding values for chronic BZ users according to Student's *t*-test for independent comparisons, $p > 0.05$.

TABLE 4. Acute Effects of Benzodiazepine Medications in Chronic Users ($N = 26$).

Behavior Test	Predrug	Postdrug
Digit-symbol substitution test	55.6 ± 2.3	57.6 ± 2.6*
Symbol copying	135.7 ± 4.1	138.1 ± 4.7
Critical flicker fusion threshold (Hz)	32.09 ± 0.61	31.06 ± 0.65*
Tapping speed	212.0 ± 7.8	216.2 ± 7.8
Choice Reaction Time:		
Recognition time (msec)	450 ± 16	441 ± 18
Travel time (msec)	259 ± 15	243 ± 18
Memory Tests:		
Immediate recall	8.7 ± 0.5	8.1 ± 0.5
Delayed recall	6.6 ± 0.5	5.0 ± 0.5*
Memorv decrement (%)	26.1 ± 3.6	41.1 ± 4.4*
Digit span	13.5 ± 0.5	13.4 ± 0.6
Mood Rating Scales:		
Mental sedation	169.4 ± 19.3	153.5 ± 14.1
Physical sedation	174.0 ± 18.0	143.4 ± 14.2*
Tranquilization	188.0 ± 24.4	249.6 ± 18.6*

All values represent the mean ± 1 SEM. (*) indicates that the value differs significantly from drug-free anxious controls according to Student's *t*-test for related comparisons, $p < 0.05$.

TABLE 5. Behavioral Responses of Chronic Benzodiazepine Users to Placebo ($N = 9$).

Behavior Test	Predrug	After Placebo
Digit-symbol substitution test	62.2 ± 4.0	62.1 ± 3.8
Symbol copying	152.5 ± 9.2	153.1 ± 10.4
Critical flicker fusion threshold (Hz)	32.49 ± 0.72	32.33 ± 0.53
Choice Reaction Time:		
Recognition time (msec)	385 ± 13	373 ± 8
Travel time (msec)	242 ± 24	262 ± 29
Free Verbal Recall:		
Immediate recall	8.2 ± 0.7	8.2 ± 0.7
Delayed recall	6.4 ± 0.7	5.7 ± 0.8
Memory decrement (%)	23.2 ± 4.4	31.8 ± 5.5
Mood Rating Scales:		
Mental sedation	108.2 ± 20.9	154.9 ± 22.2
Physical sedation	118.6 ± 26.0	130.8 ± 21.7
Tranquilization	226.4 ± 31.6	262.1 ± 25.8

All values represent the mean ± 1 SEM. No values after placebo medication differed significantly from predrug values according to Student's t-test for related comparisons, $p > 0.05$.

The pattern of behavioral effects was different under placebo administration. As shown in Table 5, performance on none of the behavior tests was altered significantly when subjects were retested shortly after taking a placebo. In addition, the subjective report of mood states on the scales of sedation and tranquilization were not altered significantly. These results suggest that the altered performance produced by acute BZ administration in chronic users was probably due to the drug rather than to characteristics of the retesting procedure or caused by previous expectations of the subjects.

Discussion

We have now examined 54 subjects that have taken BZ medications regularly for approximately 5 years with a series of objective behavioral tests. We examined a variety of skills that have been reported to be impaired by the initial administration of BZs. Our results do not support the idea that serious psychomotor or cognitive deficits are produced by the regular long-term use of BZ medications, at least when the medications are taken at therapeutically accepted doses. The chronic users of BZ medications were not impaired on any of the psychomotor tests employed at their initial interview when their performance was compared with a group of matched drug-free anxious subjects. The results presented here for 54 subjects are in agreement with our previous reports (Lucki et al., 1985, 1986). We also found that chronic BZ users were unimpaired on tests of choice reaction time, tapping rate, or digit span. On subjective report of mood states, the chronically medicated subjects did not report any increased feelings of mental or physical sedation nor did the subjects feel that they experienced drowsiness after taking their medication. However, certain behavioral differences were obtained between the chronic users and drug-free anxious controls. The chronic users reported a significantly greater degree of tranquilization than anxious control subjects. This agrees with the report from approximately 78 percent of the chronic BZ users that continued use of their medication helped to control their symptoms of anxiety. The CFF threshold was also reduced significantly in the chronic BZ users. This may reflect the reduced anxiety levels of these subjects or represent a persistent action of BZs on the central nervous system.

The behavioral effects produced acutely following the administration of BZs to chronically medicated subjects have rarely been studied (*see* Lucki et al., 1986). The time following the last dose of medication would be expected to be an important variable for assessing the behavioral effects of BZs but clinical studies may have minimal control over this variable since subjects take BZs on a variety of schedules. However, examination of the acute effects of BZs in chronically medicated subjects standardizes this factor. Acute behavioral effects may best reveal changes in the action of BZs following their long-term use. Certain behavioral effects may be detected shortly after drug intake that are not present at longer intervals.

We examined the acute effects of BZ medications in 26 subjects that were chronic users. Taken together with the behavioral performance at the initial examination, we proposed that the behavioral effects of BZs in chronically medicated subjects might be considered

TABLE 6. Different Types of Behavioral Effects to Benzodiazepine Medications Following Their Chronic Use.

I.	Persistent behavioral effects; e.g., tranquilization, reduced CFF threshold.
II.	Short-lasting behavioral effects; e.g., memory consolidation impairment.
III.	Behavioral effects that develop tolerance; e.g., mental and physical sedation, psychomotor impairment.

in three categories, as outlined in Table 6. These are: 1) behavior changes that are long-lasting or continuously present; 2) behavioral effects that are present only shortly after drug intake; and 3) behaviors that are not altered in chronic users, possibly due to the development of tolerance.

First, the increased feelings of tranquilization and the reduction of CFF threshold were most affected by long-term BZ use. Each of these behaviors was altered during the baseline examination compared with drug-free anxious controls and was changed shortly after the subjects were administered their medication. Increased tranquilization and reduced CFF threshold may also be observed acutely following the initial administration of BZs to drug-free subjects (Vogel, 1979; Wittenborn, 1979). However in chronic users, these behavioral changes occurred without accompanying subjective feelings of sedation or psychomotor impairment. Thus, tolerance does not appear to develop to these behavioral effects of BZs. It is also interesting that these two particular behaviors change in the opposite direction during withdrawal from BZs (Lucki et al., 1986).

Second, alterations in memory function, measured 60 to 90 minutes after administration of BZs to chronic users, were not observed at baseline which usually occurred several hours following the subject's previous BZ dose. Thus, memory impairment appeared to occur for only a brief time period in the chronic users, but was not continuously present despite the persistent concentrations of BZs in plasma. A variety of BZ medications has been shown to produce similar effects resembling anterograde amnesia when administered acutely to normal volunteers (Ghoneim & Mewaldt, 1975) or to anxious subjects (Angus & Romney, 1984). As recently reviewed by Lister (1985), these impairments of memory appear to be due to an inability to consolidate new information into long-term memory storage. Information learned prior to drug administration is not affected by BZs, indicating that the ability to recall information is preserved. Also, immediate memory is relatively intact following BZ administration, indicating that the information is being registered initially but not being retained adequately. Nonspecific sedative effects of drugs would be expected to affect memory by lowering immediate memory, thereby preventing information from being adequately registered. In the present study, immediate recall and digit span, both measures of immediate memory, were unaffected by BZ administration and chronic users did not report experiencing sedative effects of BZs, thereby supporting the idea that the memory deficits are not secondary to BZ's sedative effects. Ghoneim et al. (1981) reported that diazepam impaired verbal recall after 3 weeks of daily drug administration to normal volunteers, but suggested that some tolerance had developed. However, the present findings indicate that complete tolerance to memory-impairing effects of BZs does not develop in chronic users. Previously in studies with drug-free subjects, a lack of correlation was noted between the time course of memory impairment and the expected duration of plasma BZ levels (Kothary et al., 1981; File & Bond, 1979). This lack of time course between the behavioral effects and pharmacokinetics of BZ medications suggests that pharmacodynamic interactions of BZs at receptors in the central nervous system may be important in determining their behavioral effects (Ellinwood et al., 1985). These pharmacodynamic factors may apply toward understanding why the time course of memory impairment after BZ administration may be so brief and why the time course of tranquilization and reduced CFF threshold may differ from memory impairment after BZ administration.

The effect of BZ medications on memory function has potential implications for the safety of long-term clinical use of these drugs, especially since complete tolerance failed to develop in chronic users. Many patients take BZ medications several times daily and may be more susceptible to these effects while working at certain occupations. The memory-impairing effect of BZs may have a greater impact for certain kinds of patients, such as cardiac patients (Frazure-Smith & Rolicz-Woloszyk, 1982) or the elderly (Salzman et al., 1975). However, since the memory-impairing effects of BZs would be limited only to new information presented during a short critical period of susceptibility, one may wonder whether patients taking BZ medications chronically would suffer from or be aware of any changes in their memory function. The implications of these laboratory tests of verbal recall ability suggest the need for clinical studies to evaluate these effects further.

Third, chronic BZ users did not demonstrate significant impairment on the DSST, symbol copying, letter cancellation test, choice reaction time, tapping speed, nor did they report significant mental or physical sedation following the acute administration of BZ medications. These effects may represent behavioral effects that develop tolerance following the repeated use of BZ medications. Tolerance can be defined as the diminished effects of BZs on task performance following repeated administration. The suggestion that tolerance develops to the effects of BZs on these behaviors arises because an extensive previous literature indicates that these behaviors are among the most sensitive for detecting the sedative or motor-impairing effects of BZs when given initially to normal volunteers (*see* Vogel, 1979; Wittenborn, 1979; Kleinknecht & Donaldson, 1975), and that tolerance to these effects develops after regular use of BZs for just a few weeks (Aranko et al., 1983; Liljequist et al., 1979). The lack of motor impairment associated with high doses in the chronic users may be a function of the high plasma levels of BZs and metabolites these patients maintained. The doses were sufficient to cause other behavior changes in these subjects but these particular tests were unaffected. At the very least, we can conclude that chronic BZ users probably do not experience significant inpairment involving these motor skills, since the doses of BZs that we tested are those commonly recommended for medical treatment. However, we cannot conclude that we have demonstrated tolerance to the effects of BZs on these behaviors because we have not examined the behavioral effect of similar doses of BZs in drug-free subjects. Further studies are planned to do so.

Although the frequent readministration of psychomotor tests could influence performance, chronic BZ users did not demonstrate significant behavioral changes when retested after placebo administration. This suggests that the behavioral changes measured acutely after administration of BZ medications were probably due to the drug's pharmacologic effects rather than to the testing procedures or expectations of the subjects.

We have pooled the behavioral results from different BZ medications in order to conduct statistical comparisons of performance changes with adequate power. Although it is possible that the effects of individual BZ medications may differ and even that strong effects from a single medication could be diluted by pooling data, the pooled results appear to be representative for each of the medications examined (i.e., diazepam, lorazepam, clorazepate, and alprazolam). We previously (Lucki et al., 1986) failed to obtain evidence that the effects of these medications differed when we compared the BZs with longer half-lives (diazepam and clorazepate) with the BZs having shorter half-lives (lorazepam and alprazolam). Future studies will concentrate on the behavioral effects produced by individual BZ medications.

That different behaviors show different types of responses following the long-term use of BZ medications has important implications for the safety of their clinical use. That tolerance to the tranquilizing effects of BZ fails to develop rapidly in most patients, but does develop to their motor-impairing and sedative actions, has probably enabled BZs to be used chronically for the treatment of anxiety disorders with relative safety (Rickels et al., 1983; Rickels, 1978). However, the clinical significance of the lack of tolerance to the memory-impairing effects of BZs should be examined further. That tolerance develops selectively to the different behavioral effects of BZs may indicate that the separate adaptation of BZ receptors or other neuro chemical substrates is involved in modulating such behavioral effects as tranquilization and psychomotor impairment (Lippa et al., 1982).

best copy available

Acknowledgments

This research was supported by USPHS grant MH-08957. We thank Dr. George Case, Dr. Andrew Winokur, Dr. Edward Schweizer, Dr. Charlotte Swenson, Ms. Reita Fridman, Ms. Debra Toogood, and Mr. Andrew Geller for their help with various parts of this study.

References

Angus, W.R., and Romney, D.M. The effect of diazepam on patient's memory. *J. Clin. Psychopharmacol.*, 4:203–206, 1984.

Aranko, K., Mattila, M.J., and Seppala, T. Development of tolerance and cross-tolerance to the psychomotor actions of lorazepam and diazepam in man. *Br. J. Clin. Pharmacol.*, 15:545–552, 1983.

Bergman, H., Borg, S., and Holm, L. Neuropsychological impairment and exclusive abuse of sedatives or hypnotics. *Am. J. Psychiat.*, 137:215–217, 1980.

Chan, A.W.K. Effects of combined alcohol and benzodiazepine: A review. *Drug and Alcohol Dependence*, 13:315–341, 1984.

de Gier, J.J., Hart, B.J., Nelemans, F.A., and Bergman, H. Psychomotor performance and real driving performance of outpatients receiving diazepam. *Psychopharmacology*, 73:340–344, 1981.

Ellinwood, E.H., Jr., Heatherly, D.G., and Nikaido, A.M. Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. *Psychopharmacology*, 86:392–399, 1985.

File, S.E., and Bond, A.J. Impaired performance and sedation after a single dose of lorazepam. *Psychopharmacology*, 66:309–313, 1979.

File, S.E., and Lister, R.G. Does tolerance to lorazepam develop with once weekly dosing? *Br. J. Clin. Pharmacol.*, 16:645–650, 1983.

Frazure-Smith, N., and Rolicz-Woloszyk, E. Memory problems after ischemic heart disease episodes: Effects of stress, benzodiazepines and smoking. *J. Psychosomatic Res.*, 26:613–622, 1982.

Ghoneim, M.M., and Mewaldt, S.P. Effects of diazepam and scopolamine on storage, retrieval and organizational processes in memory. *Psychopharmacologia*, 44:257–262, 1975.

Ghoneim, M.M., Mewaldt, S.P., Berie, J.L., and Hinrichs, J.V. Memory and performance effects of single and 3-week administration of diazepam. *Psychopharmacology*, 73:147–151, 1981.

Hendler, N., Cimini, C., Terrence, M.A., and Long, D. A comparison of cognitive impairment due to benzodiazepines and to narcotics. *Am. J. Psychiat.*, 137:828–830, 1980.

Kleinknecht, R.A., and Donaldson, D. A review of the effects of diazepam on cognitive and psychomotor performance. *J. Nerv. Ment. Dis.*, 161:399–411, 1975.

Kothary, S.P., Brown, A.C.D., Pandit, U.A., Samara, S.K., and Pandit, S.K. Time course of antirecall effect of diazepam and lorazepam following oral administration. *Anesthesiology*, 55:641–644, 1981.

Liljequist, R., Palva, E., and Linnoila, M. Effects of learning and memory of 2-week treatments with chlordiazepoxide lactam, N-desmethyldiazepam, oxazepam and methyloxazepam, alone or in combination with alcohol. *Int. J. Pharmacopsychiat.*, 14:190–198, 1979.

Linnoila, M., Erwin, C.W., Brendle, A., and Simpson, D. Psychomotor effects of diazepam in anxious patients and healthy volunteers. *J. Clin. Psychopharmacol.*, 3:88–96, 1983.

Lippa, A.S., Meyerson, L.R., and Beer, B. Molecular substrates of anxiety: Clues from the heterogeneity of the benzodiazepine receptor. *Life Sci.*, 31:1409–1417, 1982.

Lister, R.G. The amnesic action of benzodiazepines in man. *Neurosci. Biobehav. Rev.*, 9:87–94, 1985.

Lucki, I., Rickels, K., and Geller, A.M. Psychomotor performance following the long-term use of benzodiazepines. *Psychopharmacol. Bull.*, 21:93–96, 1985.

Lucki, I., Rickles, K., and Geller, A.M. Chronic use of benzodiazepines and psychomotor and cognitive test performance. *Psychopharmacology*, 88, 1986. (In press)

Mellinger, G.D., and Balter, M.B. Prevalence and patterns of use of psychotherapeutic drugs: Results from a 1979 national survey of American adults. In: Tognoni, G., Bellantuono, C., and Lader, M. (eds.), *Epidemiological Impact of Psychotropic Drugs*, New York: Elsevier-North Holland, Inc., 1981, pp. 117–135.

Norris, H. The action of sedatives on brain stem oculomotor systems in man. *Neuropharmacology*, 10:181–191, 1971.

Paivio, A., Yuille, J.C., and Madigan, S.A. Concreteness, imagery and meaningfulness values for 925 nouns. *J. Exp. Psychol. (Suppl)*, 76:1–25, 1968.

Petursson, H., Gudjonsson, G.H., and Lader, M.H. Psychometric performance during withdrawal from long-term benzodiazepine treatment. *Psychopharmacology*, 81:345– 349, 1983.

Rickels, K. Use of antianxiety agents in anxious outpatients. *Psychopharmacology*, 58:1–17, 1978.

Rickels, K. Benzodiazepines: Use and misuse. In: Klein, D.F., and Rabkin, J. (eds.), *Anxiety: New Research and Changing Concepts*, New York: Raven Press, 1981, pp. 1–26.

Rickels, K., Case, G.W., Downing, R.W., and Winokur, A. Long-term diazepam therapy and clinical outcome. *JAMA*, 250:767–771, 1983.

Salzman, C., Shader, R.I., Harmantz, J., and Robertson, L. Psychopharmacologic investigations in elderly volunteers: Effect of diazepam in males. *J. Am. Geriatr. Soc.*, 23:451–457, 1975.

Smith, J.M., and Misiak, H. Critical flicker frequency (CFF) and psychotropic drugs in normal subjects—A review. *Psychopharmacology*, 47:175–182, 1976.

Thorndike, E.L., and Lorge, L. ***The Teachers Word Book of 30,000 Words.*** New York: Columbia University Press, 1944.

Vogel, J.R. Objective measurement of human performance changes produced by antianxiety drugs. In: Fielding, S., and Lal, H. (eds.), *Anxiolytics*, New York: Futura Publishing Co., 1979, pp. 343–374.

Wechsler, D. ***Manual for the Wechsler Adult Intelligence Scale.*** New York: The Psychological Corp., 1955.

Wittenborn, J.R. Effects of benzodiazepines on psychomotor performance. *Br. J. Clin. Pharmacol.*, 7:61S–67S, 1979.

Zimmerman-Tansella, C., Tansella, M., and Lader, M. Psychological performance in anxious patients treated with diazepam. *Prog. Neuro-Psychopharmacol.*, 3:361–368, 1978.

A Survey of Diazepam Patients

David Haskell, M.D.,[1] Jonathan O. Cole, M.D.,[2] Susan Schniebolk, B.S.,[2] and Bernard Lieberman, R.Ph., M.Sc.[1]

For a number of years following the introduction of the benzodiazepines (BZs), the medical profession generally assumed that they were free of addictive liability if taken within the recommended dose range. However, as these drugs have been available over a longer period of time, an increasing number of patients have become long-term users. In the late 1970's isolated reports began to appear in the medical literature describing addictive phenomena in patients on long-term moderate dose BZ. At the same time a great deal of media attention was focused on the possibility of over-use of diazepam, which for many years had been the most widely prescribed drug in the United States. Thus, legitimate public health questions began to be raised as to the actual extent of BZ usage and as to the long-term effects.

The extent of BZ use was well studied in a survey (Mellinger et al., 1984) which showed that 11% of Americans had taken a prescribed antianxiety agent one or more times in the 12 months before the survey. BZs accounted for 84% of the medications reported. The most common pattern of drug usage was infrequent use, but 15% reported daily use for at least 1 year. Though the regular, daily users made up a small percentage of anxiolytic drug takers, the small percentage added up to over 3,000,000 individuals, nationwide.

With so many people taking BZs on a regular basis, the issue of long-term effects is of obvious importance. The issue raises a number of questions, including:

1. Is long-term BZ ingestion harmful psychiatrically or physically?
2. Are a substantial proportion of patients obtaining continued benefit? Do their old psychiatric symptoms return when the drug is stopped?
3. Are a substantial proportion "hooked?" Are they unable to stop unnecessary BZ medications because they develop withdrawal symptoms whenever they try to stop the drug?
4. Are a substantial proportion on prolonged BZ regimens because of a mixture of patient and physician inertia? It may be easier to keep taking and keep prescribing the medication if the patient is reasonably comfortable and reluctant to stop than to mount a drug tapering and discontinuation plan.

There are several possible approaches to studying patients on long-term BZ therapy. A major problem which the authors have had to deal with in clinical practice is the difficulty of differentiating withdrawal symptoms from recurring anxiety. This can best be done after medication has been stopped and the pattern of symptom emergence observed over time. However, many patients are most reluctant to stop medication for a long enough period for such a determination to be made.

Probably the best method for studying this question is a controlled withdrawal study. Two earlier studies (Bowden & Fisher, 1980; Laughren et al., 1982) showed either questionable withdrawal symptoms or none at all after stopping long-term BZs. In studies from England 100% of patients (Petursson & Lader, 1984), or 44.4% of patients (Tyrer et al., 1983) experienced withdrawal symptoms. In the most recent and still ongoing study presented at this meeting, Rickels reported that the majority of the patients, if they could stay off medication for one month after withdrawal, were able to remain off BZ medication thereafter and felt generally better than when on BZs, after withdrawal symptoms had abated.

Another approach to patients on long-term BZ therapy would be to do an in-depth clinical study of patients on such regimens trying to understand how they came to be on the drug, why they stayed on it, and whether it appeared to have helped. This would be a considerable effort, the data would be subjective and impressionistic and, to our knowledge, has not been done. Though Lader's group has provided brief descriptions of pa-

---

[1] VA Outpatient Clinic, Boston, MA 02108.
[2] McLean Hospital, Belmont, MA 02178.

tients coming for BZ withdrawal, these patients are self-selected and the focus has been on withdrawal techniques and symptoms, not on the reasons for the long-term use or the reasons for deciding to try to stop the drug.

A third approach is to survey a large sample of BZ users, asking questions about benefit and withdrawal symptoms. The only published study of this sort is by Hallstrom and Lader (1982), who contacted members of a British self-help organization, the Phobics Society. Seventy-one individuals completed a questionnaire by mail. Of these, 80% were agoraphobics and 80% were female. Most were 30 to 60 years of age. Seventy percent had been on medication for over 4 years. Half used diazepam (mean dose 12.5 ± 7 mg), while others used chlordiazepoxide or lorazepam. Twenty-eight percent also took antidepressants or other psychotropic drugs as well. Fifty-eight of the 71 subjects had tried to taper or stop their medication. Only 5 did so easily; even these returned to later BZ use. (It is not clear whether individuals who had successfully been able to stop medication were included in the survey.) Forty-one subjects reported a return of their old symptoms while 12 believed the withdrawal-associated symptoms to be worse. Twenty-two subjects claimed they had developed tolerance to their drugs over time, and 14 of these had increased their dose. The 14 subjects who seemed to be describing probable withdrawal symptoms had all been on BZ more than 4 years. Alcohol abuse was not reported, though 14 subjects reported using alcohol to reduce symptoms.

Opportunity for a larger survey was presented at a large VA clinic, the main outpatient facility for veterans in the greater Boston area. There had been concern among clinic staff about the large number of patients taking BZs, mainly diazepam, and questions were being raised as to its clinical value and possible over-use. The clinic population is 98% male in contrast to the Hallstrom and Lader sample (80% female). Also, a survey of all patients receiving medication promised to be more inclusive than a sample recruited by a newsletter ad. The study was conducted in 1982. Only patients on diazepam were included, which accounted for over 80% of the BZs being prescribed at that time.

Procedure

A research technician was notified by the pharmacy staff when a diazepam prescription was presented. Patients were asked to participate, but assured that the survey was purely voluntary and refusal would not affect their treatment. The procedure involved completing two forms, usually accomplished within the prescription waiting time. About 400 patients were asked to participate. Of these, 210 agreed and signed a consent form. From this group, 196 completed the forms sufficiently to be included in the analyses. (These figures do not represent the total number of diazepam prescriptions dispensed at the clinic. Patients were permitted up to five refills which were usually mailed out. At the time of this survey, approximately 1,000 diazepam prescriptions in all were being filled per month.)

The forms included: (1) the Pharmacologic History Form containing medication history and demographic questions, and (2) the SCL-80, the slightly modified version of the SCL-90. The shortened version was considered more suitable for this population. This form yields scores for anxiety, depression, somatic complaints, anger-hostility, phobic anxiety, obsessive-compulsiveness, and sleep disturbance.

Results

The mean age of the sample was 51 years. Two-thirds were combat veterans. Twenty-one percent had been in Vietnam. Two-thirds received diazepam from the clinic's psychiatry service, the rest from internal medicine, neurology, and other medical services. Seventy percent were taking other medication; the categories most commonly prescribed were as follows:

Antidepressants	—	27 patients
Other BZ	—	26 patients (usually sleep medication)
Antipsychotics	—	23 patients
Antihypertensives	—	17 patients

Drug history data are summarized in Table 1.

TABLE 1. History of Valium Use ($N = 194$).

Tablet Size	Daily Dose (Percentage)	Mean (Total Group)
2 mg - 5%	<10 mg - 18%	21 mg per day
5 mg - 47.5%	10 mg - 20%	
10 mg - 47.5%	15 mg - 10%	
	20-25 mg - 18%	Valium Taken -
	30 mg - 13%	Every Day - 71%
	40 mg - 13%	Only as Needed - 29%
	>40 mg - 8%	

Duration of Valium Use		Mean Dose ($\times$Duration = p.01)	
<6 months	10%	17.5 mg	
6-24 months	14%	17.3 mg	Valium taken over this time:
2-5 years	20%	23.0 mg	"Continuously" - 66%
5-10 years	25%	24.5 mg	"On and Off" - 27%
Over 10 years	31%	25.5 mg	

Dose Changed Over Time		Mean Dose per Group (Difference sig. $p<.000$)
Increased	24%	32.8 mg
Decreased	26%	14.9 mg
No Change	50%	18.6 mg

Symptoms on Stopping Valium (question answered by only 158 patients)*

		Mean Valium Dose
Experienced No Symptoms	46 patients	17.2
Symptoms Similar to Initial Symptoms	93 patients	21.7
Symptoms Different from Initial Symptoms	19 patients	26.6

Group reporting "symptoms different" reported higher dose of Valium (26.5). Also in that group symptoms less likely to be reported on first day after stopping Valium. (Numbers small—significance tests not done.)

*Self-report from Pharmacologic History Form.

The group as a whole was taking an average of 21 mg of diazepam a day. Of these 29% took the drug only as needed, but 71% reported taking it every day, and 66% had taken diazepam "continuously" ever since the drug was first prescribed. Three-fourths had taken diazepam at least 2 years, more than half over 5 years, and only 10% for less than 6 months. Dose had been increased over time in 24% and decreased in 26%. Not surprisingly, the patients who reported increased dose were taking a higher amount (mean 32.8 mg a day). Current dose was related to duration of diazepam use ($p<0.01$). Most of the dose increase seems to have occurred around the 2-year point: (Table 1) patients on diazepam less than 2 years averaged 17.4 mg per day, whereas those over 2 years averaged 24.5 mg.

Of the 158 of the 194 patients who described ever stopping or trying to stop diazepam, only 46 patients (mean current dose 17.2 mg) reported no emergence of symptoms. Ninety-three (mean current dose 21.7 mg) reported a return of old symptoms, while 19 (mean current dose 26.6 mg) developed different, new symptoms. The occurrence of symptoms on stopping the drug was related to duration of diazepam therapy ($p = 0.05$) and to current dose ($p = 0.01$).

Overall, diazepam dose at the time of the survey was positively correlated with total symptoms reported on the SCL-80, weight, amount of VA disability, duration of diazepam therapy, and being prescribed diazepam by the psychiatric service. Age was negatively related to dose. Extent of alcohol use was positively related to the increase in diazepam dose over time. Other correlations in the data are presented in Table 2.

The SCL-80 data were scored by factor and compared with SCL-80 data obtained on patients in the pretreatment placebo phase of two unrelated drug studies, one for patients with anxiety disorder and one for patients with panic-agoraphobia, included in studies

TABLE 2. Correlational Analyses.

Variable	Positive Correlations and *p* Value
Diazepam Dose	All symptoms rated on SCL-80 (.001) Weight (.001) % Disability (.001) Duration of Diazepam Use (.01) Medical Service Prescribing Diazepam Age (Inversely)
Duration of Diazepam Use	Symptoms on Stopping Diazepam (.05)
Dose Increased Over Time	Alcohol Use (.001)
Months of Combat	Sleep Disturbance (SCL-80) - (.001) Other Medication (.001) % Disability (.05)
Cigarette Smoking	Weight (.05) Months of Combat (.01) Sleep Disturbance (SCL-80) - (.01) Depression (SCL-80) - (.05) Coffee Drinking (.001) Alcohol Use (.001)
Alcohol Use	Diazepam Dose Increased Over Time (.001) Other Medication (.01) Depression (.05) Anxiety (.05) Phobic Symptoms (SCL-80) - (.05)
Coffee Drinking	Age (.01) Other Medications (.05) Depression (.05) Anxiety (.05) Alcohol Use (.05)

carried out by McNair and collaborators at Boston University. These values are presented in Table 3. They show that the diazepam patients surveyed are more symptomatic than or as symptomatic as either comparison group except for the Phobic-Anxiety Scale where they fall between the anxiety and phobia patients groups.

Discussion

The major conclusions that may be drawn from this survey are: 1) that most patients at *this clinic* on diazepam have been taking it a long time; and 2) that they are generally *not* asymptomatic. In fact, they may be more symptomatic than patients ordinarily considered for antianxiety drug studies. They appear to believe they are obtaining continued benefit from their medication and have difficulty tapering or stopping it. It remains unclear whether this difficulty is caused by chronic anxiety symptoms only partially relieved by BZs, or results from some degree of physical dependence requiring BZ maintenance to suppress withdrawal symptoms.

TABLE 3. A Comparison of SCL-80 Scores.*

	Valium ($N = 177$)	Anxiety ($N = 185$)	Panic ($N = 34$)
Somatic	.94	.67	.70
Anxiety	1.02	1.04	1.31
Depression	1.01	.89	.93
Obsessive-Compulsive	1.01	.91	.71
Phobic-Anxiety	.70	.45	1.00
Interpersonal Sensitivity	1.09	1.00	.95
Anger-Hostility	.74	.44	.35
Sleep Difficulty	1.44	1.05	1.00

*Between VA on diazepam with patients about to enter drug trials for anxiety or for panic disorder in studies at Boston University (Dr. Douglas McNair's program)

The questions about occurrence and type of symptoms on stopping medication were intended to detect signs of withdrawal. It was expected that "symptoms different from initial symptoms" were likely to represent withdrawal symptoms rather than general anxiety. Since only 19 patients reported such a difference, the hypothesis that symptoms represent mainly withdrawal phenomena derives little support from this item in the data (though it is not known how many patients experiencing withdrawal symptoms would in fact report them as different). The "symptoms different" group were on a higher dose of diazepam, for longer duration, and were more likely to have increased their dose than the rest of the sample, though the differences were not statistically significant.

To what extent do patients develop a tolerance to the anti-anxiety effects of BZs? In this survey only one-fourth of the patients reported increasing their dose over time (probably under-reported as judged by a random check of some clinical records). The survey included an additional question as to whether dose was increased because "beginning dose not enough," or "beginning dose enough at first but needed more later on." Twenty-nine patients (mean dose 29.4 mg) checked the former, 23 patients (mean 37.0 mg), the latter.

Another possible indication of tolerance is that the longer patients were on diazepam, the higher their dose. Though many patients did increase their dose over time, there are still many who did not and who stay on a relatively low dose for many years. The data here may be consistent with Lader's suggestion of two groups of BZ takers, differing in susceptibility to the development of tolerance (Lader, 1983). One group which clinicians might expect to be at risk to become tolerant would be those with a history of alcoholism. In this survey, not surprisingly, alcohol use was highly correlated ($p = 0.001$) to increase in dose.

The overall level of symptomatology in this group of diazepam patients appears comparable to the initial levels of persons seeking treatment at outpatient psychiatric clinics. (Since it is possible that patients at a Veterans Clinic respond differently to such a questionnaire, it would be useful to test other groups of patients from the same clinic on the SCL-80.) In other studies of long-term BZ patients, patient self-rating measures of this type were not used. Laughren's long-term BZ patients had mean clinician-rated Hamilton Anxiety Scale scores of 24, quite high, while Bowden and Fisher's group averaged 14.2, below the usual minimum of 18 for a patient to be admitted to an antianxiety drug study.

An obvious limitation of this survey is that only half of the diazepam patients agreed to be tested. It would not be surprising if refusers differed from participants in important ways. It was suspected that less cooperative patients would be on a higher dose of diazepam. Pharmacy records were examined on a subsample of refusers. Their mean dose was 26 mg a day, higher, but not significantly so, than the survey group.

References

Bowden, C., and Fisher, J. Safety and efficacy of long-term diazepam therapy. *South. Med. J.*, 73:1581–1584, 1980.

Hallstrom, C., and Lader, M. The incidence of benzodiazepine dependence in long-term users. *J. Psychiatr. Treat. Eval.*, 4:293–296, 1982.

Lader, M. Dependence on benzodiazepines. *J. Clin. Psychiatry*, 44:121–127, 1983.

Laughren, T.P., Battey, Y., Greenblatt, D.J., et al. A controlled trial of diazepam withdrawal in chronically anxious outpatients. *Acta Psychiatr. Scand.*, 65:171–179, 1982.

Mellinger, G.D., Balter, M.B., and Uhlenhuth, E.H. Prevalence and correlates of the long-term regular use of anxiolytics. *JAMA*, 251:375–379, 1984.

Petursson, H., and Lader, M. *Dependence on Tranquilizers.* Oxford: University Press, 1984.

Tyrer, P., Owen, R., and Dawling, S. Gradual withdrawal of diazepam after long-term therapy. *Lancet*, 1402–1406, June 25, 1983.

Physiological and Performance Responses to Diazepam: Two Types of Effects[1]

Rudolf Hoehn-Saric, M.D.,[2] and Daniel R. McLeod, Ph.D.[2]

Introduction

The acute effects of diazepam on cognitive/psychomotor performance have been studied extensively (Hindmarch, 1980). Impairment has been found in motor performance (e.g. Linnoila et al., 1983) as well as in memory acquisition (e.g. Ghoneim et al., 1981) in subjects taking benzodiazepines. The effects of continued diazepam use are not well known. Data from a report by Lucki et al. (1985) suggest that a single dose may produce memory deficits even in people who have been taking benzodiazepines for long periods of time. Even less well known are the effects of continued benzodiazepine administration on physiological functions. The administration of benzodiazepines lowers sympathetic tone, as expressed by electrodermal activity (Boucsein & Wendt-Suhl, 1982; Brown et al., 1968; Holmberg & William-Olsson, 1964; Molander, 1982), but how long this effect persists with continued use of medication is not known. Reports of the effects of clinical doses of benzodiazepines on the cardiovascular system are inconsistent. While certain studies suggest that benzodiazepines attenuate the blood pressure increases that occur under psychological stress in normals (Holmberg & William-Olsson, 1964) or actually lower diastolic blood pressure in hypertensives (Whitehead et al., 1977a), other studies fail to support these findings (Whitehead et al., 1977b). Equally contradictory are reports on the effects of benzodiazepines on heart rate. While Brown et al. (1968) report that oxazepam lowered heart rate in normal volunteers, Biscaldi et al. (1971) did not note such an effect in anxious patients.

The data presented in this paper are part of a larger study whose aim is to examine, within the same population, the acute and subacute effects of diazepam on cognitive/psychomotor performance and physiological functions. Specifically, we report here two types of effects diazepam has on performance and physiology: 1) changes in a direction not seen following placebo; and 2) absence of change in the direction seen following placebo.

Method

Subjects

Twenty physically and psychologically healthy women with an average age of 34.7 years and an average educational level of 14.6 years were paid to participate. None had taken any medications affecting the central or autonomic nervous systems for at least 1 week. Ten subjects were randomly assigned to a diazepam group and 10 were assigned to placebo. Ten from the placebo group and 9 from the diazepam group completed the study.

General Procedure

Subjects took 15 mg diazepam (diazepam group) or three placebo capsules (placebo group) daily for 6 weeks. Psychophysiology and psychomotor performance were assessed before and after the first dose (Week 0), before and after the last dose (Week 6), and in the morning following 2 weeks without medication (Week 8). Structured rating scales were administered weekly and analog scales, used to measure subject estimates of drowsiness (and other symptoms not discussed here), were administered several times during each of the experimental test sessions.

The current report reflects a portion of a larger study. Only details germane to the points discussed in this report are presented here. Additional measures will be described elsewhere.

---

[1] This study was supported in part by USPHS Grant MH35435 from the National Institute of Mental Health.

[2] Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Meyer 144, Baltimore, MD 21205.

Experimental Sessions

In the morning of each test session, subjects sat in a comfortable reclining chair in a room kept at constant temperature and illumination. Electrodes to record physiological activity were attached and a catheter was inserted into a vein to obtain blood samples. An Apple II microcomputer was used to collect and store physiological data. Another Apple II microcomputer and a numeric key pad (The Keyboard Co.) were used to present psychomotor performance tasks.

Each session consisted of a 5-min baseline period (Baseline 1), followed by a microcomputerized Divided Attention task (5 min), a psychomotor performance battery (20 min), a Risk-Taking task (5 min), and a second 5-min baseline period (Baseline 2). Physiological activity was recorded during the two baseline segments, the Divided Attention task, and the Risk-Taking task. Following this sequence of measures, subjects were given medication and were tested again 1 hour later on Weeks 0 and 6. On Week 8, no medication was given and the sequence of measures was not repeated.

Physiological Measures

Among the physiological measures taken were skin conductance and blood pressure (systolic and diastolic). Skin conductance was measured continuously during the session segments by means of a J&J Co. Electrodermograph, with electrodes attached to the volar surfaces (middle segments) of the first and second fingers of the nondominant hand. Blood pressure was taken immediately following Baseline 1, Divided Attention, and Baseline 2 by means of a Puritan Bennett Co. Infrasonde blood pressure monitor.

Subject Ratings

Among the subject ratings taken was a measure of drowsiness. Drowsiness was rated by subjects on an analog scale (100 mm in length) following Baseline 1, Divided Attention, and Baseline 2.

Psychomotor Performance Tasks

Among the psychomotor performance tasks administered were automated versions of the Digit Symbol Substitution Test (DSST; Wechsler, 1958) and a choice reaction-time task. The automated DSST is described in detail by McLeod et al. (1982). The choice reaction time task required subjects to press one key on the numeric key pad if an even number appeared in the center of the video screen and another key if an odd number appeared. The Divided Attention task required subjects to press a key (on a numeric key pad held in their laps) upon the appearance on the video screen of one target stimulus, and also to keep track of the number of times that another target stimulus appeared on the screen. The Risk-Taking task consisted of a computerized game, similar to gambling, in which subjects could win or lose small amounts of money.

Results

Table 1 illustrates the acute effects of diazepam following subjects' first dose. For both placebo and diazepam groups, pre- and post-ingestion measures are provided for systolic blood pressure, skin conductance level, and misses of a target stimulus during the

TABLE 1. Acute Effects of 5 mg Diazepam, Baseline 1, Week 0[a].

	Placebo			Diazepam		
	Pre	Post	p	Pre	Post	p
Syst BP[b]	104.2 ± 3.2	109.6 ± 4.1	.01	107.2 ± 3.1	107.1 ± 3.5	NS
Skin Cond.	3.1 ± 0.4	2.9 ± 0.4	NS	3.5 ± 0.5	2.4 ± 0.2	.05
DA misses	0.34 ± 0.08	0.16 ± 0.08	.01	0.29 ± 0.08	0.58 ± 0.33	NS

[a] Values represent the mean ± 1 S.E.M.

[b] Abbreviations: Syst BP, Systolic blood pressure; Cond, Conductance; DA, Divided Attention.

Divided Attention task. These examples were chosen to illustrate two types of effects seen following diazepam, 5 mg. The physiological measures were taken during the Baseline 1 periods, before and after medication.

As can be seen in the Table, mean skin conductance was decreased by diazepam but not by placebo. That is, diazepam produced a change not seen with placebo. A different kind of effect was found for blood pressure and misses on the Divided Attention task. Blood pressure increased, and misses on the task decreased, for the placebo group only. In both cases, changes seen following placebo were absent following diazepam.

In Figure 1, the effects of 6 weeks of diazepam, 15 mg daily, are illustrated with two psychomotor (top panels) and two physiological (bottom panels) measures. The latter measures were taken during the Risk task. All measures were taken in the morning prior to the first dose of the day on Weeks 0 and 6. By Week 8, medication had been discontinued for 2 weeks and measures were taken at the same time of day as those taken on Weeks 0 and 6. The significance levels above the histograms reflect differences from Week 0.

Figure 1 reveals an increase in choice reaction times following 6 weeks of diazepam but not placebo, and a recovery of shorter reaction times following 2 weeks without medication. DSST performance, on the other hand, did not change following 6 weeks of diazepam but improved following placebo. Only after medication was discontinued did the performance of the diazepam group begin to improve. Thus, the two kinds of effects described above for the acute effects of diazepam were seen also following 6 weeks of medication. Diazepam produced changes in choice reaction time but prevented changes seen in the DSST performance of the placebo group.

Six weeks of diazepam produced decreases in blood pressure and skin conductance. Figure 1 shows these decreases for the morning preceding the last dose of diazepam (Week 6). Interestingly, while blood pressure returned to pre-drug levels following discontinuation of diazepam, skin conductance remained lower.

During each session, subjects rated how drowsy they felt by means of 100 mm analog

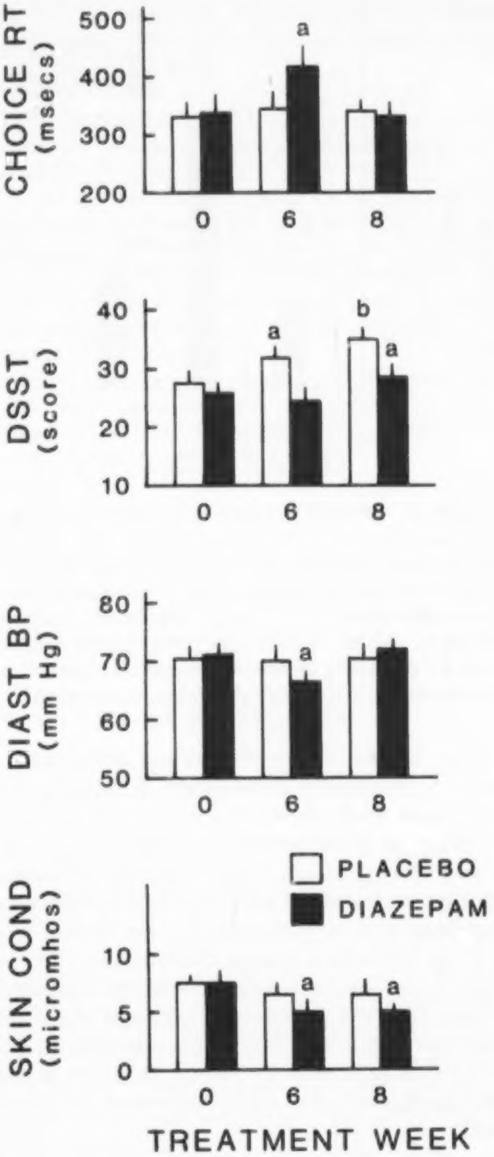


FIGURE 1. Effects of diazepam treatment for 6 weeks on psychomotor performance (upper panels) and physiological activity during the Risk task (lower panels). Data were obtained prior to the first dose of the day on Weeks 0 and 6; no medication was given after Week 6. Data points represent group mean scores ± 1 S.E.M. Scores that differ significantly from Week 0, according to Newman Keuls comparisons, are indicated by an "a" ($p<.05$) or "b" ($p<.01$) above the histograms. Dependent measures include Choice Reaction Time (CHOICE RT); Digit Symbol Substitution Test (DSST); Diastolic Blood Pressure (DIAST BP); and Skin Conductance (SKIN COND).

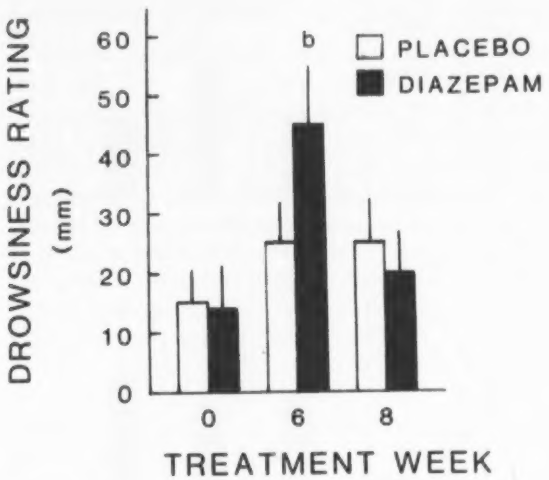


FIGURE 2. Effects of diazepam treatment for 6 weeks on analog ratings of drowsiness during the Divided Attention task. Ratings were obtained prior to the first dose of the day on Weeks 0 and 6; no medication was given after Week 6. Data points represent group mean scores ± 1 S.E.M. Scores that differ significantly from Week 0, according to Newman Keuls comparisons, are indicated by a "b" ($p < .01$) above the histograms.

rating scales. Subjects taking diazepam reported increased drowsiness following their first dose and continued to report increased drowsiness throughout the study. Figure 2 illustrates this effect by presenting drowsiness ratings on Weeks 0 and 6 prior to their morning dose and in the morning on Week 8, following 2 weeks without medication. The ratings shown were taken following completion of the Divided Attention task, and show large increases on Week 6 with a subsequent return to pre-drug levels by Week 8. The placebo group showed no such increases in drowsiness.

Discussion

Diazepam administration had two types of effects on performance and physiology: 1) changes in a direction not seen following placebo; and 2) absence of change in the direction seen following placebo. These two types of effects were seen both acutely, upon administration of diazepam, 5 mg, and following 6 weeks of diazepam, 15 mg per day.

The results of the present study show that the absence of change in psychomotor performance following diazepam does not necessarily imply an absence of drug effect. In the acute case, performance on the Divided Attention task was improved in the placebo but not the diazepam group, and in the long term, DSST performance was improved in the placebo but not the diazepam group. Thus, the *absence* of change following diazepam was an effect of the drug. This type of effect following diazepam has been observed for a variety of tasks (Ghoneim et al., 1984). The same point has to be made for the effect of diazepam on certain physiological changes. For instance, the absence of change in systolic blood pressure following diazepam in the first session is in contrast to the increase seen in the placebo group. Thus, in the assessment of drug action, it is important to ascertain effects such as failure to improve on a task or failure to show physiological responses to a stressful task.

Effects of diazepam seen after the first dose do not necessarily correspond to effects seen after continued administration. For instance, the acute effect of diazepam on systolic blood pressure was not seen 6 weeks later, while a slowing of reaction times did not appear after the first dose but was observed after 6 weeks of medication.

Physiological as well as psychomotor effects differed, depending upon the task, both after acute and prolonged administration of diazepam. Therefore, multiple measures appear to be necessary for the assessment of physiological, as well as cognitive/psychomotor effects of medications.

The most prominent subjective effect of diazepam observed in our subjects was drowsiness. This occurred both after an acute dose and after 6 weeks of medication, even *before* the first dose of the day. It is conceivable, therefore, that changes observed after medication are related to the drowsiness-inducing effect of diazepam.

The data described here were observed in normal subjects and thus may not be representative of an anxious population. Comparable examinations should be conducted in a patient population diagnosed as having generalized anxiety disorder.

References

Biscaldi, G.P., Hattab, J., Montanaro, N., and Scoz, R. Quantitative polygraphic evaluation of emotional tension in the study of a new benzodiazepine. *Curr. Ther. Res.*, 13:606–615, 1971.

Boucsein, W., and Wendt-Suhl, G. Experimental-psychologische Untersuchung psychischer und psychophysiologischer Wirkungen von Cloxazolam und Diazepam unter angstinduzierenden und Normalbedingungen bei gesunden Probanden. *Pharmacopsychiatria*, 2:48–56, 1982.

Brown, M.L., Sletten, I.W., Kleinman, K.M., and Korol, B. Effect of oxazepam on physiological responses to stress in normal subjects. *Curr. Ther. Res.*, 10:543–553, 1968.

Ghoneim, M.M., Mewaldt, S.P., Berie, J.L., and Hinrichs, J.V. Memory and performance effects of single and 3-week administration of diazepam. *Psychopharmacology*, 73:147–151, 1981.

Ghoneim, M.M., Mewaldt, S.P., and Hinrichs, J.V. Behavioral effects of oral versus intravenous administration of diazepam. *Pharmacol. Biochem. Behav.*, 21:231–236, 1984.

Hindmarch, I. Psychomotor function and psychoactive drugs. *Br. J. Clin. Pharmacol.*, 10:189–209, 1980.

Holmberg, G., and William-Olsson, U. Effects of benzquinamide, in comparison with chlordiazepoxide and placebo, on subjective experiences and autonomic phenomena in stress experiments. *Psychopharmacologia*, 5:147–157, 1964.

Linnoila, M., Erwin, C.W., Brendle, A., and Simpson, D. Psychomotor effects of diazepam in anxious patients and healthy volunteers. *J. Clin. Psychopharmacol.*, 3:88–96, 1983.

Lucki, I., Rickels, K., and Geller, A.M. Psychomotor performance following the long-term use of benzodiazepines. *Psychopharmacol. Bull.*, 21:93–96, 1985.

McLeod, D.R., Griffiths, R.R., Bigelow, G.E., and Yingling, J. An automated version of the digit-symbol substitution test (DSST). *Behav. Res. Methods Instrum.*, 14:463–466, 1982.

Molander, L. Effects of melperone, chlorpromazine, haldoperidol, and diazepam on experimental anxiety in normal subjects. *Psychopharmacology*, 77:109–113, 1982.

Wechsler, D. *The Measurement and Appraisal of Adult Intelligence.* Baltimore, MD: Williams & Wilkins, 1958.

Whitehead, W.E., Blackwell, B., and Robinson, A. Why physicians prescribe benzodiazepines in essential hypertension: a phase IV study. *Biol. Psychiatry*, 12:597–601, 1977a.

Whitehead, W.E., Blackwell, B., DeSilva, H., and Robinson, A. Anxiety and anger in hypertension. *J. Psychosom. Res.*, 21: 383–389, 1977b.

Report of the NIMH-NIH Consensus Development Conference on Electroconvulsive Therapy—

Although Electroconvulsive Therapy (ECT) has been used clinically since the late 1930's, it remains a controversial procedure. Consequently, practitioners, patients, and the public have raised questions about whether, when, how, and for whom its use is appropriate and about possible long-term effects. In an effort to address these issues and concerns, the NIMH, in conjunction with NIH Office of Medical Applications of Research, convened a Consensus Development Conference on ECT June 10–12, 1985.

As a service to the field, reprinted below is the Statement of the Censensus Development Panel (Consensus Conference-Electroconvulsive Therapy. *JAMA*, 254(15):2103-2108, 1985) followed by abstracts of presentations to the panel and conference which provided a major contribution to the scientific background for the panelists' deliberations and statement. These abstracts were designed for the use of panelists and participants in the conference and as a reference document for those interested in the conference deliberations. We are grateful to the authors who have summarized their material and made it available in a timely fashion.

JACK D. BLAINE, M.D.
National Institute of Mental Health
Rockville, Md. 20857
SUSAN M. CLARK, PH.D.
National Institutes of Health
Bethesda, Md. 20205

Statement of the Consensus Development Panel

Introduction

Electroconvulsive therapy (ECT) is a treatment for severe mental illness in which a brief application of electric stimulus is used to produce a generalized seizure. In the United States in the 1940s and 1950s, the treatment was often administered to the most severely disturbed patients residing in large mental institutions. As often occurs with new therapies, ECT was used for a variety of disorders, frequently in high doses, and for long periods. Many of these efforts proved ineffective, and some even harmful. Moreover, its use as a means of managing unruly patients, for whom other treatments were not then available, contributed to the perception of ECT as an abusive instrument of behavioral control for patients in mental institutions for the chronically ill. With the introduction of effective psychopharmacologic medications and the development of judicial and regulatory restrictions, the use of ECT has waned.

The treatment is now used primarily in general hospital psychiatric units and in psychiatric hospitals. A National Institute of Mental Health (NIMH) survey estimated that 33,384 patients admitted to hospital psychiatric services during 1980 were treated with ECT, representing approximately 2.4 percent of all psychiatric admissions.

Although ECT has been in use for more than 45 years, there is continuing controversy concerning the mental disorders for which ECT is indicated, its efficacy in their treatment, the optimal methods of administration, possible complications, and the extent of its usage in various settings. These issues have contributed to concerns about the potential for misuse and abuse of ECT and to desires to ensure the protection of patient's rights. At the same time, there is concern that the curtailment of ECT use in response to public opinion and regulation may deprive certain patients of a potentially effective treatment.

In recent decades, researchers intensified efforts to establish the effectiveness of ECT and its indications, to understand its mechanism of action, to clarify the extent of adverse effects, and to determine optimum treatment technique. Despite recent research efforts yielding substantial information, permitting professional and public evaluation of the safety and efficacy of ECT, the investigation of ECT has not generally been in the mainstream of mental health research.

To help resolve questions surrounding these issues, the National Institutes of Health, in conjunction with the NIMH, convened a Consensus Development Conference on Electroconvulsive Therapy on June 10–12, 1985. For 1½ days, experts in the field presented their findings, and an audience, including health professionals, former patients, and other interested persons, discussed the issues. A consensus panel representing psychiatry, psychology, neurology, psychopharmacology, epidemiology, law, and the general public considered the scientific evidence and agreed on answers to the following questions:

- What is the evidence that ECT is effective for patients with specific mental disorders?
- What are the risks and adverse effects of ECT?
- What factors should be considered by the physician and patient in determining if and when ECT would be an appropriate treatment?
- How should ECT be administered to maximize benefits and minimize risks?
- What are the directions for future research?

What Is the Evidence That ECT Is Effective for Patients With Specific Mental Disorders?

Published controlled studies of ECT permit evaluation of its short-term efficacy in severe major depressions (delusional and endogenous), in acute mania, and in certain schizophrenic syndromes. The available controlled clinical trials do not extend beyond the treatment of the acute episode (i.e., about 4 weeks). These studies are difficult to compare because they have used differing diagnostic systems and research designs. Further, they have measured outcome only in terms of symptom reduction, not the quality of life and social functioning.

Depression. Studies of ECT in depression have used various control conditions for comparison, including "sham" ECT (e.g., all of the elements of the ECT procedure except the electric stimulus), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOIs), combination of antidepressants and neuroleptics, and placebos. The efficacy of ECT has been established most convincingly in the treatment of delusional and severe endogenous depressions, which make a clinically important minority of depressive disorders. Some studies find ECT to be of at least equal efficacy to medication treatments, and others find ECT to be superior to medication. Not a single controlled study has shown another form of treatment to be superior to ECT in the short-term management of severe depressions. It must be noted, however, that those studies that found ECT to be superior to medication were not designed to study the persistence of this advantage of ECT beyond the short term. Moreover, the available evidence suggests that relapse rates in the year following ECT are likely to be high unless maintenance antidepressant medications are subsequently prescribed. Several studies suggest that ECT reduces symptoms in severely depressed patients who previously have not responded to adequate trials of antidepressant medication. The literature also indicates that ECT, when compared with antidepressants, has a more rapid onset of action.

Delusional Depression. ECT is highly effective in the treatment of delusional depression. It is superior to either antidepressants or neuroleptics used alone and is at least as effective as the combination of antidepressants and neuroleptics. ECT is often effective in patients who have previously failed to respond to medication. The duration of therapeutic effect beyond the initial acute episode is not clear.

Endogenous/Melancholic Depression. The severe endogenous/melancholic depressions are characterized by early morning awakening, marked weight loss, psychomotor retardation and/or agitation, diurnal variation, and lack of reactivity. ECT is at least as effective as TCA and more effective than sham ECT in the short-term treatment of these severe endogenous/melancholic depressions. ECT appears to be more effective than MAOI in the treatment of severe depressions, but available studies have generally used relatively low MAOI doses. There is evidence for the efficacy of ECT in those endogenous depressives who have not responded to an adequate trial of antidepressants. The long-term efficacy of ECT with endogenously depressed patients is not known.

Other Depression. The majority of depressed persons encountered in medical and psychiatric settings do not have the severe endogenous/melancholic or delusional depressions described above. ECT is not effective for patients with milder depressions, i.e., dysthymic disorder (neurotic depression) and adjustment disorder with depressed mood. Patients with major depression that is nonendogenous/nonmelancholic have not yet been extensively studied. Because of this, it is unclear whether their response to ECT would be more like those with dysthymic disorders or those with endogenous/melancholic features.

Acute Manic Episode. ECT and lithium appear to be equally effective for acute mania, and either is superior to hospitalization without somatic therapy. A treatment regimen in which ECT is used for the acute episode, followed by lithium maintenance, does not appear to be associated with an increased risk of early relapse compared with lithium treatment alone.

Schizophrenia. Neuroleptics are the first line of treatment for schizophrenia. The evidence for the efficacy of ECT in schizophrenia is not compelling but is strongest for those schizophrenic patients with a shorter duration of illness, a more acute onset, and more intense affective symptoms. ECT has not been useful in chronically ill schizophrenic patients. Although ECT is frequently advocated for treatment of patients with schizophreniform psychoses, schizoaffective disorders, and catatonia, there are no adequate controlled studies to document its usefulness for these disorders.

Other Disorders. There are no controlled studies supporting the efficacy of ECT for any conditions other than those designated above (i.e., delusional and severe endogenous depression, acute mania, and certain schizophrenic syndromes).

What Are the Risks and Adverse Effects of ECT?

To maximize the benefits of ECT and minimize the risks, it is essential that the patient's illness be correctly diagnosed, that ECT be administered only for appropriate indications, and that the risks and adverse effects be weighed against the risks of alternative treatments. Risks and adverse effects of ECT can be divided into two categories: 1) those medical complications that can be substantially reduced by the use of appropriately trained staff, best equipment, and best methods of administration; and 2) those side effects, such as spotty but persistent memory loss and transient posttreatment confusion, that can be expected even when an optimal treatment approach is used. In this report, we will focus on the risks still present with adequate treatment techniques.

In the early days of ECT, mortality was a significant problem. The commonly quoted overall mortality rate in the first few decades was 0.1 percent or 1 per 1,000. Over the years, safer methods of administration have been developed, including the use of short-acting anesthetics, muscle relaxants, and adequate oxygenation. Present mortality is very low. In the least favorable recent series reported, there were 2.9 deaths per 100,000 patients. In another series, 4.45 deaths per 100,000 treatments were reported. Overall, the risk is not different from that associated with the use of short-acting barbiturate anesthetics. The risk of death from anesthesia, although very small, is present and should be considered when evaluating the setting for performing ECT.

In the past, up to 40% of patients suffered from various complications, the most common being vertebral compression fractures. With present techniques, these risks have been virtually eliminated. In one recent study of almost 25,000 treatments, a complication rate of 1 per 1,300 to 1,400 treatments was found. These included laryngospasm, circulatory insufficiency, tooth damage, vertebral compression fractures, status epilepticus, peripheral nerve palsy, skin burns, and prolonged apnea.

During the few minutes following the stimulus, profound and potentially dangerous systemic changes occur. First, there may be transient hypotension from bradycardia caused by central vagal stimulation. This may be followed by sinus tachycardia and also sympathetic hyperactivity that leads to a rise in blood pressure, a response that may be more severe in patients with essential hypertension. Intracranial pressure increases during the seizure. Additionally, cardiac arrhythmias during this time are not uncommon (but usually subside without sequelae). Thus, certain patient groups that would be adversely affected by these manifestations are at increased risk.

These are two categories of central nervous system effects: the immediate consequences of the ECT seizure and the more enduring effects, both of which are affected by the treatment course. Immediately after awakening from the treatment, the patient experiences confusion, transient memory loss, and headache. The time it takes to recover clear consciousness, which may be from minutes to several hours, varies depending on individual differences in response, the type of ECT administered, the spacing and number of treatments given, and the age of the patient.

The severity of this acute confusional state is greatest after bilateral sine wave treatment and least when nondominant unilateral-pulsed ECT is administered. Severity also appears to be increased by longer seizure duration, close spacing of the treatments, increasing dosage of electrical stimulation, and each additional treatment.

Depressive disorders are characterized by cognitive deficits that may be difficult to differentiate from those due to ECT. It is, however, well established that ECT produces memory deficits. Deficits in memory function, which have been demonstrated objectively and repeatedly, persist after the termination of a normal course of ECT. Severity of the deficit is related to the number of treatments, type of electrode placement, and nature of the electric stimulus. Greater deficit occurs from bilateral than from unilateral placement. Sine-wave current has been found to impair memory more than pulsed current.

The ability to learn and retain new information is adversely affected for a time following the administration of ECT; several weeks after its termination, however, this ability typically returns to normal. There is also objective evidence, based on neuropsychological testing, of loss of memory for a few weeks surrounding the treatment; such objective tests have not firmly established persistent or permanent deficits for a more extensive period, particularly for unilateral ECT. However, research conducted as long as 3 years after treatment has found that many patients report that their memory was not as good as it was prior to the treatment. They report particular difficulties for events that occurred on average 6 months before ECT (retrograde amnesia) and on average 2 months after the treatment (anterograde amnesia). Because there is also a wide difference in individual perception of the memory deficit, the subjective loss can be extremely distressing to some and of little concern to others.

There are other possible adverse effects from ECT. Some patients perceive ECT as a terrifying experience; some regard it as an abusive invasion of personal autonomy; some experience a sense of shame because of the social stigma they associate with ECT; and some report extreme distress from persistent memory deficits. The panel heard eloquent testimony of these attitudes from former patients who had been treated with ECT. It is clear, however, that these attitudes are not shared by all ECT patients. The panel also heard moving testimony from former patients who regarded ECT as a wholly beneficial and lifesaving experience. There are insufficient systematic studies to permit any definitive assessment of the prevalence of these various perceptions among ECT patients.

Numerous ECT studies have been conducted with animal models. Many of these suffer from methodological shortcomings. In studies that have been controlled for fixation artifacts, hypoxia, and other methodological problems, neuronal cell death has not been detected. Cerebral vasospasm and alterations in capillary permeability are of short duration and of insufficient magnitude to lead to neuronal cell death. The precise mechanism of the anterograde and retrograde memory deficit has not been established; it may represent alterations in neuronal function that are not detectable with present methods. Computerized axial tomography (CAT) studies of patients who have had ECT are very preliminary and open to alternative interpretations. Definitive studies of in vivo brain metabolism with positron emission tomography (PET) and studies of tissue changes detectable by magnetic resonance imaging (MRI) remain to be done.

What Factors Should Be Considered by the Physician and Patient in Determining If and When ECT Would Be an Appropriate Treatment?

The consideration of ECT is most appropriate in those conditions for which efficacy has been established: delusional and severe endogenous depressions, acute mania, and certain schizophrenic syndromes. ECT should rarely be considered for other psychiatric conditions. The decision whether to offer ECT to an individual patient should be based on a complex consideration of advantages for ECT and for each treatment alternative. Whether to use ECT should be based on a thorough review of severity of the patient's illness, medical indications and contraindications, and nonresponsiveness to other treatments. It should be emphasized that for certain patients with very specific and narrow indications, ECT may be the only effective treatment available. In certain circumstances of acute risk to life or of medical status incompatible with the use of other effective treatments, ECT may be the first treatment.

The panel is concerned that ECT only be administered for the benefit of individual patients. Institutional factors (such as financial pressures created by prospective systems or staff convenience) should play no role in the decision to administer ECT.

Severity. Given a diagnosis for which the efficacy of ECT has been established, the immediate risk of suicide (when not manageable by other means) is a clear indication for the consideration of ECT. Acute manic episodes—especially when characterized by clouded sensorium, dehydration, extreme psychomotor agitation, high risk for serious medical complication or death through exhaustion, and nonresponse to pharmacological interventions—are also clear indications for ECT. The severe and unremitting nature of the patient's emotional suffering, or extreme incapacitation, are also important considerations.

Medical Indications and Contraindications. The patient's medical status is often the determining consideration in the use of ECT. ECT may be necessary when the patient has medical conditions that preclude the use of tricyclic antidepressants, MAOI, lithium, and neuroleptics. ECT should be considered in patients with severe depression or psychosis during the first trimester of pregnancy. Conversely, ECT is contraindicated for increased intracranial pressure, while space-occupying lesions in the brain, a recent history of myocardial infarction, and large aneurysms are relative contraindications for ECT. A personal history of nonresponsiveness to, or debilitating side effects (medical or psychological) from, ECT are also possible contraindications.

Nonresponsiveness to Other Treatments. ECT should be considered when alternative pharmacological and/or psychotherapeutic treatments have been given an adequate trial without efficacious response. When a patient is nonresponsive to other treatments, factors such as severity of the illness, its natural course, and the risk of other treatments worsening the course (as, for example, antidepressant medications precipitating a manic episode) need to be taken into account.

Informed Consent. When the physician has determined that clinical indications justify the administration of ECT, the law requires, and medical ethics demand, that the patient's freedom to accept or refuse the treatment be fully honored. An ongoing consultative process should take place. In this process, the physician must make clear to the patient the nature of the options available and the fact that the patient is entitled to choose among those options.

No uniform "shopping list" can be drawn up regarding the matters that should be discussed by patient and physician to assure a fully informed consent. They should discuss the character of the procedure, its possible risks and benefits (including full acknowledgment of posttreatment confusion, memory dysfunction, and other attendant uncertainties), and the alternative treatment options (including the option of no treatment at all). Special individual needs may also be relevant to some patients, for example, a personal situation that requires rapid remission to facilitate return to work and to reduce family disruption. In all matters, the patient should not be inundated with technical detail; the technical issues should be translated into terms meaningful and accessible to the patient.

It is not easy to achieve this ideal of "informed consent" in any aspect of medical practice; and there are special difficulties that arise regarding the administration of ECT. In particular, the patients for whom this procedure is medically appropriate may be suffering from a severe psychiatric illness that, although not impairing their legal competency to consent, may nonetheless cloud judgment in fully weighing all of the available options. Such judgmental distortion does not justify disregarding the patient's choices; rather, it makes it all the more important that the physician strive to identify and clarify the options that the patient alone is entitled to exercise.

The consent given by the patient at the outset of treatment should not be the final exchange on this issue but should be reexamined with the patient repeatedly throughout the course of the treatment. These periodic reviews should be initiated by the physician and not depend on patient initiative to "rescind" consent.

There are several reasons for this repeated consenting procedure: because of the relatively rapid therapeutic effect of the procedure itself, the patient after initial treatments is likely to have enhanced judgmental capacities; the risks of adverse effects increase with repeated treatments, so that the question of continued treatment presents a possibly charged risk/benefit assessment for the patient; and because of the short-term memory deficits that accompany each administration of ECT, the patient's recollection of the prior consenting transaction might itself be impaired, so that repeated consultations reiterating the patient's treatment options are important to protect the patient's sense of autonomy throughout the treatment process. Moveover, if the patient agrees, the family should be involved in each step of this consultative process.

In a small minority of cases, a patient will lack adequate legal capacity to consent to the proposed procedure. In such cases, timely court proceedings are necessary if treatment is to be provided. Legislation in a few states dictates that ECT may in no circumstance be provided to an involuntarily committed patient. The panel believes that such absolute bans are unduly restrictive and make treatment impossible for patients who might obtain more benefit, at acceptable levels of risk, from ECT than from alternative treatments.

It may be desirable for physicians with patients for whom the prospect of ECT is a foreseeable but not immediate possibility to discuss this in advance with the patient when his or her judgment appears least compromised by the underlying disease process. Such advance discussion would serve as a nonbinding guide both to the patient and physician and would be another means to enhance the patient's autonomous choice in weighing the risks and benefits of this procedure and its alternatives.

How Should ECT Be Administered to Maximize Benefits and Minimize Risks?

Once the patient and the physician have decided that ECT may be indicated, the patient should undergo a pretreatment medical examination that includes a history, physical, neurologic examination, electrocardiogram (ECG), and laboratory tests. Medications that affect the seizure threshold should be noted and decreased or discontinued when clinically feasible. MAOIs should be discontinued 2 weeks before treatment, and patients should be essentially lithium-free. Severe hypertension should be controlled before beginning treatment. Because some patients with compromised cardiovascular status will be receiving ECT, cardiac conditions should be evaluated and monitored closely. Educating the patient and the family through discussion and written and/or audiovisual material describing the procedure is necessary prior to obtaining written informed consent.

An area should be designated for the administration of ECT and for supervised medical recovery from the treatment. This area should have appropriate health care professionals available and should include equipment and medications that could be used in the event of cardiopulmonary or other complications from the procedure.

A health professional specifically trained and certified in the use of brief anesthetic procedures should administer the anesthesia. The treatment team should include nursing personnel trained in ECT procedures and recovery.

Typically, ECT is administered as follows: the treatment is given in the early morning after an 8- to 12-hour period of fasting. Atropine or another anticholinergic agent is given prior to the treatment. An intravenous line is placed in a peripheral vein, and access to this vein is maintained until the patient is fully recovered. The anesthetic methohexital is given first, followed by succinylcholine for muscle relaxation. Ventilatory assistance is provided with a positive pressure bag using 100% oxygen. The ECG, blood pressure, and pulse rate should be monitored throughout the procedure. Stimulus electrodes are placed either bifrontotemporally (bilateral) or with one electrode placed frontotemporally and the second electrode placed on the ipsilateral side (unilateral). Bilateral ECT may be more effective in certain patients or conditions. It has been established, however, that unilateral ECT, particularly on the nondominant side, is associated with a shorter confusional period and fewer memory deficits. Also, a brief pulse stimulus is associated with fewer cognitive defects than the traditional sine wave stimulus. Seizure threshold varies greatly among patients and may be difficult to determine; nevertheless, the lowest amount of electrical energy to induce an adequate seizure should be used. Seizure monitoring is necessary and may be accomplished by an electroencephalograph or by the "cuff" technique. In this technique, a blood pressure cuff is placed on an arm or leg and is inflated above systolic pressure prior to the injection of a muscle-relaxing agent. In unilateral ECT, the cuff should be on the same side as the electrodes to ensure that a bilateral seizure occurred.

The number of treatments in a course of therapy varies. Six to 12 treatments are usually effective. In the United States, the usual frequency is three times weekly; in the United Kingdom, the standard practice is two treatments weekly. Regressive ECT (a large number of treatments given within a short period for the purpose of achieving a persistent organic brain syndrome) is no longer an acceptable treatment form. Multiple-monitored ECT (several seizures during a single treatment session) has not been demonstrated to be sufficiently effective to be recommended. There are no controlled studies on the periodic use of ECT after remission of the acute episode or as a maintenance regimen to prevent recurrence of new episodes. Following ECT, most depressed patients should be continued on antidepressant medication or lithium to reduce relapse.

The panel is concerned that there are only limited data on the manner and extent of ECT administration in the United States and on the training of personnel involved in it. A national survey should be undertaken to assemble basic facts about the status of ECT treatment.

Medical school curricula should include education in the use of ECT. Psychiatric residency programs should include complete ECT training: indications, contraindications, risks, clinical management, informed consent, and evaluation of outcome. The American Board of Psychiatry and Neurology should include questions about ECT in its oral and written examinations.

The panel believes it is imperative that appropriate mechanisms be established to ensure proper standards and monitoring of ECT. Hospitals and centers using ECT should establish review committees modeled on other medical-surgical review committees and should formulate rules and regulations to govern the privileging of physicians giving the treatments. Stringent peer review consistent with Joint Commission for the Accreditation of Hospitals' standards should monitor ongoing utilization of ECT. Periodic inspection of the equipment is also essential. As experience accumulates, consideration should be given to the adequacy of existing monitoring and review mechanisms.

What Are the Directions for Future Research?

ECT has been underinvestigated in the past. Among the most important immediate research tasks are:

- Initiation of a national survey to assemble the basic facts about the manner and extent of ECT use, as well as studies of patient attitudes and responses to ECT. Better understanding of negative, positive, and indifferent responses should result in improved treatment practices.
- Identification of the biological mechanisms underlying the therapeutic effects of ECT and the memory deficits resulting from the treatment.
- Better delineation of the long-term effects of ECT on the course of affective illnesses and cognitive functions, including clarification of the duration of ECT's therapeutic effectiveness.
- Precise determination of the mode of electrode placement (unilateral versus bilateral) and the stimulus parameters (form and intensity) that maximize efficacy and minimize cognitive impairment.
- Identification of patient subgroups or types for whom ECT is particularly beneficial or toxic.

Conclusion

ECT is the most controversial treatment in psychiatry. The nature of the treatment itself, its history of abuse, unfavorable media presentations, compelling testimony of former patients, special attention by the legal system, uneven distribution of ECT use among practitioners and facilities, and uneven access by patients all contribute to the controversial context in which the consensus panel has approached its task.

The panel has found that ECT is demonstrably effective for a narrow range of severe psychiatric disorders in a limited number of diagnostic categories: delusional and severe endogenous depression, and manic and certain schizophrenic syndromes. There are, however, significant side effects, especially acute confusional states and persistent memory deficits for events during the months surrounding the ECT treatment. Proper administration of ECT can reduce potential side effects while still providing for adequate therapeutic effects.

The physician's decision to offer ECT to a patient and the patient's decision to accept it should be based on a complex consideration of advantages and disadvantages of ECT compared with alternative treatments. An ongoing consultative process, requiring time and energy on the part of both patient and physician, should occur.

Much additional research is needed into the basic mechanisms by which ECT exerts its therapeutic effects. Studies are also needed to better identify subgroups for whom the treatment is particularly beneficial or toxic and to refine techniques to maximize efficacy and minimize side effects. A national survey should be conducted on the manner and extent of ECT use in the United States.

These recommendations reflect the consensus of the panel. We have been careful to narrowly delineate when and how, in our judgment, ECT should be administered. To prevent misapplication and abuse, it is essential that appropriate mechanisms be established to ensure proper standards and monitoring of ECT.

Members of the Consensus Development Panel

Robert M. Rose, M.D., Panel Chairman
Professor and Chairman
Department of Psychiatry and Behavioral Sciences
University of Texas Medical Branch
Galveston, Texas

Robert A. Burt, J.D.
Southmayd Professor of Law
Yale Law School
Yale University
New Haven, Conn.

Paula J. Clayton, M.D.
Professor and Head
Department of Psychiatry
University of Minnesota
Minneapolis, Minn.

Allen Frances, M.D.
Professor of Psychiatry
Cornell University Medical College
New York, N.Y.

Arnold J. Friedhoff, M.D.
Director of Millhauser Laboratories
Professor of Psychiatry
New York University College of Medicine
New York, N.Y.

Kay Redfield Jamison, Ph.D.
Associate Professor and Director
Affective Disorders Clinic
Department of Psychiatry
University of Calif. at Los Angeles School of Medicine
Los Angeles, Calif.

David S. Janowsky, M.D.
Professor of Psychiatry and
Director, Mental Health Clinical Research Center
University of California at San Diego and
Staff Physician, San Diego VA Medical Center
La Jolla, Calif.

Jonathan Leff
Editorial Consultant and Retired Director
Consumer Reports Books
South Hero, Vt.

Ilo E. Leppik, M.D.
Associate Professor of Neurology
University of Minnesota
St. Paul Ramsey Medical Center
St. Paul, Minn.

Douglas M. McNair, Ph.D.
Professor and Director
Clinical Psychopharmacology Laboratory
Clinical Psychology Ph.D. Program
Boston University
Boston, Mass.

Leonard I. Stein, M.D.
Professor of Psychiatry
University of Wisconsin Medical School and
Medical Director
Dane County Mental Health Center
Madison, Wisc.

Verner Stillner, M.D., M.P.H.
Medical Director
Charter Ridge Hospital and
Professor of Psychiatry
University of Kentucky
Lexington, Kentucky

Myrna M. Weissman, Ph.D.
Professor of Psychiatry and Epidemiology and
Director, Depression Research Unit
Department of Psychology
Yale University School of Medicine
New Haven, Conn.

Robert P. Withrow, M.D., M.P.H.
Associate Director
Mental Health Department and
Director of Inpatient Unit
Fresno Community Hospital and Medical Center and
Assistant Clinical Professor
Department of Psychiatry
University of Calif. at San Francisco School of
Medicine
Fresno, Calif.

Members of Planning Committee

Robert M. Rose, M.D.
Panel Chairman
Professor and Chairman
Department of Psychiatry and Behavioral Sciences
University of Texas Medical Branch
Galveston, Texas

Richard Abrams, M.D.
Professor and Vice Chairman
Department of Psychiatry
University of Health Sciences and
Chicago Medical School
North Chicago, Ill.

Jack D. Blaine, M.D.
National Institute of Mental Health
Coordinator
Research Psychiatrist
National Institute of Mental Health
Rockville, Md.

Susan M. Clark
Office of Medical Applications of Research Coordinator
Social Science Analyst
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Md.

Alan J. Gelenberg, M.D.
Psychiatrist-in-Chief
The Arbour
Chief of Special Studies
Massachusetts General Hospital and
Associate Professor
Harvard Medical School
Jamaica Plain, Mass.

Michael S. Gluck, D.Sc., P.E.
Chief
Anesthesiology and Respiratory Therapy Devices Branch
Food and Drug Administration
Silver Spring, Md.

Harold Alan Pincus, M.D.
Special Assistant to the Director
National Institute of Mental Health
Rockville, Md.

William Z. Potter, M.D., Ph.D.
Chief
Section on Clinical Psychopharmacology
Laboratory of Clinical Science
National Institute of Mental Health
Bethesda, Md.

Norman Rosenberg, J.D.
Director
Mental Health Law Project
Washington, D.C.

Harold A. Sackeim, Ph.D.
Associate Professor of Psychology
New York University and
Research Scientist and Deputy Chief
Department of Biological Psychiatry
New York State Psychiatric Institute
New York, N.Y.

Richard D. Weiner, M.D., Ph.D.
Associate Professor of Psychiatry
Duke University Medical Center
Psychiatry Service
Durham VA Medical Center
Durham, N.C.

Michael J. Bernstein
Director of Communications
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Md.

Myrle Kahn
Public Information Specialist
Public Communications Branch
National Institute of Mental Health
Rockville, Md.

The Conference Was Sponsored By:

National Institute of Mental Health
Shervert Frazier, M.D., Director

Office of Medical Applications of Research
National Institutes of Health
Itzhak Jacoby, Ph.D., Acting Director

Abstracts of Presentations to the Panel and Conference—

The Use of Somatic Treatments for Psychiatric Illnesses

Gerald L. Klerman, M.D.[1]

Throughout history, various interventions, which today we would call somatic treatments, have been used for the treatment of psychiatric illnesses. The division of treatments into psychological treatments and somatic treatments reflects the mind-body dualism embodied in the philosophical writings of Descartes that has dominated Western thinking since the beginning of modern times.

The modern era of somatic treatments began in the 1930's. In that decade, Dilantin was introduced for treatment of epilepsy, and the amphetamines were used for treatment of narcolepsy and as treatment of psychomotor stimulants. Two forms of shock treatments were also introduced, Metrazol and insulin treatment. In addition, psychosurgery in the form of prefrontal lobotomy was developed by Moniz, for which he was awarded the Nobel Prize. Insulin shock treatment, also known as insulin coma treatment, was developed by Sakel in Vienna with claims for superior treatment efficacy in schizophrenia. It was the most valued treatment for schizophrenia but was also highly controversial. In the 1950's, the phenothiazines and the tranquilizers rendered insulin treatment obsolete.

The other form of shock treatment, Metrazol, was initially introduced by Van Medune in Hungary for the treatment of schizophrenia but later was found to be more effective for depressions. The term "shock treatment" has given way to the more appropriate form "convulsive therapies" because research has demonstrated that the essential therapeutic ingredient is the induction of an electrical brain discharge akin to a grand mal convulsion rather than any psychological trauma or cardiovascular shock. Over the subsequent decades, a number of convulsive therapies have been developed. Electroconvulsive therapy (ECT) has remained an important, albeit a controversial, psychiatric treatment. ECT was developed in Italy by Cerletti and Bini in 1938 and introduced to the United States in 1940. A third form of convulsive therapy, inhalation of Indoklon, was introduced after World War II. Whether the convulsion is introduced chemically (by Metrazol), electrically (by ECT), or by inhalation (Indoklon), there is evidence for the efficacy of convulsive therapy in depression and also for some other forms of acute psychosis.

Controversies in Psychiatry

The introduction of modern somatic treatments generated intense controversy, not only as to the evidence for their safety and efficacy but, more significantly, over the nature of psychiatric illness.

It has long been apparent to observers of the psychiatric scene in the United States and elsewhere that the mental health field is deeply divided into various theoretical schools. The major categories are the biological, psychodynamic, social, behavioral, and interpersonal schools. The adherents of these schools often hold intense emotional and ideologic commitments to their beliefs about the nature of mental illness, its causation, prevention and, more significantly, decisions as to the appropriateness of treatment. Among the areas of controversy is the definition of psychiatric illness per se.

---

[1] Department of Psychiatry, Cornell University Medical Center, New York, NY 10021.

The Antipsychiatry Movement

The opposition of ECT is generated not only by concerns about safety and efficacy but also by unresolved issues as to the appropriateness of the concept of mental illness. Many of the critics of ECT are involved in the antipsychiatry movement, which challenges not only the safety and efficacy of specific treatments used but more fundamentally the nature of mental illness and the legitimacy of psychiatry as a medical specialty. Antipsychiatrists, such as Laing in England, Szasz in the United States, and Foucault in France, have attached the idea of mental illness as a diagnostic class in the medical model and have asserted that psychiatry represents a form of social control in the guise of medical treatment. These antipsychiatry critics were joined in the 1960's and 1970's by the labeling theorists in sociology and social psychology who pointed out the adverse consequences for individuals who are labeled mentally ill, and the role of psychiatry as an agent of social control of deviance. Proponents of antipsychiatry have often assumed leadership roles in legal attempts to constrain the use of involuntary hospitalization (commitment) and to limit the use of biological treatments, such as psychopharmacologic agents and ECT. The legal decisions that create a "right-to-refuse treatment" reflect their success.

The Scope of Psychiatric Illness

The controversy about the value of somatic treatment involves differences of opinion with regard to the criteria for the diagnosis of psychiatric illness.

From epidemiologic data, there are a number of populations with relevance to mental health and mental illness. As shown in Figure 1, these populations consist of a core group of individuals with diagnosable mental disorders, a larger group of individuals with stress response and reactions to life events, and a group, almost without limits, of individuals who use the mental health system and its technologies, including biological treatments such as drugs, for the enhancement of their personal potential and happiness.

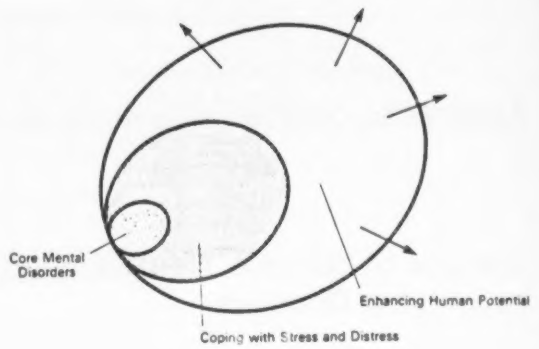


FIGURE 1

The Core Population: Individuals With Mental Disorders

At the core is the 15 percent of the population with definable and diagnosable mental disorders. Some psychiatrists would argue that within this core there is a further "inner core" of individuals with chronically disabling mental illness, particularly schizophrenia, other psychoses, and severe alcoholism.

Psychiatry began with psychotic patients, particularly those chronically disabled and requiring institutionalization, usually under public and governmental auspices. In a study prepared for the U.S. Department of Health and Human Services Task Force on the Chronically Ill, chaired by Richmond and Klerman (1982), it was estimated that there are about 1.5 million chronically mentally ill persons. It is this chronically ill group that historically has been the main concern of psychiatry, because psychiatry began as a group of physicians specializing in the care of the institutionalized mentally ill in the 19th century. Not only does this inner core reflect the historical origin of the field, but it represents a group with great social cost because of the high level of disability, demand for residential and financial supports, economic and vocational maladjustments, and frequent use of institutional settings.

Since the turn of the century, the scope of mental illness has increased so as to include various categories of neuroses, depressions, and personality disorders in addition to the psychoses. The epidemiologic evidence indicates that about 15 percent of the population in any one year suffers from such a disorder.

While 15 percent of the population represents current prevalence, epidemiologists are also interested in lifetime expectancy. Although full data are not available, it appears that about 40 percent of the population will experience some diagnosable mental illness during their lifetime. For example, the life expectancy for depression for women is about 25 percent and for men about 12 to 15 percent. To this can be added expectancies of about 10 percent alcoholism for men and various episodes of anxiety, phobia, and so forth, and it becomes clear that 40 percent is a conservative estimate.

We do not have comparable estimates of familial prevalence. It is likely that in at least 50 percent of families, at least one family member will suffer a definable mental illness at some time during the life of the family.

In addition to this core population of individuals with diagnosed illness, the Figure identifies two other populations of interest. The second population includes the large number of individuals coping with stress and life events, and the third, individuals attempting to enhance their life and achieve happiness and personal fulfillment and satisfaction.

Conclusions

Biological treatments are mainly used for individuals with the core mental disorders, especially major affective disorders, particularly depressions and bipolar illness.

Increasingly, psychopharmacologic agents are often used in the enhancement to facilitate an individual's ability to cope with stress; many individuals confronted with stressful life events use benzodiazepines and other minor tranquilizers. Physicians prescribe these drugs for patients with definable physical illness to deal with the emotional and stress consequences of having arthritis, heart disorder, and gastrointestinal disease.

ECT is usually used in the treatment of patients in the inner core of serious mental illness. As will be argued over the next days, society has yet to make a full course benefit analysis, balancing the advantages of treatment success against the adverse effects on memory and psychological functioning.

Convulsive Therapy: How It Evolved

Max Fink, M.D.[1]

Neurosyphilis was one of the main causes of insanity in the 19th century. With the discovery of the causative agent, a spirochaete, and the development of the Wasserman serological test, it was possible to clearly identify patients with this disorder. Julius Wagner-Jauregg developed malarial fever therapy for neurosyphilis and received the Nobel Prize for medicine in 1927. It is this success that encouraged the philosophy that a heroic intervention was both feasible and perhaps necessary to bring the insane back from their private hells. Such beliefs encouraged the development of prolonged sleep therapy (Klaesi), insulin coma (Sakel), leukotomy (Moniz), and convulsive therapy (Meduna) and, indeed, justified the initial trials of reserpine and chlorpromazine and the psychopharmacologic revolution of the 1950's.

Ladislas Meduna, a Hungarian neuropsychiatrist and neuropathologist, following the suggestion of a clinical antagonism between epilepsy and dementia praecox (schizophrenia), sought to influence dementia praecox by inducing epileptic fits. The first patient, a catatonic man who had been mute for 4 years, was treated on January 24, 1934. Remarkably, he recovered. Meduna repeated his success many times, and when he published his first significant report in 1937, the treatment was already in worldwide use.

The rest is a history of modifications and experimentation to reduce the risks and improve the delivery, of comparisons with psychotropic drugs, of professional and public enthusiasm and damnation, and of the recent awareness that convulsive therapy is an effective treatment in present day psychiatry whose continued use probably should be encouraged.

---

[1] Department of Psychiatry and Behavioral Sciences, SUNY at Stony Brook, Long Island, NY 11794.

Modifications

Following its success with patients with dementia praecox, convulsive therapy was soon found also to be effective in patients with mania and melancholia (1937). The Italians Cerletti and Bini simplified seizure induction by using electric currents (1938). The incidence of fractures was markedly reduced by curare (1940) and later virtually eliminated by succinylcholine (1952). Brief pulse stimuli were found effective (1944), unilateral electrode placements elicited much less amnesia (1958), and oxygenation increased seizure duration and further reduced amnesia (1953).

Not all modifications of ECT were found to be effective or safe. Trials in patients with neuroses, anxiety, obsessive compulsive disorders, hypochondriasis, hysteria, drug dependence, alcoholism, character disorder, homosexuality, and childhood schizophrenia found ECT relatively ineffective. The inhalant flurothyl (Indoklon) was found to be an effective convulsant but one that was more difficult to use (1957). Subconvulsive treatments (1942), regressive ECT (1947), and multiple monitored seizures (1967), among others, were tested, found wanting, and rejected.

The introduction of psychoactive drugs between 1953 and 1960 led to comparisons of efficacy and safety of the drugs and other somatic treatments. In direct comparisons between insulin coma and psychoactive drugs (1958), the drugs were found to be as effective as the coma treatments but clearly safer and easier and less expensive to use. Within 2 years, insulin coma was abandoned.

While direct comparisons between lobotomy and psychotropic drugs were not done, the prevailing opinion was that the drugs were as effective or more effective, and lobotomy virtually disappeared as a principal treatment by 1962.

In comparisons of the drug therapies and ECT, however, the treatments were found to be equally effective; and, indeed, in some populations, ECT was more effective. Drug therapies also replaced the use of convulsive therapy. But as some patients failed to improve with conventional drug therapies, megadoses of drugs, polypharmacy, and experimental drugs were tried. As these failed, physicians turned again to ECT with increased interest after 1967.

Professional and Public Attitudes

The initial remarkable success of the convulsive therapies (as well as insulin coma and lobotomy) led to public and professional enthusiasm that a new era for the mentally ill had finally dawned. During World War II, these somatic treatments were widely used to treat the acute psychoses occurring among military men and veterans. The success of the treatments, the ease of administration, and the many physicians trained in their use during the war years led to an explosion of use after the war and trials in many psychiatric conditions. These excesses were criticized both within and outside the profession. For example, the first report of the Group for the Advancement of Psychiatry (1947) warned against the promiscuous use of electroshock therapy.

Public confusion over differences between lobotomy, insulin coma, and electroshock, fueled by aggressive expatients and publicity-seeking psychiatrists, led to the interdiction of ECT in California in the early 1970's. This legislation led the American Psychiatric Association to establish a task force to assess the safety and efficacy of ECT in 1975; their report appeared in 1978. Similar reviews were undertaken by the Royal College of Psychiatrists in Great Britain in 1977 and 1981. Contemporaneous reviews of ECT practice by official bodies and individual scientists in Canada, Sweden, Denmark, Australia, Germany, the Netherlands, and Ireland joined the U.S. and British reports to conclude that ECT was an effective therapy for patients with major psychoses; that available procedures, if properly applied, allowed the treatments to be used safely in patients of all ages; that the training, experience, and practice of many practitioners was often wanting; that educational programs were inadequate; and that support for research into the mechanisms of convulsive therapy was almost nonexistent.

Present Practice and Future Course

These evaluations, appearing since 1976, increased interest in convulsive therapy. There are some signs that usage is increasing in individual institutions, and the number of institutions offering ECT is also apparently increasing. There is an increase in the number of publications, from a monthly average of 9.5 in 1979 to 13 Medline citations in the last half of 1984; and new textbooks and volumes of proceedings now appear at a rate of one per year. The launching in 1985 of a quarterly international scientific journal dedicated exclusively to convulsive therapy, the introduction of new instruments for ECT both in the U.S. and Great Britain, and the increase in large national and international conferences from one every few years in the 1970's to at least one each year since 1979 are other indications.

Usage will probably increase, fueled by greater professional and public acceptance of ECT in the treatment of major psychoses. Outpatient usage of ECT should increase substantially as diagnostic related groups affect medical practice. Representatives of the press and the media will become more responsible and will present the experiences of medical practice more fairly. It is hoped they will stop titillating the public by dramatic misrepresentations like those portrayed in *One Flew Over the Cuckoo's Nest*. The profession will recognize the necessity to use convulsive therapy safely and properly, pay more attention to the technical procedures, and improve training, with increased utilization of texts, videotapes, and training manuals.

One can hope that the need to replace convulsive therapy by a more elegant, simpler, and safer therapeutic practice will become a matter of public concern. The public can wait for serendipity to discover a more effective and more elegant treatment. Or, its representatives can encourage efforts to unravel the complex interactions between mood, the pathophysiology of mood disorders, brain chemistry and electrophysiology, and the effects of seizures on brain functions. Compelling clues in quantitative multilead electroencephalography and the neuroendocrine changes in cortisol and prolactin during the ECT process warrant further study. To take advantage of these observations and to encourage greater efforts among clinical and basic scientists will require changes in attitude by governmental and private committees that expend funds for research, to acknowledge that both practice and research in convulsive therapy is ethical and in the public interest. Perhaps the consensus conference will encourage such developments.

Sources

Abrams R, Essman W (eds). Electroconvulsive Therapy: Biological Foundations and Clinical Applications. New York: Spectrum Publications, 1982.

American Psychiatric Association. Electroconvulsive Therapy. Task Force Report 14. Washington, DC: American Psychiatric Association, 1978.

Fink M. Convulsive Therapy: Theory and Practice. New York: Raven Press, 1979.

Lerer B, Weiner RD, Belmaker RH (eds). ECT: Basic Mechanisms. London: John Libbey, 1984.

Palmer RL (ed). Electroconvulsive Therapy: An Appraisal. New York: Oxford, 1981.

Pippard J, Ellam L. Electroconvulsive Treatment in Great Britain, 1980. London: Gaskell, 1981.

ECT: The Historical, Social, and Professional Sources of the Controversy

David J. Rothman, Ph.D.[1]

This presentation explores the historical, social, and professional considerations that properly affect deliberations on the efficacy and side effects of electroconvulsive therapy. It analyzes the context into which findings must be placed, particularly should they demonstrate efficacy.*

---

[1] Columbia University College of Physicians and Surgeons, New York, NY 10032.

*This statement does not aim to prejudge the issue; rather, should findings point to a lack of efficacy or to unacceptable side effects, the discussion that follows becomes irrelevant. Nonefficacious treatments are simply prohibited and/or fall into disuse.

Although proponents all recognize the highly controversial character of ECT, little agreement exists on the sources of the controversy. To some, it reflects the untoward influence of sensationalist media, the power of such films as *One Flew Over the Cuckoo's Nest* to distort public opinion. Others point to the psychodynamics of displacement, whereby the patient's anger and frustration go onto the treatment. Still others cite fantasies about the nature of electricity or associations with the electric chair.

Whatever the validity of these explanations, they do not exhaust the possibilities or necessarily get to the root of the issue. All of them emphasize external factors, minimizing the history of the treatment itself or the ways that the psychiatric profession oversees the treatment. But the controversial character of ECT has many internal sources. Most notably, ECT represents a far more physically invasive procedure than is traditional to psychiatry; the profession, however, has not adequately appreciated or responded to this difference. ECT has far more in common with medical and surgical procedures than interactive procedures, but psychiatry has not adopted the comparable and standard medical and surgical regulations. Psychiatry has been proud of the medical-like quality of ECT, but generally, it has not followed medical rules with ECT; in this gap lie some of the most important sources of the controversy.

1. *Judged by the history of other medical therapies, the administration of ECT has an atypical history of significant misuse.* Although the over- or underdispensation of a new medication or procedure is not uncommon, ECT is at the high end of the scale. Debate over the conditions that warrant ECT lasts longer and remains more intense than with most other interventions. Still more important, ECT stands practically alone among medical/surgical interventions in that misuse was not to the goal of curing but of controlling the patient for the benefit of hospital staff. Whatever the misuse of penicillin or coronary artery bypass grafts, the issue of staff convenience was not nearly as prominent as with ECT. The annual reports of state hospitals through the early 1950's are replete with statements about the use of ECT for purposes of control, not therapy. Reports candidly noted that ECT was being applied to make patients "more amiable to hospital care" and "more tractable." ECT makes patients "more docile and relieves employees of the necessity of feeding or tube feeding."

In this spirit, two researchers at the Stockton (California) State Hospital reported in a 1950 article about their application of ECT to women residents on a chronic and disturbed ward. "Our goals," they explained, "were not curative; they were limited to the level of improved ward behavior." Patients who were aggressive and disturbed were selected for treatment, started on ECT once a day, and continued daily until they became manageable. Frequently "two or more seizures were induced in one day if the patient was unduly disturbed." The researchers judged ECT a success because the "physical labor of attendants was cut in half."

Although there is a distinction between managing a patient and punishing a patient, the line is very thin, often imperceptible either to patients or outside observers. Thus, it is not arbitrary or accidental that ECT earned a reputation among some patients and part of the public as a punishment. It was not the pain of the intervention but the purpose of the intervention that marked off ECT from most other medical and surgical procedures.

2. *ECT remains a controversial intervention in public perception because it is a controversial intervention among psychiatrists.* The 1978 survey of the American Psychiatric Association (APA) reported that one-third of the psychiatrists polled were "generally opposed" or "more opposed than favorable" to its use. If one removes this finding from the controversy about banning ECT and places it in a medical/surgical context, it is difficult to think of other interventions that one-third of physicians would generally oppose and two-thirds would consider highly efficacious.

3. *There are few medical/surgical interventions that proponents would insist are of great efficacy and low risk but that many of these same proponents (and others as well!) prescribe only after other usually more risky interventions have failed.* The APA Task Force reports that only 19 percent of psychiatrists gave ECT as treatment of first choice for major depression; these findings, it notes, "suggest that ECT

was not often used until other treatment approaches had been tried and found ineffective." If ECT has fewer side effects and greater efficacy than antidepressant medications, why should a patient first have to fail on a trial of antidepressants? If ECT is less intrusive and more effective than antidepressants for patients with major depressions, why the delay? Indeed, why has maintenance therapy been used so rarely? Part of the answer to these questions must rest in the psychiatric profession's own ambivalence about ECT, which it has helped to spread to the wider public.

4. *Few other interventions deemed so effective by proponents suffer from so notable a lack of attention in medical school education and residence training as ECT*. No other treatment deemed effective is so much the stepchild in training as ECT, a fact which again reduces its legitimacy among psychiatrists, other physicians, and then by extension, the public. There has been no shortage of complaints by proponents of the hit-or-miss quality of the training, but the situation has not significantly changed. The APA Task Force Report notes: "The body of information about ECT is now so large that a simple apprenticeship is of doubtful value, while thorough training courses tend to be few and far in between."

5. *Few other medical/surgical interventions deemed effective by proponents are so unevenly distributed in their usage among individual practitioners and facilities*, particularly when the equipment and the skills required are not extraordinary as, for example, with transplants. "An overview of psychiatric facilities throughout the country," reports the APA Task Force, "quickly reveals that there are centers where ECT has never been used, institutions where it has been extensively used, and all graduations in between." This uneven distribution, rare among other interventions, is yet another indication of the division of opinion and practice within the profession about ECT.

6. *Unlike other medical equipment, such as x-rays, ECT devices receive very little monitoring*, whether the devices are located in private offices or hospital settings. Regulatory procedures that, for example, cover x-ray machines rarely include ECT machines. The Joint Commission of the Accreditation of Hospitals (JCAH) has begun only now to devote attention to this matter.

7. *In few other major in-hospital interventions is there such a lack of information about the credentials of the users or so few regulations governing access to the equipment as with ECT*. That ECT is a major intervention is apparent. It relies upon general anesthesia and it is so considered by JCAH in its Consolidated Standards Manual, 1985. Indeed, JCAH is beginning to require that ECT, as a special treatment procedure, be made part of the rules and regulations of the medical staff, with a precise delineation of which professionals are going to perform what activities. JCAH officials have the impression (and in the absence of systematic investigation, these impressions must be taken seriously) that many hospitals have made little effort to regulate staff access to ECT; a few have insisted on evidence of special training, but many more make no stipulations. Indeed, JCAH is now (but only now) beginning to define the appropriate criteria, that is, the requisite educational background, training, experience, and peer review mechanisms. Such standards have long been in effect for other interventions (from access in hospitals to chemotherapeutic agents to x-ray machines). It is remarkable that ECT has for so long escaped such oversight.

This lack is all the more glaring given the findings of the survey of ECT use by Pippard and Ellam in Great Britain. They report that usually only a junior doctor is present at ECT treatment sessions (73 percent), a full 41 percent of them have had only minimal training, and supervision is lax. In many hospitals, the typical training to ECT consists of junior doctors showing other junior doctors how to use the controls, and often showing it wrong. "Half of all the clinics claim to provide supervised experience, but this is often very slight. Some hospitals regard 'supervision' as no more than having the new doctor shown how to press the button."

8. *There is a notable lack of information about the physical quality of the settings in which ECT is administered, from the privacy accorded patients to the arrangements for supervision*. Pippard and Ellam found that 27 percent of the ECT centers in Great Britain were "unsatisfactory" and had "very serious shortcomings." There

are no reliable data as to whether conditions in the United States would score higher or lower. Safety procedures, firmly in place in other medical settings (such as staff knowing how to respond to a cardiac arrest), may not be in place for ECT units. These gaps may reflect psychiatry's unfamiliarity with requisite medical/surgical procedures. Whatever the reason, inadequacies here may breed uneasiness both within and outside of the profession about ECT.

9. *Other mechanisms of peer review that are standard in medicine and surgery are lacking in ECT.* One might argue, for example, that overuse of ECT is no more common than overuse of appendectomies. However, there are no committees, such as tissue committees, to superintend the appropriateness of ECT administration. A surgeon who consistently operated without cause for an appendectomy would be brought before such a committee; ECT has no counterpart. Nor does psychiatry employ so basic a review mechanism as morbidity and mortality rounds on ECT. Although absence of these committees is true for psychiatric interventions generally, ECT is a more physical than interactive intervention and, hence, more appropriately the subject of standard medical reviews.

10. *Not many other medical interventions that proponents find efficacious simultaneously are the subject of such intense debate as ECT about proper techniques and dosage.* The current debates about the virtues of unilateral as opposed to bilateral placements of electrodes and the appropriate electrical waves suggest still another source for the controversy that surrounds ECT.

11. *It is difficult to identify other medical/surgical interventions where disagreements are as intense about the appropriate measure of outcome, that is, the criteria by which ECT effectiveness should be judged.* What proponents define as signs of recovery, critics point to as evidence of persistent brain damage. Outcome measures remain a complex problem of psychiatry generally; patients' mental health, well-being, and adjustments are not easy to define. But the problems with ECT are different and productive of still greater controversy. The point is not whether in the case of deep depression a patient's starting to eat is a good thing. (Everyone agrees it is.) Rather, the issue is whether the behavior represents improvement in attitude and functioning or is evidence of organic brain syndrome. Predictably, this type of dispute helps to make the administration of ECT the more controversial.

12. *There are few medical/surgical interventions whose proponents claim efficacy where the data about long-term effects assume so small a part of studies of efficacy. Moreover, few, if any, patient consent documents discuss the matter.* "The most striking finding," report Johnstone et al. from their comparisons of ECT and sham ECT, "is that the differences which were present at the end of the course of eight treatments had disappeared 1 month later and were undetectable also at 6 months." Weiner's recent review article cites this and other studies to the same point; he notes his reservations and then adds: "It is widely acknowledged, however, that a course of ECT produces a remission rather than a cure." That such issues are not raised in consent forms may well foster an attitude of caution and even distrust on the part of patients or observers who uncover such data.

13. *Few other medical/surgical interventions intend to cause a condition (convulsion) that is otherwise deemed a symptom of a disease.* The APA Task Force notes: "In the neurological literature, the negative effects of seizures are emphasized and concern is great to prevent them." Hence, the very nature of the procedure is almost certain to prompt professional and public uneasiness or even hostility.

14. *Although many legislatures have regulated ECT use, their efforts have not been entirely satisfactory.* Winslade et al. report that by 1983, 26 states and several courts, most notably the Federal court in Alabama, had set standards; however, "current regulation tends to have gone too far in the wrong direction [interfering with medical decisionmaking] and not far enough in the right one [protecting patients' legal rights]." State legislatures might have refrained from action—and might in the future alter their approaches—had the profession itself been more diligent in self-regulation. Certainly, it was the dismal conditions in the Alabama state mental hospital that prompted court intervention. Only a few scattered studies analyze the actual impact of state and court intervention. Indications are

that regulations may decrease ECT use, but whether the reduction is appropriate has not been adequately explored.

Policy Implications

Recognizing that many aspects of medical/surgical interventions are carefully regulated by hospital, medical, and governmental bodies, the question becomes whether ECT should remain on the lower end of the spectrum of medical regulation, where it is now, or should be moved to the higher end.

At this higher end, one finds a variety of supervisory practices. (Those who think of medicine as a comparatively unregulated field ignore a lengthy and important list of committees and rules.) They include limiting certain diagnostic or therapeutic interventions to regional centers; hospital or Federal (CDC) screening of credentials of those who would use a given diagnostic or therapeutic mechanism; Federal or state regulation, often delegated to hospital committees, for any diagnostic or therapeutic use of radioactive materials; state regulation of hospital equipment, most notably in the field of radiation safety; periods of delay before a procedure is undertaken to make certain that informed consent is authentic, as with sterilization; institutional review board oversight of human experimentation; the growing popularity of hospital ethics committees to superintend termination of treatment decisions in intensive care units; and FDA regulation of investigational drugs and medical devices.

A final determination of the appropriateness of one or more of these models for ECT must await judgments on efficacy and side effects. But whatever the finding of the consensus panel on the state of the data, the distinctions outlined above between ECT and other medical/surgical interventions clearly require greater regulation than is now standard.

Thus, the consensus panel should at a minimum offer the following recommendations:

- A task force along the lines of the British task force (as reported by Pippard and Ellam) should be created. This task force would:
  - —survey national conditions in ECT units in hospitals and other centers.
  - —survey the credentials and training of ECT users.
  - —survey patients about the quality of the treatment experience, including the consent process, the degree of privacy, aftercare, and supervision.
  - —analyze the impact of the existing regulatory process to learn whether states where regulation is more strict have appropriately or inappropriately experienced changes in ECT use.
  - —evaluate and propose standards on these issues and offer recommendations on the appropriate regulatory framework to enforce them.
- Pending the report of this task force, the consensus panel should recommend that hospitals and centers using ECT immediately establish review committees, modeled on other medical/surgical review committees. These committees would review prospectively the nonemergency use of ECT and retrospectively the emergency use of ECT to ensure that:
  - —patients have given informed consent.
  - —the therapeutic use of ECT is in keeping with the recommendations issued by the consensus panel.
  - —the ECT equipment and physical conditions are satisfactory.
  - —the personnel administering ECT have proper training.

Utilization of ECT in U.S. Psychiatric Facilities, 1975 to 1980

James W. Thompson, M.D., M.P.H.*

Data are reported on the utilization of electroconvulsive therapy (ECT) from surveys of psychiatric facilities conducted by the Nation-

---

*National Institute of Mental Health, Rockville, MD 20857.

al Institute of Mental Health (NIMH) for the years 1975 and 1980. These surveys are designed to give national estimates, using a stratified probability design selected in two stages: 1) facilities, and 2) patient admissions or discharges.

Data on trends in the use of ECT over the study period show that the number of admissions or discharges receiving ECT has decreased overall by 46 percent (from 58,667 to 31,514 cases) between 1975 and 1980, using only the 4 facility types for which data are available for both years. The largest change was in the State hospitals, which decreased ECT utilization by 74 percent during these 5 years. Private general hospitals decreased ECT utilization by 50 percent, and private psychiatric hospitals decreased ECT utilization by 61 percent. The only exception to the overall downward trend was the public general hospitals, which reported an increase in utilization of 58 percent between 1975 and 1980. The type of facility using ECT the most during both 1975 and 1980 was the private general hospital. The inpatient facilities using ECT the least in 1980 were the Veterans Administration (VA) hospitals and State hospitals.

The majority of recipients of ECT in each type of facility in 1975 and 1980 were women. Most ECT was administered to white persons, even when the relative percentages of admissions for white, black, and other persons are controlled for. As a representative example, in private general hospitals in 1970, 90 percent of admissions were white, and 96 percent of ECT was given to white patients.

TABLE 1. Numbers of Admissions or Discharges to Various Facility Types Receiving ECT, 1980 (Weighted Data, NIMH Survey of Psychiatric Facilities).

	1980	
Facility Type	Number*	Percent of Total Admissions
General Hospitals		
Multiservice	1,344	1.3
Private	20,265	4.6
Public	6,181	4.9
Private Psychiatric Hospitals	3,847	2.7
State and County Mental Hospitals	1,221	0.3
VA Hospitals	526	0.3
Totals	33,384	

* Weighted data, NIMH Surveys of Psychiatric Facilities.

Diagnostically, the majority of persons receiving ECT had affective disorders. This was true in all facility types and in all years studied. In addition, it was found that in most facility types an increasing relative proportion of ECT was being given to persons diagnosed as having affective disorders. Only in private general hospitals was this trend reversed. The data showed a trend away from the use of ECT for patients diagnosed as having a schizophrenic (including schizoaffective) disorder in public general hospitals and private psychiatric hospitals.

Patients were also studied with regard to whether they had received any prior care for mental disorders. Only in State hospitals and public general hospitals were persons who received ECT (as compared with those who did not) were more likely to have also received prior care. The percentage of persons receiving ECT who had also received prior care increased between 1975 and 1980.

Comparisons With the Literature

Hedlund et al.[1] studied the State hospital system in Missouri from 1971 to 1975 and found that 9.1 percent of schizophrenics received ECT, a figure much higher than our figures for these facilities (1.2 percent in 1975). In contrast, Weiner and Power studied the VA hospitals in 1977 and found that 0.21 percent of schizophrenic patients received ECT (roughly comparable to NIMH data for VA hospitals in 1980).[2]

The only previous national U.S. study was done in 1976 by the American Psychiatric Association (APA).[3] This study found that 88,604 patients in that year had received ECT as compared with 58,667 in the 1975 NIMH data. Different methodologies were used in these two studies, however. When the assumptions used in the statistical analysis of the APA data are reconsidered, the two figures are largely reconciled.

Babigian and Guttmacher looked at the Monroe County, New York, psychiatric case register from 1961 to 1975 and found that the prevalence of ECT use dropped over that time period.[4] They also found that patients receiving ECT tended to be female, to be over 45 years old, to be from the middle or upper socioeconomic classes, and to have an affective disorder. Over time, they found that more depressives and fewer schizophrenics were being treated with ECT. These findings are generally consistent with the present study.

Mills et al. studied several facility types in Massachusetts from 1974 to 1980.[5] They found a decrease in ECT utilization in all facility types but especially in state hospitals. These findings are similar to the present study except for the variability we found between public and private general hospitals (a distinction not made by Mills).

Similar trends toward decreased utilization of ECT and toward a relative increase in the use of ECT for affective disorders have also generally been shown in international studies, including studies by Smith and Richman in Canada,[6] Pippard and Ellam in Great Britain,[7] and Frederiksen and d'Elia in Sweden.[8]

Summary

Our findings can be summarized as follows:

- The number of persons receiving ECT decreased in most facility types during the 1970's, with the exception of the public general hospital, where its use increased.
- Women received the majority of ECT.
- Minorities received very little ECT.
- Persons with affective disorders and schizophrenia were those most likely to receive ECT, with the trend being toward relatively more use with affective-disordered persons and toward relatively less use with schizophrenic persons.
- Many recipients of ECT had received some prior psychiatric care, and the proportion receiving prior care increased over time.

References

1. Hedlund JL, Barton JL, Evenson RC, et al. Electroconvulsive therapy in Missouri state facilities: 1971–1975. J Oper Psychiatry 1978;9:40–50.
2. Weiner RD, Power DG. The use of ECT within the Veterans Administration hospital system. Compr Psychiatry 1980;21:22–9.
3. Task Force on Electroconvulsive Therapy of the American Psychiatric Association. Electroconvulsive therapy. Washington, DC: American Psychiatric Association, 1978.
4. Babigian HM, Guttmacher LB. Epidemiologic considerations in electroconvulsive therapy. Arch Gen Psychiatry 1984;41:246–53.
5. Mills MJ, Pearsall DT, Yesavage JA, et al. Electroconvulsive therapy in Massachusetts. Am J Psychiatry 1984;141:534–8.
6. Smith WE, Richman A. Electroconvulsive therapy: a Canadian perspective. Can J Psychiatry 29:693–9, 1984.
7. Pippard J, Ellam L. Electroconvulsive treatment in Great Britain. Br J Psychiatry 139:563–8, 1981.
8. Frederiksen S, d'Elia G. Electroconvulsive therapy in Sweden. Br J Psychiatry 134:283–7, 1979.

Efficacy in Depression: Controlled Trials

Sydney Brandon, M.D., F.R.C.Psych.*

Early practitioners who used ECT in psychiatric practice had few doubts regarding its efficacy.[1] By 1937, Kennedy had been able to report a successful outcome in over 70 percent of more than 1,000 patients treated by cardiazol.[2] In the latter 1940's and early 1950's, fears regarding its indiscriminate use and the introduction of alternative treatments were associated with the expression of doubts regarding its efficacy. As a result, a series of clinical trials began to appear from different parts of the world.

In 1948, Huston and Locher published a comparative study using retrospective controls.[3] Kiloh et al. in 1960 published comparisons of ECT, iproniazid, and placebo.[4,5] The major study of Greenblatt et al.[6] published in 1964 become a standard for comparison. Of 352 patients, 192 were diagnosed as endoge-

---

*Leicester Royal Infirmary, Leicester, United Kingdom.

nously depressed, and 60 were classed as neurotic depressives. In endogenous depression, 80 percent of the ECT group as compared with 30 percent of the placebo group made a good recovery, whereas in neurotic depression, the figures were 77 percent in the ECT-treated group and 71 percent in the placebo-treated group.

In Britain, the Medical Research Council trial published in 1965 compared ECT, imipramine, phenalzine, and placebo in hospitalized endogenously depressed patients and demonstrated recovery rates of 84 percent, 72 percent, 38 percent, and 45 percent, respectively.[7]

All of this generation of studies demonstrated the marked superiority of ECT over other forms of treatment in major depression, but none would claim to be free of possible bias because the ECT-treated group was evident to all.

Ulett et al. produced the first acceptably designed trial that compared ECT with convulsive and subconvulsive photic stimulation.[8] Brill and his associates simulated ECT in two groups—one with thiopentone and the other with nitrous oxide.[9] In depressed patients, 87.5 percent of those receiving ECT, 40 percent of the thiopentone group, and 30 percent of the nitrous oxide group showed marked improvement.

In 1959, Sainz found that 9 out of 10 patients given genuine ECT recovered, but only 1 in 10 of those given simulated treatment did so.[10] When the nine failures were given ECT, seven of them recovered.

In 1960, Cronholm and Ottoson used lignocaine to shorten the convulsion in one group,[11] and Harris and Robin reported their first small study.[12] In 1962, Robin and Harris compared 15 ECT-treated patients with 16 who received simulated ECT and imipramine.[13]

In 1963, Fahy et al. compared ECT simulated by Pentothal sleep with six active treatments.[14] Response rates were 35 percent with ECT, 31 percent with imipramine, and 12 percent with thiopentone. The period of observation was limited to 3 weeks, and the imipramine was given by intravenous injection, which may account for the comparatively low response rate and possibly also the equivalence between ECT and imipramine.

Wilson and colleagues compared four groups of nine patients.[15] One group received ECT plus imipramine; another, ECT plus placebo; the third, an anesthetic plus imipramine; and the fourth, anesthetic plus placebo. The improvement scores were, respectively, 15.6, 14.5, 8.4, and 8.9.

In 1966, McDonald compared ECT, amitriptyline, simulated ECT (thiopentone sleep), and placebo tablets and found a maximum improvement score of 2.4 for ECT, 2.2 for amitriptyline, and 1.5 for the control group.[16]

After a lull, a spate of new trials were reported, stimulated partly by the growth of political attempts at control or limitation of treatment and partly unsubstantiated reports of undetected defective ECT machines remaining in use for years.

In 1978, Freeman and his colleagues[17] had difficulty in persuading an ethics committee that placebo-controlled trials could be justified in severe depression. Limited agreement was secured, and patients received either real ECT or simulated ECT for the first two treatments of a course of treatment. The mean subsequent treatments were six in the ECT group and 7.15 in the placebo-initiated group.

In 1978, Lambourn and Gill reported a trial in which 32 cases of depressive psychosis received either modified unilateral ECT or simulated treatment.[18] Assessment at 2 weeks after six treatments showed both groups had a similar outcome. Only 37 percent of each group showed a substantial improvement, and a number of questions are raised by this trial, of which that of Fahy et al. is discordant with other trials.

The Northwick Park Medical Research Council group reported in 1980 a meticulously designed and executed trial.[19] The authors of this trial are less positive than many of their readers in claiming that the results of the trial demonstrate the evident superiority of ECT in the treatment of depression.

West (1981) had no such reservations, for in a placebo-controlled trial, he showed a marked superiority of ECT, and when the placebo group subsequently received ECT, they showed a dramatic improvement.[20] Bagadia and his associates (1983) reported an

Indian simulated controlled trial with a clear superiority for ECT.[21]

The Leicester ECT trial recognized that a substantial proportion of patients were regarded by their psychiatrists as benefiting from ECT as currently administered.[22] Our primary objective was to examine whether that belief was justified and, if so, whether the benefit was dependent on the electrically induced fit. Furthermore, we sought to explore these questions in a real clinical service rather than a research-based population.

All psychiatrists serving a population of 840,000 agreed to participate in notifying the research team of all patients referred for ECT as inpatients. Certain categories of patients who could not fully consent or cooperate were excluded, and 186 patients were assessed of whom 48 did not enter the trial. All patients completing the initial assessment were randomly allocated to real or sham ECT, and elaborate precautions were taken to ensure that the patient, the attending psychiatrist, the nursing staff, and the research team responsible for the assessments were unaware to which group the patient was allocated.

Patients were screened by means of the Present State Examination (PSE). The Catego Diagnosis, which was based on the PSE, identified 95 patients in the classes of major depression; 22 fulfilled the criteria for schizophrenia.

Of the 95 depressed patients, improvement on the Hamilton depressive rating scale was significantly greater in the ECT-treated group than in those in the simulated group at 2 weeks ($p = 0.014$) and 4 weeks ($p = 0.0001$). The differences were most striking in the group with depressive delusions or depressive retardation. A small number of patients diagnosed as "neurotic depression" showed no significant differences between the two groups.

For all depressed patients, no significant differences were identified at 12 and 28 weeks, that is, 8 and 24 weeks after the full range of treatments, including further real ECT. Thus, ECT showed a rapid action and striking superiority over placebo treatment at 2 and 4 weeks, which could not be attributed to factors other than the electrically induced convulsion. It was concluded that further placebo controlled trials of ECT cannot be justified in view of the weight of the evidence demonstrating its efficacy.

In summary:

- Details of these trials will be reviewed and some of the flaws discussed. On balance, one must conclude that ECT is a rapidly efficacious treatment in major depressive disorder and that the evidence suggests that this effect is due to the convulsions.
- The nature of the memory disturbance associated with ECT remains elusive and unexplained.
- The role of ECT in schizophrenia requires clarification, especially so far as catatonic symptoms are concerned. Increasing evidence of long-term adverse effects from medication makes the resolution of this problem more urgent and requires multicenter and possibly cross-national studies.
- The quantity and form of electricity or the nature and duration of the fit may be related to outcome and deserve further study.
- Biological correlates of treatment require further exploration.

References

1. Brandon S. The history of shock treatment. In: Palmer RL, ed. Electroconvulsive therapy: an appraisal. Oxford: Oxford University Press, 1981.
2. Kennedy A. Convulsion therapy in schizophrenia. J Ment Sci 1937; 83:609–29.
3. Huston PE, Locher LM. Manic-depressive psychosis: course when treated and untreated with electric shock. Arch Neurol Psychiatry 1948; 60:37–48.
4. Kiloh LG, Child JP, Latner G. A controlled trial of 1960; iproniazid in the treatment of endogenous depression. J Ment Sci 1960; 106:1139–44.
5. Kiloh LG, Child JP, Latner G. Endogenous depression treated with iproniazid—a follow up study. J Ment Sci 1960; 106:1425–8.
6. Greenblatt M, Grosser GH, Wechster H. Differential response of hospitalized depressed patients to somatic therapy. Am J Psychiatry 1964; 120:935–43.
7. Medical Research Council, Clinical Psychiatry Committee. Clinical trial of the treatment of depressive illness. Br Med J 1965; 1:881–6.
8. Ulett GA, Smith K, Gleser GC. Evaluation of convulsive and subconvulsive shock therapies utilizing

a control group. Am J Psychiatry 1956; 112:795–802.
9. Brill NQ, Crumpton E, Eiduson S, Grayson HM, Gellman LI, Richards RA. Relative effectiveness of various components of electroconvulsive therapy. Arch Neurol Psychiatry 1959; 81:627–35.
10. Sainz A. Clarification of the action of successful treatment in the depressions. Dis Nerv Syst 1959; 20(suppl):53–7.
11. Cronholm B, Ottoson J-O. Experimental studies of the therapeutic action of electroconvulsive therapy in endogenous depression. Acta Psychiatr Scand 1960; 35(suppl 145):69–101.
12. Harris JA, Robin AA. A controlled trial of phenalzine in depressive reactions. J Ment Sci 1960;106:1432–7.
13. Robin AA, Harris JA. A controlled comparison of imipramine and electroplexy. J Ment Sci 1962;106:217–9.
14. Fahy P, Imlah N, Harrington J. A controlled comparison of electroconvulsive therapy, imipramine and thiopentone sleep in depression. J Neuropsychiatry 1963; 4:310–14.
15. Wilson IC, Vernon JT, Guin T, Sandifer MG. A controlled study of treatments of depression. J Neuropsychiatry 1963; 4:331–7.
16. McDonald IM, Perkins M, Marjerrison G, Podilsky M. A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression. Am J Psychiatry 1966; 112:1427–31.
17. Freeman CPL, Basson JV, Crighton A. Double-blind controlled trial of electroconvulsive therapy (ECT) and simulated ECT in depressive illness. Lancet 1978; i:738–40.
18. Lambourn J, Gill D. A controlled comparison of simulated and real ECT. Br J Psychiatry 1978; 133:514–9.
19. Johnstone EC, Deakin JFW, Lawler P, Frith CD, Stevens M, McPherson K, Crow TJ. The Northwick Park electroconvulsive therapy trial. Lancet 1980; ii:1317–20.
20. West ED. Electroconvulsive therapy in depression: a double-blind controlled trial. Br Med J 1981; 282:355–7.
21. Bagandia VN, Abhyankar RR, Doshi J, Pradhan PV, Shah LP. Report from a WHO Collaborative Centre for Psychopharmacology in India. II. Reevaluation of ECT in depression. Psychopharmacol Bull 1983; 19:556–60.
22. Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S. Electroconvulsive therapy: results in depressive illness from the Leicestershire trial. Br Med J 1984; 288:22–5.

Efficacy in Depression: ECT Versus Antidepressants

Jan Fawcett, M.D., and William Scheftner, M.D.[1]

This presentation will address two major questions under consideration by the conference:

- Question 1—What is the evidence that ECT is effective for patients with specific mental disorders (in this case depression)?
- Question 2—What factors should be considered by the physician and patient in determining if and when ECT would be an appropriate treatment?

Our conclusions are based on a review of the literature relating to question 1 (Table 1). Table 1 illustrates that ECT has been found to be superior to simulated or placebo treatment and in comparison with tricyclic antidepressant medications, monoamine oxidase inhibitors, and neuroleptic drugs in the short term. Our review leads us to believe that the superiority of ECT over simulated treatment is not so certain with long-term cross-sectional followup and that there are really no convincing data to demonstrate whether the long-term effect of ECT compares favorably with maintenance treatment with antidepressant drugs. Based on our understanding of the literature, long-term longitudinal controlled followup studies are necessary to establish whether ECT has a significant long-term therapeutic effect. Another area that could benefit from followup studies would be a comparison of the outcome of ECT followed by maintenance therapy with tricyclic antidepressant medications or lithium carbonate against placebo in a double-blind design to test whether these medications may enhance long-term therapeutic effects following ECT therapy. In general, the literature addressing the efficacy of ECT suf-

---

[1] Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612.

TABLE 1. Efficacy of ECT in Depressive Disorders.

Comparison	Short-Term (3 to 4 weeks) Superiority	Long-Term Effect
Simulated	+	±
Tricyclics	+	No Data
Monoamine Oxidase Inhibitors	+	No Data
Neuroleptics	+	No Data

+ Indicates yes.
± Indicates questionable.

fers from noncomparability across studies because of the different methods used to assign and to administer treatment. A recent study by Janicak et al. reviewing the majority of comparative treatment studies has demonstrated the clear superiority of ECT over other forms of treatment for severe depression utilizing the Mantel-Haenszel method for the combination of fourfold tables.

Table 2 addresses question 3 and shows the therapeutic superiority of ECT as compared with tricyclic antidepressants at 3 to 4 weeks for depressions diagnosed as "manic depressive," "involutional," and "delusional" at the time the studies were done. Studies with patients diagnosed as "reactive" or "neurotic" tended to reveal no superiority of ECT over other treatments. Literature supporting the superiority of ECT over tricyclic antidepressant therapies in elderly and medically ill patients was found in our review. An effect of ECT in reducing the risk of suicide in both short-term and long-term followup versus tricyclic antidepressant therapy was evident from our review. The literature seems to rather strongly support the finding that ECT is often effective in patients who fail to respond to tricyclic antidepressant therapy at least in the short term. A number of studies indicated a more rapid onset of short-term response to ECT than was noted with other antidepressant drug therapies, a finding that may soon find application with the advent of the application of diagnostic related groups (DRGs) to reimbursement for inpatient hospital treatment by Medicare and possibly other third-party payers. Again, we find a lack of data to assess comparisons in long-term outcome between ECT and other antidepressant treatments or of adequate longitudinal studies of the risk of relapse after ECT. Studies of short- and long-term outcome of ECT versus high-dose monoamine oxidase inhibitor therapy in nonpsychotic depressions are also lacking. Our presentation will review these conclusions and the studies underlying them to assess the robustness of the conclusions as well as their implications. Areas where data are critically needed to evaluate the efficacy of ECT as compared with other treatments will be considered.

TABLE 2. Clinical Indications for ECT Versus Therapy With Tricyclic Antidepressants.

	Short-Term	Long-Term
Manic Depressive	+	No Data
Involutional	+	No Data
Delusional	++	No Data
Reactive-Neurotic	±	No Data
Elderly	+	No Data
Suicide	+	+
Rapid Response	++	No Data
Medically Ill (Anecdotal)	+	No Data
Tricyclic Nonresponders	++	No Data

+ Indicates superior to other treatment.
± Indicates not superior to other treatment.
+ + Indicates strong superiority to other treatment.

Efficacy of ECT in Schizophrenia, Mania, and Other Disorders

Joyce G. Small, M.D.*

Schizophrenia

Although severe depression is the primary indication for ECT, such treatment also has a place in the management of some other psychiatric disorders. ECT has been consigned to a secondary role in the treatment of schizophrenia since the introduction of chlorpromazine in 1954. However, it continues to

---

*Larue D. Carter Memorial Hospital, Indianapolis, IN 46202.

be clinically useful, particularly in patients who fail to respond to neuroleptic medications because of lack of effectiveness and/or toxicity, in patients with coexisting medical problems precluding the use of neuroleptics, and in individuals with prominent affective or catatonic symptoms. In general, the therapeutic benefit of ECT in schizophrenia is inversely proportional to the duration of the illness and commensurate with acuteness of onset and intensity of affective symptoms. However, evaluations of the efficacy of ECT in schizophrenia cannot be separated from issues of diagnosis. Many of the best results of the earlier studies probably occurred in patients who would now be classified as manic, depressive, or schizoaffective.

Prospective randomized controlled trials comparing real and simulated ECT showed no essential differences in chronically ill schizophrenic populations. Taylor's and Fleminger's 1980 study of a middle prognostic group on maintenance neuroleptics found that patients improved more with real ECT than with sham ECT, but group differences persisted only for 12 weeks.[1] Studies comparing ECT and neuroleptics in schizophrenic patients have shown that both treatments are effective with advantages for one or the other in different trials. A landmark study by May in 1968 demonstrated that treatment with neuroleptics was more effective than ECT, psychotherapy, or milieu therapies.[2] ECT alone had intermediate effects between neuroleptics and control treatments with better results in males than females. Two- to five-year followup established that neuroleptics and ECT were equivalent and better than nonsomatic therapies in terms of less time spent in the hospital.[3] There have been three controlled trials of ECT in combination with neuroleptics compared with drug treatment alone, all of which showed that both methods of treatment were safe and effective and that the neuroleptic/ECT combinations were superior to neuroleptics alone. Prospective and retrospective investigations have shown that unilateral and bilateral ECT are equivalent in the treatment of schizophrenia, but greater numbers of seizures are required for clinical improvement than in depression.

It can be concluded that neuroleptics are the first line of defense in the treatment of schizophrenia. ECT alone is probably less effective than drug therapy but when combined with neuroleptics provides greater therapeutic effectiveness than either treatment alone. However, the advantages may be outweighed by the difficulties with patient and family acceptance. Although ECT is frequently advocated for treatment of patients with schizophreniform psychoses, schizoaffective disorders, and catatonia, prospective studies in these areas have not been accomplished. Recognition of long-term risks with both neuroleptics and ECT requires further study of short- and long-range risk-to-benefit ratios.

Mania

Task force reports and surveys of practicing psychiatrists indicate that mania is the third most commonly listed indication for ECT. In the predrug era, some psychiatrists judged ECT to be as effective for the treatment of mania as it was for depression, whereas others considered it less so, requiring more seizures or daily or multiple daily ECT to produce remission. There was also controversy about whether ECT-treated manics were more vulnerable to relapse or early recurrence. Retrospective studies comparing ECT with neuroleptics, with lithium, and with no definitive treatment showed that all of the somatic therapies were superior to no treatment, with minimal differences between ECT and drug management.

A recent prospective controlled trial compared ECT and lithium treatment of hospitalized manic patients.[4] In both groups, lithium was withdrawn for 10 to 14 days before initiation of treatment. Neuroleptics were given as needed for the management of severe psychotic manifestations and dangerous behavior as well as to facilitate compliance. Following clinical, EEG, and neuropsychological evaluations, patients were randomly assigned to treatment with lithium or with ECT. At first, unilateral nondominant ECT was given, but this was changed to bilateral after no therapeutic benefit resulted with the former. The ECT patients received an average of 10.6 treatments, after which they were placed on lithium maintenance treatment. Analysis of the clinical rating scale data showed numerous significant group differences in the first 8 weeks of treatment, all of which favored ECT. Use of neuroleptic medications and the incidence and timing of relapses and recurrences were similar for the two treatments. It can be concluded that ECT followed by lithium maintenance is a viable alternative in the management of manic states with some short-term therapeutic advantages. It is particularly indicated when patients do not respond to lithium or other drug treatment or when life is threatened by dangerous behavior or exhaustion. Future prospective studies are necessary to corroborate these findings, including the observation that unilateral ECT is ineffective in the treatment of mania. Other research is needed to compare ECT, lithium, carbamazepine, neuroleptics, and combination therapies in the acute and maintenance treatment of manic disorders.

Other Conditions

Other indications for ECT include the "psychotic disorders not elsewhere classified" listed in DSM-III. Patients presenting with mixed syndromes with features of affective, schizophrenic, and/or confusional symptoms frequently respond well to ECT, although prospective scientific studies are lacking. Cycloid psychosis, postpartum psychosis, and late paraphrenia are specific examples. ECT is also considered effective by some clinicians in delirium and may be indicated in patients exhibiting severe agitation, confusion, perceptual disturbances, delusions, and threatening behavior requiring rapid control in situations in which psychotropic drugs may be contraindicated because of underlying medical disorders. ECT is reported to produce rapid symptom relief without exacerbating most systemic disorders. Controlled trials of ECT's effectiveness in these situations are not likely to be forthcoming because of constraints regarding informed consent, protocol selection requirements, etc.

ECT has also been recommended as a safe approach in the treatment of psychotic, manic, and/or depressive symptoms complicating the management of systemic illnesses such as parkinsonism, lupus erythmatosus, and numerous other disease states. ECT can be given with close observation and multisystem monitoring with much less risk and more rapid therapeutic effectiveness than can be achieved with drug treatment. ECT is associated with little risk in patients with cardiac and circulatory disease except in situations such as acute myocardial infarction, aortic and cerebral arterial aneurysms, and increased intracranial pressure where elevations in blood pressure must be avoided. Pregnancy and the puerperium are situations in which ECT is generally safe, while drug treatment is relatively contraindicated because of risk of fetal damage from placental transfer of drugs or their secretion in breast milk.

There is no scientific evidence supporting the use of ECT in other psychiatric disorders unless coexisting with syndromes of depression, schizophrenia, mania, or delirium. Reports of favorable results in anorexia nervosa, obsessive-compulsive disorder, hypochondriacal disorders, and neuroses have appeared in the literature, but results are inconsistent, and scientific data in these areas are unavailable. Mostly negative results have been obtained with ECT for personality problems, conduct disorders, and sexual deviation. The use of ECT as a form of restraint for control of behavior outside of the context of the syndromes described poses serious ethical problems and should not be condoned.

References

1. Taylor P., Fleminger JJ. ECT for schizophrenia. Lancet 1980;i:1380–3.
2. May PRA. Treatment of Schizophrenia. A Comparative Study of Five Treatment Methods. New York: Science House Publishers, 1968.
3. May PRA, et al. Schizophrenia—a followup study of results of treatment. Arch Gen Psychiatry 1976;33:481–6.
4. Small JG, et al. ECT in the treatment of manic episodes. Ann NY Acad Sci (in press).

ECT: Possible Mechanisms of Action

Bernard Lerer, M.D.[1]

The underlying mechanism of action of convulsive therapy has been a focus of interest since Meduna (1935) originated the therapeutic use of chemically induced seizures. Cerletti and Bini (1938), who pioneered the therapeutic use of electrically induced seizures, suggested that "the electricity itself is of little importance. . . . The important and fundamental factor is the epileptic-like seizure, no matter how it is obtained." Most researchers since Meduna and Cerletti have been guided by the same basic assumption. It is supported by the fact that seizures induced by nonelectrical means (e.g., flurothyl, pentylenetetrazol) have been effectively used for the treatment of depression. Recent controlled trials, all but one of which showed superior efficacy for real ECT over simulated ECT, further support the antidepressant role of the seizure itself and relegate to secondary importance the means by which it is induced.

Psychological Mechanisms

Most recent theories of ECT action have focused on possible biological mechanisms. Metapsychological explanation lost considerable ground with the observation that anesthetic and muscle-relaxant modified ECT were as effective as the unmodified treatment. Psychological theories have been further weakened by the demonstration of superior efficacy for real versus simulated ECT. Theories linking the amnestic effects of ECT to its antidepressant efficacy have been considerably weakened by the absence of any correlation between memory impairment and therapeutic improvement and by technical advances in electrode placement and stimulus parameters that have reduced amnestic but not antidepressant effects.

Neurophysiological Mechanisms

Biologic theories of ECT action are as numerous as the measurable physiological sequelae of the treatment. It should be stressed, however, that the association of a treatment intervention with a particular physiological consequence does not necessarily establish that consequence as a mechanism of therapeutic action. Nevertheless, a significant body of data has accumulated regarding the effects of ECT on neurophysiological parameters such as the permeability of the blood-brain barrier, regional cerebral blood flow, cerebromicrocirculation, neurometabolic activity, and brain electrical activity. Further studies are needed to expand possible mechanistic implications of these ECT effects.

An intriguing research direction links ECT effects on cerebral laterality to alterations in seizure threshold and length during the course of treatment, suggesting that regional neurometabolic suppression may underlie the therapeutic effects of the treatment. The reported mood stabilizing effects of anticonvulsant agents such as carbamazepine are an important practical correlate of this theoretical approach. Recent technological advances in brain imaging techniques reflecting neurometabolic activity will be a critical factor in the further development of these theories.

Neuroendocrine Mechanisms

Neuroendocrine effects of ECT have been most commonly used in the context of research strategies designed to test biochemical theories of ECT action. However, depression itself is associated with significant abnormalities of the hypothalamic pituitary axis, and many of these abnormalities are corrected by ECT. This fact strongly suggests that neuroendocrine mechanisms be directly considered as an explanation of the antidepressant action of the treatment. Release of hypothalamic peptides by the treatment could alter mood and cognition while reversing the vegetative abnormalities associated with the depressive state. Further research aimed at establishing which peptides are involved in this process and at testing the direct effect of such substances on the depressive state is clearly indicated.

---

[1] Jerusalem Mental Health Center, Givat Shaul, Jerusalem, Israel.

Neurochemical Mechanisms

The major emphasis of most recent research on ECT mechanisms has been on the effects of the treatment on brain neurotransmitter and receptor systems. During the past two decades, the most prominent theories of affective disorder have focused on putative abnormalities in these systems, particularly brain amines. Currently accepted explanations of the mechanism of action of both tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) relate to the effects of chronic administration of these agents on brain amines and their pre- and postsynaptic receptors. The demonstration that a particular mechanism is common to both ECT and the chemical antidepressants would lend substantial support to the putative antidepressant role of such a biochemical effect. This presentation will therefore focus on neurotransmitter and receptor effects of ECT, primarily those derived from studies on the effects of electroconvulsive shock (ECS) in laboratory animals.

The critical importance of studies demonstrating that ECS effects in healthy animals are also present in depressed humans will be stressed, and the available data will be reviewed. Important differences between the therapeutic spectra of antidepressants and ECT (which also has antimanic and generally antipsychotic properties) must be taken into account in interpreting these findings.

Noradrenergic (NA) Systems: Repeated ECS in rodents has been shown to enhance NA turnover, reduce NA uptake, and activate tyrosine hydroxylase, the rate-limiting enzyme in NA synthesis. Behavioral and biochemical strategies have demonstrated subsensitivity of presynaptic alpha-2 adrenergic receptors, which subserve NA release, although direct release studies have yielded inconclusive results. These findings are compatible with enhanced presynaptic availability of NA following ECT and thus parallel TCA and MAOI effects. TCA, MAOI, and ECS have all been shown, following chronic administration, to reduce radioligand-measured postsynaptic beta-adrenergic receptor number and beta-receptor linked adenylate cyclase activity in the cerebral cortex. It remains to be clarified what overall functional result this series of effects has on NA neurotransmission and to what extent seminal NA theories of the pathogenesis of depression will need to be modified in accordance. Studies in humans, particularly those pertaining to peripheral changes in catecholamine levels and functional effects on heart rate, provide support for amine release by ECT. However, neuroendocrine strategies that directly evaluate beta-adrenergic receptor function have not been available. Ongoing studies of ECT effects on adrenergic receptors on peripheral blood elements may provide important parallels between receptor effects in humans and those clearly demonstrated in rodent brain.

Serotonergic Systems: Chronic ECS does not substantially alter brain turnover of serotonin but may reduce serotonin uptake. Significant effects on brain serotonin receptors of the $5HT_2$ subtype have recently been demonstrated. Functional, behavioral, and radioligand binding techniques have all shown enhanced $5HT_2$ receptor sensitivity following ECS. Because a substantial body of evidence has linked depression to reduced brain serotonergic activity, the possible mechanistic relevance of this effect is evident. TCA effects on the $5HT_2$ receptor subtype, however, do not consistently parallel ECS effects, and this discrepancy remains to be explained. Further important advances have stressed possible modulatory interrelationships between serotonergic and adrenergic systems and represent a critical area for further study. Human studies utilizing serotonergic control of prolactin release as a challenge strategy have recently yielded important findings showing enhancement by TCA of serotonergic sensitivity in depressed patients. Extension of these studies to encompass ECT effects is an important step, as are studies of ECT effects on serotonin receptors in peripheral blood elements.

Dopaminergic Systems: Although less closely linked to the putative chemical pathogenesis of depression, brain DA systems are significantly affected by repeated ECS. The finding that repeated ECS enhances the functional sensitivity of striatal DA receptors, although not demonstrable by radioligand binding techiques, has had an important clinical correlate in the treatment of Parkinson's disease. Early open studies suggest a beneficial effect of ECT in patients previously unresponsive to L-dopa, which may derive from enhanced DA receptor sensitivity. Human studies utilizing growth hormone released by DA agonists as a measure of DA receptor sensitivity have yielded mixed results. However, other potential biochemical and psychophysiological strategies remain to be explored.

Cholinergic Systems: Because brain cholinergic function has been linked to both mood regulation and memory function, the potential implications of ECT effects on central cholinergic systems are considerable. Chronic ECS has been reported to reduce cortical muscarinic receptor number as measured by radioligand binding, and on the background of theories linking depression to cholinergic supersensitivity, this effect may be relevant to the antidepressant action of ECT. Alternatively, reduced cholinergic neurotransmission following ECT may underlie the amnestic effects of the treatment. Potential human strategies for investigating the cholinergic effects of ECT have hardly been explored with the exception of EEG studies and early CSF work whose findings are broadly compatible with animal receptor data.

GABA Systems: ECS has significant effects on brain GABA systems, with increased GABA concentrations and inhibition of GABA synthesis reported. GABA and benzodiazepine receptor binding are reported as unchanged. GABAergic effects of ECT may be related to the alteration in seizure threshold seen with repeated ECT. Altered GABA function may also play a role in ECT effects on brain NA and serotonin.

Endogenous Opioids: ECS has been shown to induce a spectrum of opiate-like responses in rats that are attenuated by pretreatment with an opiate antagonist. Chronic ECS sensitizes rats to opioid effects and enhances opioid receptor binding. These findings suggest activation of endogenous opioid systems by ECS and are supported by human studies showing increased plasma beta-endorphin levels following ECT. If putative antidepressant effects of opioids are confirmed, an antidepressant mechanism of ECT via endogenous opioid systems would be plausible.

Conclusions

It is clear that a wealth of data are available on the effects of ECT on neurochemical and other parameters, particularly on the basis of animal ECS studies. Such studies are likely to generate further data as newer techniques in neurophysiology, neurochemistry, and neuropharmacology are applied to ECT mechanisms. Human studies seeking support for a relationship between ECS effects in animals and the clinical efficacy of the treatment have been fewer and have thus far yielded inconclusive results, although many approaches remain to be explored. Taken together—the data already reported and the data likely to be generated if potentially promising strategies are applied—these data suggest that the mechanism of action of ECT may be far more amenable to understanding than may at first seem apparent. A close interaction between basic and clinically oriented researchers holds the key to designing studies that can answer critical questions rather than simply generating more data.

Sources

Fink M, Ottosson J-O. A theory of convulsive therapy in endogenous depression: significance of hypothalamic functions. Psychiatry Res 1980;2:49–61.

Grahame-Smith DG, Green AR, Costain DW. Mechanism of the antidepressant action of electroconvulsive therapy. Lancet 1978;i:245–56.

Lerer B. Studies on the role of brain cholinergic systems in therapeutic mechanisms and adverse effects of ECT and lithium. Biol Psychiatry 1985;20:20–40.

Lerer B, Sitaram N. Clinical strategies for evaluating ECT mechanisms: pharmacological, biochemical and psychophysiological approaches. Prog Neuropsychopharmacol Biol Psychiatry 1983;7:309–33.

Lerer B, Weiner RD, Belmaker RH (eds). ECT: basic mechanisms. London: John Libbey, 1984.

Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR. Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. Biol Psychiatry (in press).

Systemic Effects of ECT

Trevor R.P. Price, M.D.*

Modified ECT

Modified ECT, which employs short-acting barbiturate general anesthesia, succinylcholine for muscle relaxation, and assisted ventilation with 100 percent oxygen, is now and has been for the past three decades the standard form of electroconvulsive therapy in this country. It is a very safe treatment modality with low rates of morbidity and mortality.

These rates are reported to be one-third of those reported with unmodified ECT, which was the standard form of electroconvulsive treatment prior to the 1950's. Despite the higher frequency of systemic complications with unmodified ECT as compared with modified ECT, both patient acceptance and therapeutic benefit have been reported to be equivalent.[1]

Immediate Posttreatment Symptoms

A number of subjective symptoms and side effects occur very frequently and clear rapidly after ECT, whether modified or unmodified (although more often after the latter), including transient confusion and memory disturbance, headache, nausea, and muscle discomfort.

Nonetheless, most patients tolerate ECT well, indicate that they find it no more noxious than a visit to the dentist, and indicate that they would not be reluctant to have it again should it be indicated in the future.[2]

ECT-Related Morbidity and Complications

Recent studies[3,4] have reported that significant medical complications with modified ECT occur in 1 out of every 1,300 to 2,200 individual treatments (a rate of 0.073 percent to 0.045 percent) and in 1 out of every 200 to 300 patients treated (a rate of 0.46 percent to 0.29 percent).

The most common complications are transient, typically benign arrhythmias in 10 to 40 percent of patients, the type, frequency, and severity of which depend to an important extent on the kind of general anesthetic used for modification[5] and whether the patient has preexisting heart disease and transient, usually clinically insignificant blood pressure changes. More serious but fortunately much less frequent complications include serious cardiovascular complications (such as coronary insufficiency, myocardial infarctions, and congestive heart failure), aspiration, musculoskeletal injuries, prolonged seizures, laryngospasm, prolonged apnea, skin burns, damaged dentition, and oral lacerations. As previously noted, these occur in only 0.4 percent of all patients treated.

In the era of unmodified ECT, up to 40 percent of patients suffered musculoskeletal complications, most frequently vertebral compression fractures.[5] These are largely of historical interest today because the routine use of short-acting barbiturate general anesthesia and succinylcholine has virtually eliminated their occurrence.

ECT-Related Mortality

Recent reports[4,6] on mortality with modified ECT have reported rates of 2.9 deaths per 10,000 patients treated, or 0.03 percent per patient treated, and 4.5 deaths per 100,000 treatments administered, or 0.0045 percent per treatment administered.

To put these mortality rates into a meaningful context, they should be compared with the mortality rates associated with the administration of short-acting barbiturate general anesthesia alone, which range from 3.3 to 37 deaths per 100,000 inductions, or from 0.0033 percent to 0.037 percent.[7]

Various studies have reported the cause in the majority (55 to 67 percent) of ECT-related deaths to be cardiovascular,[6,8] with ventricular arrhythmias, cardiac arrests, and myocardial infarctions being most frequent. Pulmonary causes account for 31 percent, cerebrovascular accidents for 6 percent, and other miscellaneous causes for the remaining 8 percent.[8]

---

*University of Pennsylvania Hospitals, Philadelphia, PA 19104.

ECT-Related Endocrine Effects

ECT causes a wide variety of other physiological, endocrine, and neurochemical changes, which at the present time appear to have greater relevance in relation to its therapeutic efficacy than to the occurrence of clinically significant complications or side effects. A notable exception may be the effect of ECT on diabetes mellitus, which may have considerable relevance to clinical management. However, the current data are inconsistent as to whether ECT is diabetogenic or diabetolytic. Additional research to clarify this clinically important question is clearly needed.

Conclusion

When used in appropriately selected patients with proper modification techniques, ECT is an efficacious, medically safe, and well-tolerated psychiatric treatment modality. In healthy young adults, it has a very low rate of medical morbidity and a mortality rate that is on the same order of magnitude as that of short-acting barbiturate general anesthesia alone.

Even in the elderly and in patients with known cardiovascular disease, where the morbidity and mortality risks are likely to be somewhat greater, both the literature and clinical experience indicate that the risk-benefit ratio with ECT is generally favorable. This is especially true when it is compared with the use of psychotropic medications or no treatment at all.[9] With proper pretreatment selection and evaluation, use of appropriate modification techniques, and careful clinical management and monitoring during treatment, ECT is both safe and effective, even in such relatively high-risk patients as the elderly and those individuals with known cardiovascular disease.

References

1. Fink M. Risks of convulsive therapy, Chap. 4. Convulsive Therapy: Theory and Practice. New York: Raven Press, 1979.
2. Freeman CPL, Kendell RE. ECT: I. Patients' experiences and attitudes. Br J Psychiatry 1980; 137:8–16.
3. Frederiksen S-O, D'Elia G. Electroconvulsive therapy in Sweden. Br J Psychiatry 1979; 134:283–7.
4. Heshe J, Roeder E. Electroconvulsive therapy in Denmark. Br J Psychiatry 1976; 128:241–5.
5. Pitts FN Jr. Medical physiology of ECT, Chap. 4. In: Abrams R, Essman WB, eds. Electroconvulsive Therapy: Biological Foundations and Clinical Applications. New York: Spectrum Publications, 1982.
6. American Psychiatric Association. Electroconvulsive therapy. Task Force Report 14. Washington, DC: American Psychiatric Association, 1978.
7. Fink M. Risk-benefit analysis, Chap. 5. Convulsive Therapy: Theory and Practice. New York: Raven Press, 1979.
8. Maclay WS. Death due to treatment. Proc R Soc Med 1953; 46:13–20.
9. Avery D, Winokur G. Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. Arch Gen Psychiatry 1976; 33:1029–37.

Neuropathology and Cognitive Dysfunction From ECT

Peter R. Breggin, M.D.*

ECT always produces some degree of immediate brain damage and mental dysfunction, and frequently the patient never fully recovers. Permanent brain damage from ECT is demonstrated through clinical evaluations, psychological tests, EEG studies, CAT scans, human autopsy studies, and research on the effect of electrical current on the brain as well as through a variety of animal studies.

In every routine course of ECT, its devastating impact is displayed in the production of an organic brain syndrome, with severe symptoms of trauma to the brain.[1-3] In its most mild form, the organic brain syndrome takes the form of an amnestic syndrome with loss of both recent and more remote memories. Typically, "apathy, lack of initiative, and emotional blandness are common," and the emotions are "shallow."[4] More commonly, the organic brain syndrome becomes much more severe and takes the form of delirium[4] with global disruption of all mental function, including intellect, judgment, emotional sta-

---

*Center for the Study of Psychiatry, Bethesda, MD 20814.

bility, memory, and orientation to time, place, and person. Severe delirium is not uncommon in routine ECT.[1]

The brain-damaged patient tends to confabulate—to deny any mental impairment, even when it is grossly apparent to the observer.[4] This denial of impairment by many ECT patients in the face of obvious mental dysfunction unhappily lends credence to false claims that the treatment is harmless.

Because ECT always produces an organic brain syndrome, the question is not "Does ECT cause brain damage and dysfunction?" ECT always produces brain damage and dysfunction. The proper question is "How complete is recovery from this trauma?" To assume it is routinely complete after electrically induced delirium defies common sense and general medical knowledge. Among body organs, the brain is especially ill-equipped to recover from damage.

During the phase of the acute organic brain syndrome, the impaired condition of the brain is routinely reflected in a disturbed EEG pattern similar to severe chronic epilepsy, toxic states, and other serious brain diseases.[5,6]

Often this brain wave impairment becomes long lasting and even permanent.[6,7] Shrinkage of the brain may be apparent on CAT scans.[3,8,9]

Neuropathologically, the permanent damage can be visualized in human autopsies after modified ECT.[10-13] Reports show diffuse small hemorrhages throughout the brain, glial proliferation (scarring), and cell death. Extremely careful animal studies have shown similar findings.[3,8,14-17]

The worst damage results from the passage of current through the brain and has been directly visualized in animals receiving modified ECT and demonstrated by angiography. Even a very weak current of electricity passing down the blood vessels severely constricts them, cutting off the supply of nutrients and oxygen to the surrounding brain cells, eventually causing vessel wall deterioration, hemorrhage, and cell death. Advocates of ECT, such as Meldrum (1985),[18] must claim that ECT-induced convulsions are theoretically less harmful than spontaneous seizures in epilepsy; these conclusions overlook the damaging effects of the electrical current. ECT combines the brain damage caused by epilepsy with the brain damage caused by electrical trauma.

Cognitively, ECT treatment always produces some degree of permanent memory loss for events surrounding the treatment and frequently produces permanent memory loss reaching back months and years into the past.[3,19] Many cases involve losses that prohibit a return to normal activities in the home or at work. Indeed, there are repeated warnings in the literature against giving ECT to individuals who earn their living through mentally taxing work.[20] ECT can also produce ongoing problems with learning and memorizing new material, with the tragic result that the patient feels permanently defective and disabled. I have described several such desperate cases,[3,8] and many similar reports continue to flow into the Center for the Study of Psychiatry each week.

Tests that examine the most relevant function—the patient's actual memory for past events—always show serious and lasting losses following ECT. [19,21-24] Similarly, when patients are questioned years after ECT, more than 50 percent typically respond with reports of chronic memory difficulties, which they attribute to ECT (Squire, 1982, reports 58 percent; Freeman and Kendall, 1980, report 64 percent).[25,26]

Patient self-reports of permanent loss are so frequent that promoters of ECT have tried to argue that the patients have "subjective" memory losses without real or objective losses.[27] But as we have seen, patients with memory defects from brain damage of any kind tend to confabulate and deny—that is, to minimize rather than to exaggerate their defects.[4]

Squire's personally originated tests using recall for TV shows failed to show large memory losses.[28,29] But these tests are wholly of his own invention and have never been proved useful in detecting brain damage. In recent years, Squire has placed more emphasis on patient self-reports and on tests that measure the actual loss of personal memories,[24,25] both of which indicate permanent memory loss following ECT.

The modern defense of electroshock often rests on the assertion that "recent" modifications of the treatment have ameliorated its damaging effects. But the most important modification of ECT—the use of anesthetics, muscle paralyzing agents, and artificial respiration with oxygen—is not new at all. As early as 1957 there were multiple reports in the literature of brain death from modified ECT.[10] I myself administered modified ECT more than 20 years ago! The bad reputation that ECT has among many professionals and many patients, and much of the scientific data indicting ECT as a dangerous therapy, stems from more than 30 years of experience with modified ECT.

Modified ECT of necessity tends to be more damaging than the older methods. The anesthesia used in modified ECT is a sedative that suppresses the ability of the brain to have a seizure. Therefore, higher doses of offending electricity must be used in modified ECT to force a seizure from the patient's brain.[3]

Nondominant or unilateral ECT offers us no hope for a safer ECT. The fact that nondominant ECT does not so heavily affect the verbal centers on the left side of the brain makes it more difficult to measure its damaging effects; but this is merely because most of our tests are aimed at verbal memory loss. The nondominant side of the brain deals more with visual memory, musical memory, intuition, integration of knowledge, and creativity. Tests of visual memory find damage following nondominant ECT.[24]

To assume that any innovations have ameliorated the hazards of ECT remains irresponsible speculation until backed by multiple animal autopsy studies. It is in keeping with traditional medical ethics to ask the profession to ban ECT until animal studies have been conducted to test the unproven and unlikely hypothesis that the newer methods of ECT are relatively harmless.

ECT can never be made harmless. First, enough damage must be done to elicit the convulsion. Second, the damage itself produces the emotional changes—apathy and indifference, and sometimes euphoria—that are labeled an "improvement." Therefore, a relatively inoffensive ECT would be a relatively ineffective ECT.[3,8,30-32] This is consistent with Weiner et al.'s observation that the most "benign" methods of ECT may be "relatively ineffective from a therapeutic standpoint."[33] Thus, the innovations remain unpopular.

The idea that electroshock works by damaging the brain is not unprecedented in psychiatry. Before psychiatry became public–image conscious, it was commonly claimed that ECT works by damaging the brain and mind and even by killing brain cells.[34-36]

Electroshock victims can best describe the damaging effects of the treatment, and two cases will be described in the patients' own words to illustrate their anguished outcomes.

Informed consent is at the heart of the matter; the potential patient has a right to know about the controversial and dangerous nature of ECT. Kaplan and Sadock, authors of the widely read textbook of psychiatry, recently observed, "ECT remains one of the most controversial methods of treatment in psychiatry."[37] The patient has a right to be informed of this!

References

1. Daniel WF, Crovitz HF. Disorientation during electroconvulsive therapy: technical, theoretical, and neuropsychological issues. Presented at the International Conference on ECT: Clinical and Basic Research Issues, New York City, January 16–18, 1985.
2. Brengelman JC. The effect of repeated electroshock on learning in depressives. Berlin: Springer, 1959.
3. Breggin PR. Electroshock: its brain-disabling effects. New York: Springer, 1979.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association, 1980.
5. Weiner RD, Rogers HJ, Davidson JRT, Kahn EM. Effects of ECT on brain electrical activity. Presented at the International Conference on ECT: Clinical and Basic Research Issues, New York City, January 16–18, 1985.
6. Mosovitch A, Katzenelbogen S. Electroshock therapy: clinical and electroencephalographic studies. J Nerv Ment Dis 1948;107:517–30.
7. Volavka J, Feldstein S, Abrams R, et al. EEG and clinical changes after bilateral and unilateral electroconvulsive therapy. Electroencephalogr Clin Neurophysiol 1972;32:631–69.
8. Breggin PR. Disabling the brain with electroshock. In: Dongier M, Wittkower E, eds. Divergent views in psychiatry. Hagerstown: Harper and Row, 1981.

9. Calloway SP, Dolan R, Jacoby R, Levy R. ECT and cerebral atrophy: a computed tomography study. Acta Psychiatr Scand 1981;64:442–5.
10. Impastato D. Prevention of fatalities in electroshock therapy. Dis Nerv Syst 1957;18(sec 2):34–75.
11. Grabner HK, McHugh RB. Regressive electroshock therapy in schizophrenia, a controlled study (preliminary report). Lancet 1960;80:24–7.
12. McKegney FP, Panzetta AF. An unusual fatal outcome of electroconvulsive therapy. Am J Psychiatry 1963;120:398–400.
13. Erwin CW, Thompson EM. ECT in schizophrenia: a study in nosological imprecision. In: Brady J, Brodie H, eds. Controversy in psychiatry. Philadelphia: W.B. Saunders, 1978.
14. Hartelius H. Cerebral changes following electrically induced convulsions. Acta Psychiatr Neurol Scand 1952;77(suppl):1–128.
15. Ferraro A, Roizen L. Cerebral morphologic changes in monkeys subjected to a large number of electrically induced convulsions. Am J Psychiatry 1949;106:278–84.
16. Ferraro A, Roizen L. Helford M. Morphological changes in the brain of monkeys following electrically induced convulsions. J Neuropathol Exp Neurol 1946;5:285–308.
17. Friedberg J. Shock treatment, brain damage, and memory loss: a neurological perspective. Am J Psychiatry 1977;134:1010–4.
18. Meldrum BS. Neuropathological consequences of chemically and electrically induced seizures. Presented at the International Conference on ECT: Clinical and Basic Research Issues, New York City, January 16–18, 1985.
19. Janis IL, Astrachan M. The effect of convulsive treatments on memory efficiency. J Abnorm Psychol 1951;46:501–11.
20. Valentine M, Keddie HMG, Dunne D. A comparison of techniques in electroconvulsive therapy. Br J Psychiatry 1968;114:988–96.
21. Brunschwig L, Strain J, Bidder TG. Issues in the assessment of post-ECT memory changes. Br J Psychiatry 1971;119:73–4.
22. Daniel WF, Crovitz HF, Weiner RD, Rogers HF. The effects of ECT modifications on autobiographical and verbal memory. Biol Psychiatry 1982;17:919–24.
23. Taylor JR, Tomplins R, Demers R, Anderson D. Electroconvulsive therapy and memory dysfunction: is there evidence for prolonged defects? Biol Psychiatry 1982;17:1169–83.
24. Squire LR. Memory functions as affected by ECT. Presented at the International Conference on ECT: Clinical and Basic Research Issues, New York City, January 16–18, 1985.
25. Squire LR. Memory and electroconvulsive therapy (letter). Am J Psychiatry 1982;139:1221.
26. Freeman CPL, Kendall RE. ECT: I. Patients' experiences and attitudes. Br J Psychiatry 1980;137:8–16.
27. American Psychiatric Association. Task force on electroconvulsive therapy. Washington, DC: American Psychiatric Association, 1978.
28. Squire LR, Chace PM. Memory functions six to nine months after electroconvulsive therapy. Arch Gen Psychiatry 1975;32:1557–64.
29. Squire LR. A stable impairment in remote memory following electroconvulsive therapy. Neuropsychologia 1975;13:51–8.
30. Breggin PR. Psychiatric drugs: Hazards to the Brain. New York: Springer, 1983.
31. Breggin PR. Iatrogenic helplessness in authoritarian psychiatry. In: Morgan R, ed. The iatrogenics handbook. Toronto: IPI Publishing, 1983. Reprinted in Morgan R (ed). Electric Shock. Toronto: IPI Publishing, 1985.
32. Breggin PR. Electroshock therapy and brain damage: the acute organic brain syndrome as treatment. Behavioral and Brain Sciences 1984;7:24–5.
33. Weiner RD, Rogers HJ, Davidson JRT, Squire LR. Effects of stimulus parameters on cognitive side effects. Presented at the International Conference on ECT: Clinical and Basic Research Issues, New York City, January 16–18, 1985.
34. Hoch P. Discussion and concluding remarks. J Pers 1948;17:48–51.
35. Freeman W. Brain damaging therapeutics (editorial). Dis Nerv Syst 1941;2:83.
36. Wilcox PH. Brain facilitation not destruction the aim of electroshock therapy. Dis Nerv Syst 1946;7:201–7.
37. Kaplan HI, Sadock BJ. Modern Synopsis of Comprehensive Textbook of Psychiatry, III. 3rd ed. Baltimore: Williams & Wilkins, 1981.

Quantitative Neuropathology in Electrically Induced Generalized Convulsions

Agnete M. Dam, M.D., Ph.D.[1]

Background

The potential benefits of ECT, as in any treatment, will be weighed against the possi-

---

[1] University Hospital Hvidovre, Virum, Denmark.

ble risks. Brain-disabling side effects of a widespread and permanent basis have been claimed to occur. Previous experimental studies of seizures elicited by extracranial electrical stimulation have shown the occurrence of so-called "after-discharge" in the nerve cells resembling epileptic activity. Many kinds of damage to the brain have been described in experimental animals, including edema (water collection between the cells), gliosis (reaction of the supporting cells around the nerve cells), and even small bleedings in the brain tissue with loss of nerve cells. The damage has especially been found in the area underlying the electrodes. Several authors, especially Hartelius (1952), have claimed that many of these changes are due to the intensity and duration of the current and the size of the electrodes.

Hartelius himself, in a meticulously prepared study of electrically induced seizures in cats, found only slight changes, which were mostly reversible, but he described a greater variation in the animals that had seizures compared with the controls with regard to stain affinity. He stated that the irreversibility of the phenomena was debatable. Changes in the brain proteins and cell diameters have later been described in experimental studies by others, but none have described reduction in cell number.

It is important to stress that the methodology in neuropathology is very sensitive. The removal of the brain, which is soft as butter, is difficult without damaging the brain tissue and the vessels. This may result in artifacts of which one has to be aware. The brain cells die in relation to the death of the man or animal. This process starts within hours but can be delayed when the brain is cooled—a method that is applied in human pathology.

It is not possible to investigate the brain without fixation. In man, the brain has to be placed in the fixative, carefully suspended, whereas immediate fixation (by perfusion) should be used in the experimental animals. This method was not available when Hartelius made his study.

Next, the fixative is important. Fixation can be performed with different fixatives, of which formaldehyde is the most commonly used. The fixation, however, will result in a volume reduction of approximately 35 percent to which is further added a volume reduction of 15 percent because of the staining procedure. Nerve cells and other constituents of brain tissue cannot be visualized in light microscopes without stain. The above-mentioned precautions should be applied to avoid artifacts of which the so-called dark neurons (nerve cells that have attracted too much stain) are of great importance. The changes Hartelius described as possibly irreversible were similar to dark neurons.

The point is, How can we measure irreversible damage to the brain? Nerve cell death is the final and surely irreversible sign of damage to the brain. We are in fact losing up to 20 percent of our nerve cells during our lifetime without specific brain disorders; this occurs at an accelerated rate with increasing age. This does not automatically imply a marked reduction of brain function.

The nerve cells function by impulses going from one cell to another. The function will be disturbed by a number of factors. A great number of changes occur in the brain, especially in relation to ischemia (reduced blood circulation) and decrease of energy substance (i.e., glucose). Many of these changes are reversible, but if they persist for a longer time, loss of nerve cells and gliosis may be the result. Although these changes are irreversible, they should be evaluated carefully as there are, as mentioned, many possibilities of misinterpretation. Gliosis is not necessarily a sign of neuron loss. There is a great intra- and interindividual difference in neuron density—neuron loss has to be evaluated carefully when no severe lesion is present. This is not possible just by looking in a microscope. Quantitation of the neurons is necessary. It is a time-consuming method, but until now, no better method has been reached, although computer investigations with so-called classimat has been tried for this evaluation for more than 10 years. The difference between nerve cells and some supporting cells is too small, and so the evaluation is not valid.

The final problem, mentioned earlier, is that the great inter- and intraindividual variation makes it necessary to perform all of the investigations in controls, and everything has to be performed in a sufficient number of cases for statistical evaluation. Case reports are not enough to state a correlation between a method applied and changes observed.

ECT is based on the induction of generalized convulsions. Experimental convulsions elicited by either electrical stimulation or various drugs have been performed in epilepsy research for more than 40 years. The difference between epileptic convulsions and induced electroconvulsive seizures has to be noticed. The injection of epileptogenic substances results in recurrent spontaneous epileptic seizures, a characteristic feature of epilepsy. Electrically elicited generalized convulsions, except in exceptional cases, do not result in epilepsy and have mostly been used in the study of the ictal phase of epilepsy.

It has long been known that permanent changes take place in the brains of patients with epilepsy. The hippocampus in the temporal lobes, part of the limbic system, is most often involved. The pathology described ranges from total neuron loss in some part of the neuronal band to slight changes in the glial cells only. These findings are not comparable. Neuron loss, the inevitable sign of permanent brain damage, can and will be measured. The same has its effect with regard to loss of Purkinje cells in the cerebellum, which is the second place for damage in relation to epilepsy in man.

In a quantitative study of different types of epilepsy, I found a specific pattern of neuron loss in the hippocampus. It was not confined to just one area—Sommer's sector—as previously described, and the neuron loss was not especially related to temporal lobe epilepsy, as previously emphasized, but was related to many generalized convulsions. The relationship between seizures and neuron loss was in accordance with other studies that have claimed that seizures with their concomitant physiological changes are responsible for neuron loss.

Experiments

Two experimental studies were performed in brains from patients with epilepsy following these findings. The first one is of particular interest in relation to the question of possible lasting side effects of ECT. The other is mentioned in this context as a comparison to demonstrate the probable dangers of epileptic seizure activity per se.

In the first investigation, eight adult Wistar strain rats were exposed to electroconvulsive seizures through gel-soaked electrodes placed in their earholes. An alternating current of 50 nA, 50 Hz was applied for 0.9 seconds, which invariably evoked tonic-clonic convulsions that lasted approximately 50 seconds. Seizures were evoked three times daily over 50 days. The animals were sacrificed either 2 or 12 weeks after the seizure period. The neurons were counted in different subfields of the hippocampus and in the cerebellum; the counting method was similar to the one used in the studies of patients with epilepsy.

The results showed no decrease in neuron density in any of the groups of experimental animals compared with controls. A slight change in the behavior of the animals was observed as increased tension and aggression were registered after 5 to 10 seizures. A temporary increase in the body weight was found at the end of the trial. In summary, no neuron loss was disclosed in the hippocampus or cerebellum after 140 electroconvulsive seizures (i.e., approximately 3 hours of seizure time) in rats. These seizures are thought to be comparable with the seizures elicited in ECT.

The second study concerns Mongolian gerbils, which have the specific trait of having seizures when handled. The seizures comprise arrest of movement in the mildest cases and can be graded according to increased intensity ending with clonic-tonic convulsions leading to death. Each animal exhibits a stable seizure pattern. Different seizure groups and controls were studied with the quantitative method, as described in relation to the rats.

Although the gerbils had few seizures compared with the rats, neuron loss was found in the hippocampus in the animals that had convulsions and in cerebellum in all the experimental animals. The area affected in the hippocampus was not the same as that always damaged by ischemia.

Hypothesis

The hypothesis emerging from this study was that the seizure activity, present in the hippocampus of animals with spontaneous convulsions, also interictally, led to exhaustion and death of the neurons. With regard to the Purkinje cells in the cerebellum, their inhibitory action is known, and the increased demand for inhibition in relation to even small seizures could be the explanation of the loss observed.

This possible mechanism of neuronal death underlies the difference between epilepsy and ECT, also with regard to permanent brain damage.

Sources

Chapman G. In: Meldrum BS, Pedley TA, eds. Recent Advances in Epilepsy. New York: Churchill Livingstone, 1983.

Hartelius H. Cerebral changes following electrically induced convulsions: an experimental study on cats. Acta Psychiatr Neurol Scand 1952;suppl 77.

Mouritzen Dam A. Hippocampal neuron loss in epilepsy and after experimental seizures. Acta Neurol Scand 1982;66(6):601–42.

Weiner RD. Does electroconvulsive therapy cause brain damage? Behav Brain Sci 1984;7:1–22.

Acute Cognitive Side Effects of ECT

Harold A. Sackeim, Ph.D.[1]

Immediately following an ECT treatment and often lasting for a week following the ECT course, patients display a variety of cognitive side effects. The acute and subacute side effects are the most intense manifestations of the impact of ECT on cognition. The fact that ECT can produce a transient organic brain syndrome of variable duration is often a source of distress for patients and their families, can create clinical management difficulties, and may contribute to the view that the effects of ECT are brain disabling. In this presentation, we will examine the nature and timing of the acute cognitive effects of ECT and pay particular attention to the factors that can moderate their intensity and/or longevity.

Standard ECT procedures, as a consequence of general anesthesia, muscle relaxation, and the elicitation of generalized seizures, result inevitably in loss of consciousness and of spontaneous respiration. After the seizure, there is rapid return of these functions. The ECT-induced seizure, like spontaneous generalized seizures in epileptics and most acute brain injury and head trauma, results in a variable period of disorientation. Patients may not know their names, their ages, etc. When the disorientation is prolonged, it is generally referred to as an organic brain syndrome.

The duration of the period of disorientation following ECT appears to be exquisitely sensitive to treatment parameters, including the modality or electrode placement (unilateral versus bilateral), dosage of electrical stimulation and/or stimulus waveform (type of electrical stimulus used), cumulative treatment number, and temporal spacing of treatments.

In contrasting bilateral versus unilateral right electrode placements, investigators have uniformly reported that bilateral ECT results in a more prolonged disorientation. In our own trial, we have assessed orientation recovery at every treatment in 49 depressed patients randomly assigned to bilateral and unilateral right ECT. We used a low-dosage titration procedure to adjust for each patient the intensity of constant-current brief-pulse stimulation to just about seizure threshold. Various components of orientation recovery and estimates of overall time to achieve full orientation were three times more rapid in the unilateral right than bilateral ECT group. The prolongation of disorientation with bilateral ECT is attributable at least in part to greater electrical stimulation of the left hemisphere. Investigators who contrasted unilateral left and unilateral right electrode placements have found longer periods to recovery with the former modality.

It is a common statement in the field that the period of disorientation becomes pro-

---

[1] New York State Psychiatric Institute, New York, NY 10032.

gressively longer as more treatments are administered and as the treatments are more closely spaced. The period of disorientation may become so prolonged that patients are still disoriented prior to the next treatment and, at times, the treatment course may be temporarily interrupted to allow clearing of the organic brain syndrome. In our trial, using a low-dosage method and an electrically efficient stimulus waveform, we failed to observe cumulative deterioration. On the average, the bilateral ECT group oriented as quickly at the end of the ECT course as at their first two treatments. The unilateral right ECT group showed significant progressive improvement in orientation recovery, with shorter times at the end than at the beginning of the course. No patient in either group failed to meet orientation criteria prior to a treatment. Likewise, in no instance did treatment have to be interrupted because of development of an organic brain syndrome.

These findings illustrate that the type and dosage of ECT stimulation can radically alter effects on orientation processes. In the study conducted at Duke by Weiner and colleagues, it has been reported that orientation recovery on the average takes several hours in patients receiving either bilateral or unilateral sine wave stimulation. In contrast, in our study at the end of the ECT course, right unilateral patients averaged 3.99 minutes to orient following eyes opening, and bilateral patients averaged approximately 25 minutes. These findings, along with the efficacy data in these patients, indicate that the development of a prolonged organic brain syndrome is not a necessary part of the therapeutic process. There was no association between orientation recovery measures and therapeutic response.

With the recovery of orientation during the acute postictal period, patients manifest a variety of neuropsychological deficits. Retrograde memory, usually operationalized as memory for information presented just prior to the treatment, and anterograde memory, usually operationalized as memory for information presented following seizure elicitation, are often grossly disturbed. Immediate postictal deficits have been reported for other aspects of memory functioning, particularly semantic memory. More broadly, there has been relatively little investigation of possible acute postictal effects of ECT on aspects of perceptual-cognitive functioning other than memory. Nonetheless, there is evidence that ECT may temporarily disrupt basic attentional processes and may alter perceptual thresholds and sensory processing.

The cognitive deficits induced by ECT are typically most intensive during the acute postictal period (i.e., minutes to hours following seizure elicitation). Repeated testing at time points farther removed from the seizure has demonstrated rapid recovery of function. However, with traditional forms of ECT administration, given at standard intervals of twice or three times a week, recovery from memory deficits is often incomplete by the time of the next treatment. This results in characteristic cumulative deterioration in memory performance with acute repeat postictal testing over the course of treatment. The progressive cumulative decline is one of the most reliable phenomena in ECT. We identified 16 studies that examined this issue, and 13 demonstrated cumulative deterioration. Particularly with bilateral electrode placement and verbal memory tasks, a pattern of progressive deficit in postictal testing has become expected.

While the depth or intensity of postictal deficits may be related to stimulus dosage and/or waveform, number of previous treatments, and spacing of treatments, the particular areas of deficit are a function in part of electrode placement. Both anterograde memory and retrograde memory for verbal material are more disrupted by bilateral than right unilateral ECT. This underscores the fact that while generalized seizures are elicited with unilateral placements, marked asymmetries may be observed in acute postictal neuropsychological or neurophysiological measures. The pattern of effects for nonverbal information processing is less clear. Some investigators have claimed that bilateral ECT results across the board in more profound deficits. However, testing for nonverbal memory deficits has rarely used a retrograde testing format or stimuli resistant to verbal encoding.

In our study, patients were administered an 11-task neuropsychological battery at every treatment session after meeting criteria for recovery of orientation. Standard differences were obtained between bilateral and right unilateral ECT on verbal memory processes. With respect to nonverbal memory, more intense deficits were found with bilateral ECT in retrograde memory for nonsense shapes, but equivalent deficits were found between bilateral and right unilateral ECT for retrograde and anterograde neutral face recognition. This suggests that the effects of the two modalities on nonverbal information processing may be a function of the specific type of processing examined. More critically, in none of the measures in the battery was a pattern of significant cumulative deterioration obtained, despite using a wide variety of tasks designed to be sensitive to postictal deficits and testing at more treatment sessions than had been done previously. At the end of the treatment course, patients evidenced the same degree of impairment as at the beginning of the course. This suggests that, as with orientation recovery, ECT electrical dosage and/or waveform can substantially alter the intensity of postictal memory deficits.

As noted, there is rapid recovery of function from acute postictal deficits. Further, it appears that as time from the last ECT increases, the specificity of effects related to stimulus parameters and electrode placement diminishes. In the subacute period, extending from 12 hours to 7 days following the ECT course, a variety of patterns may emerge. In virtually all studies contrasting intelligence scores pre- and posttreatment, typically no change or a small increase in IQ has been observed. Frequently, scores on tasks involving nonverbal information processing are improved posttreatment relative to pretreatment. This has been interpreted as indicating that relief from depression is associated with enhanced right hemisphere processing capabilities.

Two areas in particular stand out as revealing deficits a week following the ECT course. The retrograde amnesia extends to personal and impersonal events that occurred prior to the start of the treatment course. This amnesia appears to be temporally graded in that it is most dense for events closest in time to ECT and diminishes as events become more remote. The second area of deficit pertains to anterograde memory. We have corroborated with the low-dosage technique the classic finding that the capacity to acquire new information, that is, immediate memory, is essentially unchanged by ECT. In contrast, the capacity to retain this information over a delay, that is, anterograde delayed memory, is diminished during the week following the treatment course. ECT induces a relatively pure retention deficit. Whether the extent of the subacute retrograde amnesia and the anterograde retention deficit can be moderated by manipulation of the ECT technique is presently unknown.

The Question of Long-Term Effects

Larry R. Squire, Ph.D.*

Memory impairment is a weighty issue because it is central to all discussions of long-term adverse effects of ECT. A considerable amount of experimental work has addressed the question of how severe these effects are and how long they last.[1-5]

Anterograde Amnesia

The anterograde amnesia associated with ECT diminishes between treatments and cumulates across treatments. Once the course of ECT is completed, the capacity for new learning begins to recover. The point at which new learning ability reaches normal levels is difficult to identify exactly, and estimates will vary depending on the sensitivity of the test used to assess memory. One reviewer, considering a large number of studies, found an average return to baseline functions after 72 days.[6] There are two ways to

---

*University of California at San Diego, La Jolla, CA 92093.

determine baseline. One way is to obtain pre-ECT performance scores. These scores, however, might have been lowered by the depressive illness for which ECT was prescribed, and followup scores might therefore have to exceed this baseline by some unknown amount before they can be called normal. Another way to estimate baseline functions is to compare patients who have received ECT with other similar patients who have not received ECT.

In the past several years, studies have used both of these methods.[6,7] Testing instruments have included sensitive delayed recall tests, whereby subjects are asked to produce without the help of cues information that had been presented to them up to 2 weeks earlier. One test asked subjects to recall information that had been presented to them incidentally 2 weeks earlier and that they had not been told would be later tested.[7] The results from these studies have been generally consistent. Anterograde amnesia following bilateral ECT seems to recover by 6 months after treatment. Most studies find normal performance at this time. A minority of studies have found persisting effects at several weeks after treatment, but testing was not conducted at later times.[8,9] Presumably, once treatment is completed, recovery occurs gradually in a negatively accelerated fashion over a period of many weeks.

Retrograde Amnesia

Remote memory for events that occurred before ECT can be evaluated either by tests that ask questions about public events, which are verifiable because the events were in the news, or by tests that ask about past autobiographical events. When given multiple-choice methods about past one-season television programs or sensitive recall methods that asked for details about the programs, patients receiving bilateral ECT initially exhibited a temporally limited gradient of retrograde amnesia. That is, shortly after the fifth treatment, memory was lost for programs that had appeared 1 to 3 years previously but was unaffected for programs that had appeared longer ago. This impairment gradually subsided during the weeks after treatment and was not detectable 6 months later.[10]

In a study of autobiographical memory,[10] both the patients prescribed bilateral ECT and control patients reported a large number of autobiographical details on their first testing session (about 58 details for each ECT patient and 62 details for each control patient). Following ECT, there was a sharp reduction in the number of facts that could be recalled. At the followup period 7 months later, the ECT and control patients once again performed similarly. Thus, when all 10 questions were considered together, there was no indication for a persisting deficit in remote memory.

However, a persisting impairment was present nonetheless, and this became apparent when the results were tallied separately for 3 of the 10 questions that asked about relatively recent events. One of them, a question about the details surrounding admission to the hospital, concerned an event that had occurred 11 days before treatment; another question concerned an event that had occurred 6 to 37 months before ECT; and a third question concerned an event that had occurred 14 to 19 months before ECT. The great majority of the persistent memory loss applied to the most recent event (i.e., the question about hospital admission). Further work is needed to identify the sensitive time period from which permanent memory loss can occur.[11]

Memory Complaints

Many patients who have received ECT continue to report even several months after treatment that their memory is not as good as it used to be, and they attribute their memory problem to the ECT experience.[12,13] When these reports of poor memory were evaluated with a self-rating scale, two important points emerged.[12] First, memory functions were rated considerably better 6 months after bilateral ECT than 1 week after treatment. In this respect, the reports were veridical, because it is known that memory functions do improve during this interval. Second, the quality of the memory complaints 7 months after ECT suggested that the patients may have persisted in interpreting their memory abilities just as they had experienced them shortly after ECT. That is, there could have been continuing doubts that memory had fully recovered and a tendency to refer even normal failures of memory to the ECT. A similar conclusion was suggested in a study in which patients who complained of memory problems 9 months to 30 years after ECT were given a battery of memory tests.[14] These patients performed poorly on three tests out of the battery. However, the patients had been selected by their answer to a newspaper advertisement seeking persons who felt they had been adversely affected by ECT. The significance of the positive findings is difficult to determine ambiguously. It is also possible that persisting memory complaints refer, at least in part, to the lacuna in memory that exists for the time period immediately around the treatment. As patients recover from anterograde amnesia, they do not recover the memory for events that occurred during the period of anterograde amnesia. In addition, persisting memory loss does occur for events that immediately precede the treatment course.[15]

The difference between bilateral and unilateral ECT, consistently found in formal tests of anterograde and retrograde amnesia, is also reflected in the self-ratings. In contrast to patients prescribed bilateral ECT, who report markedly reduced memory functions 1 week after treatment, patients prescribed unilateral ECT do not report that memory is more impaired after treatment than before.[15] However, a study involving randomized assignment to ECT and non-ECT groups where the role of preexisting group differences could be controlled would be required to settle this issue.

The effects of ECT on memory functions can be summarized in the following way. Patients who receive unilateral or bilateral ECT have impaired memory. Eventually, and certainly by 6 months after treatment, they perform as well on new learning tests and on remote memory tests as they performed before treatment and as well as other patients who have not received ECT. However, information acquired during the days and weeks prior to and following ECT may be permanently lost. Bilateral ECT affects memory considerably more than right unilateral ECT, and this difference is reflected as well in patients' own reports of their memory functions.

It is not known whether a similar or different story must be told for patients who have received large numbers of ECT (e.g., more than 50). In addition, it is not known whether the persisting report of memory difficulty after ECT refers entirely to problems in remembering events that occurred close to the time of treatment. The perception of memory difficulty could in part refer to a subtle compromise of memory functions, but one that would show up only on a test instrument more sensitive than any yet devised. Alternatively, a sense of continuing memory problems might occur because persons who have made a gradual recovery from amnesia tend to doubt that they are fully recovered. We all occasionally have faulty memories. How can we know when memory failures are normal and when they might be attributable to a previous course of ECT? It is not known to what extent persons in this circumstance could be helped by continued consultation or reality testing after ECT or whether such a perception would be so resistant to change that it must be considered an important cost of ECT. These and other questions remain, but science can address them all.

References

1. Price TRP. Short- and long-term cognitive effects of ECT: 1—effects on memory. Psychopharmacol Bull 1982;18:81–91.
2. Squire LR. Neuropsychological effects of ECT. In: Essman WB, Abrams R, eds. Electroconvulsive therapy. Jamaica: Spectrum Publications, Inc., 1982:169–86.
3. Squire LR. ECT and memory dysfunction. In: Lerer B, Weiner RD, Belmaker RH, eds. Basic Mechanisms of ECT. London: John Libby and Co., Ltd., 1984:156–63.
4. Taylor JR, Tompkins R, Demers R, Anderson D. Electroconvulsive therapy and memory dysfunction: is there evidence for prolonged defects? Biol Psychiatry 1982;17:1169–93.
5. Weiner RD. Does electroconvulsive therapy cause brain damage? Behav Brain Sci 1984;7:1–22.
6. Weeks D, Freeman DPL, Kendell RE. ECT III: enduring cognitive deficits? Br J Psychiatry 1980;137:26–37.
7. Squire LR, Chace PM. Memory functions six to nine months after electroconvulsive therapy. Arch Gen Psychiatry 1975;32:1557–64.

8. Halliday AM, Davison K, Browne MW, Kreeger LC. A comparison of the effects on depression and memory of bilateral ECT and unilateral ECT to the dominant and non-dominant hemisphere. Br J Psychiatry 1968;114:997–1012.
9. Cronin D, Bodley P, Potts L, Mather MD, Gardner RK, Tobin JC. Unilateral and bilateral ECT: a study of memory disturbance and relief from depression. J Neurol Neurosurg Psychiatry 1970;33: 705–13.
10. Squire LR, Slater PC, Miller PL. Retrograde amnesia and bilateral electroconvulsive therapy: long-term follow-up. Arch Gen Psychiatry 1981;38:89–95.
11. Weiner RD, Rogers HJ, Davison JRT, Squire LR. Effects of stimulus parameters on cognitive side effects. In: Malitz S, Sackeim H, eds. Conference on ECT: Clinical and Basic Issues. New York: New York Academy of Sciences (in press).
12. Squire LR, Wetzel CD, Slater PC. Memory complaint after electroconvulsive therapy: assessment with a new self-rating instrument. Biol Psychiatry 1979;14:791–801.
13. Freeman CPL, Kendell RE. ECT: I. Patients' experiences and attitudes. Br J Psychiatry 1980;137:8–16.
14. Freeman DPL, Weeks D, Kendell RE. ECT: II. Patients who complain. Br J Psychiatry 1980;137:17–25.
15. Squire LR, Slater PC. Electroconvulsive therapy and complaints of memory dysfunction: a prospective three-year follow-up study. Br J Psychiatry 1983;142:1–8.

Patients' Attitudes Toward ECT

Christopher Freeman, M.B., Ch.B., M.R.C.Psych., M.Phil.[*]

Introduction

Relatively little systematic work has been carried out in this area. There are three main sources of information: Anecdotal reports of patients and relatives who feel that ECT has been harmful, frightening, or dangerous; anecdotal reports from patients or their relatives who state that ECT has been helpful and had positive effects; and systematic inquiries that have asked patients, lay people, and relatives about their views of ECT. This paper will concentrate mainly on the third category, and the six studies that have looked at this area will be reviewed.

Anecdotal Reports

It is quite clear that negative anecdotal reports markedly outnumber positive ones. It is not true to say, as some critics of ECT state, that there are no published reports in the literature from patients who have had ECT and feel it has been helpful. I will mention only two here. The clearest account was published by Gray (1983) in the *British Journal of Psychiatry.*[1] Gray is a research neuroscientist in his fifties who had a long episode of severe endogenous depression treated with mianserin, lithium carbonate, diazepam, and subsequently electroconvulsive therapy. In his paper, he describes the different therapies he was given. In addition to the physical treatments mentioned above, he had psychotherapy, cognitive therapy, and occupational therapy. He found ECT helpful, painless, and at times even pleasant, although he did find the first treatment frightening and felt that a full explanation could have been given to him and perhaps a more powerful anxiolytic before the first treatment. I mention this account in some detail because Gray does not universally praise psychiatry; in fact, he is very critical about the counter-therapeutic effects of psychotherapy and occupational therapy. A similar rational and reasoned account is given by Sutherland in his book *Breakdown.*[2] Sutherland was a psychology professor who developed a psychiatric illness.

There are a large number of anecdotal reports about the negative effects of ECT, and many of these have been collected in Frank's book *The History of Shock Treatment.*[3] Modified ECT is grouped with unmodified ECT and insulin coma in an uncritical way as if all shock therapies are equivalent. It is also clear that many of these critical accounts of ECT are written by individuals who are critical of the whole of psychiatry and of the concept of

---

[*] Royal Edinburgh Hospital, University of Edinburgh, Edinburgh, Scotland.

psychiatric illness. The only large inquiry that has been carried out in this area is by my colleagues and me.[4] We advertised in a local paper asking people who felt they had been damaged by ECT to come forward. We also questioned all psychiatrists in the Lothian area and asked them to tell us of patients who felt they had been harmed by the treatment. Our total sample was 126. No one felt that they had been seriously brain damaged by ECT. By far the commonest complaint was of memory impairment that had not been completely resolved. This memory impairment was mild but irritating and intrusive for the patients. Much of it may have been because of continuing depressive symptoms, anxiety, alcohol intake, and drug use, but we had to conclude that we could not account for all of the apparent memory impairment in this way. There were occasional complaints of personality change, change in visual acuity, and weakness. Although this was a highly self-selected group of complainers, the most impressive thing about the individuals in this study was the reasoned and undemonstrative way they presented their complaints. They came forward seeking help and reassurance and were pleased that psychometric testing showed them to have only slight deficits. The complaints of such individuals must be taken seriously. Whether ECT does very rarely cause slight memory impairment is debatable, but there is no doubt that there are patients who have had ECT, who have memory impairment, and who make a causal connection between the two.

Systematic Studies

The first population study that looked at patients' attitudes in a systematic way was Hillard and Folger (1977).[5] They compared two wards of separate mental hospitals in North Carolina. Ward A was a high user of ECT and ward B a low user. Thirty-two subjects were interviewed in ward A and 21 in ward B. Unfortunately, the results are presented in a confusing way, and no raw scores are given. It is therefore difficult to ascertain what proportion of subjects found ECT helpful, frightening, or harmful. Their conclusions were that the patients who were treated on ward A (the high user of ECT) felt that ECT worked better and had fewer side effects. Patients on ward B felt that ECT was a more extreme measure and used for patients who showed more severe disturbance.

An interesting finding was that 90 percent of all patients mentioned other patients as their primary source of information about the treatment and that 100 percent said that other patients were an important source.

Our study consisted of interviewing all patients under the age of 70 who were given ECT in the Royal Edinburgh Hospital in 1 year.[6] Subjects were interviewed approximately 1 year after their last course of ECT using a semistructured interview. The response rate was 89 percent.

Seventy-eight percent of the subjects thought that ECT had helped them either a little or a lot. Only one person thought that ECT had made him much worse. Sixty-five percent of the people said they were willing to have treatment again. Some had been clearly put off by the side effects. Patients did not find the treatment particularly frightening or distressing. Sixteen percent said they were very anxious or frightened before the first treatment. The most common fear was of possible brain damage, but even then 77 percent of patients said they had not thought about this at all. Fifty percent of subjects felt that a trip to the dentist was more upsetting or frightening than an ECT treatment.

Side effects were troublesome, with 74 percent reporting some sort of memory disturbance and 50 percent saying this was the most troublesome side effect. Twenty-eight percent felt that ECT had caused permanent changes to their memory. The most worrysome finding concerned patients' lack of understanding of the treatment and their believing that they had not been given adequate explanation. Forty-nine percent were sure they had been given no explanation at all and struck to this view even when it was suggested to them that they might have forgotten. We did not find a very high rate of false or bizarre ideas of what the treatment involved, but we judged that only 22.9 percent had a full understanding that the treatment involved a period of unconsciousness, an electric shock, and a convulsion. We were concerned about the use of consent forms. Although 76 percent of the patients had signed a consent form themselves, many could not remember having done so, did not regard it as particularly important, and seemed quite happy to have other people, such as relatives, give consent on their behalf. We were left with a clear impression that British patients would agree to almost anything a doctor suggested.

In general, we concluded that the experience that most patients had of ECT was a positive and beneficial one, although side effects were troublesome and fuller explanations needed to be given about the treatment, both before and after it was carried out.

Hughes and colleagues (1980)[7] used our questionnaire and gave it to a sample of 72 consecutive ECT patients in Southampton, which is at the other end of the British Isles. Their results were very similar; 83 percent considered they had been improved as a result of the treatment, and 81 percent said they would have it again. Most found the experience neutral or pleasant, and 54 percent thought the dentist more distressing. Hughes and colleagues came to a different conclusion about how much patients should be told. They felt that only a few patients wanted more explanation and that most were happy with the consent procedure. Full explanations might have produced unnecessary anxiety.

Kerr and colleagues (1982), in a study carried out in New Zealand, interviewed 178 subjects.[8] Group 1 ($n = 56$) consisted of visitors to psychiatric inpatients not receiving ECT; group 2 ($n = 62$) was made up of visitors to psychiatric patients who had been given a course of ECT; and patients with experience of ECT comprised group 3 ($n = 60$). Unlike our study, they found that misconceptions were common and many ECT patients held quite bizarre beliefs about the treatment. The groups differed in their attitudes to ECT, with 50 percent of the visitors fearing ECT compared with 18 percent of the ECT group. This study supports the view of Hillard and Folger that personal experience leads to (and could propagate) the belief that the treatment is effective. Exposure to the views of friends and the media correlated strongly and positively with poorer understanding and greater fear of ECT in both visitor groups. Kerr and colleagues asked their subjects where they had obtained their information. They concluded that exposure to films and television is associated with more misconceptions and more fears of the procedure and that it is only personal experience of the treatment or having it explained by a doctor that causes this situation to improve or prevents it from developing.

Kalayam and Steinhart (1981) sent a questionnaire to 1,043 individuals but only got a 53.6 percent response rate.[9] They surveyed psychiatrists, psychiatric nurses, pychologists, social workers, and 63 patients. They found an overall positive attitude toward ECT, a finding that they said contrasted sharply with the extremely negative image of ECT in the media. In general, patients who had received the treatment were less afraid and felt more positive than the general public.

O'Shea and McGennis (1983) have conducted the only systematic survey of lay attitudes toward and experiences of ECT in Dublin.[10] They carried out a questionnaire-based survey of 100 nonpatient lay members of the public. The results indicated lay hostility to ECT, a receptivity to adverse publicity, a tendency not to question such adversity, and a proneness to blame all ills on ECT.

Conclusions and Recommendations

All of the systematic studies of patients' attitudes toward ECT indicate that the vast majority of patients find the treatment helpful and not frightening and would submit to the treatment again. A small proportion of patients, about 18 percent, finds the treatment very frightening, particularly the first application. This occurs more frequently in women. In general, patients who have experienced the treatment feel more positive about it than those who have not and much more so than the general public. There is no evidence that experience of the treatment is aversive. Side effects are common, and memory impairment is the most distressing.

In general, patients place great trust in doctors and seem to have very little understanding of what the treatment involves. Fuller explanations should be given of the treatment, and this should be done both before the treatment is given and after it is complete.

Like any psychiatric treatment, ECT is open to abuse and misuse, and there is no doubt that there is a small number of patients who have had frightening and/or damaging experiences associated with ECT. The profession should not dismiss these reports lightly, because many come from genuine and concerned individuals.

There is no evidence at all to accept the apparently widely held media view that ECT is damaging, frightening, painful, and used by psychiatrists as a method of torture.

Further studies are needed to examine attitudes before and after the treatment and to examine patients in different hospital settings, such as state mental hospitals, private clinics, and university teaching hospitals. Much more investigation is needed of patients' abilities to give informed consent and of the sort of explanation psychiatrists should be giving to patients and relatives to reassure them and not alarm them.

References

1. Gray EG. Severe depression: a patient's thoughts. Br J Psychiatry 1983;143:319–22.
2. Sutherland S. Breakdown. London: Pan Books, 1979.
3. Frank L (ed). The history of shock treatment. San Francisco: Frank, 1978 (ISBN 0-9601376-1-0).
4. Freeman CPL, Weeks D, Kendell RE. ECT II. Patients who complain. Br J Psychiatry 1980;137:17–25.
5. Hillard JR, Folger R. Patients' attitudes and attributions to electroconvulsive shock therapy. J Clin Psychol 1977;33(3):855–61.
6. Freeman CPL, Kendell RE. ECT I. Patients' experiences and attitudes. Br J Psychiatry 1980;137:8–16.
7. Hughes J, Barraclough BM, Reeve W. Are patients shocked by ECT? J R Soc Med 1981;74:283–5.
8. Kerr RA, McGraith JJ, O'Kearney RT, Price J. ECT: misconceptions and attitudes. Aust NZ J Psychiatry 1982;16:43–9.
9. Kalayam B, Steinhart MJ. A survey of attitudes on the use of electroconvulsive therapy. Hosp Community Psychiatry 1981; 32(3):185–8.
10. O'Shea B, McGennis A. ECT: lay attitudes and experiences—a pilot study. Ir Med J 1983 76(1):40–3.

Legal Parameters of Informed Consent for ECT Administered to Mentally Disabled Persons

John Parry, J.D.[1]

An Overview of the Decisionmaking Rights of Mentally Disabled Persons

The law governing the decisionmaking rights of mentally disabled persons should apply finer discriminations in the establishment and application of standards that address more precisely the abilities and disabilities of each individual patient or client. However, in the final analysis, the right of self-determination as expressed by patients themselves or by their substituted representatives usually takes legal precedence over their medical best interests alone.

Mentally disabled persons, particularly those individuals who reside in psychiatric institutions, are frequently the victims of discrimination, neglect, and abuse. While conditions have improved from the snake pits of old, serious problems persist as evidenced by recent testimony before the Senate Subcommittee on the Handicapped.

In general, mentally disabled persons are subject to overinclusive limits on their decisionmaking rights based on labels and categorizations that tend to ignore or exclude individualized assessments of their actual abilities and disabilities. The medical and social service delivery models reinforce this tendency toward overinclusive categorizations of mentally disabled people based both on sincere paternalism and professional self-interest.

The legal advocacy model tends toward underinclusive categorization based on sincere belief in the principle of self-determination and professional self-interest. In general, modern legal theory presumes that every person, mentally disabled or not, is capable of functioning normally with regard to exercising any right of privilege unless specific facts demonstrate incapacity. Except in a legiti-

---

[1] American Bar Association, Washington, DC 20036.

mate emergency, society through its laws generally endorses the principle of self-determination in decisionmaking over the best interests of the individual reflected by community or medical standards.

Mentally Disabled Persons and Voluntary, Knowing, and Competent Consent

Before major changes are recommended and implemented in the law of informed consent (actually voluntary, knowing, and competent consent), more empirical data are needed on how the law operates from the points of view of the patients, the medical establishment, and society. Relatively few empirical studies have evaluated informed consent, particularly the adequacy of the information needed for mentally disabled persons to make informed medical choices.

The most comprehensive study to date suggests that the provision of information is inadequate and that patients really are not primarily concerned with utilizing what information is available to make their own decisions. However, even this study was small in scope, focusing on just three psychiatric units—an evaluation center, a research ward, and an outpatient clinic—all associated with the same university hospital.

Voluntary Consent

The issue of whether consent is voluntary is of particular relevance to mentally disabled persons in an institution or hospital setting because so many institutional factors are present that can undercut voluntariness. Threat of force, coercion, fraud, duress, deceit, or other kinds of overreaching will compromise voluntariness if the patient's or substitute decisionmaker's decision is improperly influenced.

Whether any particular action by a hospital employee or any condition within a hospital constitutes sufficient influence by itself or together with other factors to legally invalidate the voluntariness of a decision is a matter of fact to be determined by a judge or jury. In a modern hospital environment, factors such as overreaching, deceit, duress, and threat of force are more likely to be present than actual force, coercion, and fraud. However, there are still institutions in which physical abuse, coercion, and fraud occur.

Knowing Consent

Except in an emergency or as reasonably modified by the legitimate application of the therapist's privilege, informed or knowing consent is required before any treatment may be administered. Liability to physicians for not providing informed consent is not a common occurrence.

The so-called community standard or old rule set out in *Natanson v. Kline* defined the amount and quality of information a doctor was obligated to communicate to a patient as that information required by a normal medical practice, either in a particular specialty area or in the doctor's geographical area. The so-called reasonable patient standard or modern rule set out in *Canterbury v. Spence* emphasizes the right of patients to make their own determination about medical treatment by providing them with sufficient information to understand the risks and benefits of a particular medical procedure and to evaluate the available options open to them. A number of jurisdictions mix elements of community and patient standards together or implement an entirely different approach such as the use of medical review boards.

Case law and statutes require two conditions to be present for there to be an emergency. First, the patient must be so incapacitated that he or she is incompetent to exercise his or her decisionmaking rights. Second, there must be a life-threatening disease or injury that requires immediate treatment. In certain jurisdictions, emergency also includes a condition that would substantially threaten the health of a patient even if death were not a likely result.

The therapeutic privilege, as set out in case law and statute, posits that in certain situations the total disclosure of information will have a significant negative effect on a patient's condition. In these limited situations, a physician, looking at the circumstances from the patient's point of view, may take reasonable steps to communicate or withhold information consistent with the patient's medical welfare.

A variety of defenses found mostly in the case law but also in statutes offer protections to physicians against liability and make lawsuits by patients difficult to win.

Competent Consent

What constitutes competent consent varies among jurisdictions and does not necessarily have anything to do with clinical competency. Even in the most general formulations, civil commitment is not equivalent to a competency determination. In the most precise formulations, which I favor, competency is limited to the specific decisionmaking question that is factually at issue.

Legal competency is taking on more and more characteristics of clinical competency, although there is still a significant gap between the two conceptual frameworks.

Almost no state statutes equate civil commitment with incompetency, although a couple of states such as California and Utah and the American Psychiatric Association's model commitment statute make medical decisionmaking an issue to be more decided at the civil commitment hearing. The major conceptual problems with making medical decisionmaking an issue at a commitment hearing are the timing of the hearing, which may not be close to the medical decisionmaking process; the scope of the competency determination, which does not allow for distinctions among different kinds of treatment decisions; and the implication that those who can make their own decisions should not be subjected to commitment, even if they are mentally ill and dangerous.

Except in an emergency, if there is a question about a patient's competency, a court should hear the evidence on both sides of the issue. If incompetency is determined, a substitute consent giver should be appointed.

Substitute Consent for Incompetent Persons

After a person has been adjudicated incompetent to make a specific medical decision, the court should appoint a substitute consent giver to allow the patient to properly exercise his or her right of self-determination. The court should review the decision of the patient's representative to ensure that the decision made is not inconsistent with what the patient would have favored if competent.

The traditional role of the physician as the decisionmaker, regardless of the wishes or nonmedical interests of the patient (if ever legally acceptable), is no longer accepted today. The medical decisionmaking best exercisable by physicians does not address the patient's nonmedical interests and may in fact be inconsistent with the patient's interests in self-determination.

Obviously, judges are unable to assess medical factors with the precision and accuracy of physicians, particularly the treating physician. However, by training and experience, many judges are quite capable of assessing medical testimony and are better able to assess all the legally relevant nonmedical factors, including the patient's preferences, that must be weighed if the patient's right to self-determination is to have any meaning.

Because it has been recognized that in an emergency the legal process may be too cumbersome to deal with the health needs of the patient, it is only in an emergency when a prior judicial review should be bypassed. Thus, the definition of an emergency should take into account those medical situations in which doing nothing as opposed to delivering needed medical care will in all likelihood make the patient's long-term prognosis substantially worse. If continued treatment is required, a substitute consent giver should be appointed by a court as soon as practical.

Informed Consent as Applied to ECT

Legally, ECT cannot be absolutely prohibited by statute or regulation nor can it be administered without adhering to the requirements of voluntary, knowing, and competent consent. Moreover, in the absence of an incompetency adjudication, a patient has the absolute right to accept or decline ECT and, where incompetency has been determined, the right to a substitute consent giver to exercise his or her right to accept or decline such treatment.

Competent persons, including mentally disabled individuals who have not been adjudicated incompetent, are presumed to have all the rights and privileges of citizenship, including the absolute right to approve or decline medical care. Statutes or regulations governing ECT and other medically recognized and accepted treatments that absolutely prohibit the use of such treatment or unnecessarily infringe upon the privacy interests of the patient have been found to be unconstitutional.

The majority of states that have statutes or regulations governing the administration of ECT either set out a patient's right to refuse such treatments or require informed consent from the patient. California, Illinois, and Massachusetts have the most notable schemes. Thirteen states and the District of Columbia, which have no such statutes, are governed by interpretations of Federal and state constitutions and the common law. To be certain that there will be no liability to their patients in the administration of ECT, doctors should administer each series of ECT treatments with the voluntary informed consent of the patient or the substitute consent giver.

Sources

American Psychiatric Association. Electroconvulsive therapy. Task Force Report 14. Washington, DC: American Psychiatric Association, 1978.

Appelbaum. Can mental patients say no to drugs? NY Times Magazine, March 21, 1982, p. 46.

Fink M. Convulsive Therapy: Theory and Practice. New York: Raven Press, 1979.

Frank L. The history of shock treatment. San Francisco: Frank, 1978 (ISBN 0-9601376-1-0).

Gilbert. Shock therapy and informed consent. IL Bar J 1981 Jan;272.

Halleck SL. Law in the practice of psychiatry: a handbook for clinicians. New York: Plenum Medical Book Co., 1980:97.

Katz. Disclosure and consent in psychiatric practice: mission impossible? In: Hoffling CK, ed. Law and ethics in the practice of psychiatry. New York: Brunner/Mazel, 1981:91–118.

Lidz, Meisel, Zerubavel, Carter, Sestak, Roth. Informed consent: a study of decisionmaking in psychiatry. New York: Guilford Press, 1984.

Mental and Physical Disability Law Reporter. All the case and legislative articles dealing with informed consent, substituted decisionmaking, and electroconvulsive therapy. In particular: Tenenbaum J. ECT reconsidered. MDLR 1983;7:148–57; Summary and analysis. MDLR 1983;6:62–6; and Summary and analysis. MDLR 1983;6:366.

Parry J. Decisionmaking rights over persons and property, Chap 8. In: Brakel, Parry J, Weiner RD, eds. The mentally disabled and the law. Chicago: The American Bar Association (in press).

Parry J. Incompetency, guardianship, and restoration, Chap 7. In: Brakel, Parry J, Weiner RD, eds. The mentally disabled and the law. Chicago: The American Bar Association (in press).

Plotkin. Limiting the therapeutic orgy: mental patients' right to refuse treatment. Northwestern U Law Rev 1978;72:461.

Rosoff AJ. Informed consent: a guide for health care providers. Rockville: Aspen Systems Corp., 1981.

Rozovsky. Consent to treatment: a practical guide, 1984.

Scovern. Status of electroconvulsive therapy: review of the outcome literature. Psychol Bull 1984;87(2):260–303.

Stone. Recent mental health litigation: a critical perspective. Am J Psychiatry 1977;134:273.

Stromberg, Stone. A model statute on civil commitment of the mentally ill. Harv J Legis 1983;275.

Weiner RD. Treatment rights, Chap 6. In: Brakel, Parry J, Weiner RD, eds. The mentally disabled and the law. Chicago: The American Bar Association (in press).

Winslade WJ, Liston EH, Ross JW, Weber KD. Medical, judicial, and statutory regulation of ECT in the United States. Am J Psychiatry 1984;141(11):1349–55.

Cases

Aden v. Younger, 57 Cal. 3d 662 (1978).

Aiken v. Clary, 396 S.W. 2d 668 (Mo. 1965).

Bly v. Rhoads, 222 S.E. 2d 783 (Va. 1976).

Canterbury v. Spence, 464 F.2d 772 (D.C. Cir. 1972).

Ficklin v. MacFarland, 550 P 2d 1295 (Utah 1976).

Gundy v. Pauley, 619 S.W. 2d 730 (Ky. Ct. App. 1981).

Hanes v. Ambrose, 437 N.Y.S. 2d 784 (N.Y. App. Div. 1981).

In re William M (Ohio, Franklin County Probate Ct. March 15, 1979), 3 MDLR 184.

Kaimowitz v. Michigan Dept. of Mental Health, No. 73-19434-AW (Mich. Cir. Ct., Wayne County, July 10, 1973), 1 MDLR 147.

Lester v. Aetna Casualty and Surety Company, 240 F.2d 676 (5th Cir. 1957).

Mitchell v. Robinson, 334 S.W. 2d 11 (Mo. 1960).

Natanson v. Kline, 350 P2d 1093 (Kan. 1960).

Northern California Psychiatric Society v. City of Berkeley, No. 566778-3 (Cal. Super. Ct. Sept. 14, 1983).

Price v. Sheppard, 239 N.W. 2d 905 (1966).

Salgo v. Stanford University Board of Trustees, 317 P2d 170 (1957).

Wilson v. Lehman, 379 S.W. 2d 478 (Kan. Ct. App. 1964).
Wyatt v. Hardin, No. 3195-n (M.D. Ala. Feb. 28, 1975), 1 MDLR 55.
Wyatt v. Stickney, 344 F. Supp. 373 (M.D. Ala. 1972).

Data on Informed Consent for ECT

Loren H. Roth, M.D., M.P.H.[1]

Although the informed consent requirement is relatively new to psychiatry (informed consent doctrine having come of age only over the last two decades), there is now legal, ethical, and professional consensus that informed consent should be obtained for electroconvulsive treatment. Obtaining meaningful consent for ECT permits a collaborative approach to therapy and may promote patient satisfaction with treatment. At a minimum, it is a legal requirement.

Controversy exists, however, whether severely disturbed psychiatric patients who are candidates for receiving ECT are able to give valid informed consent. Unfortunately, there is a paucity of empirical data to answer this question. In clinically based systematic studies at the University of Pittsburgh, my colleagues and I have found that informed consent works best with psychiatric patients when it is viewed as a process taking place over time, involving a discussion between physician and patient (including the patient's relatives or friends), rather than being "an event" in which a patient signs a complex form that he often does not understand. Patient education is clearly required for meaningful informed consent.

At present, obtaining informed consent for ECT usually involves securing the patient's written consent. However, the informed consent form should not be the major form of information disclosure to the patient. The only prospective empirical study on obtaining informed consent for ECT found that slightly more than one-half of the patients (54 percent) understood more than two-thirds of the information on a standard ECT consent form ($n = 57$ patients). Thirty percent of patients understood half or less of the information (Roth et al., 1982). Consent forms are typically written in too complex a manner for the average patient.

In a retrospective study, Freeman and Kendell (1980) concluded that patients wish to be told more about ECT than they remember being told. Following repeated information disclosure and teaching about ECT, however, the majority of depressed psychiatric patients are able to understand about the treatment and to give a competent consent to it. Better patient understanding and competency correlate with higher patient education and occupation, less severe illness, absence of psychosis, and the patient's ability and willingness to be taught about treatment (Roth et al., 1982). A minority of severely depressed, delusional patients are not able to give meaningful informed consent to ECT. This minority includes severely disorganized patients (both objectors and consenters), those who deny mental illness, and patients who are so hopeless or pessimistic as to be unable to appreciate the potential benefits of treatment. While the above findings about the feasibility of informed consent for ECT may be viewed optimistically or pessimistically, it should be remembered that a large number of empirical studies (totaling more than 100) have found that many medical and surgical patients also do not understand that to which they have consented (Meisel & Roth, 1983). By comparison, psychiatric patients do not do appreciably worse than other patients with respect to consent.

Patients need not understand what physicians understand to provide valid consent. A minimedical education is not required for consent. It is important when obtaining informed consent for ECT that not only the risks and benefits of ECT be told the patient but also the alternatives to ECT and their risks and benefits so that the patient can make a comparative decision.

---

[1] University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

If patients cannot give valid consent, then increasingly the practice is to involve a court to rule on patient competency for both voluntary and committed patients. Patients found incompetent by a court have guardians appointed for them to decide about treatment. In practice, court hearings occur only for a small percentage of patients who receive ECT, even in states now having complex regulatory requirements.

When a patient has only marginal understanding of treatment and there is doubt in the physician's mind about the patient's competency, then the patient's friends or relatives should be involved in decisionmaking, even though proxy consent by relatives does not provide full legal immunity for the physician.

A major controversy relating to informed consent for ECT relates to coercion. Is the institutional scene inherently coercive? Are doctors so persuasive? Or is illness so severe as to preclude voluntary patient consent—as informed consent doctrine requires? Unfortunately, no satisfactory data are available to answer these questions. Empirical observations in one university treatment setting suggests that coercion is not a problem (Lidz et al., 1984), but the generalizability of the observations from this study is not clear. Coercion is also a philosophically difficult point. It is difficult to know what proper cutoffs are between legitimate and illegitimate pressures that physicians or relatives may bring upon patients to do what is in their best interest.

Given the prominence that informed consent doctrine plays in the legal regulation of ECT, more empirical studies are needed to document the process of consent, what physicians routinely tell patients, what patients understand, and how they decide. Additional empirical research is required in the area of competency to consent to or refuse ECT. There are no fixed or universally agreed upon standards for assessing patients' competency to consent to ECT. Roth and his coworkers have delineated several standards for assessing patient competency along a sliding scale (presence of a patient decision, patient understanding, rationality, or appreciation of risks and benefits). More empirical work is required, however, to classify patients according to their abilities to meet progressively stringent standards for competency and to explore how best to integrate legal standards for competency and clinical findings so as to balance patients' rights and needs.

Sources

Appelbaum PS, Roth LH. Competency to consent to research. Arch Gen Psychiatry 1982;39:951–8.

Culver CM, Ferrell RB, Green RM. ECT and special problems of informed consent. Am J Psychiatry 1980;137:586–91.

Freeman CPL, Kendell RE. ECT: I. Patients' experience and attitudes. Br J Psychiatry 1980;137:8–16.

Kaufmann CL, Roth LH, Lidz CW, Meisel A. Informed consent and patient decisionmaking: the reasoning of law and psychiatry. Int J Law Psychiatry 1981;4:345–61.

Lidz CW, Meisel A, Zerubavel E, Carter M, Sestak RM, Roth LH. Informed consent: a study of decisionmaking in psychiatry. New York: Guilford Press, 1984.

Meisel A, Roth LH. Toward an informed discussion of informed consent: a review and critique of empirical studies. Ariz Law Rev 1983;25:265–346.

Roth LH, Lidz CW, Meisel A, Soloff PH, Kaufman K, Spiker DG, Foster FG. Competency to decide about treatment or research: an overview of some empirical data. Int J Law Psychiatry 1982;5:29–50.

Roth LH, Meisel A, Lidz CW. Tests of competency to consent to treatment. Am J Psychiatry 1977; 134:279–84.

Taylor PJ. Consent, competency and ECT: a psychiatrist's view. J Med Ethics 1983;9:146–51.

Winslade WJ, Liston EH, Ross JW, Weber KD. Medical, judicial, and statutory regulation of ECT in the United States. Am J Psychiatry 1984;141:1349–55.

Clinical Strategies in Choice and Timing of ECT

Richard Abrams, M.D.[1]

This presentation will, of necessity, be largely based on accumulated clinical wisdom and experience because few hard research data are available to guide the physician in determining the choice and timing of ECT. The following presentation is concerned with questions of diagnosis, timing, and technique of administration.

---

[1] University of Health Sciences and Chicago Medical School, North Chicago, IL 60064.

Diagnosis

Within the broad diagnostic classes to be considered, the following subgroups, subsyndromes, individual symptoms, historical facts, and laboratory tests may identify individual patients as particularly good candidates for ECT.

Melancholia/Endogenous Depression

ECT response is substantially better in persons with these disorders than in nonmelancholic major depressives and is considered particularly favorable in the presence of certain symptoms (early waking, retardation, agitation, delusions/psychosis, ruminations, guilt/self-reproach, weight loss), historical features (prior to ECT, a family history of depression, history of mania, cyclothymic personality), certain laboratory results (positive sedation threshold test, positive dexamethasone suppression test), and the pseudodementia syndrome (diffuse cognitive impairment coexisting with depressive symptoms in an older patient).

Febrile Mania (Bell's Mania, Stauder's Lethal Catatonia, Febrile Catatonia)

This syndrome of acute mania with fever, dehydration, tachycardia, and severe insomnia bears some resemblance to neuroleptic malignant syndrome. It is generally unresponsive to or aggravated by neuroleptics and may terminate fatally unless ECT is rapidly instituted.

Catatonia

This nonspecific motor syndrome of stupor, mutism, negativism, and accessory features is frequently associated with a primary diagnosis of affective disorder and is very sensitive to ECT. Temporary alleviation of these motor symptoms by intravenous barbiturates (the "sodium Amytal interview") augurs well for a striking ECT response.

Acute, Schizophreniform, Schizoaffective, or Good-Prognosis Schizophrenia

These related subsyndromes are difficult or impossible to differentiate from bipolar affective disorder and show a uniformly good response to ECT (in marked contrast to chronic schizophrenia).

Timing

Use as Initial Treatment

ECT is often considered the initial treatment of choice over medications in seriously suicidal or psychotic depressives; patients in catatonic stupor; pregnant patients (any trimester) requiring immediate antidepressant, antimanic, or neuroleptic drug therapy; patients whose major medical disorders render them unsuitable candidates for drug treatment (e.g., melancholiacs with heart block, psychotic patients with prostatic hypertrophy); and patients with PCP-induced psychoses.

Drug Nonresponders

Many depressed, manic, or psychotic patients who fail to respond to appropriate drug therapy may eventually recover with ECT. The point at which a given patient becomes a drug nonresponder is difficult or impossible to determine precisely, especially in outpatients suffering from the less severe syndromes. In hospitalized patients, ECT should be seriously considered for any melancholic patient who has shown no response at all to 1 week of appropriate antidepressant therapy (or a minimal response to 2 weeks of therapy); any acute manic (or acute, schizophreniform, schizoaffective, or good-prognosis schizophrenic) who has shown no response at all to 5 to 7 days of high-dose parenteral neuroleptics, with or without additional lithium; or any subacute manic who has shown no response at all to 2 weeks of lithium therapy at satisfactory blood levels, with or without additional neuroleptics.

Emergency ECT

Defined as the administration of ECT on the same day as the decision to give it is made, emergency ECT is usually justified in the presence of a serious suicidal or self-mutilative attempt or in a patient whose condition suddenly and unexpectedly deteriorates while on drug therapy (e.g., a manic who develops the febrile syndrome over a weekend or a melancholiac who stops eating and rapidly loses weight).

Financial Considerations

With diagnostic-related groups and other financial constraints on patient care and duration of therapy, the ability of a patient or his insurer to pay for treatment may partially determine choice of treatment. In the hypothetical case of reimbursement for a maximum of 2 weeks of hospitalization for melancholia, the choice of ECT will be dictated as a method that is capable of inducing a full remission in this time span in contrast to available drugs, which are not capable of inducing a full remission.

Technique

The considerations in unilateral versus bilateral ECT substantially overlap with those concerning choice of ECT versus drug therapy. Where symptoms are very severe or life-threatening or where a rapid, assured response is required (e.g., melancholiacs with delusions, psychosis, suicidal intent/ruminations, stupor, or agitation; manics; catatonics), bilateral ECT should be chosen. Patients of any diagnosis who do not respond to five to seven unilateral ECT treatments are also candidates for switching to bilateral ECT.

Unilateral ECT should be considered first in all other patients as well as in those whose occupations or personal convictions would render intolerable any significant degree of clinical confusion or amnesia.

General Technique of ECT

Ferris N. Pitts, Jr., M.D.[1]

Modified ECT has been shown to be an extremely safe and effective psychiatric treatment for depressive disorders, for anorexia nervosa, and for a wide variety of toxic and metabolic psychoses. The safe and effective administration of ECT requires a thorough evaluation of the patient's physical condition (with appropriate treatment of certain abnormalities prior to the ECT) and a thorough knowledge of the medical physiology of the treatment. It also requires a thorough knowledge of the techniques and experience in the administration of brief anesthesia.

Mortality with ECT (even when unmodified) has always been extremely low, and with modern brief anesthetic techniques, the mortality is nearly zero—even in patients with advanced age, extreme debilitation, and/or severe heart disease. Morbidity in unmodified ECT was chiefly because of vertebral compression fractures (50 percent of patients); fractures, sprains, or dislocations of long bones and joints (10 percent of patients); pneumonitis due to aspiration of secretions or gastric contents; and hypoxia due to apnea and/or bradycardia during and following the seizure. These morbidities can be almost completely avoided with modern preanesthetic measures and brief anesthetic techniques.

This presentation examines the specifics of the pretreatment evaluations, the details of the treatment procedures, and the events of posttreatment (recovery) management of the ECT patient. Many general physiologic effects of ECT, the reasons for introduction of specific anesthetic-resuscitative measures, and the equipment and personnel needed to administer the treatment (and provide emergency care when necessary) are to be detailed. Systematic studies of the ECT procedure are reviewed and assessed. Future studies are suggested. After this presentation, the

---

[1] University of Southern California School of Medicine, Los Angeles, CA 90033.

panel should be able to envision the setting, the equipment, and the procedure itself. The panel should also become fully cognizant of the marked specific and relative safety of the ECT procedure.

Pretreatment Evaluations

ECT is given under a brief anesthesia, and all patients receive complete medical, neurologic, and psychiatric examinations. Specific tests required by different institutions vary, but CBC, urinalysis, FBS, BUN, electrolytes, chest x-ray, and EKG are ordinarily obtained. Many add a serum chemistry panel, thyroid battery, and serum cholinesterase to the pretreatment screening process. All abnormal conditions should be delineated with further studies and treated prior to ECT, but the ECT procedure is so safe and simple that no condition absolutely precludes its use. Spine x-rays, skull x-rays, computerized tomographic studies of the CNS, and electroencephalograms are often obtained as part of a complete workup or in response to a bureaucratic requirement. Medical specialist evaluations are often advisable for assessment and most effective management of particular disease states prior to ECT. The decision to administer ECT is made by the treating psychiatrist; he writes the orders for the procedure and ordinarily administers the treatment.

The ECT Procedure

ECT is ordinarily given in the early morning after an 8- to 12-hour period of fasting, although other times of the day after briefer fasting periods have been used. Atropine, or another anticholinergic drug, is given prior to the treatment to prevent paroxysmal vagal discharge with ECT. Vagal discharge can cause sufficient profuse upper respiratory secretions to result in pulmonary aspiration with resuscitation and/or spontaneous respiration; it can also cause a particularly profound and dangerous bradycardia. Atropine is given in 1.0 to 1.2 mg dosage intramuscularly (30 to 60 minutes), subcutaneously (45 to 90 minutes), or intravenously (5 minutes) before treatment. A butterfly needle is placed in a peripheral vein, and access to this vein is maintained until the patient has been fully resuscitated. Anesthetic medications are administered by rapid-push (bolus) injection or rapid infusion. Methohexital is given first in the initial dosage of 0.9 to 1.0 mg/kg, followed immediately by succinylcholine in the initial dosage of about 0.5 mg/kg. The dosages of both these medications are adjusted in subsequent ECT treatments according to anesthetic response (duration of post-ECT apnea, vigorousness of muscle movements with the seizure). A soft rubber bite plate and oropharyngeal airway are introduced just before, or just after, the anesthetic medications. Methohexital anesthetic induction takes one arm-to-tongue circulation time (10 to 20 seconds), and the succinylcholine depolarizing neuromuscular blockade takes about 60 (50 to 80) seconds following injection. During the postanesthetic/pre-ECT period, the patient is resuscitated through a positive-pressure bag and mask with 100 percent oxygen at 2 to 5 liters per minute (room air is equally effective at this time and at post-ECT) at about 9 to 12 full respirations per minute. This resuscitation may be continued during the seizure, which is triggered by one of the electrical pulses from one of the instruments considered in detail by Dr. Weiner and which lasts 28 ± 6 (SEM) seconds, although most wait until after the seizure to resume this oxygenation process. The post-ECT apneic period is ordinarily 90 seconds (total apneic period, counted from the administration of succinylcholine, is 300 ± 12 seconds) with this method. The rate of new or increased abnormal EKG findings during the following ECT is about 9 percent in patients with and without heart disease using this method. The new or increased abnormal EKG findings with this method are evanescent and minor. With unmodified ECT and with other anesthetic procedures, especially with other anesthetic medications, the EKG abnormalities are far more frequent, persistent, and severe, and differences are even greater for patients with heart disease. Nevertheless, in over (approximately) 1 million ECT treatments given with this method to patients, including those with severe heart disease, there has been no fatality, no apnea prolonged beyond 10 minutes, and no serious medical consequence. ECT involves an anesthetic procedure given to an ill individual. The ECT suite should, therefore, be equipped with the most modern instruments and drugs for monitoring and managing the cardiopulmonary status of the patient, and those administering the treatment should be trained in their use.

Electrical Dosage, Stimulus Parameters, and Electrode Placement

Richard D. Weiner, M.D., Ph.D.*

Electrode Placement

Introduction

ECT involves the passage of an electrical stimulus between two electrodes placed on the scalp. In practice, stimulus electrodes are placed either bifrontotemporally (bilateral [BL] ECT) or with one electrode placed frontotemporally and a second electrode placed in any of a variety of ipsilateral scalp locations (unilateral [UL] ECT). The latter configurations are usually described with respect to the cerebral hemisphere felt to mediate verbal function, that is, unilateral dominant (ULD) versus unilateral nondominant (ULND) ECT.

Key Points and Conclusions

Regardless of the type of electrode placement, the induction of a bilaterally generalized seizure is felt to be integral to a successful therapeutic outcome, although it is recognized that seizures with UL are less intense within the cerebral hemisphere contralateral to the side stimulated.[1] Likely due to this asymmetry, there is a relative sparing of contralateral hemispheric cognitive function with UL ECT.[2] With ULND ECT, for example, verbal memory function is considerably less affected than with either BL or ULD ECT. Because most individuals are much more sensitive to verbal as opposed to nonverbal memory deficits, ULND has received acceptance as the preferred type of UL ECT, at least for the treatment of depressive disorders. This conclusion is also supported by evidence that ULD ECT may be less therapeutically effective than ULND ECT in this population.[3]

While ULND ECT produces clearly less memory dysfunction over a course of ECT than does BL ECT, the possibility that such a difference might persist for weeks to months following completion of the treatment course has not been as carefully investigated. Because ECT-induced memory deficits rapidly diminish with time, it is not surprising that the only positive findings to date have resulted from the assessment of recall for autobiographic events occurring prior to the ECT course[4] and of self-rated memory function.[5,6] In each case, however, negative reports also exist.[7]

A large number of investigations have considered the relative efficacy of UL versus BL ECT.[8-13] Of 38 reports contrasting ULND and BL ECT, 20 (53 percent) found equivalence. Of the remaining 18 studies in which at least a trend was present, 16 favored BL treatments, although the difference was statistically significant in only two cases.

When these studies are analyzed critically, two points are clear. First, the more methodologically rigorous investigations, in terms of factors such as subject selection, blindness, and outcome measures, were more likely to show equivalence between the two modalities. Second, there seemed to be a relationship between the use of "optimal" UL ECT and the absence of significant differences, with optimal technique defined as the use of a high centroparietal location for the second stimulus electrode, proper attention to electrode-scalp coupling, the assurance of suprathreshold stimuli, and the incorporation of seizure monitoring of some sort.

Despite the above arguments, however, many psychiatrists remain concerned about the relative efficacy of ULND ECT. The possibility has been raised, for example, that particular patient subgroups might respond preferentially to BL treatments, such as has recently been reported for those with manic symptomatology.[14]

---

*VA Medical Center, Durham, NC 27705.

Areas Requiring Further Research

Given the substantially lower extent of cognitive deficits associated with ULND ECT, it will be important to demonstrate a clear therapeutic advantage for BL ECT to justify its continued use. Such an advantage could not only be in terms of clinically definable subgroups of patients for whom it might be more effective in producing a remission but also could be in terms of either the rapidity of response or the duration of the induced remission. Further comparative studies designed to clarify the presence and extent of long-lasting memory effects with ULND and BL ECT are also indicated to clarify pertinent risk-benefit considerations.

A final area for additional research in the area of electrode placement relates to the desirability of understanding how ULND-induced seizures are able to produce a beneficial effect while sparing verbal memory function. Perhaps the neuronal activation necessary for the potent efficacy of ECT is in fact focal rather than diffuse. If such is the case, it might, in the future, be possible to devise means of selective noninvasive stimulation of pertinent brain structures, thereby not only obviating cognitive disruption but also removing much of the unsavory aura that has surrounded ECT from its very beginnings.

Stimulus Waveform

Introduction

The electrical signal used to trigger an induced seizure with ECT can be described in terms of its waveform, that is, its voltage or current fluctuations as a function of time. In the early days of ECT, the choice of stimulus waveform was based simply on what was available for use—the line frequency sine wave. It was not long, however, before research began to characterize waveforms that were more energy efficient in inducing seizure activity.[18] As a product of this work, for example, it was found that brief pulse stimuli, which consist of a train of short bursts of current flow interrupted by much longer periods of electrical inactivity, required considerably lower energy content than the sine wave to elicit seizures. Over the years, equipment producing a wide variety of stimulus waveforms has been developed for use with ECT. In the United States, devices utilizing either sine wave or brief pulse stimuli are presently available commercially, while elsewhere machines using waveforms with energy efficiency between these are also common.

Key Points and Conclusions

The use of low-energy stimulus waveforms is predicated on the hypothesis that lower energy means less central nervous system (CNS) toxicity. Five of seven studies have, in fact, reported less cognitive impairment with lower energy waveforms, either during the ECT course or within the first few days following its completion.[4,7,16,17] On the other hand, none of six studies that considered the possibility of more persistent differences observed such phenomena.[4,7,16,17] Although the increase in acute amnestic and encephalopathic dysfunction on the basis of higher energy waveforms is less likely than that ascribable to BL versus ULND electrode placement, the use of appropriately sensitive measures reveals that these differences are, in fact, substantial.[4,17]

Most (six of eight) studies that compared the therapeutic efficacy of different stimulus waveforms reported no significant differences.[4,7] Interestingly, both investigations that found an average for the higher energy waveform used "ultrabrief" pulses, that is, less than 0.5 msec pulse duration, for the lower energy alternative.[18,19] This may indicate that a certain energy content must be present for each repetition of the stimulus waveform to assure sufficient depolarization of relevant neuronal structures.[20]

Areas Requiring Further Research

At present, there appears to be evidence for a therapeutic equivalency between high- and low-energy stimuli, although this may not be the case regarding stimuli at the ultra-low-energy end of the spectrum. In addition, patients receiving low-energy stimuli appear to have less acute cognitive and electrophysiologic deficits. For these reasons, it will be important, if high-energy stimuli such as the sine wave are to remain viable, to provide conclusive evidence that they are more rapid or more effective in certain patient subgroups or that they offer a greater degree of protection against early relapse. In addition, the mechanisms of greater encephalopathic changes with higher energy stimulus waveforms and of decreased therapeutic potency with ultra-low-energy waveforms are unclear and await exploration.

Stimulus Intensity

Introduction

Regardless of stimulus waveform, the practitioner still must decide how to match the intensity of the stimulus with respect to the seizure threshold. Given an enormous degree of both inter- and intraindividual variability in seizure thresholds, there has been much uncertainty as to the proper stimulus dosing regimen.[21,22] This has resulted in clinical practices ranging from closely titrated stimuli, resulting in numerous missed seizures and restimulations, to fixed high-intensity stimulation, leading to the use of intensities that are grossly suprathreshold for the great majority of patients. At present, however, it appears that most ECT users have adopted a technique that represents a tradeoff between avoidance of maximal stimuli and missed seizures.

Stimulus intensity is actually a function of a number of electrical factors, each of which may or may not be adjustable depending on the specific ECT device used.[15] Because research into differences among the effects of various intensity measures has not yet produced scientifically based clinical guidelines, practitioners have tended either to follow suggestions given in device user manuals or to empirically derive their own choice of settings. Alternatively, some equipment manufacturers have dealt with this matter by limiting the number of adjustable settings on their devices. In the extreme case, for example, some European devices, no modifiable intensity parameters are present, assuring the use of a fixed, usually maximally suprathreshold stimulus at all times.

Key Points and Conclusions

Early studies comparing different stimulus intensities suggested that the threshold for neuropathologic changes was much greater than that utilized in clinical practice.[7] Later work focused on intensity-related effects on cognitive performance and the EEG in humans and in animals. While the evidence is clear that the greater portion of adverse CNS effects associated with ECT appear to be secondary to the seizure rather than to the stimulus itself,[23,24] there are also some suggestive data to support the possibility of a direct electrical effect on cognitive performance, at least for high-energy stimulus waveforms.[4,25]

Very little attention has been given to the effects of stimulus intensity on therapeutic outcome. With BL ECT, a single study found that grossly suprathreshold stimuli produced no added improvement over a course of treatments.[25] Another quite recent investigation, however, using barely threshold stimuli, reported that ULND ECT was significantly less effective than BL ECT,[13] thereby suggesting that a more moderate choice of stimulus intensity might prove beneficial.

Areas Requiring Further Research

A consideration of the limited data dealing with stimulus intensity and its effect on indices of adverse and therapeutic response allows only the tentative conclusions that the conservative approach to intensity dosing used by most practitioners is probably the most rational and that devices that produce only a fixed unmodifiable stimulus intensity may sometimes result in increased toxicity. Clearly, more research in these areas is indicated. In addition, which intensity parameters are the most relevant also needs to be clarified.

References

1. Weiner RD. EEG related to electroconvulsive therapy. In: Hughes JR, Wilson WP, eds. EEG and Evoked Potentials in Psychiatry and Behavioral Biology. Boston: Butterworths, 1983.
2. Fromm-Auch D. Comparison of unilateral and bilateral ECT: evidence for selective memory impairment. Br J Psychiatry 1982;141:608–13.
3. Cronin D, Bodley P, Potts L, et al. Unilateral and bilateral ECT: a study of memory disturbance and relief from depression. J Neurol Neurosurg Psychiatry 1970;33:705–13.
4. Weiner RD, Rogers HJ, Davidson JRT, et al. Effects of stimulus parameters on cognitive side effects. Ann NY Acad Sci (in press).
5. Small IF. Inhalant convulsive therapy. In: Fink M, Kety S, McGaugh J, et al., eds. Psychobiology of Convulsive Therapy. Washington: VH Winston & Sons, 1974.
6. Squire LR, Chace PM. Memory functions six to nine months after ECT. Arch Gen Psychiatry 1975; 32:1557–64.
7. Weiner RD. Does electroconvulsive therapy cause brain damage? Behav Brain Sci 1984;7:1–54.
8. d'Elia G, Raotma H. Is unilateral ECT less effective than bilateral? Br J Psychiatry 1975;126:83–9.
9. Welch CA. The relative efficacy of unilateral nondominant and bilateral stimulation. Psychopharmacol Bull 1982;18:68–70.
10. Abrams R, Taylor MS, Faber R, et al. Bilateral vs. unilateral ECT: some new data. Am J Psychiatry 1983;140:463–465.
11. Janicak PG, Davis JM, Gibbons RD, et al. Efficacy of ECT: a metaanalysis. Am J Psychiatry 1985; 142:297–302.
12. Stromgren LS. Is bilateral ECT ever indicated? Acta Psychiatr Scand 1984;69:484–90.
13. Malitz S, Sackeim HA, Decina P, et al. Dose/response interactions with modality. Ann NY Acad Sci (in press).
14. Small JG, Small IF, Milstein V, et al. Manic symptoms: an indication for bilateral ECT. Biol Psychiatry 1985;20:125–34.
15. Weaver LA Jr, Williams RW. The electroconvulsive therapy stimulus. In: Abrams R, Essman WB, eds. Electroconvulsive Therapy, Biological Foundations and Clinical Applications. New York: SP Medical & Scientific Books, 1982;129–56.
16. Warren EW, Groome DH. Memory test performance under three different waveforms of ECT for depression. Br J Psychiatry 1984;144:370–5.
17. Weiner RD, Rogers HJ, Davidson JRT, et al. Effects of ECT upon brain electric activity. Ann NY Acad Sci (in press).
18. Cronholm B, Ottosson JO. Ultrabrief stimulus techniques in ECT. 1. Influence of retrograde amnesia. J Nerv Ment Dis 1963;137:117–23.
19. Robin A, de Tissera S. A double-blind controlled comparison of the therapeutic effects of low and high energy electroconvulsive therapies. Br J Psychiatry 1982;141:357–66.
20. Valentine M, Keddie KMG, Dunne D. A comparison of techniques in electroconvulsive therapy. Br J Psychiatry 1968;114:989–96.
21. Weaver LA Jr, Ives J, Williams R. The threshold number of pulses in bilateral and unilateral ECT. Biol Psychiatry 1978;13:227–41.
22. Malitz S, Sackeim HA, Decina P, et al. Low dosage ECT: electrode placement and acute physiological and cognitive effects. Am J Soc Psychiatry 1984;IV:47–53.
23. Zornetzer S. Retrograde amnesia and brain seizures in rodents: electrophysiology and neuroanatomical analyses. In: Fink M, Kety S, McGaugh J, et al., eds. Psychobiology of Convulsive Therapy. Washington: VH Winston & Sons, 1974.
24. Pacella BL. Varieties of electrical shock therapy. J Nerv Ment Dis 1949;109:396–404.
25. Ottosson JO. Experimental studies on the mode of action of electroconvulsive therapy. Acta Psychiatr Scand 1960;35(suppl 145):1–141.

Articles—

Major Depression and Panic Disorder: Diagnostic and Neurobiological Relationships[1]

Dennis S. Charney, M.D.,[2] George R. Heninger, M.D.,[2] Lawrence H. Price, M.D.,[2] and Alan Breier, M.D.[2]

There has been considerable research attempting to define the relationship between anxiety states and depressive illness. Most of the current research has focused on the relationship of panic disorder and agoraphobia with panic attacks to major depression. Patients with agoraphobia and panic disorder (agoraphobia-panic disorder) are usually considered together because panic attacks usually occur with agoraphobia and play a critical role in its pathogenesis (Klein, 1981).

Studies indicate that agoraphobia-panic disorder and major depression are responsive to similar treatments and may be genetically linked. It has been documented that first-degree relatives of patients with agoraphobia-panic disorder have high rates of major depression (Leckman et al., 1983). Controlled therapeutic trials demonstrate that drugs such as imipramine and phenelzine, which have antidepressant efficacy, are also effective for the treatment of agoraphobia-panic disorder (Sheehan et al., 1980; Zitrin et al., 1983). These investigations have raised questions regarding the frequency with which patients may experience both depressive and panic disorder symptoms, the existence of a common neurobiological dysfunction involving both disorders, and the mechanisms by which the same drug can be both antidepressant and antipanic.

In the present paper, we reviewed the results of a series of investigations conducted at our facility designed to examine these questions as to the etiological, diagnostic, and therapeutic relationships between agoraphobia-panic disorder and major depression.

Lifetime Occurrence of Major Depression in Panic Disorder

The longitudinal course of anxiety and depressive symptoms in 60 patients consecutively admitted to the Anxiety Disorder Clinic on the Clinical Research Unit of the Connecticut Mental Health Center was evaluated. The methodology used in this study has been detailed elsewhere (Breier et al., 1984). Briefly, all patients had the following characteristics: a history of spontaneous panic attacks; a current Research Diagnostic Criteria (RDC) diagnosis of agoraphobia, mixed phobia and/or panic disorder; age between 18 and 65 years; good physical health, as determined by physical and laboratory examinations; and no history of psychotic disorders or current substance abuse. Presence or absence of affective disorder was not considered in the admission screening. Structured interviews and a comprehensive year-by-year analysis of the agoraphobia-panic disorder and major depression were used for data collection. The major focus was to document the occurrence of major depressive episodes, which were also diagnosed using RDC criteria, and the relationship of such episodes to the onset and clinical course of the agoraphobia-panic disorder. The structured instrument used in the interview was a version of the SADS-L which included a new anxiety section developed by Fayer and Endicott. Ratings of the worst past level of impairment for panic attacks and agoraphobia (on a scale from 1 to 8 and 1 to 6, respectively) are included in this anxiety sec-

---

[1] This study was supported in part by USPHS Grants MH-25642, MH-36229, MH-38007, and MH-30929 from the National Institute of Mental Health and by the State of Connecticut. The laboratory, clinical, secretarial, and pharmacy staff of the Ribicoff Research Facilities are gratefully acknowledged.

[2] Clinical Research Unit, Ribicoff Research Facilities, Connecticut Mental Health Center, Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06508.

tion and were used in this study. In addition to the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L), a semistructured interviewing guide was developed to more carefully detail the longitudinal course of agoraphobia and panic and their temporal relationship to depressive illness.

The current level of symptomatology was assessed by research nurses who were blind to the longitudinal data obtained from the structured interview. The clinician rated scales used were the Hamilton Anxiety Scale (HAM-A) and the Hamilton Depression Scale (HAM-D). Patient-rated scales used were the Patient-Rated Anxiety Scale, a modified Wolpe-Lange Fear Survey, and a Panic Attack Inventory that documented the type of stimulus and the frequency of the panic attacks that occurred during the preceding 7-day period.

The major finding of this study was the high frequency with which depression occurred in patients presenting with agoraphobic and panic disorder symptoms. Forty-one of the 60 patients (68%) had had an episode of major depression. Thirty-five of these 41 patients had had at least one episode of an endogenous type major depression. The major depression was primary in 20 patients in that its onset had preceded that of the agoraphobia-panic disorder. The mean duration between the end of the last primary episode of major depression and the first panic attack was approximately 3 years. Seven of the 20 patients with a primary major depression had gone on to have an episode of secondary major depression. A total of 28 patients had had at least one secondary major depressive episode. The mean duration between the end of the last episode of secondary major depression and admission to the study was approximately 56 months. Eleven patients met criteria for both major depression and agoraphobia-panic disorder on admission.

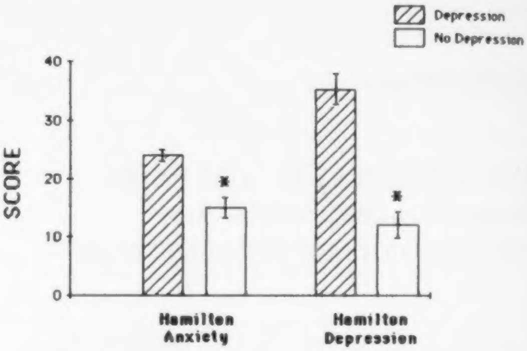


FIGURE 1. Hamilton Anxiety Scale and Hamilton Depression Scale scores in Agoraphobic-Panic Disorder patients with ($N = 41$) and without ($N = 19$) a past or current major depressive episode. (*$p < .001$)

There appeared to be a relationship between the severity of agoraphobia-panic disorder and the history of major depression. The patients with past or current depression had substantially higher scores on all symptom scales used at admission, which included both clinician-rated and patient-rated instruments. The patients with past or current depression had higher scores on the clinician rated HAM-A and HAM-D (Figure 1). In addition, mean scores on the Patient Rated Anxiety Scale, Wolpe-Lange Fear Survey, and the Panic Attack Inventory were also significantly higher for patients with depression than those patients with no history of depression (Figure 2).

The current presence or absence of major depression had no influence on the above findings. The past worst level of impairment was significantly greater for patients with past or current depression for both impairment associated with panic attacks and agoraphobia (Figure 3). In the patients with a history of secondary major depression, the past

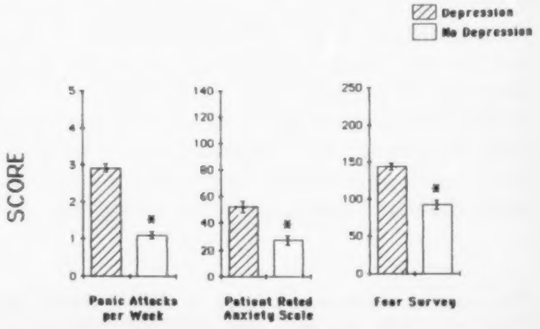


FIGURE 2. Patient-Rated Anxiety Scale, Wolpe-Lange Fear Survey, and Panic Attack Inventory Scores in Agoraphobic-Panic Disorder patients with ($N = 41$) and without ($N = 19$) a past or current major depressive episode. (*$p < .001$)

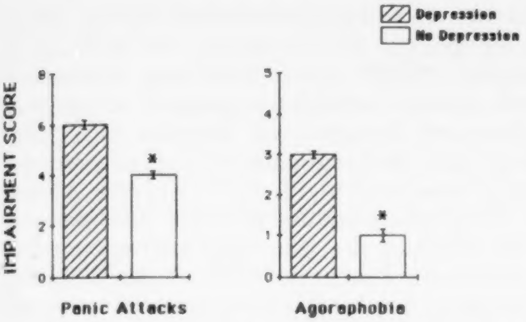


FIGURE 3. The past worst level of impairment associated with panic attacks and agoraphobia in Agoraphobic-Panic Disorder patients with ($N = 41$) and without ($N = 19$) a past or current major depressive episode. (*$p < .001$)

worst impairment secondary to panic attacks did not uniformly occur at the time of the episode of major depression. Thirty-one percent of secondary episodes occurred at a time when impairment secondary to agoraphobia was not most severe. Thirty-nine percent of the secondary episodes occurred when impairment to panic attacks was not most severe. This finding is consistent with the impression that many secondary episodes of major depression were not occurring when panic and phobic symptoms were most severe. The patients with primary depression and those with secondary depression without primary major depression did not differ from each other on measures of severity.

The Effect of Yohimbine in Panic Disorder and Major Depression

It is not known whether the occurrence of the symptoms of major depression and agoraphobia-panic disorder in the same patient represent separate psychiatric disorders, each with a distinct etiology, natural course, and treatment response, or are representative of a common psychophysiologic condition. Of the many brain neuronal systems hypothesized to be involved in human anxiety and depression, the noradrenergic system has been among the most extensively studied in patients with anxiety disorders and major depression. Clinical evidence now provides strong support for the hypothesis that increased noradrenergic function is of etiologic significance in at least some forms of human anxiety (Charney et al., 1984a). There are also data suggesting that a subgroup of depressed patients may exhibit noradrenergic hyperactivity (Esler et al., 1982; Koslow et al., 1983; Lake et al., 1982). Taken together, these studies have led to a hypothesis that increased noradrenergic activity may be involved in the etiology of some forms of panic disorder and major depression.

This hypothesis was studied in a series of investigations in which the regulation of noradrenergic function was evaluated in patients with a diagnosis of Agoraphobia with Panic Attacks or Panic Disorder, and patients with Major Depression (Breier et al., 1984; Price et al., 1984). The ability of yohimbine to increase plasma free 3-methoxy-4-hydroxyphenylglycol (MHPG) levels by blocking the alpha-adrenergic autoreceptor was used to assess presynaptic noradrenergic neuronal regulation in these patient groups in comparison with a healthy control population. The ability of yohimbine to raise blood pressure and to produce subjective anxiety and somatic symptoms was used to provide a more general index of the effect of increased noradrenergic function.

The patients, who were free of major medical problems based upon a physical examination and laboratory tests, were treated as either inpatients or outpatients on the Clinical Research Unit of the Connecticut Mental Health Center. Thirty-nine patients were studied who met a DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) criteria of either agoraphobia with panic attacks (33 patients) or panic disorder (6 patients). There were 28 females and 11 males with median ages of 36 and 35, respectively. Fifty-five patients were studied who met DSM-III criteria for major depression, with 25 of these patients also meeting criteria for melancholia. There were 38 females and 17 males with median ages of 37 and 35, respectively. Twenty healthy subjects (11 females, 9 males) also participated in the study. The healthy subjects were determined to be free of medical and psychiatric disorders on the basis of physical examination, laboratory tests, and a psychiatric interview. The median age of the healthy subjects was 39 for women and 39 for men.

In the agoraphobic-panic disorder patients the severity of clinical symptoms at the time of yohimbine testing was assessed by the HAM-A, the Clinical Global Impression Scale, the Patient Rated Anxiety Scale, and a Panic Attack Inventory that documented the type of stimulus and the frequency and severity of panic attacks that occurred during the preceding 7-day period. The severity of clinical symptoms in the depressed patients was assessed using the HAM-D.

The yohimbine challenge procedure has been described in detail elsewhere (Charney et al., 1984a). Each subject participated in 2 test days. They received four placebo yohimbine capsules on the first test day and four capsules each containing 5 mg of yohimbine on the second test day. Blood samples were obtained for plasma-free MHPG at 15 and 0.5 minutes prior to the yohimbine dose and at 120, 180, and 240 minutes after the dose. Sitting and standing blood pressure and pulse rate were measured at 15 minutes before and 60, 90, 120, 180, and 240 minutes following the dose. Behavioral ratings were administered at 15 minutes before and 60, 90, 120, 180, and 240 minutes following the yohimbine dose. Visual analog scales completed by the subjects were used to evaluate the change of ten different mood status (happy, sad, drowsy, anxious, nervous, energetic, calm, fearful, high, and mellow). The scales were scored in millimetre from the left hand side of 100 mm line to a perpendicular mark made by the subject at the point corresponding to his feeling state at the time. Patients and healthy subjects also completed a 12-item physical symptom scale designed to measure the severity of somatic symptoms commonly associated with states of increased noradrenergic function. Each of the following symptoms were rated on a 4-point scale of 1 = not at all to 4 = severe: nausea, urinary frequency, perspiration, palpitations, restlessness, anorexia, tremulousness, piloerection, hot and cold flashes, lacrimation, rhinorrhea, and muscle aches.

Effects of Yohimbine on Plasma MHPG. Yohimbine significantly increased plasma MHPG in healthy subjects, agoraphobic-panic disorder patients, and depressed patients. At none of the time points measured was the yohimbine-induced increase in plasma-free MHPG significantly different among these three groups. In comparing the increase in plasma MHPG levels following yohimbine with clinical variables, a positive correlation was noted between the increase in MHPG level and the frequency of patient-reported panic attacks ($r = .44$, $p < .05$) in the Agoraphobic-Panic Disorder patients. This correlation indicates that patients experiencing frequent panic attacks have an enhanced MHPG response to yohimbine in comparison to patients with less frequent panic attacks. When a subgroup of patients reporting frequent panic attacks (greater than 2.5 per week, $N = 15$) were compared to a matched control group ($N = 12$), the MHPG rise following yohimbine was significantly greater in the patient group at 120 and 180 minutes in comparison to the healthy controls. There was no difference in the MHPG rise following yohimbine between patients with melancholic and non-melancholic major depression. The MHPG rise following yohimbine in the different groups is shown in Figure 4.

Behavioral Effects of Yohimbine. Yohimbine did not produce marked effects on the visual analog ratings of mood states in either healthy subjects or depressed patients. In contrast, yohimbine had marked anxiogenic

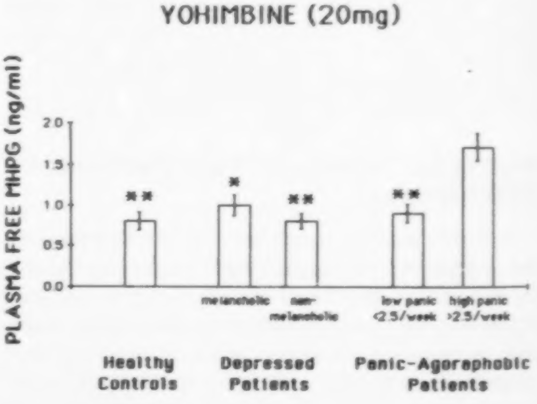


FIGURE 4. Yohimbine-induced increase in plasma-free MHPG ([mean MHPG 2 and 3 hours following yohimbine administration minus baseline] minus [mean MHPG 2 and 3 hours following placebo administration minus baseline]) in Healthy subjects ($N = 20$), Depressed patients ($N = 55$), and Agoraphobic-Panic Disorder patients ($N = 39$). (*$p < .05$ vs high panic Agoraphobic-Panic Disorder patients; **$p < .001$ vs high panic Agoraphobic-Panic Disorder patients)

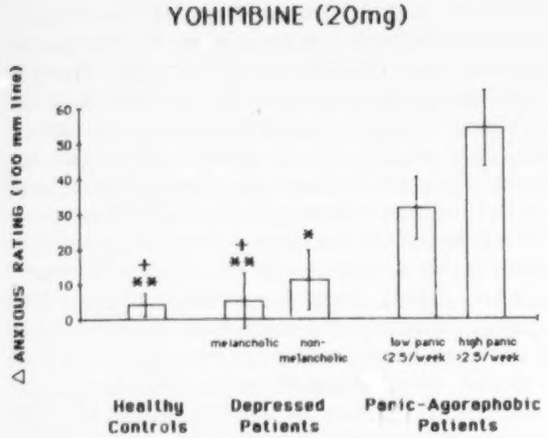


FIGURE 5. Peak increases in patient-rated anxiety ([peak anxiety following yohimbine administration minus baseline] minus [peak anxiety following placebo administration minus baseline]) in Healthy subjects ($N = 20$), Depressed patients ($N = 55$), and Agoraphobic-Panic Disorder patients ($N = 39$). ($+p < .05$ vs low panic Agoraphobic-Panic Disorder patients; $^*p < .05$ vs high panic Agoraphobic-Panic Disorder patients; $^{**}p < .001$ vs high panic Agoraphobic-Panic Disorder patients)

effects in agoraphobic-panic disorder patients. Patients reported that the anxiety produced by yohimbine was similar in quality to that experienced during panic attacks. These effects on anxiety and nervous ratings in the agoraphobic-panic disorder group were significantly different from those experienced by healthy control subjects and patients with depression. Patients with melancholic and non-melancholic major depression did not differ in their behavioral response to yohimbine. This is illustrated in Figure 5, in which the peak increases in anxiety following yohimbine in healthy subjects, depressed patients, and agoraphobic-panic disorder patients are compared.

Effects of Yohimbine on Somatic Symptoms. In healthy subjects yohimbine produced only modest effects on somatic symptoms. Significant increases in comparison to placebo were found only for urinary frequency and piloerection. In contrast, in depressed patients, there were significant increases at one or more time points in all of the somatic symptoms evaluated except for anorexia and lacrimation. The increases in nausea, perspiration, palpitations, restlessness, tremors, hot and cold flashes, and muscle aches were significantly greater than those in healthy subjects at one or more time points. Yohimbine had similar effects on somatic symptoms in the agoraphobia-panic disorder patients. On all 12 somatic symptoms, ratings following yohimbine were significantly higher in patients than in healthy subjects at one or more time points. There were no differences between depressed patients and agoraphobic patients in the yohimbine-induced changes in somatic symptoms.

Effects of Yohimbine on Blood Pressure. Yohimbine produced greater increases in blood pressure in the depressed and agoraphobic-panic disorder patients in comparison to healthy subjects. This was most apparent with sitting systolic blood pressure. The increase in sitting systolic blood pressure following yohimbine in comparison to placebo was significantly greater in the agoraphobia-panic disorder and depressed patients than in healthy subjects at 60 and 90 minutes after the dose. There was no difference between the agoraphobic-panic disorder patients and the depressed patients in the blood pressure response following yohimbine.

Summary

The findings of these investigations of the response to yohimbine in agoraphobic-panic disorder patients, depressed patients, and healthy subjects provides additional evidence supporting a relationship between increased noradrenergic activity and anxiety. Agoraphobic patients with a high frequency of panic attacks demonstrate increased behavioral sensitivity and an increased MHPG response to yohimbine. These findings support the hypothesis that relates increased presynaptic brain noradrenergic activity to the development of panic anxiety. Agoraphobic patients with a low frequency of panic attacks demonstrate increased behavioral sensitivity to yohimbine but their plasma MHPG response to yohimbine does not differ from healthy subjects or depressed patients. It is possible that the enhanced behavioral response to yohimbine in this group is due to abnormal functional sensitivity of postsynaptic alpha-1, alpha-2, or beta-adrenergic receptors.

The plasma MHPG and behavioral response to yohimbine in the depressed patients was no different than that of the healthy subjects. This finding, taken with other studies in the literature, suggests that the regulation of presynaptic brain noradrenergic activity may not be dysfunctional in most depressed patients. The depressed patients did demonstrate an enhanced autonomic and blood pressure response to yohimbine in comparison to healthy subjects. The mechanism responsible for this effect is unclear. However, it may relate to increased peripheral sympathetic activity that has been shown to occur in some depressed patients (Esler et al., 1982; Koslow et al., 1983; Lake et al., 1982). The differential MHPG and anxiogenic response to yohimbine between the patients with frequent panic attacks and depressed patients does not provide support for the hypothesis that increased noradrenergic activity is a common etiology for both panic disorders and major depression.

The Mechanism of Action of Antidepressant and Antipanic Treatment

Elucidation of the mechanism of action of different antidepressant and antipanic drugs should yield important data regarding the etiology of major depression and panic disorders. Tricyclic antidepressants, monoamine oxidose inhibitors, and other antidepressant drugs have important effects on noradrenergic and serotonergic function. In laboratory animals long-term administration of these drugs have been shown to decrease the sensitivity of beta adrenergic and to increase alpha-1 and serotonin receptor sensitivity. Some, but not all, of these drugs have been demonstrated to reduce alpha-2 adrenergic autoreceptor sensitivity, and effects on monoamine turnover is variable (Charney et al., 1981a). It has not been determined which of these effects are responsible for antidepressant and antipanic efficacy. It is possible that different biological effects are responsible for these two clinical properties. Recent work on the spectrum of antidepressant drugs effective for reducing panic attacks provides important data relevant to this question.

There is emerging evidence that the antipanic efficacy of some antidepressant drugs may be due to regulatory effects on noradrenergic function related to decreased beta adrenergic receptor sensitivity, decreased locus coeruleus neuronal firing rate, and decreased brain norepinephrine turnover. Clinical studies have shown that the antidepressants desipramine, imipramine, and amitriptyline reduce plasma MHPG levels or "total body" norepinephrine turnover (Charney & Heninger, in press; Charney et al., 1981b, 1983; Ko et al., 1983; Linnoila et al., 1982). The effects on plasma MHPG occur following a single dose and persist for at least several weeks of treatment (Charney et al., 1981b). In panic disorder patients, the decrease in plasma MHPG induced by imipramine is correlated with a reduction in the signs and symptoms of panic attacks (Ko et al., 1983).

Trazodone and bupropion, drugs with established antidepressant efficacy, have recently been demonstrated not to have antipanic properties (Charney et al., in preparation; Sheehan et al., 1983). Bupropion does not decrease rat brain beta adrenergic receptors or norepinephrine turnover (Ferris & Beaman, 1983). In depressed patients bupropion decreases plasma MHPG less than half the magnitude produced by imipramine, desipramine, and amitriptyline (Charney et al., in preparation). Trazodone does decrease rat brain beta adrenergic receptors, but fails to decrease locus coeruleus firing rate or the spontaneous activity of cortical neurons receiving noradrenergic innervation (Peterson et al., 1983; Shvee-Moreau & Dresse, 1982). In depressed patients trazodone does not significantly decrease plasma MHPG (Price et al., in press). These findings support the hypothesis that the antipanic effects of tricyclic antidepressants and monoamine oxidase inhibitors may be related to actions on noradrenergic function. Alternatively, their antidepressant properties and those of other antidepressant drugs may be due to an ability to increase serotonin function (Charney et al., 1984b).

Benzodiazepine drugs, with the exception of alprazolam, have not been demonstrated to be effective in reducing panic attacks (Klein et al., 1978). This contrasts with the therapeutic actions of these agents for generalized anxiety symptoms. Many of the pharmacological actions of the benzodiazepines can be attributed to their ability to facilitate gamma-aminobutyric acid (GABA) transmission in the brain. The specific enhancement of GABA function is initiated by the interaction of benzodiazepines with benzodiazepine receptors at a variety of central neuronal sites (Tallman et al., 1980).

There have been few preclinical and clinical studies of the effects of benzodiazepines on brain noradrenergic function. Acute administration of diazepam, chlordiazepoxide, and alprazolam reduce the firing rate of the locus coeruleus, probably by activating a benzodiazepine-GABA receptor complex (Grant et al., 1980, 1984). High doses of benzodiazepines (10 mg/kg) reduce baseline norepinephrine (NE) turnover or stress-induced increases in NE turnover (Corrodi et al., 1967, 1971; Fuxe et al., 1975; Taylor & Laverty, 1969). Long-term alprazolam, but not diazepam, administration prevents the reserpine-induced increases in beta adrenergic receptors (Sethy & Hodges, 1982). The effects of diazepam on noradrenergic function were recently studied in healthy subjects (Charney et al., 1983b). Single doses of diazepam (10 mg) did not change blood pressure or plasma MHPG levels. In contrast, in a separate study alprazolam (1.5 mg) significantly decreased systolic and diastolic blood pressure and plasma MHPG in healthy subjects (Charney et al., 1986). The different effects of single doses of alprazolam and diazepam on NE turnover and blood pressure in healthy subjects may be related to the general clinical impression that alprazolam is more efficacious in the treatment of panic disorders than diazepam (Chouinard et al., 1982; Sheehan et al., 1979; Charney & Heninger, 1985a). It will be important to determine if other benzodiazepines with high affinity for benzodiazepine receptors are also antipanic and whether they have similar actions on noradrenergic function as alprazolam.

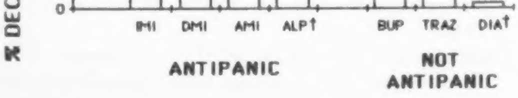


FIGURE 6. The effects of long term treatment with imipramine (IMI), desipramine (DMI), amitriptyline (AMI), alprazolam (ALP), bupropion (BUP), and trazodone (TRAZ) on plasma free MHPG levels. †Diazepam (DIA) effects are from single 10 mg dose. Alprazolam effects are those of long-term and single 1.5 mg dose. (*$p<.05$ from baseline.)

A summary of the effects of the tricyclic antidepressants, bupropion, trazodone, alprazolam, and diazepam on plasma MHPG levels is shown in Figure 6.

Future Directions

The data from the lifetime occurrence study suggest a common vulnerability in some patients for both panic disorder and major depressive illness. However, the neurobiological basis for such a vulnerability has not been identified. An alternative to the common underlying neurobiological disturbance concept is that the presence of one disorder (e.g., panic disorder) might lead to the development of a second disorder (e.g., major depression) with a different pathophysiologic state. One theoretical neurobiologic mechanism for this phenomenon is the functional interactions of different neuronal systems in the brain. For example, dysfunction of one system (e.g., noradrenergic) resulting in panic disorder could cause altered function in a second system (e.g., serotonin) and produce depression. Additional studies are needed to examine both noradrenergic and serotonin function in agoraphobia-panic disorder patients, major depression patients, and patients with a history of both panic disorder and major depression at times in which each disorder is manifested. The studies of the mechanism of antipanic and antidepressant efficacy provide preliminary support for the hypothesis that antipanic effects are related to regulatory actions on noradrenergic function, and antidepressant effects to an enhancement of serotonin function. Assessment of the effects of a spectrum of drugs with antidepressant and/or antipanic efficacy on serotonin and noradrenergic function will provide important additional data relevant to this hypothesis.

References

Breier, A., Charney, D.S., and Heninger, G.R. Major depression in patients with agoraphobia and panic disorder. *Arch. Gen. Psychiatry*, 41:1129–1135, 1984.

Charney, D.S., Breier, A., Jatlow, T.I., and Heninger, G.R. Behavioral, biochemical, and blood pressure responses to alprazolam in healthy subjects: Interactions with yohimbine. *Psychopharmacology*, 88: 133–140, 1986.

Charney, D.S., and Heninger G.R. Noradrenergic function and the mechanism of action of antianxiety treatment: I. The effect of long-term alprazolam treatment. *Arch. Gen. Psychiatry*, 42:458–467, 1985a.

Charney, D.S., and Heninger, G.R. Noradrenergic function and the mechanism of action of antianxiety treatment: II. The effect of long-term imipramine treatment. *Arch. Gen. Psychiatry*, 42:473–481, 1985b.

Charney, D.S., Menkes, D.B., and Heninger, G.R. Receptor sensitivity and the mechanism of action of antidepressant treatment: Implications for the etiology and therapy of depression. *Arch. Gen. Psychiatry*, 38:1160–1180, 1981a.

Charney, D.S., Heninger, G.R., Sternberg, D.E., et al. Plasma MHPG in depression: Effects of acute and chronic desipramine treatment. *Psychiatry Res.*, 5:217–229, 1981b.

Charney, D.S., Heninger, G.R., and Sternberg, D.E. Alpha-2 adrenergic receptor sensitivity and the mechanism of action of antidepressant therapy: The effect of long-term amitriptyline treatment. *Br. J. Psychiatry*, 142:265–275, 1983a.

Charney, D.S., Heninger, G.R., and Redmond, D.E., Jr. Yohimbine induced anxiety and increased noradrenergic function in humans: Effects of diazepam and clonidine. *Life Sci.*, 33:19–29, 1983b.

Charney, D.S., Heninger, G.R., and Breier, A.B. Noradrenergic function in panic anxiety. *Arch. Gen. Psychiatry*, 41:751–764, 1984a.

Charney, D.S., Heninger, G.R., and Sternberg, D.E. Serotonin function and the mechanism of action of antidepressant treatment. *Arch. Gen. Psychiatry*, 41:359–365, 1984b.

Chouinard, G., Annable, L., and Fontaine, R., et al. Alprozolam in the treatment of generalized anxiety and panic disorders: A double-blind, placebo-controlled study. *Psychopharmacolgy*, 77:229–233, 1982.

Corrodi, H., Fuxe, K., Lidbrink, P., and Olson, L. Minor tranquillizers, stress and central catecholamine neurons. *Brain Res.*, 29:1–16, 1971.

Corrodi, H., Fuxe, K., and Hokfelt, T. The effect of some psychoactive drugs on central monoamine neurons. *Eur. J. Pharmacol.*, 1:363–368, 1967.

Esler, M., Turbott, J., and Schwartz, R., et al. The peripheral functions of norepinephrine in depressive illness. *Arch. Gen. Psychiatry*, 39:295–300, 1982.

Ferris, R.M., and Beaman, O.J. Bupropion: A new antidepressant drug, the mechanism of action of which is not associated with down-regulation of postsynaptic β-adrenergic, serotonergic (5-HT$_2$), α_2-adrenergic, imipramine, and dopaminergic receptors in brain. *Neuropharmacology*, 22:1257–1267, 1983.

Fuxe, K., Agnati, L.F., and Bolme, P., et al. The possible involvement of GABA mechanisms in the action of benzodiazepines on central catecholamine neurons. In: Costa, E. and Greengard, P. (eds.), *Mechanism of Action of Benzodiazepines*. New York: Raven Press, 1975, pp. 45-61.

Grant, S.J., Mayor, R., and Redmond, D.E., Jr. Effects of alprozolam, a novel triozolobenzodiazepine, on locus coeruleus unit activity. *Neurosci Abstr*, 10:952, 1984.

Grant, S.J., Huang, Y.H., and Redmond, D.E., Jr. Benzodiazepines attenuate single unit activity in the locus coeruleus. *Life Sci.*, 27:2231–2236, 1980.

Klein, D.F. Anxiety reconceptualized. In: Klein, D.F., and Raskin, J. (eds.), *Anxiety: New Research and Changing Concepts*. New York: Raven Press, 1981, pp. 235-263.

Klein, D.F., Zitrin, C.M., Woerner, M. Antidepressants, anxiety, panic and phobia. In: Lipton, M.A., DiMascio, A., Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*, New York: Raven Press, 1978, pp. 1401–1410.

Ko, G.N., Elsworth, J.D., Roth, R.M., et al. Panic induced elevation of plasma MHPG in phobic anxious patients: Effects of clonidine or imipramine. *Arch. Gen. Psychiatry*, 40:425–430, 1983.

Koslow, S.H., Maas, J.W., Bowden, C.L., et al. Cerebrospinal fluid and urinary biogenic amines and metabolites in depression and mania: A controlled univariate analysis. *Arch. Gen. Psychiatry*, 40:999–1010, 1983.

Lake, C.R., Pickar, D., Ziegler, M.G., et al. High plasma norepinephrine levels in patients with major affective disorder. *Am. J. Psychiatry*, 139:1315–1318, 1982.

Leckman, J.F., Weissman, M.M., Merikangas, K.R., et al. Panic disorder increases risk of major depression, alcoholism, panic, and phobic disorders in affectively ill families. *Arch. Gen. Psychiatry*, 40:1055–1060, 1983.

Linnoila, M., Karoum, F., Calil, H.M., et al. Alteration of norepinephrine metabolism with desipramine and zimelidine in depressed patients. *Arch. Gen. Psychiatry*, 39:1025–1028, 1982.

Peterson, S.L., Tapier, T.C., and Rigdon, G.C. Dissimilar responses of cortical neurons to chronic trazodone or desipramine treatment. *Prog. Neuro-Psychopharm. Biol. Psychiatry*, 7:175–181, 1983.

Price, L.H., Heninger, G.R., and Charney, D.S. Effects of alpha-2 adrenoceptor blockade in depression. Proceedings of the annual meeting of the American Psychiatric Association, Los Angeles, May, 1984.

Price, L.H., Charney, D.S., and Heninger, G.R. Effects of trazodone treatment on alpha-2 adrenoceptor function in depressed patients. *Psychopharmacology*. (In press.)

Sethy, V.H., and Hodges, D.H., Jr: Alprazolam in a biochemical model of depression. *Biochem. Pharmacol.*, 31:3155–3157, 1982.

Sheehan, D.V., Davidson, J., Manschrek, T., et al. Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. *J. Clin. Psychopharmacol.*, 3:28–31, 1983.

Sheehan, D.V., Coleman, J.H., Greenblatt, D.J., et al. Some biochemical correlates of panic attacks and their response to a new treatment. *J. Clin. Psychopharmacol.*, 25:519–526, 1979.

Sheehan, D.V., Ballenger, J., and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch. Gen. Psychiatry*, 37:51–59, 1979.

Shvee-Moreau, J., and Dresse, A. Effect of trazodone on firing rate of central monoaminergic neurons in comparison with various antidepressants. *Arch. Int. Pharmacodyn. Ther.*, 260:299–301, 1982.

Tallman, J.F., Paul, S.M., Skolnick, P., and Gallagher, D.T. Receptors for the age of anxiety: Pharmacology of the benzodiazepines. *Science*, 207:274–281, 1980.

Taylor, K.M., and Laverty, R. The effect of chlordiazepoxide, diazepam and nitrazepam on catecholamine metabolism in regions of the rat brain. *Eur. J. Pharmacol.*, 8:296–301, 1969.

Zitrin, G.M., Klein, D.F., Woerner, M.G., and Ross, D.C. Treatment of Phobias: Comparison of imipramine and placebo. *Arch. Gen. Psychiatry*, 40:125–138, 1983.

The Role of the Locus Coeruleus—Limbic Noradrenergic Transmission in the Action of Antidepressant Drugs[1]

Wojciech Kostowski, M.D.,[2] Adam Plaźnik, M.D.,[2] and Wojciech Danysz, M.A.[2]

Results of many studies indicate that the deficit in noradrenergic (NE) neurotransmission is critically involved in the mechanism of at least certain types of depression (Review: Maj et al., 1984; Schildkraut, 1965; Sugrue, 1983; Vetulani, 1984). The clinical effects of antidepressive drugs are, in accordance with NE concept of depression, explained as resulting from enhancing NE concentration in the synaptic cleft due to different mechanisms. There is, however, a controversy as to the acceptance of this explanation. The effect of NE uptake inhibition, which is characteristic for numerous tricyclic antidepressants, occurs immediately after administration of drugs whilst the therapeutic effects appear after several weeks of treatment. Some well-known amine uptake blockers such as cocaine and amphetamine are poor antidepressants. Moreover, clinically effective new or "atypical" drugs lacking NE uptake inhibiting activity have been found (e.g., mianserine, trazodone, or citalopram). These and other controversies prompted numerous investigators to undertake intensive studies on the mechanism of action of chronically administered antidepressants.

The important finding in this field was that of the Sulser group (Sulser et al., 1978; Vetulani & Sulser, 1975; Vetulani et al., 1976) showing that repetitive (but not single) doses of various antidepressants produced a decrease in the cyclic AMP-generating system response to NE in the rats' cerebral cortex and limbic forebrain. That result was subsequently confirmed and extended in other laboratories including the finding that chronic antidepressants and other antidepressive therapies such as electroconvulsive treatment (ECT) not only did reduce sensitivity of NE receptors associated with the cyclic AMP-generating system, i.e., beta receptors, but also in some cases reduced the number of beta receptors. This phenomenon, called beta adrenoceptor "down regulation," was proposed as the common mechanism of antidepressant action (Mobley & Sulser, 1981, for review).

Further studies have revealed that chronic treatment with antidepressants leads to changes in sensitivity and/or density of alpha adrenoceptors belonging to $alpha_1$ and $alpha_2$ subgroups. Radioligand binding studies have demonstrated increased ^{3}H-prazosin (a selective antagonist of $alpha_1$ receptors) binding sites in the rats' brain (Campbell & McKernan, 1982; Vetulani & Pilc, 1982; Vetulani et al., 1983) but the results with another less selective $alpha_1$ ligand—^{3}H-WB4101—were less conclusive (Peroutka & Snyder, 1979). The findings indicating the $alpha_1$ adrenoceptor "up-regulation" are consistent with other studies which reveal that chronic antidepressants may affect behavioral and electrophysiological responses in a manner indicating increasing NE transmission mediated by postsynaptic $alpha_1$ receptors (Maj et al., 1981; Menkes & Aghajanian, 1981). These receptors seem to mediate exitatory signals at electrophysiological level and to mediate stimulatory behavioral effects (Aghajanian, 1984; Maj et al., 1981).

The concept of $alpha_1$ receptor up-regulation is generally in accordance with the "classical" theory of monoamine deficiency in depression and underlies the fact that antidepressant drugs may increase NE output through excitatory $alpha_1$ receptors (Vetulani, 1984).

The third line of receptor studies concerns the role of inhibitory $alpha_2$ adrenoceptors in depression and the mode of action of antidepressants. These receptors located both pre- and postsynaptically play an inhibitory role in NE transmission. Presynaptic $alpha_2$ adrenoceptors are involved in inhibition of

---

[1] This study was supported by the Ministry of Health, Grant MZ-V-0202, and the Polish Academy of Sciences, Grant Nr. 10.4.

[2] Department of Pharmacology and Physiology of the Nervous System, Psychoneurological Institute, 02-957 Warszawa, Sobieskiego 1-9, Poland.

NE release from nerve endings (Starke, 1977), while postsynaptic receptors inhibit bioelectrical activity of neurons (Svensson et al., 1975). An agonist of alpha$_2$ adrenoceptors, clonidine produces well-known signs of behavioral depression such as sedation (Delini-Stula et al., 1979; Kostowski & Malatyńska, 1983), suppression of avoidance reactions (Robson et al., 1978), and inhibition of self-stimulation in laboratory animals (Franklin & Herberg, 1977) as well as synchronization in the cortical EEG pattern (Florio et al., 1975). Results of many recent studies indicate that antidepressants reduce sensitivity of alpha$_2$ receptors. First, clonidine has been found to produce less marked biochemical and behavioral effects in animals receiving repetitive doses of antidepressants (Kostowski & Malatyńska, 1983; Pilc & Vetulani, 1982) and then, chronic administration of antidepressants reduces clonidine-induced synchronization in the EEG pattern (Kostowski et al., 1984a; Passarelli & Scotti de Carolis, 1982). Studies with ^{3}H-clonidine binding revealed less conclusive results, but generally, when antidepressants were administered for sufficiently long periods (3 weeks and more) they tended to reduce the density of clonidine binding sites (Campbell & McKernan, 1982; Pilc & Vetulani, 1982; Smith et al., 1981; Vetulani, 1984).

Studies on the Role of the Locus Coeruleus (LC) System

These and other findings not discussed here suggest that long-acting administration of antidepressants produces multidirectional changes in the brain adrenoceptors. The functional consequences of this phenomenon are, however, not clear. First of all, the knowledge of the physiological role of adrenoceptors, particularly in regulation of behavioral processes, remains only partially elucidated. Further, only a few studies deal with the correlation between receptor sensitivity and/or density and given behavioral phenomena. One approach to elucidate the functional aspects of receptor changes following chronic antidepressive therapy is to study the behavioral effects of selective lesions and stimulations of NE neurons in the brain. Such experiments were initiated several years ago in pharmacological laboratory at the Psychoneurological Institute in Warszawa (Kostowski, 1980, 1981). One line of that study focused on the possible role of ascending NE systems such as the LC and the ventral bundle (VB) in the mechanism of depression and the mode of action of antidepressants. Following biochemical, pharmacological, and behavioral studies in rats with lesioned NE systems the investigators hypothesized that a defect in the LC function might be responsible for depressive symptoms (Kostowski, 1980, 1981). More recently the investigators found that a bilateral lesion of the LC either electrolytic or induced by 6-hydroxydopamine (6-OHDA) markedly reduced characteristic effects of desipramine in two tests commonly used in studies on antidepressants, i.e., clonidine-induced hypothermia and so-called behavioral despair. Chronic but not acute administration of antidepressant drugs has been reported to antagonize hypothermic action of clonidine in rats (von Voiglander et al., 1978). Since clonidine hypothermia is mediated mostly through alpha$_2$ adrenoceptors, the finding that clonidine produces less marked effect in animals pretreated with antidepressants suggested that this treatment may "down regulate" alpha$_2$ receptors (Vetulani, 1984). The other test, more psychologically oriented, is based on the finding that antidepressants reduce the "immobility" of rats and mice submitted to the unescapable forced swim situation (Porsolt et al., 1979). This test is supposed to reflect the effect of drugs upon NE transmission while the drugs acting upon serotonergic mechanisms are less active (Borsini et al., 1981). The behavioral despair (or forced swim) test is sensitive for single doses of antidepressants but some drugs at least, e.g., desipramine (DMI), produce even stronger characteristic effect, i.e., reduce immobility when administered chronically. Interestingly, the action of DMI and amitryptiline (AMI) in clonidine hypothermia tests was abolished by LC lesions (Figure 1) but also following the administration of DSP-4, a new neurotoxin depleting NE concentrations within the areas innervated by the LC system, e.g., the hippocampus and cerebral cortex (Danysz et al., 1985). Both lesions of the LC

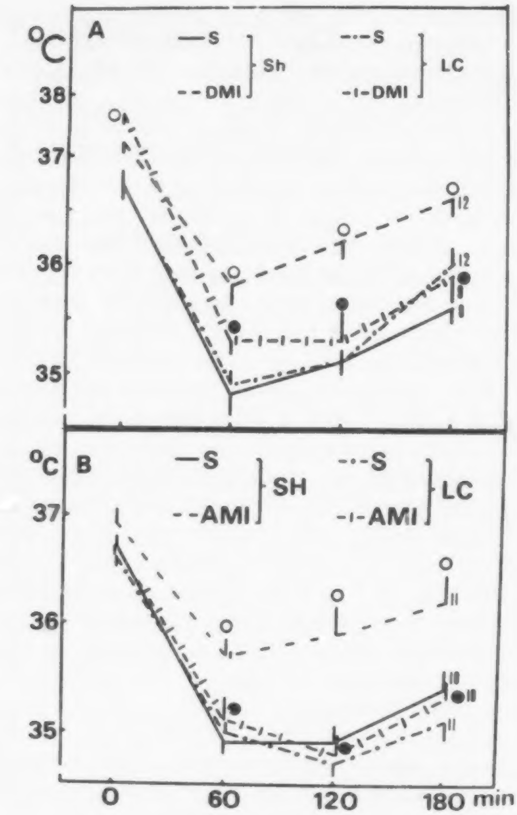


FIGURE 1. Effects of DMI and AMI given chronically (3 weeks, 10 mg/kg i.p. once a day) on clonidine-induced hypothermia (0.2 mg/kg i.p.) in rats with 6-OHDA lesions of the locus coeruleus (LC)(SH = sham-lesioned rats). Mean values SEM, number of animals in each group marked in the figure. Vertical scale: rectal temperature (°C), horizontal scale: time after clonidine injection (in minutes). 6-OHDA was injected bilaterally into the LC (8 µl/µl) 7 days before clonidine (control animals received microinjection of saline). ○ = $p<0.05$ in respect to sham-lesioned saline group, ● = $p<0.05$ in respect to sham-lesioned DMI group (Student's "t" test two-tailed).

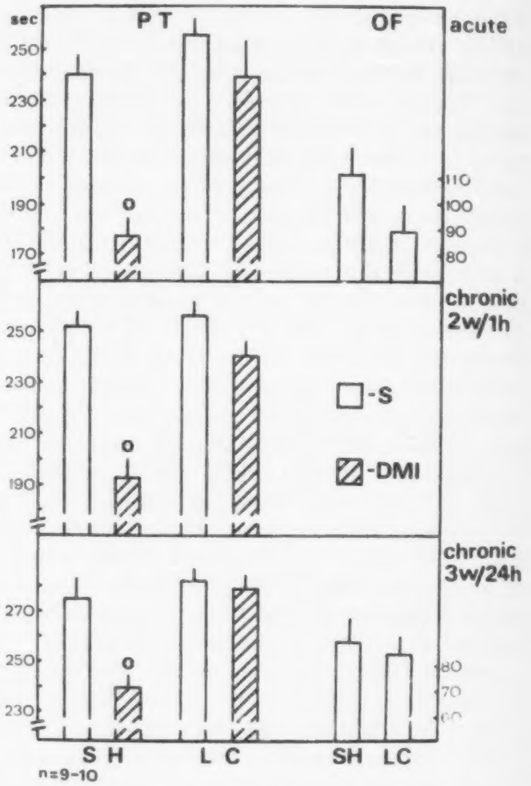


FIGURE 2. Effect of DMI on rats' behavior in the behavioral dispair (forced swim) test. LC = rats with 6-OHDA bilateral lesions of the locus coeruleus, SH = sham-lesioned animals, mean values from 9 to 10 experiments SEM. Upper panel: the animals treated with single dose of DMI (10 mg kg^{-1} i.p.) 7 days after 6-OHDA and then tested 1 hr later in the behavioral dispair (Porsolt) test (PT) (acute treatment). Middle and lower panels: rats treated chronically with DMI (10 mg kg^{-1} i.p. once a day) or saline (S), lesioned and then tested 1 hr after 14th dose of DMI and again 24 hrs after 21st dose of DMI. 6-OHDA lesions were performed on the 7th day of treatment. Both lesioned and sham-lesioned rats (untreated) were tested additionally in the open field (OF) 1 day after PT. Vertical scale = time of immobility in sec (PT) or activity in the OF (number of squares crossed during 5 min of observation). ○ = $p<0.05$ in respect to saline (Student's "t" test, two-tailed). Note that 6-OHDA lesions abolished DMI action in the PT.

and DSP-4 administration were also noticed to prevent the effects of single doses of DMI in the behavioral despair paradigm. The investigators found, moreover, that the effect of chronic (3 weeks) DMI administration on rats' behavior in this test was abolished by a 6-OHDA lesion of the LC (Figure 2). Lesioning of the VB remained, however, uneffective (Danysz et al., 1985; Kostowski et al., 1984b).

Despite the clear-cut effect of LC lesion on AMI action in clonidine hypothermia, the anti-immobility effect of AMI in behavioral despair test remained unchanged following LC lesion. The findings indicate that anatomical integrity of the LC system is critical for DMI action in animal tests commonly used for evaluation of antidepressive effect; it is difficult, however, to ascertain at present whether this hypothesis is true for other antidepressants.

In another set of experiments the investigators found that electrical stimulation of the LC, though not that of the VB, increased the rats' activity in the forced swim (behavioral despair) test, thus producing an effect similar to that brought about by the administration of antidepressants (Danysz et al., 1985; Kostowski et al., 1984b,c). It is of particular interest to note that this effect occurred even after a single stimulation session (30 Hz, 60 minute period of stimulation) and disappeared 24 hours after stimulation (Figure 3). Stimulation of the LC did not produce any behavioral effect in the open field, thus indicating that reduction in immobility was not simply due to an increase in the general activity of rats.

Further study showed that stimulation effect was reduced by pretreatment with phenoxybenzamine, the antagonist of alpha$_1$ adrenoceptors, but not by propranolol, thus indicating that the "antidepressive" effect of LC stimulation was mediated through alpha$_1$ but not beta receptors (Danysz & Kostowski, in press). It is noteworthy that DMI action in the behavioral despair test also could be blocked by alpha$_1$ antagonists (Kitada et al., 1983) but not by propranolol (Danysz & Kostowski, in press) (Figure 4). These results imply the similarity between the stimulation of the LC and DMI action and support our previous hypothesis concerning the possible role of this structure in the mechanism of affective disorders (Kostowski, 1981). It also indicates the role of the alpha$_1$ adrenoceptor system in mediating the antidepressive effect.

Regarding the possible implication of the LC system in both depression and the mode of action of antidepressants, some recent findings from the literature should be mentioned. Interestingly enough, the LC has been found to contain a high density of DMI binding sites (Biegon & Rainbow, 1983). Lesion of this area has been reported to prevent the decrease in beta adrenoceptor sensitivity following long-term DMI administration (Janowsky et al., 1982). Both acute and chronic DMI therapy reduces the firing of LC cells, the chronic treatment, however, prevents the further reduction of firing by the alpha$_2$ ad-

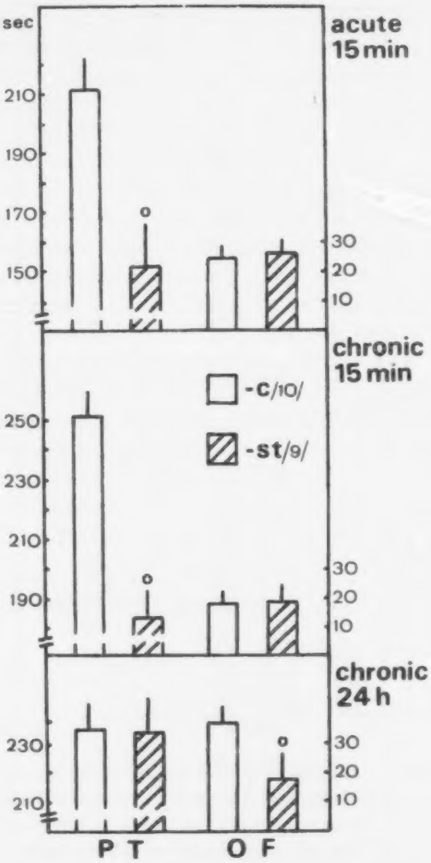


FIGURE 3. Effect of unilateral stimulation of the LC (30 Hz, 2 to 4 V, stimulation session 45 min) on rats' activity in the behavioral despair test (PT) and open field (OF) test. Mean values from 9-10 rats SEM, c = control (unstimulated), st = stimulated. Vertical scale = time of immobility in sec (PT) and activity in the OF (the number of squares crossed during 5 min of observation). Upper panel: the effect of single stimulation session (the rats were tested 15 min after the stimulation in the OF and then immediately in the PT. Middle and lower panels: the same rats were tested 15 min and 24 hrs after 6th stimulation session (one stimulation session daily). ○ = $p < 0.05$ in respect to unstimulated animals (Student's "t" test, two-tailed). Note that stimulation (both single and repetitive) reduced rats' immobility shortly after the stimulation but failed to change the animals' behavior in the PT 24 hrs after the stimulation. Stimulation failed to modulate the rats' activity in the OF 15 min after single session but reduced the activity 24 hrs after the 6th session.

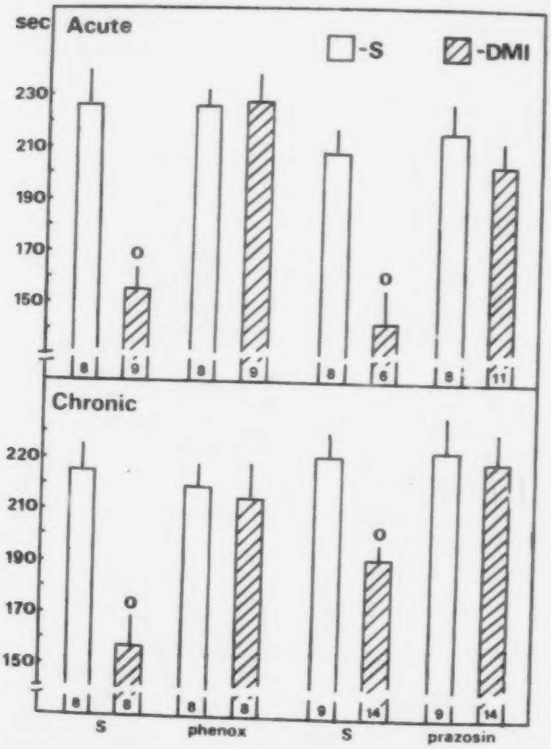


FIGURE 4. Effects of single dose (10 mg kg^{-1} i.p.) and chronic administration (10 mg kg^{-1} i.p. once a day for 3 weeks) of DMI on animals' behavior in behavioral despair test. The animals received 70 minutes before testing single dose of phenoxybenzamine (phenox, 10 mg kg^{-1} i.p.) or prazosin (5 mg kg^{-1} i.p.). In an acute experiment rats were tested 1 hr after DMI while in chronic experiments the immobility was measured 24 hrs after the last (i.e., 21st) dose of DMI. Mean values = SEM (number of rats marked in columns), s = saline group. o = $p<0.05$ in respect to saline.

renoceptor agonist, clonidine (Svensson & Usdin, 1978). Furthermore, Weiss et al. (1981) reported that the time course for the behavioral disturbances induced by unescapable shock in a forced swim task paralleled the NE reduction in the LC more closely than NE alterations on other brain areas.

Possible Role of the Hippocampal NE Transmission

The ascending projection from the LC innervates not only the neocortex but also limbic areas such as hippocampus, amygdaloid complex, and septum (Lindvall & Björklund, 1978). The results of studies upon the LC system prompted the investigators from the Psychoneurological Institute, Warsaw, to analyze the possible role of NE transmission within target areas of this system in the action of antidepressants. Recent experiments focused upon the hippocampus, the structure involved in the regulation of numerous behavioral processes (e.g., emotions, motivations, learning, and memory) which are implicated in phenomenology of depression. This structure has been considered as a promising target area for action of antidepressants for many reasons. First, it contains high density receptor binding sites for ^{3}H-labeled imipramine and desipramine (Sherman & Allers, 1980) and high correlation had been found between imipramine concentration in the rat's hippocampus and positive effect of the drug in the forced swim test. Also, chronic treatment with DMI increased MHPG (3-methoxy-4-hydroxy-phenylethylene glycol, the main NE metabolite in the brain) concentrations in the hippocampus (Miyauchi et al., 1982) as well as the basal firing rate of rat hippocampal neurones (Huang, 1979). Furthermore, the investigators found that DMI was able to produce the "antidepressive" effect in the behavioral despair test when injected into the dorsal hippocampus (Danysz & Kostowski, in press), while extensive electrolytic lesions of the structure completely abolished the effect of drug in this test (A. Plaźnik, personal communication).

The investigators attempted, therefore, to study the effects of agonists of alpha and beta adrenoceptors injected intrahippocampally and to assess the possible changes in their actions after single and multiple doses of antidepressants. Microinjections of NE increased rats' activity in the open field (Plaźnik et al., 1983) and activated the animals in the forced swim (behavioral despair) situation. The effect must have been mediated through both $alpha_1$ and beta receptors since it was attenuated by phenoxybenzamine as well as by propranolol (Plaźnik & Kostowski, in press). A single dose of DMI (10 mg kg^{-1} i.p.) failed to modulate NE action but chronic treatment (3 weeks) markedly potentiated NE effects in both tests mentioned above (Plaźnik & Kostowski, in press; Plaźnik et al., 1984). Both phenylephrine, a selective alpha$_1$ adrenoceptor agonist, and isoprenaline, an agonist of beta receptors, when given in sufficient doses also produced stimulatory effects but only phenylephrine action was potentiated by chronic (but not acute) treatment with DMI (Figure 5). A microinjection of clonidine reduced rats' activity in the open field but failed to produce significant change in the animals' behavior in behavioral despair situation. In rats chronically treated with DMI, clonidine uniformly activated the behavior in both experimental paradigms (Plaźnik & Kostowski, in press; Plaźnik et al., 1984).

The results indicate that chronic desipramine potentiates behavioral phenomena mediated through hippocampal alpha$_1$ receptors and attenuates or even reverses, as in the open-field, inhibitory effects mediated through hippocampal alpha$_2$ adrenoceptors. Interestingly enough, behavioral effects associated with beta adrenoceptors remained unchanged following DMI. This finding indicates the apparent involvement of behavioral effects mediated through the alpha, though not beta, hippocampal adrenoceptors in the action of long-term DMI. This finding, although not supporting the functional role of beta adrenoceptors in the action of antidepressant drugs, is generally in agreement with the results of other authors showing hypersensitivity and increased density of alpha$_1$ adrenoceptors following antidepressant therapy and with those stressing the reduced sensitivity and/or density of inhibitory alpha$_2$ adrenoceptors (Vetulani, 1984).

It is possible that other antidepressants including novel "atypical" drugs modulate the

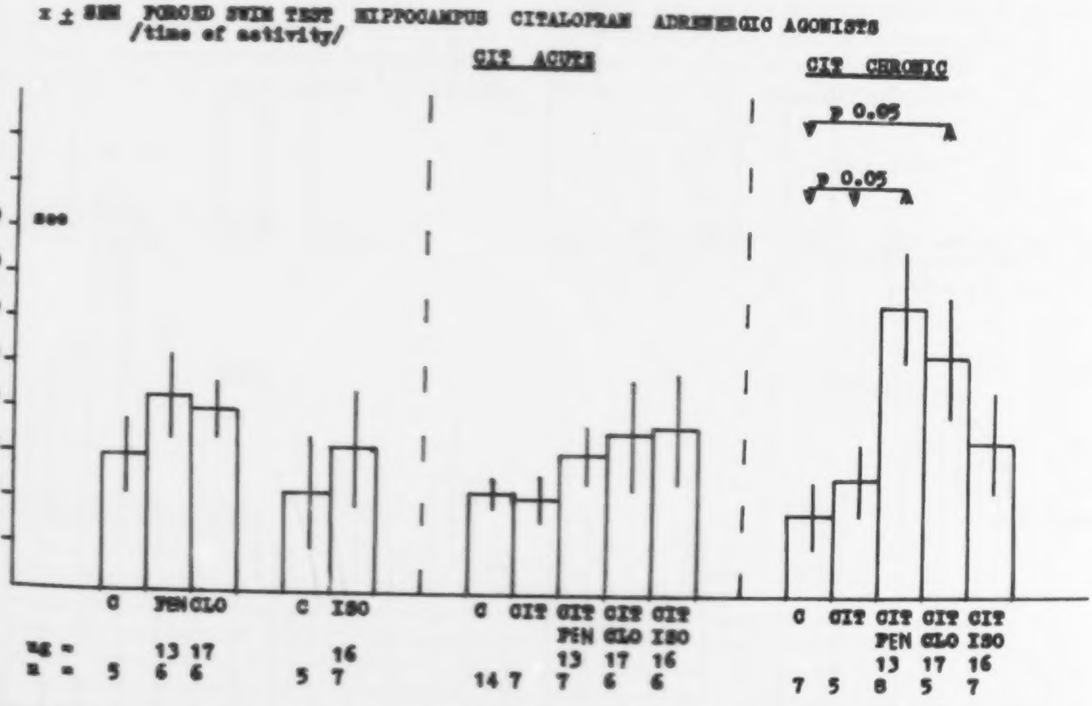


FIGURE 5. Effects of noradrenergic agonists— fenylephrine (FEN, 13 μg), clonidine (CLO, 17 μg) and isoprenaline (ISO, 16 μg) (the doses equimolar to 20 μg of NE, pure substance) injected bilaterally into the dorsal hippocampus—on rats' behavior in the behavioral despair (forced swim) test after acute and chronic pretreatment with DMI. Mean values SEM (*N* = number of rats, C = control). Acute DMI treatment consisted of two daily doses of 10 mg kg^{-1} i.p., the animals were tested 24 hrs after the second dose. Chronic treatment consisted of 21 doses of DMI (10 mg kg^{-1} i.p. once a day), the rats were tested 24 hrs after the last dose, 10 min after intrahippocampal injection of saline. Note that FEN and CLO (but not ISO) produce significant activation in rats treated chronically with DMI (time of activity of animals in vertical scale).

behavioral responses associated with hippocampal alpha adrenoceptors. Most recently the investigators found that citalopram, an atypical drug acting selectively upon serotonin uptake mechanism (Hyttel, 1982) like DMI changed the effects of intrahippocampal phenylephrine and clonidine but failed to potentiate the NE and isoprenaline action. The effect of citalopram occurred, moreover, only in behavioral despair but not the open field (Plaźnik & Kostowski, in press) (Figure 6).

Possible Involvement of Other Limbic Structures

It is likely that limbic structures other than the hippocampus also play a role in the action of antidepressants. Preliminary data indicate that microinjections of NE into the nucleus accumbens produce similarly to intrahippocampal injections, stimulation of rats' behavior in both open field and forced swim test; the latter effect, however, does occur earlier (5 min) than the former (15 min after microinjection) (Plaźnik & Kostowski, in press). Other adrenergic agonists such as phenylephrine, clonidine, and isoprenaline slightly activated the animals' behavior in the forced swim in control (untreated) rats, while in the animals pretreated with multiple doses of DMI both phenylephrine and clonidine (though not isoprenaline) produced strong stimulatory effect. More recent data indicate that dopamine injected into the nucleus accumbens activates the animals' behavior in the forced swim situation, the effect being potentiated following multiple doses of DMI (A. Plaźnik, personal communication). Thus, these preliminary results suggest that NE and possibly also dopaminergic transmission within the nucleus accumbens play a role in the action of DMI.

Conclusion

The results presented here indicate that noradrenergic neurotransmission associated with the LC-hippocampal system (and proba-

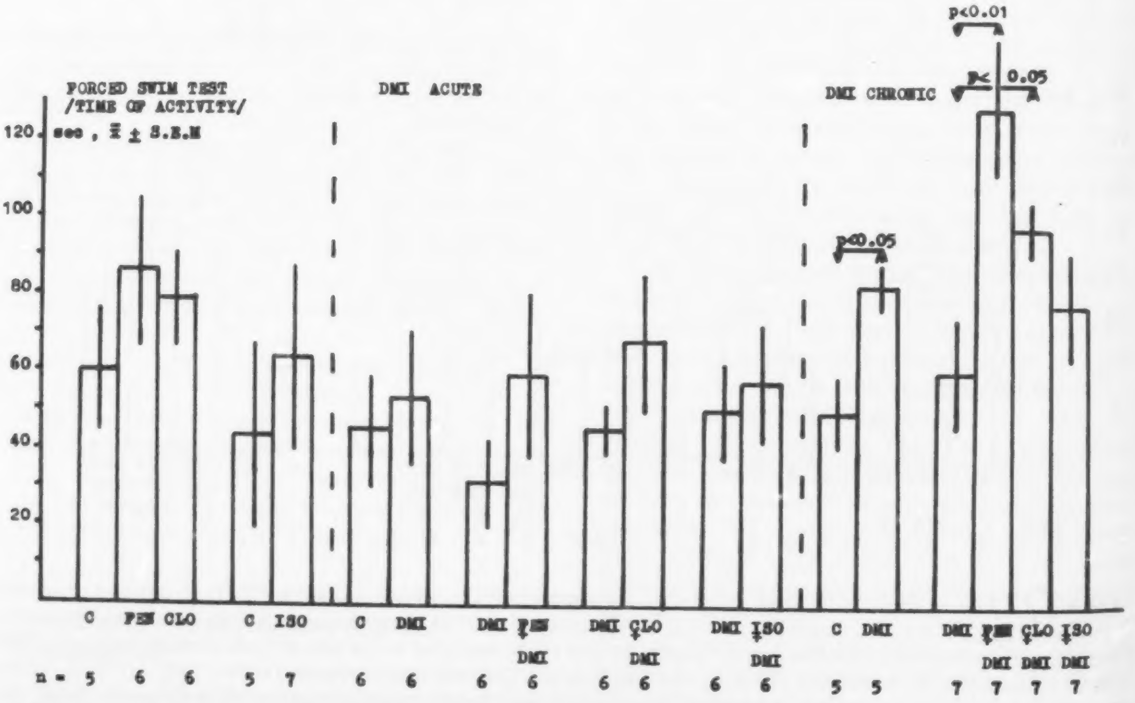


FIGURE 6. Effects of noradrenergic agonists injected intrahippocampally on rats' behavior in the forced swim test after acute and chronic pretreatment with citalopram (the dosage similar to that of DMI: *see* Figure 5 for details). Note that FEN and CLO produce significant activation in rats treated chronically with citalopram (CIT).

bly the other limbic structures) is critically involved in the mode of action of DMI and apparently at least some other antidepressants. The functional consequences of reduction of behavioral responses mediated through alpha$_2$ adrenoceptors are illustrated by the results of the experiments with clonidine. Clonidine inhibits locomotion and exploratory behavior in rats, mice, and other laboratory animals (Delini-Stula et al., 1979; Lal & Shearman, 1981) and produces other symptoms of behavioral depression. The investigators focused recently upon the clonidine effect on dominance behavior in rats competing for food or water (Malatyńska & Kostowski, in press). Clonidine when injected to the dominant rat reduces the dominance and reverses the hierarchy order in the pair of rats (the dominant animal becames submissive). Repetitive doses of tricyclic antidepressants as well as novel "atypical" drugs such as iprindol, mianserine, and salbutamol antagonize clonidine-induced suppression of dominance (Figure 7). This phenomenon seems to be particularly characteristic and selective for antidepressants thus providing the promising possibility to study this group. The finding may reflect also some "psychological" aspects of modulation of alpha$_2$ receptor system in the brain. It is likely that alterations in NE neurotransmission (and perhaps in other transmitter systems) which take place within

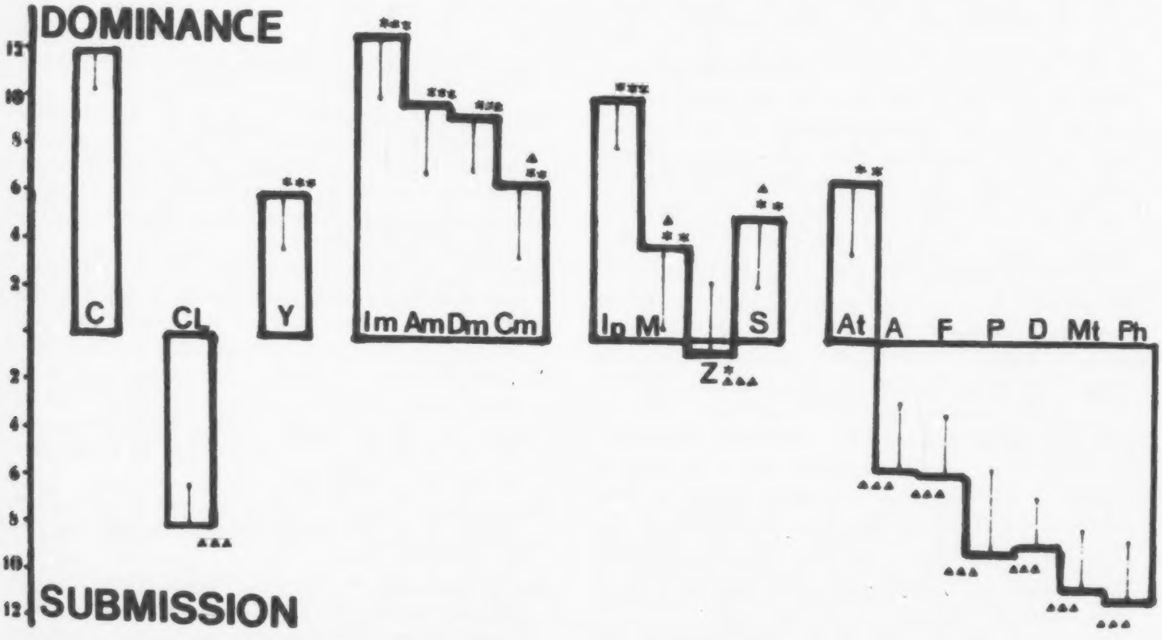


FIGURE 7. Effects of drugs belonging to different groups on dominance behavior in rats competing for food (sweetened milk). Vertical scale: score of dominance expressed as a difference in drinking time between dominant and submissive animals (each 5 sec of drinking was calculated as 1 point). Mean values SEM from 10 to 14 pairs of rats. C = control (saline), CL = clonidine (0.1 mg kg^{-1} i.p.). Drugs were injected once a day in 5 consecutive doses 1 hr before clonidine to the dominant rat (CL group received saline). The test was performed 1 hr after 5th dose of drug-clonidine (or saline-clonidine) combination. Drugs given in combination with clonidine: Y = yohimbine (2.5 mg kg^{-1}), Im = imipramine (2.5 mg kg^{-1}), Am = amitryptiline (2.5 mg kg^{-1}), Dm = desipramine (2.5 mg kg^{-1}), Cm = clomipramine (2.5 mg kg^{-1}), Ip = iprindol (5.0 mg kg^{-1}), M = mianserine (5.0 mgkg^{-1}), Z = zimelidine (5.0 mg kg^{-1}), S = salbutamol (2.0 mg kg^{-1}), At = atropine (1.0 mg kg^{-1}), A = amphetamine (1.0 mg kg^{-1}), F = flupentixol (2 mg kg^{-1} on the 1st day and 1 mg kg^{-1} on the 3rd day), P = pimozide (0.25 mg kg^{-1}), D = diazepam (1.0 mg kg^{-1}), Mt = metergoline (2.0 mg kg^{-1}), and Ph = antazoline (2.5 mg kg^{-1}. ▲ = $p < 0.05$, ▲▲▲ = $p<0.01$ in respect to control (C), x = $p<0.05$, xx = $p<0.02$, xxx = $p<0.01$ in respect to clonidine (CL) group (Student's "*t*" test). Note that only antidepressants (belonging to different groups) and atropine were able to reverse depressive action of clonidine upon the dominance.

the limbic structures and the LC system in the course of chronic antidepressive therapy lead to profound behavioral and psychological effects which are of importance to the mechanism of action of antidepressant drugs.

Summing up, it may be suggested that NE transmission associated with LC- limbic structures is involved in the action of antidepressants. The anatomical and functional integrity of the LC is important for the expression of at least some of the behavioral effects of DMI and AMI. It also seems likely that behavioral phenomena which might be of significance for antidepressive action (e.g., activation of animals' behavior in the behavioral despair situation) are mediated through the alpha$_1$ adrenoceptors rather than beta receptors. Furthermore, the hippocampal alpha adrenoceptors seem to be of particular importance in mediating "antidepressive" behavioral phenomena induced by chronic administration of antidepressants. It was intriguing to establish that the hippocampal (and probably nucleus accumbens) beta adrenoceptors did not participate in the modulation of rats' behavior following long-term DMI and citalopram. The role of beta adrenoceptors in behavioral processes is poorly known, and some authors tend to stress the beta receptor involvement in the control of trophic-metabolic function (Vetulani, 1984).

In conclusion, antidepressants produce characteristic changes in LC-limbic transmission resulting in the facilitation of excitatory signals (e.g., mediated through alpha$_1$ receptors), and in the attenuation of inhibitory signals (e.g., alpha$_2$ receptors). It seems likely that other excitatory signals (e.g., associated with dopaminergic receptors within the nucleus accumbens) could be potentiated following the chronic antidepressants. Further experiments are obviously needed to elucidate this problem.

The "common mechanism" of action of antidepressants should, therefore, be discussed in more functional and anatomical categories. In other words, no conclusion can be drawn from various receptor and metabolic changes until these phenomena are correlated with the function of particular brain structures.

References

Aghajanian, G.K. The physiology of central α and β adrenoceptors. In: *Central Nervous System—Theoretical Aspects.* New York: Allan R. Liss, Inc., 1984, pp. 85–92.

Biegon, A., and Rainbow, T.C. Localization and characterization of ^{3}H-desmethylimipramine binding sites in rat brain by quantitative autoradiography. *J. Neurosci.*, 3:1063–1073, 1983.

Borsini, F., Bondotti, V., Velkov, V., et al. Immobility test: Effects of 5-hydroxytryptaminergic drugs and role of catecholamines in the activity of some antidepressants. *J. Pharm. Pharmacol.*, 33:33–37, 1981.

Cambell, I.C., and McKernan, R.M. Central and peripheral changes in alpha adrenoceptors in the rat after chronic tricyclic antidepressants. *Br. J. Pharmacol.*, (suppl.) 75:100P, 1982.

Danysz, W., Kostowski, W., and Hauptmann, M. Evidence for the locus coeruleus involvement in desipramine action in animal models of depression. *Pol. J. Pharmacol. Pharm.*, 37, 1985. (In press)

Delini-Stula, A., Bauman, P., and Buch, O. Depression of exploratory activity by clonidine in rats as a model for the detection of relative pre- and postsynaptic central noradrenergic receptor selectivity of alpha-adrenolytic drugs. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 307:115–122, 1979.

Florio, V., Bianchi, L., and Longo, V.G. A study of the central effects of sympathomimetic drugs: EEG and behavioral investigations on clonidine and naphazoline. *Neuropharmacology*, 14:707–714, 1975.

Franklin, K.B., and Herberg, L.J. Presynaptic alpha adrenoceptors: The depression of self-stimulation by clonidine and its restoration by piperoxane but not phentolamine or phenoxybenzamine. *Eur. J. Pharmacol.*, 43:33–38, 1977.

Huang, Y.H. Chronic desipramine treatment increases activity of noradrenergic postsynaptic cells. *Life Sci.*, 25:709–716, 1979.

Hyttel, J. Citalopram: Pharmacological profile of a specific serotonin uptake inhibitor with antidepressive activity. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 6:277–295, 1982.

Janowsky, A., Steranka, L.R., Gillespie, D.D., and Sulser, F. Role of neuronal signal input in the down-regulation of central noradrenergic receptor function by antidepressant drugs. *J. Neurochem.*, 39:290–292, 1982.

Kitada, Y., Miyauchi, T., Kanazawa, Y., et al. Involvement of alpha and beta adrenergic mechanisms in the immobility-reducing action of desipramine in the forced swim test. *Neuropharmacology*, 22:1055–1060, 1983.

Kostowski, W. Noradrenergic interactions among central neurotransmitters. In: Essman, W.B. (ed.). *Neurotransmitters, Receptors, and Drug Action*. New York: Spectrum Publications, Inc., 1980, pp. 47–65.

Kostowski, W. Brain noradrenaline, depression and antidepressant drugs: Facts and hypothesis. *Trends Pharmacol. Sci.*, 3:314–317, 1981.

Kostowski, W., and Malatyńska, E. Antagonism of behavioral depression produced by clonidine in the Mongolian gerbil: A potential screening test for antidepressant drugs. *Psychopharmacology*, 79:203–208, 1983.

Kostowski, W., Dyr, W., and Zachcarski, B. A study of the effects of clonidine on the EEG in rats treated with single and multiple doses of antidepressants. *Psychopharmacology*, 84:85–90, 1984a.

Kostowski, W., Danysz, W., and Nowakowska, E. Studies on brain noradrenergic neurons in animal model for antidepressive activity. *Psychopharmacol. Bull.*, 20:320–323, 1984b.

Kostowski, W., Danysz, W., Plaźnik, A., and Nowakowska, E. Studies on the locus coeruleus system in an animal model for antidepressive activity. *Pol. J. Pharmacol. Pharm.*, 36:523–530, 1984c.

Lal, H., and Sherman, G.T. Psychotropic actions of clonidine. In: Lal, H., and Fielding, S. (eds.). *Psychopharmacology of Clonidine*. New York: Alan R. Liss Inc., 1981, pp. 99–145.

Lindvall, O., and Björklund, A. Organization of catecholamine neurons in the rat central nervous system. In: Iversen, L.L., Iversen, S.D., and Snyder, S.H. (eds.). New York: Plenum Press, Inc., Vol. 9, 1978, pp. 139–222.

Maj, J., Mogilnicka, E., Klimek, V., and Kordecka-Magiera, A. Chronic treatment with antidepressants: Potentiation of clonidine-induced aggression in mice via noradrenergic mechanism. *J. Neural. Transm.*, 52:189–197, 1981.

Maj, J., Przegalińcki, E., and Mogilnicka, E. Hypothesis concerning the mechanism of action of antidepressant drugs. *Rev. Physiol. Biochem. Pharmacol.*, 100:1–74, 1984.

Menkes, D.B., and Aghajanian, G.K. Alpha$_1$-adrenoceptor mediated responses in the lateral geniculate nucleus are enhanced by chronic antidepressant treatment. *Eur. J. Pharmacol.*, 74: 27–35, 1981.

Miyauchi, T., Kitada, Y., and Satoh, S. Effect of acute and chronic treatment with cyclic antidepressants on 3-methoxy-4-hydroxy-phenylethylene glycol (MHPG-SO$_4$) contents in various regions of rat brain. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 6: 137–147, 1982.

Mobley, P.L., and Sulser, F. Downregulation of the central noradrenergic receptor system by antidepressant therapies: Biochemical and clinical aspects. In: Enna, S.J., Malick, B.J., and Richelson, F., (eds.). New York: Raven Press, 1981, pp. 31-51.

Passarelli, F., and Scotti de Carolis, A. Effects of chronic treatment with imipramine on the behavioural and electroencephalographic modifications induced by clonidine in the rat. *Neuropharmacology*, 21:591–593, 1982.

Peroutka, S.J., and Snyder, S.H. Multiple serotonin receptors: Differential binding of ^{3}H-5-hydroxytryptamine, ^{3}H-lysergic acid diethylamide and ^{3}H-spiroperidol. *Mol. Pharmacol.* 16:687–699, 1979.

Pilc, A., and Vetulani, J. Attenuation by chronic imipramine treatment of ^{3}H-clonidine binding to cortical membranes and of clonidine-induced hypothermia: The influence of central chemosympathectomy. *Brain Res.*, 238:499–504, 1982.

Plaźnik, A., Danysz, W., and Kostowski, W. Some behavioral effects of microinjections of noradrenaline and serotonin into the hippocampus of the rat. *Physiol. Behav.*, 31:625–631, 1983.

Plaźnik, A., Danysz, W., and Kostowski, W. Behavioral evidence for alpha$_1$-adrenoceptor up and alpha$_2$-adrenoceptor down-regulation in the rat hippocampus after chronic desipramine treatment. *Eur. J. Pharmacol.* 101:305–306, 1984.

Plaźnik, A., and Kostowski, W. Modification of behavioral responses to intrahippocampal injections of noradrenaline and noradrenergic agonists by chronic treatment by desipramine and citalopram: Functional aspects of adaptive receptor changes. *Eur. J. Pharmacol.*, 1985. (In press).

Porsolt, R.D., Anton, N., Blavet, N., and Jalfre, M. Behavioral despair in rats: A new animal model sensitive to antidepressant treatment. *Eur. J. Pharmacol.*, 47: 379–391, 1979.

Robson, R.D., Antonaccio, M.J., Saelens, J.K., and Lebman, J. Antagonism by mianserine and classical alpha adrenoceptor blocking drugs on some cardiovascular and behavioral effects of clonidine. *Eur. J. Pharmacol*, 47:413–442, 1978.

Schildkraut, J.J. The catecholamine hypothesis of affective disorder. *Am. J. Psychiatry*, 122:509–522, 1965.

Sherman, A.D., and Allers, G.L. Relationship between regional distribution of imipramine and its effect on learned helplessness in the rat. *Neuropharmacology* 19:159–162, 1980.

Smith, C.B., Garcia-Sevilla, J.A., and Hollingsworth, P.J. Alpha$_2$ adrenoceptors in rat brain are decreased after long-term tricyclic antidepressant drug treatment. *Brain Res.*, 210:413–418, 1981.

Starke, K. Regulation of noradrenaline release by presynaptic receptor systems. *Rev. Physiol. Biochem. Pharmacol.*, 77:1–124, 1977.

Sugrue, M. Chronic antidepressant therapy and associated changes in central monoaminergic receptor functioning. *Pharmac. Ther.*, 21:1–33, 1983.

Sulser, F., Vetulani, J., and Mobley, P.L. Mode of action of antidepressant drugs. *Biochem. Pharmacol.*, 27:257–260, 1978.

Svensson, T.H., Bunney, B.S., and Aghajanian, G.K.

Inhibition of both noradrenergic and serotonergic neurons in brain by the alpha adrenergic agonist clonidine. *Brain Res.*, 92:291–305, 1975.

Svensson, T.H., and Usdin, T. Feedback inhibition of brain noradrenaline neurons by tricyclic antidepressants: Alpha receptor mediation. *Science*, 202: 1089–1091, 1978.

Vetulani, J., and Sulser, F. Action of various antidepressant treatment reduces reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. *Nature*, 257:495–496, 1975.

Vetulani, J., Stawarz, R.J., Dingell, J.V., and Sulser, F. A possible common mechanism of action of antidepressant drugs. Reduction in the sensitivity of noradrenergic cyclic AMP generating system. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 293: 109–114, 1976.

Vetulani, J., and Pilc, A. Postdecapitation convulsions in the rat measured with an animex motility meter: Relation to central alpha adrenoceptors. *Eur. J. Pharmacol.*, 85:269–275, 1982.

Vetulani, J., Antkiewicz-Michaluk, L., Rokosz-Pelc, A., and Pilc, A. Chronic electroconvulsive treatment enhances the density of ^{3}H-prazosin binding sites in the central nervous system of the rat. *Brain Res.*, 275:392–395, 1983.

Vetulani, J. Complex action of antidepressant treatment on central adrenergic system: Possible relevance to clinical effects. *Pharmacopsychiatry*, 17: 16–21, 1984.

Voiglander, P.T. von, Triezenberg, H.J., and Losey, E.G. Interaction between clonidine and antidepressant drugs: A method for identyfing antidepressant-like agents. *Neuropharmacology*, 17:375–381, 1978.

Weiss, J.M., Goodman, P.A., and Lesito, B.G. Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine and serotonin levels in various regions of the rat brain. *Brain Res. Rev.*, 3:167–205, 1981.

Eating Disorders: A Bibliography (Major Emphasis on Psychopharmacology)

Natalie Reatig[1]

EATING DISORDERS: GENERAL

Andersen, A.E. Anorexia nervosa and bulimia in adolescent males. *Pediatr. Ann.*, 13(12):901–904, 907, 1984.

Autry, J.H., Stover, E.S., and Reatig, N. Anorexia nervosa and bulimia. Nutrition Symposium. *Ann. Rev. Publ. Health*, Vol. 7, 1986.

Carter, P.I., and Moss, R.A. Screening for anorexia and bulimia nervosa in a college population: Problems and limitations. *Addict. Behav.*, 9(4):417–419, 1985.

Bayer, A.E. Eating out of control: Anorexia and bulimia in adolescents. *Children Today*, 13(6):7–11, 1984.

Eating disorders: Too little or too much? (Editorial). *Biol. Psychiatry*, 29(3):233–234, 1985.

Garner, D.M., Olmstead, M.P., Bohr, Y., and Garfinkel, P.E. The Eating Attitudes Test: Psychometric features and clinical correlates. *Psychol. Med.*, 12:871–878, 1982.

Garner, D.M., Olmstead, M.P., and Polivy, J. Development and validation of a multidimensional eating disorder inventory for anorexia nervosa and bulimia. *Int. J. Eating Disord.*, 2:15–34, 1983.

Gwirtsman, H., Kaye, W., Weintraub, M., and Jimerson, D.C. Pharmacologic treatment of eating disorders. *Psychiatr. Clin. No. Am.*, 7(4):863–878, 1984.

Hatsukami, D.K., Mitchell, J.E., and Eckert, E.D. Eating disorders: a variant of mood disorders? *Psychiatr. Clin. No. Am.*, 7(2):349–365, 1984.

Herzog, D.B. Pharmacotherapy of anorexia nervosa and bulimia. *Pediatr. Ann.*, 13(12):915, 918–919, 923, 1984.

Herzog, D.B. Are anorexic and bulimic patients depressed? *Am. J. Psychiatry*, 141(12): 1594–1597, 1984.

Herzog, D.B., and Copeland, P.M. Eating disorders. *N. Engl. J. Med.*, 313(5):295–303, 1985.

Herzog, D.B., and Norman, D.K. Subtyping eating disorders. *Compr. Psychiatry*, 26(4): 375–380, 1985.

Hillard, J.R., and Hillard, P.J. Bulimia, anorexia nervosa, and diabetes: Deadly combinations. *Psychiatr. Clin. No. Am.*, 7(2): 367–379, 1984.

Hudson, J.I., and Hudson, M.S. Endocrine dysfunction in anorexia nervosa and bulimia: Comparison with abnormalities in other psychiatric disorders and disturbances due to metabolic factors. *Psychiatr. Dev.*, 2(4): 237–272, 1985.

Hudson, J.I., Pope, H.G. Jr., and Jonas, J.M. Psychosis in anorexia nervosa and bulimia. *Br. J. Psychiatry*, 145(Oct):420–423, 1984.

Hudson, J.I., Pope, H.G., Jr., Jonas, J.M., and Yurgelun-Todd, D. Family history study of anorexia nervosa and bulimia. *Br. J. Psychiatry*, 142:133–138, 1983.

Hudson, J.I., Pope, H.G. Jr., Jonas, J.M., and Yurgelun-Todd, D. Phenomeologic relationship of eating disorders to major affective disorder. *Psychiatr. Res.*, 9(4):345–354, 1983.

Johnson, C., Stuckey, M., and Mitchell, J. Psychopharmacological treatment of anorexia nervosa and bulimia: Review and synthesis. *J. Nerv. Ment. Dis.*, 171(9):524–534, 1983.

Katz, J.L., Kuperberg, A., Pollack, C.P., et al. Is there a relationship between eating disorder and affective disorder? New evidence from sleep recordings. *Am. J. Psychiatry*, 141(6):753–759, 1984.

Kog, E., and Vandereycken, W. Family characteristics of anorexia nervosa and bulimia: A review of the critical literature. *Clin. Psychol. Rev.*, 5(2):159ff. 1985.

Kaye, W.H., Ebert, M.H., Gwirtsman, H.E., and Weiss, S.R. Differences in brain serotonergic metabolism between nonbulimic and bulimic patients with anorexia nervosa. *Am. J. Psychiatry*, 141(12):1598–1601, 1984.

---

[1] Program Specialist, Special Populations Section, Pharmacologic and Somatic Treatments Research Branch, National Institute of Mental Health, 5600 Fishers Lane, Rockville, MD 20857. Currently in the Office of the Director, Division of Education and Service, Systems Liaison, Rm. 11C27

Male anorectics and bulimics: Study finds evidence of sexual inactivity, homosexuality. *Med. World News*, 25(190):67, 1984.

Murphy, D.L., Siever, L.J., and Insel, T.R. Therapeutic responses to tricyclic antidepressants and related drugs in non-affective disorder patient populations. Prog. Neuropsychopharmacol. *Biol. Psychiatry*, 9(1):3–13, 1985.

Mallick, M.J. Anorexia nervosa and bulimia: Questions and answers for school personnel. *J. School Health*, 54(8):299–301, 1984.

Piran, N., Kennedy, S., Garfinkel, P.E., et al. Affective disturbance in eating disorders. *J. Nerv. Ment. Dis.*, 173(7):395–400, 1985.

Pope, H.G., Hudson, J.I., and Yugelun-Todd, D. Anorexia nervosa and bulimia among 300 suburban women shoppers. *Am. J. Psychiatry*, 141(2):292–294, 1984.

Viesselman, J.O., and Roig, M. Depression and suicidality in eating disorders. *J. Clin. Psychiatry*, 46(4):118–124, 1985.

ANOREXIA NERVOSA

Agras, W.S., and Kraemer, H.C. The treatment of anorexia nervosa: Do different treatments have different outcomes? Research publications: *Assoc. Res. Nerv. Ment. Dis.*, 62:193–207, 1984.

Altshuler, K.Z., and Weiner, M.F. Anorexia nervosa and depression: A dissenting view. *Am. J. Psychiatry*, 142(3):328–332, 1985.

Andersen, A.E., and Mickalide, A.D. Anorexia nervosa in the male: An underdiagnosed disorder. *Psychosomatics*, 24(12): 1066–1075, 1983.

Baranowska, B., Rozbicka, G., Jeske, W., and Abdel-Fattah, M.H. The role of endogenous opiates in the mechanism of inhibited luteinizing hormone (LH) secretion in women with anorexia nervosa: The effect of naloxone on LH, follicle-stimulating hormone, prolactin, and beta-endorphin secretion. *J. Clin. Endocrin. Metab.*, 59(3): 412–416, 1984.

Beaumont, P.J.V. Further categorization of patients with anorexia nervosa. *Aust. NZ J. Psychiatry*, 11:223–226, 1977.

Beaumont, P.J.V., George, G.C.W., and Smart, D.E. Dieters and vomiters and purgers in anorexia nervosa. *Psychol. Med.*, 6:617–622, 1976.

Beaumont, P.J.V., Simpson, K.G., and Abraham, S.F. The psychosexual histories of adolescent girls and young women with anorexia nervosa. *Psychol. Med.*, 11:131–140, 1981.

Biederman, J., Herzog, D.B., Rivinus, T.M., et al. Urinary MHPG in anorexia nervosa patients with and without a concomitant major depressive disorder. *J. Psychiatry Res.*, 18(2):149–160, 1984.

Biederman, J., Herzog, D.V., Rivinus, T.M., et al. Amitriptyline in the treatment of anorexia nervosa: A double-blind, placebo-controlled study. *J. Clin. Psychopharmacol.*, 5(1):10–16, 1985.

Biederman, J., Rivinus, T.M., Herzog, D.B., et al. High frequency of HLA-Bw16 in patients with anorexia nervosa. *Am. J. Psychiatry*, 141(9):1109–1110, 1984.

Biederman, J., Rivinus, T.M., Herzog, D.B., et al. Platelet MAO activity in anorexia nervosa patients with and without a major depressive disorder. *Am. J. Psychiatry*, 141(10):1244–1247, 1984.

Boag, F., Weerakoon, J., Ginsburg, J., Havard, C.W., and Dandona, P. Diminished creatinine clearance in anorexia nervosa: Reversal with weight gain. *J. Clin. Pathol.*, 38(1):60–63, 1985.

Buchan, T. and Gregory, L.D. Anorexia nervosa in a black Zimbabwean. *Br. J. Psychiatry*, Sept(145):326–330, 1984.

Burns, T., and Crisp, A.H. Outcome of anorexia nervosa in males. *Br. J. Psychiatry*, 145:319–325, 1984.

Casper, R.C. Hypothalamic dysfunction and symptoms of anorexia nervosa. *Psychiatry Clin. No. Am.*, 7(2):201–213, 1984.

Casper, R.C., Halmi, K.A., Goldberg, S.C., et al. Disturbances in body image estimation as related to other characteristics and outcome in anorexia nervosa. *Br. J. Psychiatry*, 134:60–66, 1979.

Collipp, P.J. Anorexia nervosa and binge vomiting. *Pediatr. Ann.*, 13(7):538–542, 1984.

Crisp, A.H. Some aspects of the evolution, presentation and follow-up of anorexia nervosa. *Proc. R. Soc., (Lond.) Med.*, 58: 814–820, 1965.

Crisp, A.H. Anorexia nervosa. *Br. Med. J.*, 287:855–858, 1983.

Crisp, A.H. *Anorexia nervosa: Let Me Be.* London: Academic Press, 1980.

Crisp, A.H., Kalucy, R.S., Lacey, J.H., et al. Long-term prognosis in anorexia nervosa: Some factors predictive of outcome. In: Vigersky, R.A. (ed.), *Anorexia Nervosa.* New York: Raven Press, 1977.

Dally, P.J., Oppenheim, G.B., and Sargant, W.A. A new treatment of anorexia nervosa (chlorpromazine). *Br. Med. J.*. 2:633, 1958.

Dally, P.J., and Sargant, W.A. A new treatment for anorexia nervosa. (chlorpromazine). *Br. Med. J.*, 1:1770–1773, 1960.

Darby, PL., Garfinkel, P.E., Garner, D.M., and Coscina, D.V. (eds.) *Anorexia Nervosa: Recent Developments in Research.* New York: Alan Liss, (In press)

Eckert, E.D., Goldberg, S.C., and Halmi, K.A. Behavior therapy in anorexia nervosa. *Br. J. Psychiatry*, 134:55–59, 1979.

Eckert, E.D., Goldberg, S.C., Halmi, K.A., et al. Depression in anorexia nervosa. Psychol. Med., 11:1–8, 1981.

Eckert, E.d., Goldberg, S.C., Halmi, K.A., et al. Alcoholism in anorexia nervosa.In: Pickens, R.W., and Heston, L.L. (eds.), Psychiatric Factors in Drug Abuse. New York: Grune and Stratton, 1979, pp. 267-283.

Falk, J.R., Halmi, K.A., Eckert, E., and Casper, R. Primary and secondary amenorrhea in anorexia nervosa. In: S. Golub (ed.), *Proceedings of the Society for Menstral Cycle Research: Menarche - An Interdisciplinary Review.* New York: Springer (In press)

Falk, J.R., and Halmi, K.A. Amenorrhea in anorexia nervosa: Examination of the critical body weight hypothesis. *J. Biol. Psychiatry.* (In press)

Garfinkel, P.E., Brown, G.M., and Darby, P.L. The psychoendocrinology of anorexia nervosa. *Int. J. Ment. Health*, 9:162–193, 1981.

Garfinkel, P.E., and Garner, D.M. *Anorexia Nervosa: A Multidimensional Perspective.* New York: Brunner/Mazel, 1982.

Garner, D.M., and Bemis, K. A cognitive behavioral approach to anorexia nervosa. *Cogn. Ther. Res.*, 6:1–27, 1982.

Garner, D.M., and Garfinkel, O. An overview of sociocultural factors in the development of anorexia nervosa. In: P. Darby, P.E. Garfinkel, D.M., Garner, et. al. (eds.) *Anorexia Nervosa: Recent Developments in Research.* New York: Alan R. Liss, Inc. 1983.

Garner, D.M., and Garfinkel, P.E. The Eating Attitudes Test: An index of the symptoms of anorexia nervosa. *Psychol. Med.*, 9:273–279, 1979.

Garner, D.M., Olmsted, M.P., Polivy, J., and Garfinkel, P.E. Comparison between weight-preoccupied women and anorexia nervosa. *Psychosom. Med.*, 46(3):255–266, 1984.

Gerner, R.H., Cohen, D.J., Fairbanks, L., et al. CSF neurochemistry of women with anorexia nervosa and normal women. *Am. J. Psychiatry*, 141(11):1441–1444, 1984.

Gerner, R.H., and Gwirtsman, H.E. Abnormalities of dexamethasone suppression test and urinary MHPG in anorexia nervosa. *Am. J. Psychiatry*, 138:650–653, 1981.

Gershon, E.S., Hamovit, J.R., Schreiber, J.L. et al. Anorexia nervosa and major affective disorders associated in families: A preliminary report. In:Guze, S.B., and Earls, F.J. (eds.), *Childhood Psychopathology and Development.* New York: Raven Press, 1983.

Gershon, E.S., Schreiber, J.L., Hamovit, J.R., et al. Clinical findings in patients with anorexia nervosa and affective illness in their relatives. *Am. J. Psychiatry*, 141(11):1419–1422, 1984.

Goldberg, S.C., Eckert, E.D., Casper, R.C., et al. Factors influencing hospital differences in weight gain in anorexia nervosa. *J. Nerv. Ment. Dis.*, 168:181–183, 1980.

Goldberg, S.C., Eckert, E.D., Halmi, K.A., et al. Cyproheptadine in the treatment of anorexia nervosa. *Arch. Gen. Psychiatry*, 37:1060, 1980.

Goldberg, S.G., Eckert, E.D., Halmi, K.A., et al. Effects of cyproheptadine on symptoms and attitudes in anorexia nervosa. (Letter to the editor). *Arch. Gen. Psychiatry*, 30:1083, 1980.

Goldberg, S.C., Halmi, K.A., Eckert, E.D., et al. Attitudinal dimensions in anorexia nervosa. *J. Psychiatry Res.*, 15:239–251, 1980.

Goldberg, S.C., Halmi, K.A., Eckert, E.D., et al. Cyproheptadine in anorexia nervosa. *Br. J. Psychiatry*, 134:67–70, 1979.

Golden, N., and Sacker, I.M. An overview of the etiology, diagnosis, and management of anorexia nervosa. *Clin Pediatr.* (Phila)., 23(4):209–214, 1984.

Gordon, D.P., Halmi, K.A., and Ippolito, P.M. A comparison of the psychological evaluation of adolescents with anorexia nervosa and of adolescents with conduct disorders. *J. Adolesc.*, 7(3):245–266, 1984.

Gross, H.A., Ebert, M.H., Faden, V.B., et al. A double-blind controlled trial of lithium carbonate in primary anorexia nervosa. *J. Clin. Psychopharmacol.*, 1:376–381, 1981.

Gross, H., Ebert, M.H., Faden, V.B., et al. A double-blind trial of delta-9 Tetrahydrocannabinol in primary anorexia nervosa. *J. Clin. Psychopharmacol.*, 3(3):165–171, 1983.

Gross, H.A., Lake, C.R., Ebert, M.H., et al. Catecholamine metabolism in primary anorexia nervosa. *J. Clin. Endocrinol. Metab.*, 49:805–809, 1979.

Hall, A., Slim, E., Hawker, F., and Salmond, C. Anorexia nervosa: long-term outcome in 50 female patients. *Br. J. Psychiatry*, 145:407–413, 1984.

Halmi, K.A. The state of research in anorexia nervosa and bulimia. *Psychiatry Dev.*, 1(3):247–262, 1983.

Halmi, K.A. Behavior and drug therapy for anorexia nervosa. *Behav. Med. Update*, 4(3):13–15, 1983.

Halmi, K.A., Casper, R.C., Eckert, E.D., et al., Unique features associated with age of onset of anorexia nervosa. *Psychiatry Res.*, 1:209–215, 1979.

Halmi, K.A., Dekirmenjian, H., Davis, J.M., et al. Catecholamine metabolism in anorexia nervosa. *Arch. Gen. Psychiatry*, 35:458–460, 1978.

Halmi, K.A., Eckert, E., and Falk, J.R. Cyproheptadine, an antidepressant and weight-inducing drug for anorexia nervosa. *Lancet*, 1:1357–1358, 1982.

Halmi, K.A., and Falk, J.R. Pretreatment and post-treatment discriminators of outcome in anorexia nervosa. Proceedings of the Third World Congress of Biological Psychiatry, Stockholm, Sweden, 1981.

Halmi, K.A., and Falk, J.R. Anorexia nervosa: A study of outcome discriminators in exclusive dieters and bulimics. *J. Acad. Child Psychiatry.* (In press)

Halmi, K.A., and Falk, J.R. Common physiological changes in anorexia nervosa. *Int. J. Eat Disord.*, 1:16–27, 1981.

Halmi, K.A., and Falk, J.R. Anorexia nervosa: a study of outcome discriminators in exclusive dieters and bulimics. *J. Acad. Child Psychiatry.* (In press)

Halmi, K.A., Goldberg, S.C., Eckert, E., et al. Preatreatment evaluation in anorexia nervosa. In: Vigersky, R.A. (ed.), *Anorexia Nervosa*, New York: Raven Press, 1977.

Halmi, K.A., Goldberg, S.C., Casper, R.C., et al. Pretreatment predictors of outcome in anorexia nervosa. *Br. J. Psychiatry*, 134: 71–78, 1979.

Halmi, K.A., Powers, P., and Cunningham, S. Treatment of anorexia nervosa with behavior modification. *Arch. Gen. Psychiatry*, 32:93–96, 1975.

Halmi, K.A., and Sherman, B.M. Prediction of treatment response in anorexia nervosa. (Series: *Biological Psychiatry Today*) Amsterdam: Elsevier/North-Holland Biomedical Press, 1979, pp. 609-614.

Hall, A., Slim, E., Hawker, F., and Salmond, C. Anorexia nervosa: Long-term outcome in 50 female patients. *Br. J. Psychiatry*, 145(Oct):407–413.

Hawley, R.M. The outcome of anorexia nervosa in younger subjects. *Br. J. Psychiatry*, 146(June):657–660, 1985.

Hendren, R.L. Depression in anorexia nervosa. *J. Am. Acad. Child Psychiatry*, 22:59–62, 1983.

Holland, A.J., Hall, A., Murray, R., et al. Anorexia nervosa: A study of 34 twin pairs and one set of triplets. *Br. J. Psychiatry*, 145:414–419, 1984.

Hsu, L.K.G., Crisp, A.H., and Harding, B. Outcome of anorexia nervosa. *Lancet*, 1:61–65, 1979.

Hsu, L.K.G. Outcome of anorexia nervosa. A review of the literature (1954-1978). *Arch. Gen. Psychiatry*, 37:1041–1046, 1980.

Hudson, J.I., Pope, H.G., Jonas, J.M., and Yurgelun-Todd, D. Treatment of anorexia nervosa with antidepressants. *J. Clin. Psychopharmacol.*, 5(1):17–23, 1985.

Huse, D.M., and Lucas, A.R. Dietary patterns in anorexia nervosa. *Am. J. Clin. Nutr.*, 40(2):251–254, 1984.

Johanson, A.J., and Knorr, N.J. L-Dopa as treatment for anorexia nervosa. In: Vigersky, R.A., (ed.) *Anorexia Nervosa.* Raven Press: New York, 1977, pp. 363-372.

Johanson, A.J., and Knorr, N.J. Treatment of anorexia nervosa by levodopa. *Lancet*, 2:591, 1974.

Johnston, J.L., Leiter, L.A., Burrow, G.N., et al Excretion of urinary catecholamine metabolites in anorexia nervosa: Effect of body composition and energy intake. *Am. J. Clin. Nutr.*, 40(5):1001–1006, 1984.

Jones, D.J., Fox, M.M., Babigian, H.M., et al. Epidemiology of anorexia nervosa in Monroe County, N.Y. 1960-1976. *Psychosom. Med.*, 42:551–558, 1980.

Kaye, W.H., Ebert, M.H., Raleigh, M., and Lake, R. Abnormalities in CNS monoamine metabolism in anorexia nervosa. *Arch. Gen. Psychiatry*, 41(4):350–355, 1984.

Kuhs, H., and Mester, H. [Dexamethasone suppression test in anorexia nervosa]. *Eur. Arch. Psychiatry Neurol. Sci.*, 234(5):335–340, 1985.

Lacey, J.H., and Crisp, A.H. Hunger, food intake and weight: The impact of clomipramine on a refeeding anorexia nervosa population. *Post Grad. Med. J.*, 56:79–85, 1980.

McSherry, J.A. The diagnostic challenge of anorexia nervosa. *Am. Fam. Physician*, 29(2):141–145, 1984.

Miller, D., and Carlton, B.S. The etiology and treatment of anorexia nervosa. *Adolesc. Psychiatry*, 12:219–232, 1985.

Moldofsky, H., Jeuniewic, N., and Garfinkel, P.E. Preliminary report on metoclopramide in anorexia nervosa. In: Vigersky, R.A. (ed.) *Anorexia Nervosa*. New York: Raven Press, 1977.

Moore, D.C. Amitriptyline therapy in anorexia nervosa. *Am. J. Psychiatry*, 134: 1303–1304, 1977.

Moore, R., Mills, I.H., and Forster, A. Naloxone in the treatment of anorexia nervosa: Effect on weight gain and lipolysis. *J. R. Soc. (Lond.) Med.*, 74:129–131, 1981.

Morgan, H.G., Purgold, J., and Welbourne, J. Management and outcome in anorexia nervosa. A standardized prognostic study. *Br. J. Psychiatry*, 143(Sept.):282–287, 1983.

Morgan, H.G., and Russell, G.F. Value of family background and clinical features as predictors of long-term outcome in anorexia nervosa: Four year follow-up study of 41 patients. *Psychol. Med.*, 5:355–371, 1975.

Munford, P.R., Tarlow, G., and Gerner, R. An experimental analysis of the interaction of chemotherapy and behavior therapy in anorexia nervosa. *J. Nerv. Ment. Dis.*, 172(4):228–231, 1984.

Munoz, R.A. The basis for the diagnosis of anorexia nervosa. *Psychiatry Clin. N. Am.*, 7(2):215–221, 1984.

Needleman, H.L, and Waber, D. The use of amitriptyline in anorexia nervosa. In: Vigersky, R.A. (ed.), *Anorexia Nervosa*. New York: Raven Press, 1977.

Nussbaum, M., Shenker, I.R., Baird, D., et al. Follow-up investigation in patients with anorexia nervosa. *J. Pediatr.*, 106(5):835–840, 1985.

Pawlowski, C.T. Cyproheptadine: Weight-gain and appetite stimulation in essential anorexia patients. *Curr. Ther. Res.*, 18: 673–678, 1975.

Plantley, F. Pimozide in treatment of anorexia nervosa. (Letter) *Lancet*, 1:1105, 1977.

Powers, P.S., and Powers, H.P. Inpatient treatment of anorexia nervosa. *Psychosomatics*, 25:7:512–527, 1984.

Pumariega, A.J., Edwards, P., and Mitchell, C.B. Anorexia nervosa in black adolescents. *J. Am. Acad. Child Psychiatry*, 23(1): 111–114, 1984.

Rivinus, T.M., Biederman, J., Herzog, D.B., et al. Anorexia nervosa and effective disorders: A controlled family history study. *Am. J. Psychiatry*, 141(11):1414–1418, 1984.

Rockwell, W.J., Nishita, J.K., and Ellinwood, E.H. Jr. Anorexia nervosa: Current perspectives in research. *Psychiatr. Clin. No. Am.*, 7(2):223–233, 1984.

Sargent, J., and Liebman, R. Outpatient treatment of anorexia nervosa. *Psychiatr. Clin. N. Am.*, 7(2):235–245, 1984.

Schleimer, K. Dieting in teenage schoolgirls. A longitudinal prospective study. *Acta Paediatr. Scand. [Suppl.], 312:1–54, 1983.*

Skoog, D.K., Andersen, A.E., and Laufer, W.S. Personality and treatment effectiveness in anorexia nervosa. *J. Clin. Psychol.*, 40(4):955–961, 1984.

Silber, T.J. The role of the pediatrician in the diagnosis and management of anorexia nervosa. *Pediatr. Ann.*, 13(12):886–890, 1984.

Stein, G.S., Hartshorn, J., Jones, J., et al. Lithium in a case of severe anorexia nervosa. *Br. J. Psychiatry*, 140:526–528, 1982.

Steinhausen, H.C., and Glanville, K. A long-term follow-up of adolescent anorexia nervosa. *Acta. Psychiatr. Scand.*, 68(1):1–10, 1983.

Strober, M., Salkin, B., Burroughs, J., et al. Validity of the bulimia-restricter distinction in anorexia nervosa: Parental personality characteristics and family psychiatric morbidity. *J. Nerv. Ment. Dis.*, 170:345–351, 1982.

Suematsu, H., Koboki, T., and Itoh, T. Statistical studies on the prognosis of anorexia nervosa. *Psychother. Psychosom.*, 43(2):104–112, 1985.

Suematsu, H., Ishikawa, H., Kuboki, T., and Itoh, T. Statistical studies on anorexia nervosa in Japan: Detailed clinical data on 1,011 patients. *Psychother. Psychosom.*, 43(2):96–103, 1985.

Tan, T.L., Handford, H.A., and Soldatos, C.R. Current therapy of eating disorders I: Anorexia nervosa. *Rational Drug Ther.*, 18(1):1–6, 1984.

Thomas, J.P., and Szmukler, G.I. Anorexia nervosa in patients of Afro-Caribbean extraction. *Br. J. Psychiatry*, 146(June): 653–656, 1985.

Tolstrup, K., Brinch, M., Isager, T., et al. Long-term outcome of 151 cases of anorexia nervosa. The Copenhagen Anorexia Nervosa Follow-up Study. *Acta Psychiatr. Scand.*, 71(4):380–387, 1985.

Touyz, S.W. and Beumont, P.J. Anorexia nervosa. A follow-up investigation. *Med. J. Austr.*, 141(4):219–222, 1984.

Vandereycken, W. Neuroleptics in the short-term treatment of anorexia nervosa: A double-blind placebo-controlled study with sulpiride. *Br. J. Psychiatry*, 144:288–292, 1984.

Vandereycken, W., and Pierloot, R. Pimozide combined with behavior therapy in the short-term treatment of anorexia nervosa: A double-blind placebo-controlled crossover study. *Acta Psychiatr. Scand.*, 60:446–451, 1982.

Vandereycken, W., and Van den Broucke, S. Anorexia nervosa in males. A comparative study of 107 cases reported in the literature (1970–1980). *Acta Psychiatr. Scand.*, 70(5):447–454, 1984.

Vigersky, R.A., and Loriaux, D.L. The effect of cyproheptadine in anorexia nervosa: A double-blind trial. In: Vigersky, R.A., (ed.), *Anorexia Nervosa*. New York: Raven Press, 1977, p. 349–356.

Waldhauser, F., Toifl, K., Spona, J., et al. Diminished prolactin response to thyrotropin and insulin in anorexia nervosa. *J. Clin. Endocrinol. Metab.*, 59(3):538–541, 1984.

Walker, J., Roberts, S.I., Halmi, K.A., and Goldberg, S.C. Caloric requirements for weight gain in anorexia nervosa. *Am. J. Clin. Nutr.*, 32(July):1396–1400, 1979.

Walsh, T., Katz, J.L., Levin, J., et al. Adrenal activity in anorexia nervosa. *Psychosom. Med.*, 40:499–506, 1978.

White, J.H., and Schnaultz, N.L. Successful treatment of anorexia nervosa with imipramine. *Dis. Nerv. Syst.*, 38:567–568, 1977.

Winokur, A., March, V., and Mendels, J. Primary affective disorder in relatives of patients with anorexia nervosa. *Am. J. Psychiatry*, 137:695–698, 1980.

Witt, E.D., Ryan, C., and Hsu, L.K.G. Learning deficits in adolescents with anorexia nervosa. *J. Nerv. Ment. Dis.*, 173(3): 182–184, 1985.

Yellowlees, A.J. Anorexia and bulimia in anorexia nervosa: A study of psychosocial functioning and associated psychiatric symptomatology. *Br. J. Psychiatry*, 146(June):648–652, 1985.

Ziesat, H.A. Jr., and Ferguson, J.M. Outpatient treatment of primary anorexia nervosa in adult males. *J. Clin. Psychol.*, 52(3):423–428, 1984.

BULIMIA

Abraham, S.F., and Beumont, P.J.V. How patients describe bulimia or binge-eating. *Psychol. Med.*, 12:625–635, 1982.

Boskind-Lodahl, M., and White, W.C. The definition and treatment of bulimarexia in college women: A pilot study. *J. Am. Coll. Health*, 27:84–86, 1978.

Brotman, A.W., Herzog, D.B., and Woods, S.W. Antidepressant treatment of bulimia: The relationship between bingeing and depressive symptomatology. *J. Clin. Psychiatry*, 45(1):7–9, 1984.

Casper, R.C. On the emergence of bulimia nervosa as a syndrome: A historical view. *Int. J. Eat. Disord.*, 2:3–16, 1983.

Casper, R.C., Eckert, E.D., Halmi, K.A., et al. Bulimia: Its incidence and clinical importance in patients with anorexia nervosa. *Arch. Gen. Psychiatry*, 37(Sept.):1030–1035, 1980.

Conner, C.S. Treatment of bulimia. *Drug Intell. Clin. Pharm.*, 17(11):815–816, 1983.

Cooper, P.J., and Fairburn, C.G. Binge-eating and self-induced vomiting in the community - a preliminary study. *Br. J. Psychiatry*, 142:139–144, 1983.

Dalvit-McPhillips, S. A dietary approach to bulimia treatment. *Physiol. Behav.*, 33(5): 769–775, 1984.

Dupont, R.L. Bulimia: A modern epidemic among adolescents. *Pediatr. Ann.*, 13(12):908–909, 912,914, 1984.

Fairburn, C.G. Binge eating and its management. *Br. J. Psychiatry*, 141:631–633, 1982.

Fairburn, C.G. and Cooper, P.J. Self-induced vomiting and bulimia nervosa: An undetected problem. *Br. Med. J.*, 284:1153–1155, 1982.

Fairburn, C.G. Bulimia: Its epidemiology and management. In: Stunkard, A.J. and Stellar, E. (eds), *Eating and Its Disorders*. (Research Publications: Assoc. for Research in Nervous and Mental Disease.) Vol. 62. New York: Raven Press, 1984. pp. 235–258.

Fairburn, C.G., and Cooper, P.J. The clinical features of bulimia nervosa. *Br. J. Psychiatry*, 144:238–246, 1984.

Fairburn, C.G., and Cooper, P.J. Binge-eating, self-induced vomiting and laxative abuse: A community study. *Psychol. Med.*, 14(2):401–410, 1984.

Garfinkel, P.E., Moldofsky, H., and Garner, D.M. The heterogeneity of anorexia nervosa: Bulimia as a distinct subgroup. *Arch. Gen. Psychiatry*, 37:1036–1040, 1980.

Garner, D.M., Garfinkel, P.E., and O'Shaughnessy, M. The validity of the distinction between bulimia with and without anorexia nervosa. *Am. J. Psychiatry*, 142(5):581–587, 1985.

Grace, P.S., Jacobson, R.S., and Fullager, C.J. A pilot comparison of purging and non-purging bulimics. *J. Clin. Psychol.*, 41(2):173–180, 1985.

Green, R.S., and Rau, J.H. Treatment of compulsive eating disturbances with anticonvulsant medication. *Am. J. Psychiatry*, 131:428–432, 1974.

Green, R.S., and Rau, J.H. The use of diphenylhydantoin in compulsive eating disorders: Further studies. In: Vigersky, R.A., (ed.), *Anorexia Nervosa*. New York: Raven Press, 1977.

Gwirtsman, H.E., Rery-byrne, P., Yager, J., et al. Neuroendocrine abnormalities in bulimia. *Am. J. Psychiatry*, 140:559–563, 1983.

Halmi, K.A., Falk, J.R., and Schwartz, E. Binge-eating and vomiting: A survey of a college population. *Psychol. Med.*, 11:697–706, 1981.

Hart, K.J., and Ollendick, T.H. Prevalence of bulimia in working and university women. *Am. J. Psychiatry*, 142(7):851–854, 1985.

Herridge, P.L., and Pope, H.G. Jr. Treatment of bulimia and rapid-cycling bipolar disorder with sodium valproate: A case report. *J. Clin. Psychopharmacol.*, 5(4):229–230, 1985.

Hsu, L.K.G. Treatment of bulimia with lithium. *Am. J. Psychiatry*, 141:10:1260–1262, 1984.

Hudson, J.I., Laffer, P.S., and Pope, H.G., Jr. Bulimia related to affective disorder by family and response to the dexamethasone suppression test. *Am. J. Psychiatry*, 139:685–687, 1982.

Hudson, J.I., Pope, H.G. Jr., and Jonas, J.M. Treatment of bulimia with antidepressants: Theoretical considerations and clinical findings. In: Stunkard, A.J., and Stellar, E. (eds.), *Eating and Its Disorders*. Research Publications: Association for Research in Nervous and Mental Disease. Vol. 62, New York: Raven Press 1984. pp.259-273.

Hudson, J.I., Pope, H.G. Jr., Jonas, J.M., et al. Hypothalamic-pituitary adrenal axis hyperactivity in bulimia. *Psychiatr. Res.*, 8:111–117, 1983.

Johnson, C.J., and Larson, R. Bulimia: An analysis of moods and behavior. *Psychosom. Med.*, 44:333–345, 1982.

Johnson, C., Lewis, C., and Hagman, J. The syndrome of bulimia. Review and synthesis. *Psychiatr. Clin. No. Am.*, 7(2):247–273, 1984.

Johnson, C., Lewis, C., Love, S., et al. Incidence and correlates of bulimic behavior in a female high school population. *J. Youth Adolesc.*, 13(1):15–26, 1984.

Johnson, C.L., Stuckey, M.K., Lewis, L.D., and Schwartz, D.M. Bulimia: A descriptive

best copy available

survey of 316 cases. *Int. J. Eat. Disord.*, 2:3–16, 1982.

Johnson-Sabine, E.C., Wood, K.H., and Wakeling, A. Mood changes in bulimia nervosa. *Br. J. Psychiatry*, 145:512–516, 1984.

Johnson, W.G., and Brief, D.J. Bulima. *Behav. Med. Update*, 4(3):16–21, 1983.

Jonas, J.M., Pope, H.G., Jr., and Hudson, J.I. Treatment of bulimia with MAOI's. *J. Clin. Psychopharmacol.*, 3:59–60, 1983.

Kaplan, A.S., Garfinkel, P.E., Darby, P.L., and Garner, D.M. Carbamezepine in the treatment of bulimia. *Am. J. Psychiatry*, 140(9):1225–1226, 1983.

Katzman, M.A., and Wolchik, S.A. Bulimia and binge eating in college women: A comparison of personality and behavioral characteristics. *J. Consult. Clin. Psychol.*, 52(3):423–428, 1984.

Kirkley, B.G., Schneider, J.A., Agras, W.S., and Bachman, J.A. Comparison of two group treatments for bulimia. *J. Consult. Clin. Psychol.*, 53(1):43–48, 1985.

Lacey, J.H. Bulimia nervosa, binge-eating, and psychogenic vomiting. A controlled treatment study and long-term outcome. *Br. Med. J.*, 286:1609–1613, 1983.

Liskin, B., Roose, S.P., Walsh, B.T., and Jackson, W.K. Acute psychosis following phenelzine discontinuation. *J. Clin. Psychopharmacol.*, 5(1):46–47, 1985.

Lowenkopf, E.L. Bulimia: Concept and therapy. *Compr. Psychiatry*, 26(6):546–554, 1983.

Maceyko, S.J., and Nagelberg, D.B. The assessment of bulimia in high school students. *J. School Health*, 55(4):135–137, 1985.

Mitchell, J.E., and Bantle, J.P. Metabolic and endocrine investigations in women of normal weight with the bulimia syndrome. *Biol. Psychiatry*. (In press)

Mitchell, J.E., and Goff, G. Bulimia in male patients. *Psychosomatics*, 25(12):909–924, 1984.

Mitchell, J.E., and Groat, R. A placebo-controlled, double-blind trial of amitriptyline in bulimia. *J. Clin. Psychopharmacol.*, 4(4):186–193, 1984.

Mitchell, J.E., Hosfield, W., and Pyle, R.L. EEG findings in patients with the bulimia syndrome. *Int. J. Eat. Disord.* (In press)

Mitchell, J.E., Pyle, R.L., and Eckert, E.D. Frequency and duration of binge-eating episodes in patients with bulimia. *Am. J. Psychiatry*, 138:835–836, 1981.

Mitchell, J.E., Pyle, R.L., Eckert, E.D., et al. Electrolyte and other physiological abnormalities in patients with bulimia. *Psychol. Med.*, 13:273–278, 1983.

Mitchell, J.E., Pyle, R.L., Hatsukami, D., and Boutacoff, L.I. The dexamethasone suppression test in patients with bulimia. *J. Clin. Psychiatry*, 45:508–511, 1984.

Mizes, J.S., and Lohr, S.M. The treatment of bulimia (binge-eating and self-induced vomiting). *Int. J. Eat. Disord.*, 2:59–60, 1983.

Musisi, S., and Garfinkel, P. Comparative dexamethasone suppression test measurements in bulimia, depression and normal controls. *Can. J. Psychiatry*, 30(3):190–194, 1985.

Norman, D.K., and Herzog, D.B. Persistent social maladjustment in bulimia: A 1-year follow-up. *Am. J. Psychiatry*, 141(3):444–446, 1984.

Ong, Y.L, Checkley, S.A., and Russell, G.F. Suppression of bulimic symptoms with methylamphetamine. *Br. J. Psychiatry*, 143(Sept.):288–293, 1983.

Pirke, K.M., Pahl, J., Schweiger, U., et al. Metabolic and endocrine indices of starvation in bulimia: A comparison with anorexia nervosa. *Psychiatr. Res.*, 15(1):33–41, 1985.

Pope, H.G. Jr., and Hudson, J.I. Treatment of bulimia with antidepressants. *Psychopharmacology*, 78:176–179, 1982.

Pope, H.G. Jr., Hudson, J.I., and Jonas, J.M. Antidepressant treatment of bulimia: Preliminary experience and practical recommendations. *J. Clin. Psychopharmacol.*, 3(5):274–281, 1983.

Pope, H.G., Jr., Hudson, J.I., Jonas, J.M., and Yurgulen-Todd, D. Bulimia treated with imipramine: A placebo-controlled double-blind study. *Am. J. Psychiatry*, 140:554–558, 1983.

Pyle, R.L., Mitchell, J.E., and Eckert, E.D. Bulimia: A report of 34 cases. *J. Clin. Psychiatry*, 42:60–64, 1981.

Pyle, R.L., Mitchell, J.E., Eckert, E.D., et al. The incidence of bulimia in freshman college students. *Int. J. Eat. Disord.*, 2:75–85, 1983.

Robinson, P.H., Checkley, S.A., and Russell, G.F.M. Suppression of eating by fenfluramine in patients with bulimia nervosa. *Br. J. Psychiatry*, 146 (Feb.): 169–176, 1985.

Russell, G.F.M. Bulimia nervosa: An ominous variant of anorexia nervosa. *Psychol. Med.*, 9:429–448, 1979.

Sabine, E.J., Yonace, A., Farrington, A.J., et al. Bulimia nervosa: a placebo controlled double-blind therapeutic trial of mianserin. *Br. J. Clin. Pharmacol.*, 15:195S–202S, 1983.

Smith, M.C., and Thelen, M.H. Development and validation of a test for bulimia. *J. Consult. Clin. Psychol.*, 52:5:863–872, 1984.

Stern, S.L., Dixon, K.N., Nemzer, E., et al. Affective disorder in the families of women with normal weight bulimia. *Am. J. Psychiatry*, 141(10):1223–1227, 1984.

Stewart, J.W., Walsh, B.T., Wright, L., et al. An open trial of MAO inhibitors in bulimia. *J. Clin. Psychiatry*, 45:217–219, 1984.

VanThorre, M.D., and Vogel, F.X. The presence of bulimia in high school females. *Adolescence*, xx(77):45–52, 1985.

Walsh, B.T., Roose, S.P., Glassman, A.H., et al. Bulimia and depression. *Psychosom. Med.*, 47(2):123–131, 1985.

Walsh, B.T., Roose, S.P., Glassman, A.H., et al. Bulimia and depression. *Psychosom. Med.*, xlvii(2):123–131, 1985.

Walsh, B.T., Stewart, J.W., Wright, L., et al. Treatment of bulimia with monoamine oxidase inhibitors. *Am. J. Psychiatry*, 139(12):1629–1630, 1982.

Walsh, B.T., Stewart, J.W., Roose, S.P., et al. Treatment of bulimia with phenelzine: A double-blind, placebo-controlled study. *Arch. Gen. Psychiatry*, 41:1105–1109, 1984.

Weiss, S.R., and Ebert, M.H. Psychological and behavioral characteristics of normal-weight bulimics and normal-weight controls. *Psychosom. Med.*, 45:293–303, 1983.

Weiss, T., and Levitz, L. Diphenylhydantoin treatment of bulemia (Letter to the editor). *Am. J. Psychiatry*, 133:1093, 1976.

Wermuth, B.M., Davis, K.L., Hollister, L.E., and Stunkard, A.J. Phenytoin treatment of the binge-eating syndrome. *Am. J. Psychiatry*, 134:1249–1253, 1977.

Attention Deficit Disorders: A Bibliography

(Contains references from 1/1/84 to 9/30/85)

Natalie Reatig[1]

Index

I. General References
II. Etiology
III. Diagnosis and Characteristics:
  A. General
    1) Rating and Assessment Instruments
  B. Pre-School Age
  C. Adolescence and Follow-Up Studies
    1) Substance Abuse
  D. Adults
IV. Treatment:
  A. Drugs:
    1) General References
    2) Stimulants
      a) Effects on Behavior and Learning
      b) Effects on Growth
      c) Physiological Effects/ Pharmacology
      d) Comparison with Other Drug Classes
    3) Other Drug Classes
    4) Compliance
  B. Behavioral Approaches
  C. Diet, Megavitamins, Caffeine, etc.
  D. Electromyographic (EMG) Feedback
V. Prevalence of the Hyperkinetic Behavior Syndrome
VI. Prevalence of Drug Treatment

I. General References

Aman, M.G. Hyperactivity: Nature of the syndrome and its natural history. *J. Aut. Devel. Disord.*, 14:39–56, 1984.

Bloomingdale, L.M., and Swanson, J.M. (eds.) *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Camp, J.A., and Winsberg, B.G. Clinical utility of animal models of childhood hyperkinesis. *Clin. Neuropharmacol.*, 7(3):185–221, 1984.

Campbell, S.B., and Werry, F.S. Attention deficit disorder (Hyperactivity). In: Quay, H.C., and Werry, J.S. (eds.). *Psychological Disorders of Childhood*, (Third Edition), New York: Wiley & Sons. (In press)

Cantwell, D.P. The attention deficit disorder syndrome: Current knowledge, future needs. (Editorial) *J. Am. Acad. Child Psychiatry*, 23:315–318, 1984.

Hadley, J. Facts about childhood hyperactivity. *Children Today*. 13(1):8–18, 1984.

Poole, S.R. Hyperactivity. *Primary Care*, 11(3):431–442, 1984.

Shaywitz, S.E., and Shaywitz, B.A. Diagnosis and management of attention deficit disorder: A pediatric perspective. *Pediatr. Clin. No. Am.*, 31(2):429–457, 1984.

Vivian, D., and O'Leary, K.D. Effects of the label "hyperactive". *Psychol. in the Schools*, 21(3):356–359, 1984.

Whalen, C.A., and Henker, B. Hyperactivity and the Attention Deficit Disorders: Expanding frontiers. *Pediatr. Clin. No. Am.*, 141: 7:906–908, 1984.

II. Etiology

Bloomingdale, L.M., Davies, R.K., and Gold, M.S. Some possible neurological substrates in Attention Deficit Disorder. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding*. New York: Spectrum Publications, Inc., 1984, pp. 37–66.

Corbuz, R.J., and Cuenod, M. Biological correlates of ADD. In: Bloomingdale, L.M., (ed), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding*. New York: Spectrum Publications, Inc., 1984, pp. 11–36.

Hagerman, R., Kemper, M., and Hudson, M. Learning disabilities and attentional problems in boys with the fragile X syndrome. *Am. J. Dis. Children*, 139(7):674–678, 1985.

Hartsough, C.S., and Lambert, N.M. Medical factors in hyperactive and normal children:

---

[1] National Institute of Mental Health

Prenatal, developmental, and health history findings. *Am. J. Orthopsychiatry.* 55(2): 190–201, 1985.

McGee, R., Williams, S., and Silva, P.A. Background characteristics of aggressive, hyperactive, and aggressive-hyperactive boys. *J. Am. Acad. Child Psychiatry*, 23(3):280–284, 1985.

Raskin, L.A., Shaywitz, S.E., Shaywitz, B.A. et al. Neurochemical correlates of attention deficit disorder. *Pediatr. Clin. No. Am.*, 31(2):387–396, 1984.

Serfontein, G.L., Earl, J.W., and Johnston, L.F. Neurotransmitter metabolites in children with Attention Deficit Disorder. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Wender, P.H. Remarks on the neurotransmitter hypothesis. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding*. New York: Spectrum Publications, Inc., 1984.

Zametkin, A.J., Karoum, F., Rapoport, J.L., et al. Phenylethylamine excretion in attention deficit disorder. *J. Am. Acad. Child Psychiatry*, 3:310–314, 1984.

III. Diagnosis and Characteristics

A. General

Bloomingdale, L.M. Whither ADD (Attention Deficit Disorder)? *Psychiatr. J. Univ. Ottawa*, 9(4):175–186, 1984.

Bloomingdale, L.M. (ed.) *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding*. New York: Spectrum Publications, Inc., 1984.

Bloomingdale, L.M. (ed.) *Attention Deficit Disorder: Identification, Course, and Rationale*, Vol. 2. New York: Spectrum Publications, Inc., 1985.

Christie, D., DeWitt, R.A., Kaltenbach, P., and Reed, D. Hyperactivity in children: Evidence for differences between parents' and teachers' perceptions of predominant features. *Psychol. Rep.*. (June):771–775, 1984.

DeHaas, P.A., and Young, R.D. Attention styles of hyperactive and normal girls. *J. Abnorm. Child Psychol.*, 12(4):531–546, 1984.

Douglas, V.I. The psychological processes implicated in ADD. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding*. New York: Spectrum Publications, Inc., 1984, pp. 147–161.

Edelbrock, C. Identifying the attention deficit disorder syndrome. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale*, Vol. 2. New York: Spectrum Publications, Inc., 1985.

Edelbrock, C., Costello, A.J., and Kessler, M.D. Empirical corroboration of Attention Deficit Disorder. *J. Am. Acad. Child Psychiatry*, 23(3):285–290, 1984.

Halperin, J.M., Gittelman, R., Klein, D.F., and Rudel, R.G. Reading-disabled hyperactive children: A distinct subgroup of Attention Deficit Disorder with hyperactivity. *J. Abnorm. Child Psychol.*, 12(1):1–14, 1984.

Johnston, C.J., Pelham, W.E., and Murphy, H.A. Peer relationships in ADDH and normal children: A developmental analysis of peer and teacher ratings. *J. Abnorm. Child Psychol.* (In press)

Kinsbourne, M. Beyond attention deficit: Search for the disorder in ADD. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding*. New York: Spectrum Publications, Inc., 1984, pp. 133–145.

Klorman, R., Salzman, L.F., and Borgstedt, A.D. Brain event-related potentials in evaluation of cognitive deficits in Attention Deficit Disorder and outcome of stimulant therapy. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Lahey, B.B., Schaughency, E.Z., Strauss, C.C., and Frame, C.L. Are Attention Deficit Disorders with and without hyperactivity similar or dissimilar disorders? *J. Am. Acad. Child Psychiatry*, 23(3):302–309, 1984.

McCulture, F.D., and Gordon, M. Performance of disturbed hyperactive and nonhyperactive children on an objective measure of hyperactivity. *J. Abnorm. Child Psychol.*, 12(4):561–572, 1984.

McGee, R., Williams, S., and Silva, P.A. Behavioral and developmental characteristics of aggressive, hyperactive and aggressive-hyperactive boys. *J. Am. Acad. Child Psychiatry,* 23(3):270–279, 1984.

McMahon, R.C. Hyperactivity as dysfunction of activity, arousal, or attention: A study of research relating to DSM-III's Attention Deficit Disorder. *J. Clin. Psychol.*, 40(6): 1300–1307, 1984.

Milich, R., and Landau, S. A comparison of the social status and social behavior of aggressive and aggressive/withdrawn boys. *J. Abnorm. Child Psychol.*, 12(2):277–288, 1984.

Milich, R., and Landau, S. The social status and social behavior or hyperactive, aggressive, and hyperactive/aggressive boys. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, 1986.

Pelham, W.E., and Milich, R. Peer relations in children with hyperactivity/Attention Deficit Disorder. *J. Learn. Disabil.*, 17(9): 560–567, 1984.

Quay, H.C. Aggression, conduct disorder, and attention problems. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale, Vol 2.* New York: Spectrum Publications, Inc., 1985.

Rubinstein, R.A., and Brown, R.T. An evaluation of the validity of the diagnostic category of attention deficit disorder. *Am. J. Orthopsychiatry,* 54(3):398–414, 1984.

Sargeant, J.A. Functional deficits in Attentional Deficit Disorder? In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Shaffer, D., and Schonfeld, I. A critical note on the value of attention deficit as a basis for a clinical syndrome. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding.* New York: Spectrum Publications, Inc., 1984, pp. 119–131.

Tarver-Behring, S., Barkeley, R.A., and Karlsson, J. The mother-child interactions of hyperactive boys and their normal siblings. *Am. J. Orthopsychiatry,* 55(2):202–209, 1985.

Ullman, R.K., Sleator, E.K., and Sprague, R.L. ADD children: Who is referred from the schools? *Psychopharmacol. Bull.*, 20(2):308–311, 1984.

Weithorn, C.J., Kagen, E., and Marcus, M. The relationship of activity level ratings and cognitive impulsivity to task performance and academic achievement. *J. Child Psychol. Psychiatry,* 25(4):587–606, 1984.

A. General

1) Rating and Assessment Instruments

Atkins, M.S., Pelham, W.E., and Licht, M.H. A comparison of objective classroom measures and teacher ratings of Attention Deficit Disorder. *J. Abnorm. Child Psychol.*, 13(1):155–168, 1985.

Breen, M.J., and Barkley, R.A. Psychological adjustment in learning disabled hyperactive, and hyperactive/learning disabled children as measured by the Personality Inventory for Children. *J. Clin. Child Psychol.*, 13(3):232–236, 1984.

Bruening, S.E., and Ackles, P.K. Evaluation of outcome. *Psychiatr. Ann.*, 15(2):108–109, 113-114, 1985.

Ferguson, H.B., and Simeon, J.G. Evaluating drug effects on children's cognitive functioning (bupropion and alprazolam). *Prog. Neuropsychopharmacol., Biol., Psychiatry,* 8(4-6):683–686, 1984.

Fullard, W., McDevitt, S.C., and Carey, W.B. Assessing temperament in one to three-year-old children. *J. Pediatr. Psychol.*, 9(2):205–218, 1984. 9(2):205–218, 1984.

Gurlong, M.J., and Fortman, J.B. Factor analysis of the abbreviated Conners Teacher Rating Scale: Implications for the assessment of hyperactivity. *Psychol. in the Schools*, 21(3):289–293, 1984.

Holborow, P.L., Berry, P., and Elkins, J. Prevalence of hyperkinesis: A comparison of three rating scales (Conners, Queensland, Pittsburgh). *J. Learn. Disabil.*, 17(7):411–417, 1984.

McClure, F.D., and Gordon, M. Performance of disturbed hyperactive and nonhyperactive children on an objective measure of hyperactivity (Delay Task, Gordon Diagnostic System). *J. Abnorm. Child Psychol.*, 12(4):561–572, 1984.

Milich, R., and Fitzgerald, G. Validation of inattention/overactivity and aggression ratings with classroom observations: *J. Consult. Clin. Psychol.*, 53(1):139–140, 1985.

Oettinger, D.R., Halpin, B., Miller, et al. Evaluating drug effectiveness in an office setting for children with Attention Deficit Disorders. *Clin. Pediatr.* (Phila.) 24(5):245–251, 1985.

Roberts, M.A., Ray, R.S., and Roberts, R.J. A playroom observational procedure for assessing hyperactive boys. *J. Pediatr. Psychol.*, 9(2):177–192, 1984.

Thivierge, J., Caperaa, P., Boudreault, M., et al. Reliability and principal component analysis (PCA) of the Conners Teacher Questionnaire. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Thivierge, J., Caperaa, P., Boudreault, M., et al. The sudden interruption of continuity (SIC) as a new screening test for MBD. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale, Vol 2.* New York: Spectrum Publications, Inc., 1985.

Trites, R.L. The Conners Teacher Rating Scale: Reliability, validity, and normative data. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Tyron, W.W. Measuring activity using actometers: A methodological study. *J. Behav. Assess.*, 6(2):147–154, 1984.

Ullmann, R.K. ACTeRS useful in screening learning disabled from Attention Deficit Disordered (ADD-H) children. *Psychopharmacol. Bull.*, 21(2):339–348, 1985.

Ullmann, R.K., Sleator, E.K., and Sprague, R.L. A new rating scale for diagnosis and monitoring of ADD children (ACTeRS). *Psychopharmacol. Bull.*, 20(1):160–164, 1984.

B. Pre-School Age

Campbell, S.B. Early identification and follow-up of parent-referred "hyperactive" toddlers. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale,* Vol. 2. New York: Spectrum Publications, Inc., 1985.

Campbell, S.B., Breaux, A.M., Ewing, L.J., and Szumowski, E.K. A one-year follow-up study of parent-referred hyperactive preschool children. *J. Am. Acad. Child Psychiatry,* 23(3):243–249, 1984.

Fullard, W., McDevitt, S.C., and Carey, W.B. Assessing temperament in one- to three-year-old children. *J. Pediatr. Psychol.*, 9(2):205–218, 1984.

C. Adolescence and Follow-up Studies

Brown, R.T., Borden, K.A., and Clingerman, S.R. Pharmacotherapy in ADD adolescents with special attention to multimodality treatments. *Psychopharmacol. Bull.*, 21(2):192–211, 1985.

Cantwell, D.P. Pharmacotherapy of ADD in adolescents: What do we know, where should we go, how should we do it? (A summary of workshop proceedings). *Psychopharmacol. Bull.*, 21(2):251–257, 1985.

Conners, C.K. Issues in the study of adolescent ADD-hyperactivity. *Psychopharmacol. Bull.*, 21(2):243–250, 1985.

Eichlseder, W. Ten years of experience with 1,000 hyperactive children in a private practice. *Pediatrics*, 76(2):176–184, 1985.

Garfinkel, B.D. Neuroendocrine and cognitive responses to amphetamine in adolescents with a history of ADD. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding.* New York: Spectrum Publications, Inc., 1984, pp. 163–178.

Garfinkel, B.D., and Klee, S.H. Behavioral and personality characteristics of adolescents with a history of childhood ADD. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale,* Vol. 2. New York: Spectrum Publications, Inc., 1985.

Gastfriend, D.R., Biederman, J., and Jellinek, M.S. Desipramine in the treatment of adolescents with Attention Deficit Disorder. *Am. J. Psychiatry,* 141(7):906–908, 1984.

Gittelman, R., and Mannuzza, S. Diagnosing ADD-H in adolescents. *Psychopharmacol. Bull.* 21(2):237–242, 1985.

Hechtman, L. Adolescent outcome of hyperactive children treated with stimulants in childhood: A review. *Psychopharmacol. Bull.* 21(2):178–191, 1985.

Hechtman, L., Weiss, G., and Perlman, T. Hyperactives as young adults: Past and current substance abuse and antisocial behavior. *Am. J. Orthopsychiatry,* 54(3):415–425, 1984.

Howell, D.C., Huessy, H.R., and Hassuk, B. Fifteen-year follow-up of a behavioral history of Attention Deficit Disorder. *Pediatrics*, 76(2):185–190, 1985.

Huessy, H.R., and Howell, D.C. The behaviors associated with ADD followed from age seven to twenty-one: Difference between males and females. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder,* Vol. 3. New York: Spectrum Publications, Inc., 1986.

Klorman, R. Attention deficit disorder in adolescence. In: Feldman, R.A., and Stiffman, A.R., (eds.) *Advances in Adolescent Mental Health*. Greenwich, Conn: JAI Press. (In press)

Mannuzza, S., and Gittelman, R. The adolescent outcome of hyperactive girls. *Psychiatry Res.*, 13(1):19–30, 1984.

Safer, D.J. Subgrouping conduct disordered adolescents by early risk factors. *Am. J. Orthopsychiatry*, 54(4):603–612, 1984.

Safer, D.J., and Krager, J.M. Prevalence of medication treatment for hyperactive adolescents. *Psychopharmacol. Bull.*, 21(2): 212–215, 1985.

Satterfield, H. Psychosocial effects on delinquency rates in ADD youths and control subjects: An eight-year prospective study. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Thomas, A., and Chess, S. Genesis and evolution of behavioral disorders: From infancy to early adult life. *Am. J. Psychiatry*, 141:1–9, 1984.

Varley, C.K. A review of studies of drug treatment efficacy with Attention Deficit Disorder with hyperactivity in adolescents. *Psychopharmacol. Bull.*, 21(2):216–221, 1985.

Weiss, G. Follow-up studies on outcome of hyperactive children. *Psychopharmacol. Bull.*, 21(2):169–177, 1985.

1) Substance Abuse

Beck, L., Langford, W.S., MacKay, M., and Sum, G. Childhood chemotherapy and later drug abuse and growth curve: A follow-up study of 30 adolescents. *Am. J. Psychiatry*, 132:436–438, 1975.

Blouin, A., Bornstein, R., and Trites, R. Teenage alcohol use among hyperactive children: a five year follow-up study. *J. Pediatr. Psychol.*, 3(4):188–195, 1978.

Eyre, S.L., Rounsaville, B.J., and Kleber, H.D. History of childhood hyperactivity in a clinic population of opiate addicts. *J. Nerv. Ment. Dis.*, 170(9):522–529, 1982.

Hechtman, L., Weiss, G., and Perlman, T. Hyperactives as young adults: Past and current substance abuse and antisocial behavior. *Am. J. Orthopsychiatry,* 54(3):415–425, 1984.

Hechtman, L., and Weiss, G. Controlled prospective fifteen-year follow-up of hyperactives as adults: Non medical drug and alcohol use and antisocial behavior. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. Spectrum Publications, Inc., 1986.

Henker, B., Whalen, C.K., Bugental, D.B., and Barker, C. Licit and illicit substance use patterns in stimulant-treated children and their peers. In: Gadow, K., and Loney, J. (eds.), *Psychosocial Aspects of Drug Treatment for Hyperactivity.* Boulder, Colo.: Westview Press, 1981.

Huessy, H.R. Genetics of alcoholism. (Letter on ADD,RT) *Hosp. Commun. Psychiatry,* 35(6):620–621, 1984.

Kramer, J., and Loney, J. Childhood hyperactivity and substance abuse: A review of the literature. In: Gadow, K., and Bailer, I. (eds.), *Advances in Learning and Behavioral Disabilities*, (Vol. 1), Greenwich, Conn: JAI Press, (In press)

Lambert, N.M. Overview of the data base for the Berkeley Hyperactivity Studies and some preliminary findings related to substance use and mental health outcomes. Paper presented at the NIMH Attention Deficit Disorder Workshop, Washington, D.C., April 14–15, 1983.

Loney, J. The Iowa theory of substance abuse among hyperactive adolescents. In: Lettieri D.J., Sayers M., and Peterson H.W. (eds.), *Theories on Drug Abuse*. National Institute of Drug Abuse Research, Monograph 30, U.S. Department of Health and Human Services, Washington, D.C. 1980, pp. 132–136.

D. Adults

Gauthier, M. Stimulant medications in adults with Attention Deficit Disorder. *Can. J. Psychiatry*, 29(5):435–440, 1984.

Hechtman, L., and Weiss, G. Controlled prospective fifteen-year follow-up of hyperactives as adults: Non medical drug and alcohol use and antisocial behavior. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. Spectrum Publications, Inc., 1986.

Hechtman, L., Weiss, G., and Perlman, T. Young adult outcome of hyperactive children who received long-term stimulant treatment. *J. Am. Acad. Child Psychiatry*, 23(3):261–269, 1984.

Hechtman, L., Weiss, G., Perlman, T., and Amsel, R. Hyperactives as young adults: Initial predicators of adult outcome. *J. Am. Acad. Child Psychiatry*, 23(3):250–260, 1984.

Hooberman, D., and Stern, T.A. Treatment of Attention Deficit and Borderline Personality Disorders with psychostimulants: Case report. *J. Clin. Psychiatry*, 45(10): 441–442, 1984.

Huessy, H.R. Genetics of alcoholism. (Letter on ADD,RT) *Hosp. Commun. Psychiatry*, 35(6):620–621, 1984.

Huey, L.Y., Janowsky, D.S., Judd, L., et al. Effects of methylphenidate in adult psychiatric inpatients: A preliminary report. *Psychopharmacol. Bull.*, 20(1):10–17, 1984.

Klorman, R., Bauer, L.O., Coons, H.W., et al Enhancing effects of methylphenidate on normal young adults' cognitive processes. *Psychopharmacol. Bull.*, 20(1):3–9, 1984.

Mattes, J.A., Boswell, L., and Oliver, H. Methylphenidate effects on symptoms of Attention Deficit Disorder in adults. *Arch. Gen. Psychiatry*, 41:1059–1963, 1984.

Reimherr, F.W., Wender, P.H., Ebert, M.H., and Wood, D.R. Cerebrospinal fluid homovanillic acid and 5-hydroxy-indoleacetic acid in adults with Attention Deficit Disorder, Residual Type. *Psychiatry Res.*, 11:71–78, 1984.

Weiss, G. Psychiatric status of hyperactives as adults: A controlled prospective 15-year follow-up of 63 hyperactive children. *J. Am. Acad. Child Psychiatry*, 24(2):211–220, 1985.

Wender, P.H., Reimherr, M.D., and Wood, D.R. Stimulant therapy of 'Adult Hyperactivity'. (Letter to the Editor; Letter in Reply by Jeffrey A. Mattes). *Arch. Gen. Psychiatry*, 42(8):834ff, 1985.

Wender, P.H., Reimherr, F.W., Wood, D., and Ward, M. A controlled study of methylphenidate in the treatment of Attention Deficit Disorder, Residual Type, in adults. *Am. J. Psychiatry*, 142(5):547–552, 1985.

Wender, P.H., Wood, D., and Reimherr, F. Studies in Attention Deficit Disorder, Residual Type (minimal brain dysfunction in adults). *Psychopharmacol. Bull.*, 20(1):18–20, 1984.

Wender, P.H., Wood, D.R., and Reimherr, F.W. Pharmacological treatment of Attention Deficit Disorder/Residual Type (ADD/RT, "Minimal Brain Dysfunction", "Hyperactivity", in Adults. *Psychopharmacol. Bull.* 21(2):222–231, 1985.

Wood, D.R., Reimherr, F.W., and Wender, P.H. Amino acid precursors for the treatment of Attention Deficit Disorder, Residual Type. *Psychopharmacol. Bull.*, 21(1):146–149, 1985.

IV. Treatment

A. Drugs

1) General References

Dulcan, M.K. The psychopharmacologic treatment of children and adolescents with Attention Deficit Disorder. *Psychiatr. Annal.*, 15(2):69–86, 1985.

Gualtieri, C.T., and Hicks, R.E. Stimulants and neuroleptics in hyperactive children, (letter). *J. Am. Acad. Child Psychiatry*, 24(3):363–364, 1985.

Volkmar, F.R., Hoder, E.L., and Cohen, D.J. Inappropriate uses of stimulant medications. *Clin. Pediatr.*, (Phila.), 24(3): 127–130, 1985.

Wiener, J.M. Psychopharmacology in childhood disorders. *Psychiatr. Clin. No. Am.*, 7(4): 831–843, 1984.

2a) Stimulants: Effects on Behavior and Learning

Abikoff, H., and Gittelman, R. The normalizing effects of methylphenidate on the classroom behavior of ADDH children. *J. Abnorm. Child Psychol.* 13(1):33–44, 1985.

Amery, B., Minichiello, M.D., and Brown, G.L. Aggression in hyperactive boys: Response to d-amphetamine. *J. Am. Acad. Child Psychiatry*, 23(3):291–294, 1984.

Ballinger, C.T., Varley, C.K., and Nolen, P.A. Effects of methylphenidate on reading in children with Attention Deficit Disorder. *Am. J. Psychiatry,* 141(12):1590–1593, 1984.

Barkley, R.A., Karlsson, J., Strzelecki, E., and Murphy, J.V. Effects of age and Ritalin dosage on the mother-child interactions of hyperactive children. *J. Consult. Clin. Psychol.*, 52(5):750–758, 1984.

Becker-Mattes, A., Mattes, J.A., Abikoff, H., and Brandt, L. State-dependent learning in hyperactive children receiving methylphenidate. *Am. J. Psychiatry,* 142(4):455–459, 1985.

Brown, R.T., Slimmer, L.W., and Wynne, M.E. How much stimulant medication is appropriate for hyperactive school children? *J. School Health,* 54(3):128–130, 1984.

Brown, R.T., Wynne, M.E., and Slimmer, L.W. Attention Deficit Disorder and the effect of methylphenidate on attention, behavioral, and cardiovascular functioning. *J. Clin. Psychiatry,* 45:473–476, 1984.

Callaway, E. Human information-processing: Some effects of methylphenicate, age, and scopolamine. *Biol. Psychiatry,* 19(5): 649–662, 1984.

Caresia, L., Pugnetti, L., Besana, R., et al. EEG and clinical findings during pemoline treatment in children and adults with attention deficit disorder: An 8-week open trial. *Neuropsychobiology,* 11(3):158–167, 1984.

Golinko, B.E. Side effects of dextroamphetamine and methylphenidate in hyperactive children - A brief review. *Prog. Neuro-psychopharmacol. Biol. Psychiatry,* 8:1–8, 1984.

Hunt, R.D. Clonidine benefits children with ADDH. *J. Am. Acad. Child Psychiatry,* (In press)

Peeke, S., Halliday, R., Callaway, E., et al. Effects of two doses of methylphenidate on verbal information processing in hyperactive children. *J. Clin. Psychopharmacol.*, 4(2):82ff., 1984.

Pelham, W.E. The effects of stimulant drugs on learning and achievement in hyperactive and learning-disabled children. In: Torgesen, J.K., and Wong, B. (eds.), *Learning Disabilities: Some New Perspectives.* New York:Academic Press. (In press)

Pozzi, M., and Hartley, L. Hyperactivity, drugs and attention deficit. *Br. J. Clin. Psychol.*, 23:217–223, 1984.

Rapport, M.D., Stoner, G., DuPaul, G.J., et al. Methylphenidate in hyperactive children: Differential effects of dose on academic, learning and social behavior. *J. Abnorm. Child Psychol.*, 13(2):227–244, 1985.

Reid, M.K., and Borkowski, J.G. Effects of methylphenidate (Ritalin) on information processing in hyperactive children. *J. Abnorm. Child Psychol.*, 12(1):169–186, 1984.

Schmidt, K., Solanto, M.V., Sanchez, M., et al. The effect of stimulant medication on academic performance, in the context of multimodal treatment, in Attention Deficit Disorders with hyperactivity: Two case reports. *J. Clin. Psychopharmacol.*, 4(2): 100–103, 1984.

Solanto, M.V. Behavioral effects of low-dose methylphenidate. *J. Am. Acad. of Child Psychiatry.* (In press)

Stephens, R.S., Pelham, W.E., and Skinner, R. State-dependent and main effects of methylphenidate and pemoline on paired-associate learning and spelling in hyperactive children. *J. Consult. Clin. Psychol.*, 52(1):104–113, 1984.

Sustained-release methylphenidate. *Med. Lett. Drugs Ther.*, 26(673):97–98, 1984.

Varley, C.K. A review of studies of drug treatment efficacy with Attention Deficit Disorder with Hyperactivity in adolescents. *Psychopharmacol. Bull.*, 21(2):216–221, 1985.

Weber, K. Methylphenidate: Rate-dependent effects in hyperactive boys. *Psychopharmacology* (Berlin), 85(2):231–235, 1985.

2b) Stimulants: Effects on Growth

Golinko, B.E. Side effects of dextroamphetamine and methylphenidate in hyperactive children - A brief review. *Prog. Neuro-Psychopharmacol., Biol. Psychiatry,* 8:1–8, 1984.

Greenhill, L.L., Puig-Antich, J., Novacenko, H., et al. Prolactin, growth hormone and growth responses in boys with attention deficit disorder and hyperactivity treated with methylphenidate. *J. Am. Acad. Child Psychiatry,* 23(1):58–67, 1984.

2c) Stimulants: Physiological Effects / Pharmacology

Ackerman, P.T., Holcomb, P.J., and Dykman, R.A. Effects of reward and methylphenidate on heart rate response morphology of augmenting and reducing children. *Int. J. Psychophysiol.* 1(4):301–316, 1984.

Brown, R.T., Wynne, M.E., and Slimmer, L.W. Attention Deficit Disorder and the effect of methylphenidate on attention, behavioral, and cardiovascular functioning. *J. Clin. Psychiatry*, 45:473–476, 1984.

Camp, J.A., and Winsberg, B.G. Clinical utility of animal models of childhood hyperkinesis. *Clin. Neuropharmacol.*, 7(3):185–221, 1984.

Caresia, L., Pugnetti, L., Besana, R., et al. EEG and clinical findings during pemoline treatment in children and adults with attention deficit disorder: An 8-week open trial. *Neuropsychobiology*, 11(3):158–167, 1984.

Collier, C.P., Soldin, S.J., Swanson, J.M., et al., Pemoline pharmacokinetics and long term therapy in children with Attention Deficit Disorder and hyperactivity. *Clin. Pharmacokin.*, 10(3):269–278, 1985.

Conners, C.K., and Solanto, M.V. The psychophysiology of stimulant drug response in hyperkinetic children. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder Diagnostic, Cognitive, and Therapeutic Understanding.* New York: Spectrum Publications, Inc., 1984, pp. 191–204.

El-Defrawi, M.H., and Greenhill, L.L. Substituting stimulants in treating behavior disorders. (Letter: Acute dyskinetic movement disorder in a child treated with methylphenidate). *Am. J. Psychiatry*, 141(4):610, 1984.

Gualtieri, C.T., Hicks, R.E., Mayo, J.P., and Schroeder, S.R. The persistence of stimulant effects in chronically treated children: Further evidence of an inverse relationship between drug effects and placebo levels of response. *Psychopharmacology*, 83(1):44–47, 1984.

Gualtieri, C.T., Hicks, R.E., Evans, R.W., and Patrick, K. The clinical importance of methylphenidate blood level determinations. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Gualtieri, C.T., Hicks, R.E., Patrick, K., et al. Clinical correlates of methylphenidate blood levels. *Ther. Drug Monit.*, 6(4): 379–392, 1984.

Hicks, R.E., Gualtieri, C.T., Mayo, J.P., et al. Methylphenidate and homeostasis: Drug effects are inversely related to placebo levels of responses. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale*, Vol. 2. New York: Spectrum Publications, Inc., 1985.

Hunt, R.D., Cohen, D.J., Anderson, G., and Clark, L. Possible change in noradrenergic receptor sensitivity following methylphenidate treatment. Growth hormone and MHPG response to clonidine challenge in children with Attention Deficit Disorder and hyperactivity. *Life Sci.*, 35(8):885–897, 1984.

Kinsbourne, M. Base-state dependency of stimulant effects on the cognitive performance of hyperactive children. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale*, Vol. 2. New York: Spectrum Publications, Inc., 1985.

Sallee, F., Stiller, R., Perel, J., et al., Oral pemoline kinetics in hyperactive children. *Clin. Pharmacol. Ther.*, 37(6):606–609, 1985.

Shaywitz, B.A. Pharmacokinetic, neuroendocrine and behavioral substrates of ADD: In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive and Therapeutic Understanding.* New York: Spectrum Publications, Inc., 1984.

Shen, Y.C., and Wang, Y.F. Urinary 3-methoxy-4-hydroxyphenylglycol sulfate excretion in seventy-three schoolchildren with Minimal Brain Dysfunction Syndrome. *Biol. Psychiatry*, 19(6):861–870, 1984.

Solanto, M.V. Neuropharmacological basis of stimulant drug action in Attention Deficit Disorder with Hyperactivity: A review and synthesis. *Psychol. Bull.*, 5(3):387–409, 1984.

Solanto, M.V. Behavioral effects of low-dose methylphenidate in childhood Attention Deficit Disorder: Implications for a mechanism of stimulant drug action. *J. Am. Acad. Child Psychiatry.* (In press)

Steinhausen, H.C., Romahn, G., and Gobel, D. Computer analyzed EEG in methylphenidate-responsive hyperactive children. *Neuropediatrics*, 15:1:28–32, 1984.

Swanson, J.M. Correlations of blood levels and response to stimulants in ADD+H children. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Zametkin, A.J., Brown, G.L., Karoum, F., et al. Urinary phenethylamine response to d-amphetamine in 12 boys with Attention Deficit Disorder. *Am. J. Psychiatry*, 141(9): 1055–1058, 1984.

Zametkin, A.J. Karoum, F., Linnoila, M., et al. Stimulants, urinary catecholamines, and indoleamines in hyperactivity. *Arch. Gen. Psychiatry*, 42(3):251–258, 1985.

2d) Stimulants: Comparison with Other Drug Classes

Butter, H.J., Lapierre, Y., Firestone, P., and Blank, A. Efficacy of ACTH 4-9 analog, methylphenidate, and placebo on Attention Deficit Disorder with hyperkinesis. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 8(4-6):661–664, 1984.

Pozzi, M., and Hartley, L. Hyperactivity, drugs and attention deficit. (methylphenidate and imipramine.) *Br. J. Clin. Psychol.*, 23:217–223, 1984.

Weizman, A., Weitz, R., Szekely, G.W., et al. Combination of neuroleptic and stimulant treatment in Attention Deficit Disorder with hyperactivity. *J. Am. Acad. Child Psychiatry*, 23(3):295–298, 1984.

3) Other Drug Classes

Campbell, M. On the use of neuroleptics in children and adolescents. *Psychiatr. Ann.*, 15(2):101–107, 1985.

Campbell, M., Perry, R., and Green, W.H. Use of lithium in children and adolescents. *Psychosomatics*, 25(2):95–106, 1984.

Ferguson, H.B., and Simeon, J.G. Evaluating drug effects on children's cognitive functioning (bupropion and alprazolam). *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 8(4-6):683–686, 1984.

Gastfriend, D.R., Biederman, J., and Jellinek, M.S. Desipramine in the treatment of adolescents with Attention Deficit Disorder. *Am. J. Psychiatry*, 141:7:906–908, 1984.

Gastfriend, D.R., Biederman, J., and Jellinek, M.S. Desipramine in the treatment of Attention Deficit Disorder in adolescents. *Psychopharmacol. Bull.*, 21(1):144–145, 1985.

Hunt, R.D., Cohen, D.J., Anderson, G., and Minderra, R. Noradrenergic mechanisms in ADD+H. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Rapoport, J.L., Zametkin, A., Donnelly, M., and Ismond, D. New drug trials in Attention Deficit Disorder. *Psychopharmacol. Bull.*, 21(2):232–236, 1985.

Simeon, J., Ferguson, B., Rochon, R., et al. Bupropion effects in children with Attention Deficit and Conduct Disorders. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

4) Compliance

Brown, R.T., Borden, K.A., and Clingerman, S.R. Adherence to methylphenidate therapy in a pediatric population: A preliminary investigation. *Psychopharmacol. Bull.*, 21(1):28–36, 1985.

Rosse, R.B., and Licamele, W.L. Slow-release methylphenidate: Problems when children chew tablets. (Letter) *J. Clin. Psychiatry*, 45(12):525, 1985.

Slimmer, L.W. Parents' decision-making process in methylphenidate administration: Educational policy considerations. Univ. Illinois, Chicago, Unpublished Ph.D. dissertation, 1984.

Varni, J.W., and Wallander, J.L. Adherence to health-related regimens in pediatric chronic disorders. *Clin. Psychol. Rev.* 4(5):585ff. 1984.

B. Behavioral Approaches

Abikoff, H., and Gittelman, R. Does behavior therapy normalize the classroom behavior of hyperactive children? *Arch. Gen. Psychiatry*, 41(5):449–454, 1984.

Brown, R.T., Borden, K.A., and Clingerman, S.R. Pharmacotherapy in ADD adolescents with special attention to multimodality treatments. *Psychopharmacol. Bull.*, 21(2): 192–211, 1985.

Brown, R.T., Wynne, M.E., and Medenis, R. Methylphenidate and cognitive therapy: A comparison of treatment approaches with hyperactive boys. *J. Abnorm. Child Psychol.*, 13(1):69–88, 1985.

Christie, D.J., Hiss, M. and Lozanoff, B. Modification of inattentive classroom behavior: Hyperactive children's use of self-recording with teacher guidance. *Behav. Modif.*, 8(3):391–406, 1984.

Douglas, V.I. The response of ADD children to reinforcement: Theoretical and clinical implications. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Identification, Course, and Rationale*, Vol. 2. New York: Spectrum Publications, Inc., 1985.

Hinshaw, S.P., Henker, B., and Whalen, C.K. Cognitive-behavioral and pharmacologic interventions for hyperactive boys: Comparative and combined effects. *J. Consult. Clin. Psychol.*, 57(5):739–749, 1984.

Hinshaw, S.P., Henker, B., and Whalen, C.K. Self-control in hyperactive boys in anger-inducing situations: Effects of cognitive-behavioral training and methylphenidate. *J. Abnorm. Child Psychol.*, 12(1):55–77, 1984.

Pelham, W.E. The combination of pharmacological and behavioral treatments for Attention Deficit Disorders. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Pollack, E., and Gittelman, R. Practical problems encountered in behavioral treatment with hyperactive children. (Mss. available from the authors at: Child Development Clinic, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 11042).

Quay, H.C. The behavioral reward and inhibition system in childhood behavior disorders. In: Bloomingdale, L.M., and Swanson, J.M. (eds.), *Attention Deficit Disorder*, Vol. 3. New York: Spectrum Publications, Inc., 1986.

Rosen, L.A., O'Leary, S.G., Joyce, S.A., et al. The importance of prudent negative consequences for maintaining the appropriate behavior of hyperactive students. *J. Abnorm. Child Psychol.*, 12(4):581–604, 1984.

Schmidt, K., Solanto, M.V., Sanchez, M., et al. The effect of stimulant medication on academic performance, in the context of multimodal treatment, in Attention Deficit Disorders with hyperactivity: Two case reports. *J. Clin. Psychopharmacol.*, 4(2): 100–103, 1984.

Sprague, R.L. Behavior modification and educational techniques (a review). In: Rutter, M. (ed.), *Developmental Neuropsychiatry*. New York: The Guilford Press, 1983.

C. Diet, Megavitamins, Caffeine, etc.

Arnold, L.E. Diet and hyperkinesis. *Integrative Psychiatry*, 2(5): 188–200, 1984.

Haslam, R.H., Dalby, J.T., and Rademaker, A.W. Effects of megavitamin therapy on children with Attention Deficit Disorders. *Pediatrics*, 74(1):103–111, 1984.

Rapoport, J.L., Berg, C.J., Ismond, D.R., et al. Behavioral effects of caffeine in children. *Arch. Gen. Psychiatry*, 41:1073–1079, 1984.

Schechter, M.D., and Timmons, G.D. Objectively measured hyperactivity; II. Caffeine and amphetamine effects. *J. Clin. Pharmacol.*, 25(4):276–280, 1985.

Taylor, E. Diet and behavior. *Arch. Dis. Childhood*, 59:97–98, 1984.

Varley, C.K. Diet and the behavior of children with Attention Deficit Disorder. *J. Am. Acad. Child Psychiatry*, 23(2):182–185, 1984.

Wells, S.J. Caffeine: Implications of recent research for clinical practice. *Am. J. Orthopsychiatry*, 54(3):375–389, 1984.

Wolraich, M., Milich, R., Stumbo, P., and Schultz, F. Effects of sucrose ingestion on the behavior of hyperactive boys. *J. Pediatr.*, (April):675–682, 1985.

D. EMG Feedback

Denkowski, K.M., and Denkowski, G.C. Is group progressive relaxation training as effective with hyperactive children as individual EMG biofeedback treatment? *Biofeedback Self-Reg.*, 9(3):353–365, 1984.

Denkowski, K.M., Denkowski, G.C., and Omizo, M.M. Predictors of success in the EMG biogeedback training of hyperactive male children. *Biofeedback Self-Reg.*, 9(2):253–264, 1984.

Estrada, N., Kelso, H.G., and Gladman, A.E. Integrating biofeedback training within a multimodal treatment model for Attention Deficit Disorder. *Am. J. Clin. Biofeedback*, 7(1):22–30, 1984.

Lubar, J.O., and Lubar, J.F. Electroencephalographic biofeedback of SMR and Beta for treatment of attention deficit disorders in a clinical setting. *Biofeedback Self-Reg.*, 9(1): 1–24, 1984.

V. Prevalence of ADD(H)

Holborow, P.L., Berry, P., and Elkins, J. Prevalence of hyperkinesis: A comparison of three rating scales (Conners, Queensland, Pittsburgh). *J. Learn. Disabil.*, 17(7):411–417, 1984.

Huessy, H.R. Remarks on the epidemiology of MBD/ADD. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding.* New York: Spectrum Publications, Inc., 1984.

Sprague, R.L. Preliminary report of cross-cultural study and cognitive strategies of ADD children. In: Bloomingdale, L.M. (ed.), *Attention Deficit Disorder: Diagnostic, Cognitive, and Therapeutic Understanding.* Spectrum Publications, Inc., 1984, pp.211-219.

Taylor, E., and Sandberg, S. Hyperactive behavior in English schoolchildren: A questionnaire survey. *J. Abnorm. Child Psychol.*, 12(1):143–156, 1984.

VI. Prevalence of Drug Treatment

Safer, D.J., and Krager, J.M. Prevalence of medication treatment for hyperactive adolescents. *Psychopharmacol. Bull.*, 21(2):212–215, 1985.

Safer, D.J., and Krager, J.M. Trends in medication treatment of hyperactive school children: Results of six biannual surveys. *Clin. Pediatr.*, 22(7):500–504, 1983.

Safer, D.J., and Krager, J.M. Trends in medication therapy for hyperactivity: National and international perspectives. In: Gadow, K. (ed.), *Advances in Behavior and Learning*, Vol. 3. (In press)

Introduction and Summary: Psychobiological Markers for Schizophrenia: State of the Art and Future Perspectives[1,2]

Joseph Zubin, Ph.D.[3]

Introduction

The purpose of the panel on psychobiological markers for schizophrenia was to update the state of the art since 1977 when the last report was presented to the American College of Neuropsychopharmacology (Zubin, 1979).

During the past 7 years, several developments have taken place which will affect future markers studies. As far as the etiological models which underlie the markers are concerned, the old neuropathological model has been revived in the wake of the new methodologies for brain scanning. The neurophysiological model has been extended to include more neurohumoral and endocrinological factors and immunological system factors, indicating the revival of what used to be called the psychosomatic model (Ader, 1981). In genetics, molecular genetics and mapping (HLA) have developed very rapidly. Some of these advances in etiological models are providing new potential markers for schizophrenia.

Perhaps one of the most striking developments during the past septennial was the provision of systematic structured and semistructured interviews for diagnosis, resulting in a high degree of reliability in the classification of the mentally ill. As a consequence, it became possible to provide research diagnostic criteria based on these interviews and a new codification of the Diagnostic and Statistical Manual—DSM-III (American Psychiatric Association, 1980) that laid a firmer foundation for specificity in the search for markers. There has also developed a stronger interest in fractionating schizophrenia and also depression into subcategories. In schizophrenia, the use of positive and negative symptoms and their relation to drug effects has provided some tentative new classifications of subgroups which may provide new markers. The positive symptoms seem to characterize patients during their episode, since the symptoms often wax and wane with the episode. The negative symptoms are alleged to be more persistent but there seems to be some doubt whether they are indigenous parts of schizophrenia (Zubin, 1985). Despite these efforts at subcategorization of schizophrenia, there has been a revival of the unitary hypothesis of the functional disorders (Bleuler, 1972; Meltzer, 1984) so that we may find the same markers identifying both the schizophrenias as well as the affective disorders. Another new development has arisen from the results of the long-term follow-up studies of schizophrenia (Bleuler, 1972; Ciompi, 1980; Harding & Strauss, in press; Huber et al., 1980), which seem to cast doubt on the malignant chronic character that has been attributed to schizophrenia, changing it to a more benign disorder. The vulnerability model also points to a change in that direction, substituting a vulnerability to schizophrenia for the belief that it is a persistent deteriorating process. This vulnerability may or may not lead to episodes, but the episodes, according to the vulnerability model, are intermittent, leading eventually to a good outcome in the majority of patients (Bleuler, 1972; Ciompi, 1980; Harding & Strauss, in press; Huber et al., 1980). Thus, episode markers may assume greater importance because they can help in determining beginnings and ends of episodes.

One methodological innovation during the past 7 years was the introduction of information processing procedures in the quest for markers (Kietzman et al., 1984). Since one of the behavioral deviations in schizophrenia is in the domain of information reception and transmission, especially in the cognitive domain, it is clear why information processing is so important in the search for markers. In

---

[1] This paper was incorrectly printed with some lines out of place in Vol. 21, No. 3, 1985. We are reprinting it here in its entirety, as corrected.

[2] This study was supported by the Medical Research Service of the Veterans Administration.

[3] VA Medical Center, and Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15206.

earlier days, the mere finding of a difference between schizophrenic and non-schizophrenic patients and normals was regarded as a remarkable achievement in itself. Today, such a finding is only the beginning. It becomes necessary to find just where the deviation occurs in the processing of the information under examination, in which time period and how it relates to the preceding and succeeding processing procedures. Furthermore, the vast knowledge of information processing that has accumulated in the last few decades in normal functioning lays the foundation for detecting deviation in abnormal functioning and thus provides a solid framework for the search for markers. Instead of depending upon serendipity alone, a systematic search can be launched.

The role of information processing in providing a systematic framework for the search for markers is most strikingly illustrated in studies of attention. It is perhaps the most popular area for schizophrenia research. On the one hand, in order to be able to carry out any experimental task, the schizophrenic must apply attention; but, on the other hand, we hypothesize with Kraepelin and many others that attention is somehow deviant in schizophrenics. How can we trust the outcome of an experiment to reflect performance of the task itself when deviations in attention rather than in the functions under investigation may explain the deviant performance? The results of many experiments in psychopathology have run afoul of the general deficit syndrome. The performance of patients (slowness or less accuracy) may be poor simply because they are not motivated, do not understand the instructions, or cannot attend to the task requirements.

Our first attempt to deal with this problem was to ignore it by designing tasks in which deviation in attention could probably not affect the results. We chose tasks that resulted in responses occurring within the first 1,000 msec following stimulation. In such tasks, attention could play either no role or a minor role because they did not depend upon the engagement of awareness and cognitions of a high order, reducing the role of attention to a minimum. To attain this end we developed the cross-modality reaction-time task (Sutton et al., 1961). This task consists of responding with the same simple finger lift as each stimulus appears and the reaction time of the cross-modal stimuli was compared with ipsimodal stimuli where any deviation in attention, if it did occur, could cancel out.

Another strategy was to devise tasks in which schizophrenics excelled normals, so that the general deficit syndrome could not be used to explain the results. An example of this type of strategy is the recent perceptual organization research devised by Place and Gilmore (1980) in which schizophrenic patients perform more rapidly than normal controls under some conditions. This better performance is attributable to the fact that the control subjects' perception seems to be influenced by the organizational complexities of the visual stimuli and they, therefore, take longer to count the stimuli while the schizophrenics blithely ignore these organizational complexities and finish the counting task more quickly.

Another answer to this question was the statistically controlled design due to the Chapmans (1973), which, by the way, was successfully applied to the cross-modality technique by Manuzza et al. (1984). They demonstrated that our initial assumption that attention played no differential role for normals in the cross-modality reaction-time task was verified. The distribution of ipsimodal and cross-modal functions were found to be psychometrically equivalent in normals, requiring no equating. It is ironic that our attempt to ignore attention, though successful in normals, revealed the deviation that schizophrenics display in shifting attention.

In the dichotic listening studies of Dr. Spring (1985), the various tasks in her experiments were also equated on the normal control group, thus eliminating the possibility of the general deficit syndrome as an explanation of her findings.

Finally, a frontal attack on attention itself was made in such techniques as the Continuous Performance Task (CPT) and Span of Apprehension. Although it is quite clear that these techniques reveal differences between schizophrenics, their unaffected first-degree relatives, and contrasted normal controls, to my knowledge the Chapman argument and the general deficit factor were never addressed in these techniques. Similarly, I do not know whether attention and the general deficit syndrome play a role in the smooth pursuit eye movement task. The fact that Shagass et al. (1976) showed that forcing attention to the numerals on the swinging pendulum reduces the phenomenon, makes one wonder whether attention may not be a factor.* Not all of these measures of attention have been shown to be vulnerability markers and some may turn out to be episode or residual markers.

In the psychosocial sphere, social networks, family deviance and emotional expression in families with highly critical members, as contrasted with nurturing accepting members, have developed prominently as factors in vulnerability, especially in the study of relapses. Whether they can serve as vulnerability markers or episode markers remains to be seen.

The question of whether markers may now serve as the independent variable for classifying mental disorders has arisen. A more equitable approach is the iterative method where either the marker or the diagnostic category can serve alternatingly as the initial entry point. Then the independent variable can change places with the dependent variable, the latter becoming the independent variable and a new analysis made of the data. In this way, both the marker and the diagnostic categories can be further refined.

In line with the need for a "trigger" to trip an episode in the vulnerable, the rapid developments in the field of immunological studies have indicated that stressors seem to lead to a breakdown in the immune system and hence this system could be used to detect triggering stressful events and thus serve to mark the beginnings and ends of episodes (Ader, 1981).

As far as episode markers are concerned, the work on chemical as well as behavioral challenges may show the way for determining the beginnings and ends of episodes (van Kammen, 1985).

As for residual markers, only a comparison of patients who do not show residual markers with those that do can throw light on the indigenous character of residual markers or defects.

Future Perspectives

As for the future, there seems to be a greater tendency to accept the concept of non-familial schizophrenia or phenocopies to use the genetic term. Some of the positive evidence for non-genetic etiology of schizophrenia are the role of perinatal factors, ophthalmological, and other congenital deviations (Zubin, 1979) and the potential of persistent long-term stress for inducing a schizophrenic episode (Dohrenwend & Dohrenwend, 1981). On the negative side, it seems that the role of penetrance in studies of sporadic schizophrenics has not been fully appreciated. For the monogenic hypothesis, the degree of penetrance is on the order of .25. If this is accepted, it can readily be shown that a minimum of 20 first-degree relatives for a single proband is necessary before dismissing the role of genetics on the .95 level of confidence. Since very few probands would have as many as 20 first-degree relatives, it becomes necessary to examine for each proband separately by means of a 4-fold table comparing the number of affected and unaffected first-degree relatives with chance expectancy and the value of chi square computed for each of these 4-fold tables. The distribution of these chi square values should not differ from its expected chance distribution if we are to conclude that probands suffer from a nonfamilial disorder. How to determine the minimum number of first-degree relatives for multiple families and for polygenic hypotheses needs to be worked out. If a threshold value for determining the dichotomy into vulnerable-invulnerable individuals can be developed, the polygenic model can also be dealt with in a manner analogous to the monogenic model and the minimal number of first-degree relatives determined in like manner.

In considering the variety of possible markers (Zubin, 1985) it can be shown that in addition to vulnerability markers there are at least two types of invulnerability markers. Thus, a marker which is present premorbidly, morbidly, and postmorbidly but occurs in unaffected first-degree relatives with no greater frequency than chance expectancy, can be regarded as an invulnerability marker since its absence seems to protect the first-degree relatives from developing an episode. By the same token, if a marker occurs in the unaffected first-degree relatives with a frequency exceeding chance, but does not occur in the probands, it could be interpreted as an invulnerability marker, since its presence in the first-degree relatives probably protects them against developing an episode, and its absence in the proband permitted the development of an episode.

---

*Philip Holzman has addressed this question in his Dean Award Lecture, in press.

At this point one may raise the question of what is meant by a genetic disorder. Since, in the last analysis, the human organism can react only in ways permitted by its genome, every disorder must be genetically compatible with the genome of the organism. What then is meant by a genetic disorder? Woodworth (1941) long ago pointed out that the relative proportion of the variance of a trait attributable to hereditary or environmental factors is what determines our decision as to whether the trait is hereditary or environmental in origin. Thus, if all the members of the group under study have identical genomes, any variation in a trait must be due to environment and mutatis mutandis for identical environments. But even such disorders as phenylketonuria (PKU) or Tay Sachs disease may be genetic disorders only in our social-cultural physical environment. Perhaps we call a disorder genetic when we have some evidence for genetic transmission but are ignorant of the required environmental assists. Similarly, we may call a disorder environmental when we know the noxious environmental agents but have not yet discovered the genetic factors.

Finally, the increase in interest in psychosocial aspects of vulnerability, though it may not contribute to etiology (although some theorists claim that it does) (Dohrenwend & Dohrenwend, 1981), certainly contributes to the triggering, maintenance, and recurrence of episodes It becomes necessary to determine the link between external factors producing stress with the internal responses to stress in the immunological, endocrinological systems in their interaction with the central nervous system. The study of the psychosocial factors may lead to a better understanding of chronicity and recidivism, and may point to the entry path for intervention.

It is also important to determine whether the markers are associated with the disorder (pathophysiological markers) or have no direct association with the disorder (linkage type). The former may be prodromal in character in so far as they may develop only after the incipient onset of the disorder and hence may serve more as episode markers than vulnerability markers, although some markers may serve both as episode and vulnerability markers, e.g., P300. The linkage type markers may occur coincidentally with schizophrenia rather than causally, e.g., are located on the same chromosomes close to the alleles determining schizophrenia, and hence can be depended upon to distinguish unaffected first-degree relatives. Pathophysiological markers that occur in unaffected first-degree relatives strengthen the possibility that they are at least in part vulnerability rather than episode markers.

It should also be borne in mind that not all individuals will develop an episode even if they possess the marker identifying them as vulnerable and are subjected to sufficiently noxious stressors. Certain moderating variables such as social networks, ecological niches, and premorbid personality may absorb the stress and prevent the episode if they are favorable, or enhance the probability of a developing episode if they are unfavorable (Zubin et al., 1985).

Finally, the response to treatment may itself serve as a marker, differentiating those who benefit from those who do not.

Summary of Panel Presentations

Some of the outstanding contributions of the present panel summarizing the state of the art as of 1985 are as follows:

Generally, markers of vulnerability can be found not only in the genetic domain but also in any of the other seven domains of the etiological models of schizophrenia (Zubin et al., 1981). One model, the neurophysiological model, seems to possess certain transcending characteristics which need to be pointed out. Since neurophysiology underlies all behavior, deviations in this carrier wave for behavior should accompany any of the disordered behavior by which we now recognize the presence of schizophrenia. As an example, P300 transcends the characteristics of the stimulus which elicits it, appearing independently of the modality in which it arises and of some of the other properties of the stimulus which elicit it. Hence, it becomes an independent indicator of brain function, independent of its origin, and is an endogenous brain response to stimulation. Consequently, P300 and other components of the event-related potentials are excellent measures of the deviations in information processing which may characterize schizophrenia. In contrast with other techniques which can not always transcend the concrete matrix from which they emanate, physiological indicators may be free of them. It may serve the same purpose in analyzing brain function that factor analysis serves in analyzing the common elements in many performances. Another virtue of physiological indicators is that they can be repeated as often as required (within limits of adaptation). Consequently, the final averaged result is relatively free of noise.

One finding reported by Steinhauer (1985) is that the pattern of response of P300 to the various degrees of uncertainty of the stimulus is quite different in schizophrenics than in normals. This additional possibility of determining a pattern over several degrees of uncertainty makes the analysis more flexible, so that individuals can be clustered in accordance with the pattern they exhibit. Since the likelihood of finding pathognomonic markers is rather low, the pattern across different markers may also help to group individuals into like-minded clusters. Thus, instead of being merely a group phenomenon, the marker or markers can pin-point the single individual and his peers and, therefore, can be used meaningfully in dealing with them.

An interesting example of how the different characteristics of a disorder vary in the degree of their pathognomicity is found in PKU. Taking the marker of the concentration of phenylalanine in the blood plasma, the distribution for normals is from 0 to about 2%, while the distribution for PKU patients is from about 15% to 40%, with no overlap. However, if IQ is taken as a marker, the distribution for PKU overlaps with the distribution for normals between IQs of 20 and 125. Similarly, in the distribution for head size PKU overlaps with that of normals between 300 and 350 mm. For hair color reflectance, the PKU distribution overlaps with the normal distribution almost completely—from 0 to 30%. However, it is possible that if the pattern of IQ status, head size, and hair color reflectance were obtained for PKU for each patient and for each normal, the overlap between the patterns would be reduced considerably. Our markers for schizophrenia resemble more the hair color reflectance measure than the phenylalanine concentration in blood plasma, and that is why we need to be satisfied with patterns of markers rather than search for pathognomonic markers (Levitan & Montagu, 1977).

At present, the beginnings and terminations of episodes are based purely on clinical observations and hunches. Dr. van Kammen (1985) has pointed out that it may be possible to develop objective episode markers which would enable us to recognize the imminence of an incipient episode or the imminence of its termination. The ability to perceive the approaching episode may help in the selection of suitable intervention strategies, while knowledge that the episode is terminating may be of value in altering the treatment regimen. The question raised by Dr. van Kammen is whether we can find suitable biochemical challenges to serve as episode markers. If this can be done, they could serve as indicators for the beginning and end of treatment. We may possibly be able to abort incipient episodes or prevent needless continuation of drug treatment with its dangers of inducing tardive dyskinesia. Among the candidates for episode markers are (1) growth hormone responses to apomorphine, (2) psychotogenic response to amphetamine and methylphenidate, and (3) relative cerebrospinal fluid/norepinephrine levels (van Kammen, 1985).

These challenges can serve as chemical stressors, even as high emotional expression in families serve as environmental stressors. The controlled graduated stress which can be induced by amphetamine may serve to trigger a miniepisode in those who are still in their episode, while this chemical challenge may produce little or no effect in those in whom the episode is ended. It is likely that behaviorally induced stressors may serve the same purpose (Zubin & Steinhauer, 1981).

In the cognitive domain, Dr. Spring (1985) has added a new marker of vulnerability—intrusions in dichotic listening with distractors, especially in delusional schizophrenics. The performance of these schizophrenics on the shadowing task itself is not impaired but, unlike their controls, they make intrusions from the non-target ear in their shadowing. This holds true not only of the schizophrenic probands but also of their first-degree relatives, and does not seem to disappear in remitted cases. It also does not characterize nonparanoid schizophrenics and nonschizophrenic mental patients and their relatives. Dr. Spring suggests that the deviation in information processing which this marker presents may be due to a difference in the allocation of attention capacity. The schizophrenic may be allocating more processing capacity to performance on this task than normals, without interfering with accuracy of shadowing on the main channel. According to this suggestion, schizophrenics may be excelling in their performance since, despite instructions to monitor only the main channel, they succeed in monitoring even the forbidden channel to some extent.

In the perceptual domain, Dr. Kietzman (1985) has pointed out that the speed of visual information processing is characteristically slowed down in schizophrenics. Two techniques for measuring the speed of processing are now available: span of apprehension and backward masking. Dr. Knight has suggested that the slowed processing may be a long-term characteristic product of a perceptual organization deficiency in schizophrenics with poor premorbid personalities (Knight, 1984).

All in all, the last 7 years have been a period of consolidation and gradual rather than rapid further development. In a sense it was the sabbatical year for markers; nevertheless, the impact of information processing as a framework has been strongly felt. Several of the markers have entrenched themselves more firmly by providing evidence of their existence in unaffected first-degree relatives—a requirement for establishing them as vulnerability markers.

In the 1977 report (Zubin, 1979) the following potential vulnerability markers (as determined by presence in unaffected first-degree relatives) were reported: (1) Cancro's measures of blinking during visual mental tasks, (2) Holzman's smooth pursuit eye movements, (3) Cromwell's cross-over index in reaction time, and (4) Rosvold's and Orzack's vigilance task of continuous performance.

Today, the list of potential vulnerability markers is as follows: cross-over reaction time, span of apprehension, CPT, backward masking, smooth pursuit eye movements and dichotic listening with distraction. Those awaiting vulnerability status are: cross-modality reaction time, evoked potentials, pupillographic responses, and heart rate.

Very little progress has been made in the area of residual markers, an area which is in need of further development, though it has been suggested that some negative symptoms may qualify as residual markers. The other types of markers and their usefulness are waiting for further research.

References

Ader, R. (ed.). *Psychoneuroimmunology.* New York: Academic Press, 1981.

American Psychiatric Association, *Diagnostic and Statistical Manual*—DSM-III, Washington, D.C.: The Association, 1980.

Bleuler, M. *The Schizophrenic Disorders: Long-Term Patient and Family Studies.* (Die Schizophrenen Geistesstorungen im Lichte Langjahriger Kranken, Stuttgart, Thieme Verlag, 1972) New Haven: Yale University Press, 1978.

Chapman, L.J., and Chapman, J.P. Problems in the measurement of cognitive deficit. *Psychol. Bull.*, 79:380–385, 1973.

Ciompi, L. The natural history of schizophrenia in the long term. *Br. J. Psychiatry*, 136:413–420, 1980.

Dohrenwend, B.S., and Dohrenwend, B.P. (eds.). Life stress and illness: Formulation of the issues. In: *Stressful Events and Their Contexts.* New York: Prodist, 1981.

Harding, C.M., and Strauss, J.S. In: Alpert, M. (ed.), *The Course of Schizophrenia: An Evolving Concept, Controversies in Schizophrenic Changes and Constances.* New York: Guilford Press. (In press)

Huber, G., Gross, G., Schuttler, R., and Linz, M. Longitudinal studies of schizophrenic patients. *Schizophr. Bull.*, 6:592–605, 1980.

Kietzman, M.L., Sensory and perceptual behavioral markers of schizophrenia. *Psychopharmacol. Bull.*, 21(3):518–522, 1985.

Kietzman, M.L., Spring, B., and Zubin, J. Perception, cognition, and information processing. In: Kaplan, H.I., and Sadock, B.J. (eds.), *Comprehensive Textbook of Psychiatry*, 4th ed. Chapt. 4. Baltimore: Williams & Wilkins, 1984, pp. 157–158.

Knight, R.A. Converging models of cognitive deficit in schizophrenia. In: Spaulding, W.D., and Cole, J.K. (eds.), *Theories of Schizophrenia and Psychosis: Nebraska Symposium on Motivation, 1983*. Lincoln, Neb.: University of Nebraska Press, 1984, pp. 93–156.

Levitan, M., and Montagu, A. *Textbook of Human Genetics*, 2nd ed. New York: Oxford University Press, 1977.

Manuzza, S., Kietzman, M.L., Berenhaus, I.J., et al. The modality shift effect in schizophrenia: Fact or artifact? *Biol. Psychiatry*, 19(9):1317–1331, 1984.

Meltzer, H.Y. Schizoaffective disorder: Is the news of its nonexistence premature? *Schizophr. Bull.*, 10(1): 11–13, 1984.

Place, E.J.S., and Gilmore, G.C. Perceptual organization in schizophrenia. *J. Abnorm. Psychol.*, 89: 409–418, 1980.

Shagass, C., Roemer, R.A., and Amadeo, M. Eye-tracking performance and engagement of attention. *Arch. Gen. Psychiatry*, 33:121–125, 1976.

Spring, B. Distractibility as a marker of vulnerability to schizophrenia. *Psychopharmacol. Bull.* 21(3):509–512, 1985.

Steinhauer, S.R. Neurophysiological aspects of information processing in schizophrenia. *Psychopharmacol. Bull.*, 21(3):513–517, 1985.

Sutton, S., Hakerem, G., Zubin, J., and Portnoy, M. The effect of shift of sensory modality on serial reaction times: A comparison of schizophrenics and normals. *Am. J. Psychol.*, 74:224–232, 1961.

van Kammen, D.P., Rosen, J.P., Peters, J., et al. Are there state-dependent markers in schizophrenia? *Psychopharmacol. Bull.*, 21(3):497–502, 1985.

Woodsworth, R.S. Heredity and environment: A critical survey of recently published material on twins and foster children. Social Science Research Council Bulletin No. 47, 1941.

Zubin, J. Summary of the session on markers of vulnerability to mental disorders. *Psychopharmacol. Bull.*, 15(1):47–79, 1979.

Zubin, J. Negative symptoms: Are they indigenous to schizophrenia? *Schizophr. Bull.*, 11:461–470, 1985.

Zubin, J. Implications of the vulnerability model for DSM-IV in contemporary issues in psychopathology. In: Millon, T., and Klerman, G. (eds.) (In press)

Zubin, J., and Steinhauer, S.R. How to break the logjam in schizophrenia: A look beyond genetics. *J. Nerv. Ment. Dis.*, 169:477–492, 1981.

Zubin, J., Steinhauer, S.R., Day, R., and van Kammen, D.P. Schizophrenia at the crossroads: A blueprint for the 80's. *Compr. Psychiatry*, 26:217–240, 1985; also In: Alpert, M. (ed.), *Controversies in Schizophrenia: Changes and Constancies*. New York: Guilford Press. (In press)

Psychopharmacology—A Recurring Bibliography—

The bibliography below is offered to our readers to alert them to recent papers on psychopharmacology from the world literature. It was computer-generated by the Medical Literature Analysis and Retrieval System (MEDLARS) of the National Library of Medicine, National Institutes of Health, and represents papers which were entered into the system during the 3 months before this issue of the *Bulletin* went to press.

The subject headings from Index Medicus were selected at the NIMH to reflect significant current interest of the international scientific community. Some nonrelevant citations may appear, and some relevant ones may be absent, but this is usual for machine-generated searches.

ISSN 0048–5764

BIBLIOGRAPHY

ACEPROMAZINE

Premedication of dogs with acepromazine or pentazocine before euthanasia with carbon monoxide. Dallaire A, et al. **Can J Comp Med** 1985 Apr;49(2):171–8

ACETYLCHOLINE

Increase in transmitter release from motor nerve terminals induced by some pyridine derivatives. Montoya GA, et al. **Acta Physiol Pharmacol Latinoam** 1984;34(4):409–18

Positive inotropic effect of acetylcholine in canine cardiac Purkinje fibers. Gilmour RF Jr, et al. **Am J Physiol** 1985 Oct;249(4 Pt 2):H735–40

Enzymes of acetylcholine metabolism in the rat cochlea. Godfrey DA, et al. **Ann Otol Rhinol Laryngol** 1985 Jul–Aug;94(4 Pt 1):409–14

Enhancement of acetylcholine–evoked catecholamine release from perfused dog adrenals by elevating cyclic AMP levels. Morita K, et al. **Arch Int Pharmacodyn Ther** 1985 Jun;275(2):208–16

Effects of gastrointestinal hormones on Oddi's sphincter and duodenal myoelectric activity and pancreatobiliary pressure. Studies in the opossum. Coelho JC, et al. **Arch Surg** 1985 Sep;120(9):1060–4

Open channel noise. I. Noise in acetylcholine receptor currents suggests conformational fluctuations. Sigworth FJ. **Biophys J** 1985 May; 47(5):709–20

Acetylcholine acts on m2–muscarinic receptors to excite rat locus coeruleus neurones. Egan TM, et al. **Br J Pharmacol** 1985 Aug; 85(4):733–5

Two types of receptors for 5–hydroxytryptamine on the cholinergic nerves of the guinea–pig myenteric plexus. Kilbinger H, et al. **Br J Pharmacol** 1985 Jun;85(2):529–39

Single acetylcholine channel currents in sympathetic neurons. Schofield GG, et al. **Brain Res** 1985 Sep 2;342(1):200–3

ACh and 5–HT stimulated thermogenesis at different core temperatures in the He–Cold hypothermic hamster. Simpson CW, et al. **Brain Res Bull** 1985 Aug;15(2):123–7

Acetylcholine supersensitivity in the rat heart produced by neonatal sympathectomy. Ishii K, et al. **Can J Physiol Pharmacol** 1985 Jul; 63(7):898–9

The characterization of a sodium–dependent high affinity choline uptake system unassociated with acetylcholine biosynthesis. Ivy MT, et al. **Comp Biochem Physiol [C]** 1985;81(2):351–7

Seasonal variations in the muscarinic regulation of acetylcholine release from Torpedo electric organ nerve terminals. Pinchasi I, et al. **Comp Biochem Physiol [C]** 1985;81(2):439–44

Effect of microelectrophoretically applied acetylcholine, noradrenaline, dopamine and serotonin on the discharge of paraventricular oxytocinergic neurones in the rat. Honda K, et al. **Endocrinol Jpn** 1985 Feb;32(1):127–33

Corticoidogenic effect of acetylcholine in bovine adrenocortical cells. Kawamura M, et al. **Endocrinol Jpn** 1985 Feb;32(1):17–9

The antagonism of acetylcholine excitatory and inhibitory responses of Helix central neurones, by some neuromuscular blocking drugs. Bokisch AJ, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):405–9

Histamine–mediated acetylcholine release in the guinea–pig ileum. Rubinstein R, et al. **Eur J Pharmacol** 1985 May 8;111(2):245–50

Antipsychotic drugs depress acetylcholine release in the Torpedo electric organ, a purely cholinergic system. Schaller–Clostre F, et al. **Eur J Pharmacol** 1985 May 28;112(1):27–37

Biochemical evidence that acetylcholine release from cholinergic nerve terminals is mostly vesicular. Michaelson DM, et al. **FEBS Lett** 1985 Sep 2;188(2):389–93

Temporal coincidence between synaptic vesicle fusion and quantal secretion of acetylcholine. Torri–Tarelli F, et al. **J Cell Biol** 1985 Oct; 101(4):1386–99

Improved analysis of acetylcholine and choline in canine brain and blood samples by capillary gas chromatography–mass spectrometry. Singh AK, et al. **J Chromatogr** 1985 Apr 12;339(1):170–4

Effect of perfusion rate of cholinergic agonist on sinus node automaticity. Loeb JM, et al. **J Electrocardiol** 1985 Jul;18(3):287–94

Synaptosomal phospholipase D potential role in providing choline for acetylcholine synthesis. Hattori H, et al. **J Neurochem** 1985 Nov; 45(5):1578–84

Neurally mediated nonadrenergic relaxation in cat airways occurs independent of cholinergic mechanisms. Altiere RJ, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):590–7

Trace amines inhibit the electrically evoked release of [3H]acetylcholine from slices of rat striatum in the presence of pargyline: similarities between beta–phenylethylamine and amphetamine. Baud P, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):220–9

Acetylcholine– and 5–hydroxytryptamine–stimulated contraction and calcium uptake in bovine coronary arteries: evidence for two populations of receptor–operated calcium channels. Ratz PH, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):641–7

Cyclooxygenase inhibitors affect Met–enkephalin– and acetylcholine–stimulated motility of the isolated rat colon. Scheurer U, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):742–6

Long–term potentiation of synaptic acetylcholine release in the superior cervical ganglion of the rat. Briggs CA, et al. **J Physiol (Lond)** 1985

BIBLIOGRAPHY

Jun;363:181-90

Lack of nicotinic supersensitivity in frog sympathetic neurones following denervation. Dunn PM, et al. **J Physiol (Lond)** 1985 Jun;363:211-25

Acetylcholine-evoked potassium release in the mouse pancreas. Petersen OH, et al. **J Physiol (Lond)** 1985 Aug;365:319-29

Age-related reductions in rat atrial high affinity choline uptake, ACh synthesis, and ACh release. A brief note. Meyer EM, et al. **Mech Ageing Dev** 1985 May 13;30(2):221-5

Intracerebroventricular administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its metabolite 1-methyl-4-phenylpyridinium ion (MPP+) decrease dopamine and increase acetylcholine in the mouse neostriatum. Cavalla D, et al. **Neuropharmacology** 1985 Jun;24(6):585-6

Intracerebroventricular administration of ethylcholine mustard aziridinium ion (AF64A) reduces release of acetylcholine from rat hippocampal slices. Leventer S, et al. **Neuropharmacology** 1985 May; 24(5):453-9

Anti-acetylcholine antibodies and first immunocytochemical application in insect brain. Geffard M, et al. **Neurosci Lett** 1985 Jun 4;57(1):1-6

Effect of ketamine on amino acid-evoked release of acetylcholine from rat cerebral cortex in vitro. Lodge D, et al. **Neurosci Lett** 1985 May 23;56(3):371-5

Laminar distributions of neurons sensitive to acetylcholine, noradrenaline and dopamine in the dorsolateral prefrontal cortex of the monkey. Sawaguchi T, et al. **Neurosci Res** 1985 Apr;2(4):255-73

Noradrenergic modulation of 4-aminopyridine-induced acetylcholine release from rat cerebral cortex. Magnani M, et al. **Pharmacol Res Commun** 1985 Jul;17(7):653-8

Acetylcholine and phorbol esters inhibit potassium currents evoked by adenosine and cAMP in Xenopus oocytes. Dascal N, et al. **Proc Natl Acad Sci USA** 1985 Sep;82(17):6001-5

Two types of muscarinic response to acetylcholine in mammalian cortical neurons. McCormick DA, et al. **Proc Natl Acad Sci USA** 1985 Sep; 82(18):6344-8

Calcium entry induced by acetylcholine action on snail neurons. Eusebi F, et al. **Proc R Soc Lond [Biol]** 1985 Jul 22;225(1238):55-62

The effect of Na+ and Cl- removal and of loop diuretics on acetylcholine-evoked membrane potential changes in mouse lacrimal acinar cells. Suzuki K, et al. **Q J Exp Physiol** 1985 Jul;70(3):437-45

Relationship between pelviureteral peristaltic frequency and urine flow change evoked by autonomic drug administration. Morita T, et al. **Tohoku J Exp Med** 1985 Jul;146(3):265-71

[Changes in acetylcholine contractions induced by carnitine in coronary vessels isolated 'in vitro'] Bettini V, et al. **Acta Vitaminol Enzymol** 1985; 7(1-2):61-9 (Eng. Abstr.) **(Ita)**

[Effect of acetylcholine on the structuro-functional characteristics of bush-like interoceptors of the urinary bladder of the frog] Podol'skaia LA, et al. **Arkh Anat Gistol Embriol** 1985 Jul;89(7):28-35 (Eng. Abstr.) **(Rus)**

[Dynamics of changes in the spontaneous quantum and nonquantum secretion of acetylcholine from the motor nerve endings after nerve dissection] Nikol'skiĭ EE, et al. **Dokl Akad Nauk SSSR** 1985; 281(3):762-4 **(Rus)**

[Effect of serotonin and acetylcholine on the electrical activity of isolated cortex in the rabbit] Ignat'ev DA, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):733-41 (Eng. Abstr.) **(Rus)**

[Differences in the cholinergic effects of eserine and pilocarpine on the uvea and retina of the bovine eye] Kováčik L, et al. **Bratisl Lek Listy** 1985 Jul;84(1):45-9 (Eng. Abstr.) **(Slo)**

ACHIEVEMENT

Methylphenidate and children with attention deficit disorder. Dose effects on classroom academic and social behavior. Pelham WE, et al. **Arch Gen Psychiatry** 1985 Oct;42(10):948-52

ADJUSTMENT DISORDERS

Depression and anxiety: mianserin and nomifensine compared in a double-blind multicentre trial. Granier F, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:67-74

An evaluation of alprazolam in the treatment of reactive or neurotic (secondary) depression. Imlah NW. **Br J Psychiatry** 1985 May; 146:515-9

Biochemical and diagnostic classification and serum drug levels: relation to antidepressive effect of imipramine. Møller SE, et al. **Neuropsychobiology** 1985;13(4):160-6

Cianopramine and amitriptyline in the treatment of depressed patients—a placebo-controlled study. Hormazabal L, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):205-8

AFFECT

Anorectic behavior, mood, and metabolic and endocrine adaptation to starvation in anorexia nervosa during inpatient treatment. Pahl J, et al. **Biol Psychiatry** 1985 Aug;20(8):874-87

The conditioned place preference is affected by two independent reinforcement processes. White NM, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):37-42

AFFECTIVE DISORDERS

Circadian rhythm in primary affective disorder. Faravelli C, et al. **Compr Psychiatry** 1985 Jul-Aug;26(4):364-9

Practical therapeutics: the use of carbamazepine in affective disorders. Obel AO, et al. **East Afr Med J** 1985 Mar;62(3):224-8

Mood-independent aberrancies in associative processes in bipolar affective disorder: an apparent stabilizing effect of lithium. Pons L, et al. **Psychiatry Res** 1985 Apr;14(4):315-22

Studies of beta-adrenergic receptors in leukocytes of patients with affective illness and effects of antidepressant drugs. Pandey GN, et al. **Psychopharmacol Bull** 1985;21(3):603-9

AFFECTIVE DISORDERS, PSYCHOTIC

How many, and which patients with affective disorders need long-term maintenance therapy? Angst J, et al. **Adv Biochem Psychopharmacol** 1985;40:169-72

Changes in the diagnoses of the functional psychoses associated with the introduction of lithium. Parker G, et al. **Br J Psychiatry** 1985 Apr; 146:377-82

Successful treatment of psychotic depression with carbamazepine. Schaffer CB, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):233-5

Mood-independent aberrancies in associative processes in bipolar affective disorder: an apparent stabilizing effect of lithium. Pons L, et al. **Psychiatry Res** 1985 Apr;14(4):315-22

[Administration of maintenance therapy in endogenous psychoses in out-patient practice] Mrña B, et al. **Cesk Psychiatr** 1985 Aug; 81(4):273-5 (Eng. Abstr.) **(Cze)**

AGGRESSION

The participation of serotoninergic system in the regulation of emotional-defensive behavior evoked by intrahypothalamic carbachol injections in the cat. Golebiewski H, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(1-2):25-36

Metoprolol for intermittent explosive disorder. Mattes JA. **Am J Psychiatry** 1985 Sep;142(9):1108-9

Maternal aggression in mice: effects of treatments with PCPA, 5-HTP and 5-HT receptor antagonists. Ieni JR, et al. **Eur J Pharmacol** 1985 May 8;111(2):211-20

Animal models of behavioral pathology and violent aggression. Valzelli L. **Methods Find Exp Clin Pharmacol** 1985 Apr;7(4):189-93

The effect of milenperone on the aggressive behavior of psychogeriatric patients. A double-blind placebo-controlled study. De Cuyper H, et al. **Neuropsychobiology** 1985;13(1-2):1-6

The role of central noradrenergic neurons in electroconvulsive shock-induced muricide inhibition in olfactory bulbectomized rats. Liou SY, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):65-70

Benzodiazepine-receptor mediated inhibition of isolation-induced aggression in mice. Skolnick P, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):17-20

Evidence of norepinephrine-mediated suppression of para-chlorophenylalanine-induced muricidal behavior. Pucilowski O, et al. **Pharmacol Res Commun** 1985 May;17(5):457-62

Human aggression and the role of central serotonin. Mühlbauer HD. **Pharmacopsychiatry** 1985 Mar;18(2):218-21

The cholinergic influences on aggression in isolated mice. Herbut M, et al. **Pol J Pharmacol Pharm** 1985 Jan-Feb;37(1):1-10

Maternal aggression in rats: effects of chlordiazepoxide and fluprazine. Olivier B, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):68-76

[Change in certain forms of aggressive behavior and the concentration of monoamines in the brain during selection of wild rats for taming] Nikulina EM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):703-9 (Eng. Abstr.) **(Rus)**

[Discrete and continuous mathematical models of intraspecific behavior in the pharmacoethology of the mouse] Poshivalov VP, et al. **Zh Vyssh Nerv Deiat** 1985 May-Jun;35(3):487-96 (Eng. Abstr.) **(Rus)**

AMINO ACIDS

Moroamine, amino acid and cholinergic interactions in slices of rat cerebral cortex. Flint RS, et al. **Brain Res Bull** 1935 Aug; 15(2):197-202

Effectors of amino acid transport processes in animal cell membranes. Lerner J. **Comp Biochem Physiol** [A] 1985;81(4):713-39 (194 ref.)

Characteristics and hormonal regulation of amino acid transport system A in isolated rat hepatocytes. Kilberg MS, et al. **Curr Top Cell Regul** 1985;25:133-63 (79 ref.)

Interplay of nutrients and hormones in the regulation of insulin release. Pipeleers DG, et al. **Endocrinology** 1985 Sep;117(3):824-33

Interplay of nutrients and hormones in the regulation of glucagon release. Pipeleers DG, et al. **Endocrinology** 1985 Sep;117(3):817-23

Relationship of brain glutamine and brain neutral amino acid concentrations after portacaval anastomosis in rats. Jeppsson B, et al. **Eur J Clin Invest** 1985 Aug;15(4):179–87

Differential effects of dextrorphan and levorphanol on the excitation of rat spinal neurons by amino acids. Church J, et al. **Eur J Pharmacol** 1985 May 8;111(2):185–90

Blocking action of pentobarbital on receptors for excitatory amino acids in the guinea pig hippocampus. Sawada S, et al. **Exp Brain Res** 1985; 59(2):226–31

Reversed-phase high-performance liquid chromatographic separation and quantitation of phenylthiohydantoin derivatives of 25 amino acids, including those of cysteic acid, 4-hydroxyproline, methionine sulfone, S-carboxymethylcysteine and S-methylcysteine. Kolbe HV, et al. **J Chromatogr** 1985 Jun 26;327:1–7

Determination of amino acids by separation of their ion pairs with dodecyl sulphate. Seiler N, et al. **J Chromatogr** 1985 May 31;341(1):11–21

1-Piperideine as an in vivo precursor of the gamma-aminobutyric acid homologue 5-aminopentanoic acid. Callery PS, et al. **J Neurochem** 1985 Sep;45(3):946–8

Excitatory effect of amino acids on identified neuron R14 of Aplysia. II. Neutral amino acids and structure-activity relationships. Ichinose M, et al. **J Neurosci Res** 1985;14(1):145–58

Potassium movements associated with amino acid and sugar transport in enterocytes isolated from rabbit jejunum. Brown PD, et al. **J Physiol (Lond)** 1985 Jun;363:271–85

Effect of excitatory amino acids on gamma-aminobutyric acid release from frog horizontal cells. Cunningham JR, et al. **J Physiol (Lond)** 1985 May;362:51–67

Amino acids release somatostatin-like immunoreactivity from isolated rat glomeruli. Fujibayashi S, et al. **Mol Cell Endocrinol** 1985 Jul; 41(2-3):263–7

Stability of the amino acid content of nerve endings after administration of gamma-aminobutyrate agonists and antagonists. Wood JD, et al. **Neuropharmacology** 1985 Jul;24(7):685–7

Dopaminergic toxicity after the stereotaxic administration of the 1-methyl-4-phenylpyridinium ion (MPP+) to rats. Heikkila RE, et al. **Neurosci Lett** 1985 Aug 16;59(1):135–40

Effect of ketamine on amino acid-evoked release of acetylcholine from rat cerebral cortex in vitro. Lodge D, et al. **Neurosci Lett** 1985 May 23;56(3):371–5

Antagonistic effect of delta-aminovaleric acid on bicuculline-insensitive gamma-aminobutyric acid B (GABA B) sites in the rat's brain. Nakahiro M, et al. **Neurosci Lett** 1985 Jun 24;57(3):263–6

Correlation between cytochrome oxidase staining and the uptake and laminar distribution of tritiated aspartate, glutamate, gamma-aminobutyrate and glycine in the striate cortex of the squirrel monkey. Carroll EW, et al. **Neuroscience** 1985 Aug;15(4):959–76

Antramine (antral histamine) antagonizes somatostatin inhibition on endogenous gastrin-induced gastric secretion. A new hypothesis for the role of histamine in gastric secretion regulation. Vatier J, et al. **Scand J Gastroenterol** 1985 Aug;20(6):671–6

[Course of the concentration of serum free amino acids as a function of time and the method of preservation] Hainque B, et al. **Ann Biol Clin (Paris)** 1985;43(3):221–6 (Eng. Abstr.) **(Fre)**

[Conformation study, using an empirical atom-atom potential, of biologically active amino acids as neurotransmitters] Jáuregui EA, et al. **Acta Cient Venez** 1984;35(5-6):337–41 (Eng. Abstr.) **(Spa)**

AMITRIPTYLINE

A placebo controlled comparison of the effects of pirenzepine and amitriptyline on the tyramine pressor test in healthy volunteers. Wilkins MR, et al. **Br J Clin Pharmacol** 1985 Jun;19(6):829–31

Discrepancies between pharmacokinetic studies of amitriptyline. Schulz P, et al. **Clin Pharmacokinet** 1985 May–Jun;10(3):257–68 (43 ref.)

Long-term amitriptyline in chronic depression. Giller E Jr, et al. **Hillside J Clin Psychiatry** 1985;7(1):16–33

Cerebrospinal fluid levels of amitriptyline, nortriptyline, imipramine and desmethylimipramine. Relationship to plasma levels and treatment outcome. Hanin I, et al. **J Affective Disord** 1985 Jul;9(1):69–78

Determination of citalopram, amitriptyline and clomipramine in plasma by reversed-phase high-performance liquid chromatography. Rop PP, et al. **J Chromatogr** 1985 Feb 27;338(1):171–8

Patterns of attrition for psychosocial and pharmacologic treatments of depression. Last CG, et al. **J Clin Psychiatry** 1985 Sep;46(9):361–6

Repeated treatment with imipramine or amitriptyline increases the locomotor response of rats to (+)-amphetamine given into the nucleus accumbens. Maj J, et al. **J Pharm Pharmacol** 1985 May;37(5):362–4

Electro-acupuncture vs. amitriptyline in the treatment of depressive states. Luo HC, et al. **J Tradit Chin Med** 1985 Mar;5(1):3–8

Antidepressant treatment of children: clinical relapse is unrelated to tricyclic plasma concentrations. Olig RM, et al. **Percept Mot Skills** 1985 Jun;60(3):879–89

Serotonin uptake and imipramine binding in rat platelets after chronic dexamethasone and amitriptyline treatment. Chan MY, et al. **Pharmacol Res Commun** 1985 Jul;17(7):619–32

Amitriptylinoxide: receptor-binding profile compared with other antidepressant drugs. Borbe HO, et al. **Pharmacopsychiatry** 1985 Sep; 18(5):314–9

Single oral dose pharmacokinetics of amitriptylinoxide and amitriptyline in humans. Kuss HJ, et al. **Pharmacopsychiatry** 1985 Jul; 18(4):259–62

Cardiovascular effects of single doses of the antidepressants amitriptyline and lofepramine in healthy subjects. Stern H, et al. **Pharmacopsychiatry** 1985 Jul;18(4):272–7

Cardiovascular effects of amitriptyline in the treatment of elderly depressed patients. Christensen P, et al. **Psychopharmacology (Berlin)** 1985;87(2):212–5

Cianopramine and amitriptyline in the treatment of depressed patients—a placebo-controlled study. Hormazabal L, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):205–8

Evaluation of amitriptyline pharmacokinetics during peritoneal dialysis. Tasset JJ, et al. **Ther Drug Monit** 1985;7(3):255–7

[Measurement of basal plasma levels of 3 anterior pituitary hormones during acute or chronic treatment with tricyclic antidepressants] Goyot C, et al. **Encephale** 1985 Mar–Apr;11(2):45–51 (Eng. Abstr.) **(Fre)**

[Serum levels of amitriptyline and nortriptyline in a case of poisoning (letter)] Fernández de Gatta M, et al. **Med Clin (Barc)** 1985 May 18; 84(19):798–9 **(Spa)**

AMOBARBITAL

Toxicological analysis of amobarbital and glutethimide from bone tissue. Benkö A. **J Forensic Sci** 1985 Jul;30(3):708–14

AMPHETAMINE

Succinic and malic dehydrogenase histochemical activities in cerebral, cerebellar and neostriatum sections incubated in presence of d-amphetamine. Martínez-Murillo R, et al. **Acta Neuropathol (Berl)** 1985;67(1-2):81–5

Amphetamine's effects on terminal excitability of noradrenergic locus coeruleus neurons are impulse-dependent at low but not high doses. Ryan LJ, et al. **Brain Res** 1985 Aug 19;341(1):155–63

Differential biochemical and behavioral effects of single and chronic administration of amphetamine and apomorphine. Bernardi MM, et al. **Gen Pharmacol** 1985;16(4):407–10

Differential alterations in brain sensitivity to amphetamine and pentylenetetrazol in socially deprived mice. Faggin BM, et al. **Gen Pharmacol** 1985;16(3):299–302

Trace amines inhibit the electrically evoked release of [3H]acetylcholine from slices of rat striatum in the presence of pargyline: similarities between beta-phenylethylamine and amphetamine. Baud P, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):220–9

Sensitization to stress: the enduring effects of prior stress on amphetamine-induced rotational behavior. Robinson TE, et al. **Life Sci** 1985 Sep 16;37(11):1039–42

Ten years of experience with 1,000 hyperactive children in a private practice. Eichlseder W. **Pediatrics** 1985 Aug;76(2):176–84

Comparative effects of cathinone and amphetamine on fixed-interval operant responding: a rate-dependency analysis. Goudie AJ. **Pharmacol Biochem Behav** 1985 Sep;23(3):355–65

Asymmetrical effect of unilateral cortical lesions and amphetamine on DRL-20: a time-loss analysis. Kubos KL, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):1001–6

Persistent effects of amphetamine, p-chloroamphetamine, and related compounds on central dopamine and serotonin neurons in rodents. Fuller RW. **Psychopharmacol Bull** 1985;21(3):528–32

Drug preference in normal volunteers: effects of age and time of day. de Wit H, et al. **Psychopharmacology (Berlin)** 1985;87(2):186–93

Evaluation of signal detection theory on the effects of psychotropic drugs on critical flicker-fusion frequency in normal subjects. MacNab MW, et al. **Psychopharmacology (Berlin)** 1985;85(4):431–5

The abolition of the partial reinforcement extinction effect (PREE) by amphetamine. Weiner I, et al. **Psychopharmacology (Berlin)** 1985; 86(3):318–23

AMPHETAMINES

A reevaluation of psychotomimetic amphetamine derivatives in humans. Cassels BK, et al. **J Psychoactive Drugs** 1985 Apr–Jun;17(2):129–30

Persistent effects of amphetamine, p-chloroamphetamine, and related compounds on central dopamine and serotonin neurons in rodents. Fuller RW. **Psychopharmacol Bull** 1985;21(3):528–32

Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. Ricaurte G, et al. **Science** 1985 Sep 6;229(4717):986–8

ANGER

Metoprolol for intermittent explosive disorder. Mattes JA. **Am J Psychiatry** 1985 Sep;142(9):1108–9

ANOREXIA NERVOSA

Anorectic behavior, mood, and metabolic and endocrine adaptation to starvation in anorexia nervosa during inpatient treatment. Pahl J, et al. **Biol Psychiatry** 1985 Aug;20(8):874–87

Monoamine oxidase inhibitor therapy for anorexia nervosa and bulimia: a preliminary trial of isocarboxazid. Kennedy SH, et al. **J Clin Psychopharmacol** 1985 Oct;5(5):279–85

The management of bulimia nervosa. Fairburn CG. **J Psychiatr Res** 1985; 19(2–3):465–72

Altered norepinephrine metabolism following long–term weight recovery in patients with anorexia nervosa. Kaye WH, et al. **Psychiatry Res** 1985 Apr;14(4):333–42

Disturbances of norepinephrine metabolism and alpha–2 adrenergic receptor activity in anorexia nervosa: relationship to nutritional state. Kaye WH, et al. **Psychopharmacol Bull** 1985;21(3):419–23

[Low blood values of prolactin in women with psychogenic amenorrhea and anorexia nervosa] Natoli A, et al. **Clin Ter** 1985 Jun 30; 113(6):499–501 (Eng. Abstr.) **(Ita)**

ANTIDEPRESSIVE AGENTS

From clomipramine to mianserin: therapeutic relevance of interactions with serotonin uptake and storage, as studied in the blood platelet model. Lingjaerde O. **Acta Psychiatr Scand [Suppl]** 1985;320:10–9 (18 ref.)

Profiles of antidepressant activity with the Montgomery–Asberg Depression Rating Scale. Montgomery SA, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:38–42

Adrenoreceptor interactions of the enantiomers and metabolites of mianserin: are they responsible for the antidepressant effect? Pinder RM. **Acta Psychiatr Scand [Suppl]** 1985;320:1–9 (29 ref.)

Approach to chronic and treatment–resistant depressions. Akiskal HS. **Adv Biochem Psychopharmacol** 1985;40:159–63

How many, and which patients with affective disorders need long–term maintenance therapy? Angst J, et al. **Adv Biochem Psychopharmacol** 1985;40:169–72

Attenuation by antidepressant drugs of alcohol intake in rats. Daoust M, et al. **Alcohol** 1984 Sep–Oct;1(5):379–83

Alprazolam as an antidepressant [letter] Empson P. **Aust NZ J Psychiatry** 1985 Jun;19(2):197

Differential effect of anionic and cationic drugs on the synaptosome–associated acetylcholinesterase activity of dog brain. Deliconstantinos G, et al. **Biochem J** 1985 Jul 1;229(1):81–6

Guidelines for the pharmacological management of depression. Creelman W, et al. **Conn Med** 1985 Sep;49(9):565–9

Influence of renal failure on the kinetics of zimeldine and norzimelidine. Ferry N, et al. **Eur J Clin Pharmacol** 1985;28(4):453–6

Pharmacokinetics and bioavailability of viqualine, a new antidepressant. Fourtillan JB, et al. **Eur J Drug Metab Pharmacokinet** 1985 Jan–Mar; 10(1):3–10

Chronic antidepressant treatment increases enkephalin levels in n. accumbens and striatum of the rat. De Felipe MC, et al. **Eur J Pharmacol** 1985 May 28;112(1):119–22

Behavioral and eegraphic changes induced by dopaminergic antidepressants in rabbits. Bo P, et al. **Farmaco [Sci]** 1985 Aug; 40(8):608–16

Simultaneous measurement of various antidepressants in the plasma of depressed patients by high performance liquid chromatography. Yufu N, et al. **Folia Psychiatr Neurol Jpn** 1984;38(1):57–64

A video analysis of the non–verbal behaviour of depressed patients before and after treatment. Ulrich G, et al. **J Affective Disord** 1985 Jul; 9(1):63–7

Determination of diclofensine, an antidepressant agent, and its major metabolites in human plasma by high–performance liquid chromatography with fluorometric detection. Strojny N, et al. **J Chromatogr** 1985 Jun 14;341(2):313–31

A proposed clinical approach to chronic and 'resistant' depressions: evaluation and treatment. Akiskal HS. **J Clin Psychiatry** 1985 Oct; 46(10 Pt 2):32–7

The new generation antidepressants: promising innovations or disappointments? Ostrow D. **J Clin Psychiatry** 1985 Oct; 46(10 Pt 2):25–31

Design, synthesis, and pharmacological activities of 2–substituted 4–phenylquinolines as potential antidepressant drugs. Alhaider AA, et al. **J Med Chem** 1985 Oct;28(10):1394–8

Effects of rolipram, a novel antidepressant, on monoamine metabolism in rat brain. Kehr W, et al. **J Neural Transm** 1985;63(1):1–12

Determination of indeloxazine in plasma by liquid chromatography and gas chromatography–mass spectrometry. Kamimura H, et al. **J Pharm Sci** 1985 May;74(5):559–61

Binedaline binding to plasma proteins and red blood cells in humans. Morin D, et al. **J Pharm Sci** 1985 Jul;74(7):727–30

Rapid down regulation of beta adrenergic receptors by combining antidepressant drugs with forced swim: a model of antidepressant–induced neural adaptation. Duncan GE, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):402–8

Upregulation of gamma–aminobutyric acid (GABA) B binding sites in rat frontal cortex: a common action of repeated administration of different classes of antidepressants and electroshock. Lloyd KG, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):191–9

Re–evaluation of antidepressant effect of tetrahydrobiopterin [letter] Fleischhacker WW, et al. **Lancet** 1985 Aug 17;2(8451):387

Synergistic interaction between alpha– and beta–adrenergic receptors in rat brain slices: possible site for antidepressant drug action. Pilc A, et al. **Life Sci** 1985 Sep 30;37(13):1183–94

Clinical use of antidepressant blood levels and the electrocardiogram [editorial] Salzman C. **N Engl J Med** 1985 Aug 22;313(8):512–3

Presynaptic serotonin receptor–mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Goodwin GM, et al. **Nature** 1985 Oct 10–16;317(6037):531–3

Behavioral evidence for beta–adrenoceptor subsensitivity after subacute antidepressant/alpha 2–adrenoceptor antagonist treatment. Goldstein JM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun; 329(4):355–8

Pharmacological studies on the serotoninergic and nonserotonin–mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pretreatment with fluoxetine, indalpine, PCPA, and L–tryptophan. Van de Kar LD, et al. **Neuroendocrinology** 1985 Oct; 41(4):283–8

Neuronal sensitivity to substance P is increased after repeated treatment with tranylcypromine, carbamazepine or oxaprotaline, but decreased after repeated electroconvulsive shock. Jones RS, et al. **Neuropharmacology** 1985 Jul;24(7):627–33

Increase in levels and ex vivo release of thyrotrophin–releasing hormone (TRH) in specific regions of the CNS of the rat by chronic treatment with antidepressants. Lighton C, et al. **Neuropharmacology** 1985 May; 24(5):401–6

Early visual information processing in depressive patients treated with ORG 2766 (an ACTH 4–9 analogue). d'Elia G, et al. **Neuropsychobiology** 1985;13(1–2):63–8

Suppressant effect of REM sleep deprivation on neophobia in normal rats and in rats with selective DSP–4 induced damage of locus coeruleus neurons. Mogilnicka E, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):93–7

Amitriptylinoxide: receptor–binding profile compared with other antidepressant drugs. Borbe HO, et al. **Pharmacopsychiatry** 1985 Sep; 18(5):314–9

The importance of brain serotonergic receptor mechanisms for the action of antidepressant drugs. Ogren SO, et al. **Pharmacopsychiatry** 1985 Mar; 18(2):209–13

Oxaprotiline in the treatment of endogenous depressed inpatients an early clinical trial. Schmauss M, et al. **Pharmacopsychiatry** 1985 Jul; 18(4):282–5

The central action of carbamazepine as a potential antidepressant drug. Maj J, et al. **Pol J Pharmacol Pharm** 1985 Jan–Feb;37(1):47–56

The GABA hypothesis of depression and antidepressant drug action. Bartholini G, et al. **Psychopharmacol Bull** 1985;21(3):385–8

Serotonergic modulation of cortical rat noradrenergic system in the mechanism of action of antidepressant drugs. Brunello N, et al. **Psychopharmacol Bull** 1985;21(3):379–84

Melancholia in rodents: neurobiology and pharmacology. Henn FA, et al. **Psychopharmacol Bull** 1985;21(3):443–6

Studies of beta–adrenergic receptors in leukocytes of patients with affective illness and effects of antidepressant drugs. Pandey GN, et al. **Psychopharmacol Bull** 1985;21(3):603–9

Panic attacks in outpatients with depression: response to antidepressant treatment. Robinson DS, et al. **Psychopharmacol Bull** 1985; 21(3):562–7

The serotonin/norepinephrine–linked beta–adrenoceptor system and the mode of action of antidepressants. Sanders–Bush E, et al. **Psychopharmacol Bull** 1985;21(3):373–8

Delayed biochemical changes following antidepressant treatment. Sugrue MF. **Psychopharmacol Bull** 1985;21(3):619–22

Ro 11–2465 (cyan–imipramine), citalopram and their N–desmethyl metabolites: effects on the uptake of 5–hydroxytryptamine and noradrenaline in vivo and related pharmacological activities. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):156–63

Behavioral screen for antidepressants: the effects of drugs and electroconvulsive shock on performance under a differential–reinforcement–of–low–rate schedule. Seiden LS, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):55–60

Antidepressants and serotonergic neurotransmission: an integrative review. Willner P. **Psychopharmacology (Berlin)** 1985;85(4):387–404 (244 ref.)

Informed consent in psychiatric research: preliminary findings from an ongoing investigation. Benson PR, et al. **Soc Sci Med** 1985; 20(12):1331–41

Experience with a specific request form for antidepressant drug monitoring. Fraser AD. **Ther Drug Monit** 1985;7(3):299–302

[Action of clovoxamine on the sleep of depressed patients. 'Polygraphic recordings'] Minot R, et al. **Encephale** 1985 Mar–Apr;11(2):65–70 (Eng. Abstr.) **(Fre)**

[Bicyclic antidepressants based on phthalans and their sulfur analogs] Oparin DA, et al. **Farmakol Toksikol** 1985 Jul–Aug;48(4):115–9 (68 ref.) **(Rus)**

[Toxicological study of the Soviet tetracyclic antidepressant inkazan] Verstakova OL, et al. **Farmakol Toksikol** 1985 Jul–Aug;48(4):99–103

(Eng. Abstr.) (Rus)

[Development of passivity in the rat: effect of tranquilizers and antidepressants] Khonicheva NM, et al. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):339–47 (Eng. Abstr.) **(Rus)**

ANXIETY

Separate and combined anxiolytic and anti-depressant treatment of mixed anxiety/depression. A double-blind, placebo controlled comparison. Sussex Clinical Trials Group. **Acta Psychiatr Scand** 1985 Jul; 72(1):81–8

Depression and anxiety: mianserin and nomifensine compared in a double-blind multicentre trial. Granier F, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:67–74

Chronic anxiolytic treatment: benefit and risk. Marks J. **Adv Biochem Psychopharmacol** 1985;40:173–83

Indications and contraindications for chronic anxiolytic treatment: is there tolerance to the anxiolytic effect? Rickels K, et al. **Adv Biochem Psychopharmacol** 1985;40:193–204

Biological stress responses in high and low trait anxious students. Davis DD, et al. **Biol Psychiatry** 1985 Aug;20(8):843–51

Correlation of [3H]diazepam binding density with anxiolytic locus in the amygdaloid complex of the rat. Thomas SR, et al. **Brain Res** 1985 Sep 2;342(1):85–90

Effect of beta-receptor blockade on anxiety with reference to the three-systems model of phobic behavior. Fagerström KO, et al. **Neuropsychobiology** 1985;13(4):187–93

Studies on the suanzaorentang in the treatment of anxiety. Chen HC, et al. **Psychopharmacology (Berlin)** 1985;85(4):486–7

[Questionnaires for anxiety and depression] Harlay A. **Infirm Fr** 1985 Apr; (264):15–22 **(Fre)**

[Treatment of anxious-depressive syndromes with Mianserin hydrochloride. Statistical evaluation of the data by Student's 't test'] Spinetti G, et al. **Minerva Psichiatr** 1985 Jan–Mar;26(1):79–86 (Eng. Abstr.) **(Ita)**

ANXIETY DISORDERS

Treatment outlines for the management of anxiety states. The Quality Assurance Project. **Aust NZ J Psychiatry** 1985 Jun;19(2):138–51

Topographic EEG changes with benzodiazepine administration in generalized anxiety disorder. Buchsbaum MS, et al. **Biol Psychiatry** 1985 Aug;20(8):832–42

Anxiety: the pharmacological and sociological interface. Proceedings of a symposium. Englefield Green, Surrey, 29 November–1 December, 1984. **Br J Clin Pract [Symp Suppl]** 1985 May;38:1–107

Buspirone: its potential role in the treatment of general practice anxiety. Beaumont G. **Br J Clin Pract [Symp Suppl]** 1985 May;38:100–6

Models of anxiety. File SE. **Br J Clin Pract [Symp Suppl]** 1985 May; 38:15–20

Anxiety, performance and anti-anxiety drugs. Hindmarch I. **Br J Clin Pract [Symp Suppl]** 1985 May;38:53–8

The pharmacological treatment of anxiety. Jenner FA, et al. **Br J Clin Pract [Symp Suppl]** 1985 May;38:48–52

Clinical profile of buspirone. Knapp JE. **Br J Clin Pract [Symp Suppl]** 1985 May;38:95–9

Anxiety disorders: diagnosis and treatment. Jack RA, et al. **Compr Ther** 1985 Jul;11(7):31–7

A multi-centre, double-blind parallel trial of bromazepam ('Lexotan') and lorazepam to compare the acute benefit-risk ratio in the treatment of patients with anxiety. Cordingley GJ, et al. **Curr Med Res Opin** 1985; 9(7):505–10

Thyroid indices in panic disorder. Fishman SM, et al. **J Clin Psychiatry** 1985 Oct;46(10):432–3

Beta-blockers in situational anxiety [editorial] **Lancet** 1985 Jul 27; 2(8448):193

The influence of ritanserin, a serotonin antagonist, in anxiety disorders: a double-blind placebo-controlled study versus lorazepam. Ceulemans DL, et al. **Pharmacopsychiatry** 1985 Sep;18(5):303–5

Initial study of methylclonazepam in generalized anxiety disorder. Evidence for greater power in the cross-over design. Ansseau M, et al. **Psychopharmacology (Berlin)** 1985;87(2):130–5

Metoprolol, a new selective beta-blocker in anxiety neurosis. Chaturvedi SK. **Psychopharmacology (Berlin)** 1985;85(4):488

[Clinical experiences with the new-generation anxiolytic agent cloxazolam—a double-blind study] Zmorski T, et al. **Schweiz Rundsch Med Prax** 1985 Jul 2;74(27):728–34 (Eng. Abstr.) **(Ger)**

APOMORPHINE

Effects of single and repeated application of clonazepam and diazepam combined with cyproheptadine on apomorphine stereotypy in rats. Georgiev VP, et al. **Agressologie** 1985 Jan;26(1):57–60

Apomorphine's antipsychotic activity [letter] Schaffer MH, et al. **Arch Gen Psychiatry** 1985 Sep;42(9):927–8

The effect of dopamine, apomorphine and piribedil on the mesenteric blood flow of the cat. György L, et al. **Arch Int Pharmacodyn Ther** 1985 May;275(1):22–32

Vasomotor responses of cerebral arterioles in situ to putative dopamine receptor agonists. Edvinsson L, et al. **Br J Pharmacol** 1985 Jun; 85(2):403–10

Clonidine sensitizes mice for apomorphine-induced stereotypic gnawing: antagonism by neuroleptics and cholecystokinin-like peptides. Zetler G. **Eur J Pharmacol** 1985 May 20;111(3):309–18

Determination of apomorphine in rat plasma and brain by high-performance liquid chromatography with electrochemical detection. Bianchi G, et al. **J Chromatogr** 1985 Feb 27;338(1):230–5

Effect of ergometrine on methamphetamine and apomorphine stereotypy in the guinea-pig. Balsara JJ, et al. **J Pharm Pharmacol** 1985 Jul; 37(7):514–7

Effects of isomers of apomorphines on dopamine receptors in striatal and limbic tissue of rat brain. Kula NS, et al. **Life Sci** 1985 Sep 16; 37(11):1051–7

Quantification of dopaminergic supersensitization using apomorphine-induced behavior in the mouse. Randall PK. **Life Sci** 1985 Oct 14;37(15):1419–23

S(+)Apomorphines. Selective inhibition of excitatory effects of dopamine injected into the limbic system of the rat. Campbell A, et al. **Neuropharmacology** 1985 May;24(5):391–9

Effects of the contraceptive pill on sedative responses to clonidine and apomorphine in normal women. Chalmers JS, et al. **Psychol Med** 1985 May;15(2):363–7

Lidocaine kindling is accompanied by an increase in apomorphine stereotypy and mesolimbic dopamine D2 receptor density. Csernansky JG, et al. **Psychopharmacol Bull** 1985;21(3):707–11

Dopamine agonist action in mesolimbic, cortical and extrapyramidal areas to modify spontaneous climbing behaviour of the mouse. Costall B, et al. **Psychopharmacology (Berlin)** 1985;86(4):452–7

Yawning elicited by systemic and intrastriatal injection of piribedil and apomorphine in the rat. Dourish CT, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):175–81

Repeated treatment with imipramine potentiates the locomotor effect of apomorphine administered into the hippocampus in rats. Smiałowski A, et al. **Psychopharmacology (Berlin)** 1985;86(4):468–71

REM sleep deprivation effect on apomorphine-induced gnawing is reversed by dexamethasone. Nez L, et al. **Sleep** 1985;8(3):283–7

[Effect of 2 new GABA-ergic agents on apomorphine stereotypy in the rat] Vamvakidès A. **Agressologie** 1985 Jan;26(1):63–5 (Eng. Abstr.) **(Fre)**

[Effect of arachidonic acid on stereotyped behavior in the rabbit induced by a dopamine receptor agonist] Kurchikov AL, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):783–5 **(Rus)**

APPETITE

The effect of captopril on sodium appetite in adrenalectomized and deoxycorticosterone-treated rats. Elfont RM, et al. **J Physiol (Lond)** 1985 Aug;365:1–12

The dependence of the salt appetite of the rat on the hormonal consequences of sodium deficiency. Epstein AN. **J Physiol (Paris)** 1984; 79(6):496–8

AROMATIC AMINO ACID DECARBOXYLASES

1-DOPA decarboxylase and dopamine-beta-hydroxylase isolated from sympathetic splenic nerves estimated by sodium dodecyl sulphate polyacrylamide gel electrophoresis with and without mercaptoethanol. Husseini HS, et al. **J Chromatogr** 1985 Jul 19;329(2):300–6

AROUSAL

Effect on postural sway of various benzodiazepine tranquillizers. Patat A, et al. **Br J Clin Pharmacol** 1985 Jul;20(1):9–16

Effects of a new benzodiazepine derivative, ethyl loflazepate (CM6912), on the arousal level of normal humans assessed by the averaged photopalpebral reflex. Tanaka M, et al. **Clin Neuropharmacol** 1985; 8(3):271–9

The conditioned place preference is affected by two independent reinforcement processes. White NM, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):37–42

Effects of the contraceptive pill on sedative responses to clonidine and apomorphine in normal women. Chalmers JS, et al. **Psychol Med** 1985 May;15(2):363–7

Evaluation of signal detection theory on the effects of psychotropic drugs on critical flicker-fusion frequency in normal subjects. MacNab MW, et al. **Psychopharmacology (Berlin)** 1985;85(4):431–5

ASSOCIATION

Mood-independent aberrancies in associative processes in bipolar affective disorder: an apparent stabilizing effect of lithium. Pons L, et al. **Psychiatry Res** 1985 Apr;14(4):315–22

ATTENTION

Effect of neuroleptic treatments on attention, information processing, and thought disorder. Spohn HE, et al. **Psychopharmacol Bull** 1985; 21(3):582-7

[A study on application of the function of maintaining concentration (TAF) for chronic schizophrenia] Okamoto Y, et al. **Hokkaido Igaku Zasshi** 1985 May;60(3):445-9 (Eng. Abstr.) **(Jpn)**

ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY

Hyperactive children treated with stimulants. Is cognitive training a useful adjunct? Abikoff H, et al. **Arch Gen Psychiatry** 1985 Oct; 42(10):953-61

Methylphenidate and children with attention deficit disorder. Dose effects on classroom academic and social behavior. Pelham WE, et al. **Arch Gen Psychiatry** 1985 Oct;42(10):948-52

Treatment of hyperactive children with monoamine oxidase inhibitors. I. Clinical efficacy. Zametkin A, et al. **Arch Gen Psychiatry** 1985 Oct; 42(10):962-6

Treatment of hyperactive children with monoamine oxidase inhibitors. II. Plasma and urinary monoamine findings after treatment. Zametkin A, et al. **Arch Gen Psychiatry** 1985 Oct;42(10):969-73

Attention deficit disorder children with or without hyperactivity. Which behaviors are helped by stimulants? Ullmann RK, et al. **Clin Pediatr (Phila)** 1985 Oct;24(10):547-51

Pemoline pharmacokinetics and long term therapy in children with attention deficit disorder and hyperactivity. Collier CP, et al. **Clin Pharmacokinet** 1985 May-Jun;10(3):269-78

Treatment of chronic cocaine abuse and attention deficit disorder, residual type, with magnesium pemoline. Weiss RD, et al. **Drug Alcohol Depend** 1985 May;15(1-2):69-72

Separating psychological factors from brain trauma in treating a hyperactive child. Frances A, et al. **Hosp Community Psychiatry** 1985 Jul;36(7):711-3

Clonidine benefits children with attention deficit disorder and hyperactivity: report of a double-blind placebo-crossover therapeutic trial. Hunt RD, et al. **J Am Acad Child Psychiatry** 1985 Sep; 24(5):617-29

Developmental changes in the mother-child interactions of hyperactive boys: effects of two dose levels of Ritalin. Barkley RA, et al. **J Child Psychol Psychiatry** 1985 Sep;26(5):705-15

Catecholamine metabolism in the attention deficit disorder: implications for the use of amino acid precursor therapy. McConnell H. **Med Hypotheses** 1985 Aug;17(4):305-11

Ten years of experience with 1,000 hyperactive children in a private practice. Eichlseder W. **Pediatrics** 1985 Aug;76(2):176-84

Rate-dependency and hyperactivity: methylphenidate effects on operant responding. Rapport MD, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):77-83

Neuropharmacological basis of stimulant drug action in attention deficit disorder with hyperactivity: a review and synthesis. Solanto MV. **Psychol Bull** 1984 May;95(3):387-409 (195 ref.)

AUDITORY THRESHOLD

Effects of diazepam and triazolam on auditory and visual thresholds and reaction times in the baboon. Lukas SE, et al. **Psychopharmacology (Berlin)** 1985;87(2):167-72

AUTISM, INFANTILE

[Clinical (behavior scale items), electrophysiologic (conditioned evoked potentials) and biochemical (urinary homovanillic acid) markers in infantile autism] Barthelemy C, et al. **Encephale** 1985 May-Jun; 11(3):101-6 (33 ref.) (Eng. Abstr.) **(Fre)**

AVOIDANCE LEARNING

Relationship between the release and uptake of noradrenaline by rat brain synaptosomes in the formation of defensive conditioned reflex. Bazyan AS, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(1-2):37-46

Memory effects of GABA-ergic antagonists in rats trained with two-way active avoidance tasks. Yonkov DI, et al. **Acta Physiol Pharmacol Bulg** 1985;11(2):44-9

Neocortical involvement in the acquisition and retention of learned alcohol aversions in rats. Kiefer SW, et al. **Alcohol** 1985 Jul-Aug; 2(4):597-601

Role of ethanol in conditioning aversion to alcoholic beverages in rats. Franchina JJ, et al. **Behav Res Ther** 1985;23(5):521-9

A response-specific conditioned aversion to rewarding hypothalamic stimulation in rats. Greenshaw AJ, et al. **Brain Res** 1985 Jul 22; 339(1):130-5

Comparisons between discrete lever-press and shuttle avoidance responses in mice: acquisition processes and effects of psychoactive drugs. Kuribara H, et al. **Jpn J Pharmacol** 1985 Jun;38(2):141-51

A comparison of physostigmine and soman using taste aversion and nociception. Romano JA, et al. **Neurobehav Toxicol Teratol** 1985 May-Jun;7(3):243-9

Effects of intracerebroventricular administration of ovine corticotropin-releasing factor (CRF 1-41) on passive avoidance behaviour: lack of influence on monoamine contents of limbic brain areas. Fekete M, et al. **Neuropeptides** 1985 Jul;6(4):283-292

Forebrain serotonergic involvement in avoidance learning. Ogren SO, et al. **Neurosci Lett** 1985 Aug 5;58(3):305-9

Central serotonin neurones in avoidance learning: interactions with noradrenaline and dopamine neurones. Ogren SO. **Pharmacol Biochem Behav** 1985 Jul;23(1):107-23

The role of trazodone metabolism in its inhibitory action on avoidance response. Sansone M, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):137-40

The effect of chronic administration of trazodone on the acquisition of avoidance behavior in mice. Sansone M, et al. **Pol J Pharmacol Pharm** 1985 Mar-Apr;37(2):173-8

Effects of phencyclidine on active avoidance and escape in rats. Martin P, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):237-40

The effect of stimulus preexposure upon the context effect in taste-aversion learning in noradrenaline-depleted rats. Archer T, et al. **Scand J Psychol** 1985;26(2):158-69

[Effect of a cyclic analog of enkephalin on learning and memory in the mouse] Getsova VM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug; 35(4):710-7 (Eng. Abstr.) **(Rus)**

AZEPINES

Worker exposure during aerial application of a liquid and a granular formulation of Ordram Selective Herbicide to rice. Knarr RD, et al. **Arch Environ Contam Toxicol** 1985 Sep;14(5):523-7

Spectrophotometric study of drugs containing the 1,4-diazepine-2-thione group. Fernández-Arciniega MA, et al. **Boll Chim Farm** 1985 Jan; 124(1):19-26

Effects of cetiedil on the oxidative metabolism of activated polymorphonuclear leucocytes. Kohzaki H, et al. **Br J Haematol** 1985 Jul;60(3):531-9

Relationship between alpha 2-adrenoceptor occupancy and response for B-HT 933 in canine saphenous vein. Ruffolo RR Jr, et al. **Eur J Pharmacol** 1985 May 8;111(2):267-71

Effect of the absorption enhancer, Azone, on the transport of 5-fluorouracil across hairless rat skin. Sugibayashi K, et al. **J Pharm Pharmacol** 1985 Aug;37(8):578-80

Characterization of alpha 2-adrenoceptor binding properties of imidazoline-like drugs, azoloazepine derivatives and beta-phenethylamine-like drugs in human platelet membranes. Vago T, et al. **J Pharm Pharmacol** 1985 Aug;37(8):593-6

Amelioration of albuminuria induced by dilazep administration in aminonucleoside nephrosis of rats. Nagase M, et al. **Nippon Jinzo Gakkai Shi** 1985 Mar;27(3):385-91

Sexual excitement and stretching and yawning induced by B-HT 920. Ferrari F. **Pharmacol Res Commun** 1985 Jun;17(6):557-64

Effect of dilazep on coronary and systemic circulations. Marzilli M, et al. **Pharmacology** 1985;31(2):82-7

BEHAVIOR

The effects of dietary neurotransmitter precursors on human behavior. Lieberman HR, et al. **Am J Clin Nutr** 1985 Aug;42(2):366-70

BEHAVIOR, ANIMAL

Effects of amiflamine and related compounds on the accumulation of biogenic monoamines in rat brain slices in vitro and ex vivo in relation to their behavioural effects. Rényi L, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):416-26

Effects of histamine and H1 and H2-receptor antagonists on the wet-dog-shaking episodes in rats induced with lithium chloride. Rajtar G, et al. **Acta Physiol Pol** 1984 Mar-Apr;35(2):131-5

Cholecystokinin potentiation of dopamine-mediated behaviors in the nucleus accumbens. Crawley JN. **Ann NY Acad Sci** 1985;448:283-92

Unilateral odor deprivation: effects on the development of olfactory bulb catecholamines and behavior. Brunjes PC, et al. **Brain Res** 1985 Sep; 354(1):1-6

In vivo voltammetric and behavioural evidence for somatodendritic autoreceptor control of mesolimbic dopamine neurones. Maidment NT, et al. **Brain Res** 1985 Jul 15;338(2):317-25

Behavioral study after local injection of 6-hydroxydopamine into the nucleus accumbens in the rat. Taghzouti K, et al. **Brain Res** 1985 Sep 30;344(1):9-20

Biochemical and behavioral changes in rats during and after chronic d-amphetamine exposure. Vogel WH, et al. **Drug Alcohol Depend** 1985 Jun;15(3):245-53

DSP-4 lesioning prevents the enhancement of dopamine and 5-hydroxytryptamine mediated behavioural changes by repeated electroconvulsive shock. Heal DJ, et al. **Eur J Pharmacol** 1985 Sep

10;115(1):117–21

Does a single priming injection of clenbuterol alter behavioral response to beta-adrenoceptor agonists and antagonists in mice through a time-dependent process? Martin P, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):91–6

Pharmacologic therapeutic window of pramiracetam demonstrated in behavior, EEG, and single neuron firing rates. Poschel BP, et al. **Experientia** 1985 Sep 15;41(9):1153–6

Behavioral and eegraphic changes induced by dopaminergic antidepressants in rabbits. Bo P, et al. **Farmaco [Sci]** 1985 Aug; 40(8):608–16

Differential biochemical and behavioral effects of single and chronic administration of amphetamine and apomorphine. Bernardi MM, et al. **Gen Pharmacol** 1985;16(4):407–10

Behavioral and neurochemical aspects of prostaglandins in brain function. Chiu EK, et al. **Gen Pharmacol** 1985;16(3):163–75 (115 ref.)

Differential vulnerability of male and female rats to the timing of various perinatal insults. Grimm VE, et al. **Int J Neurosci** 1985 Aug; 27(3–4):155–64

Source of stray voltage and effect on cow health and performance. Appleman RD, et al. **J Dairy Sci** 1985 Jun;68(6):1554–67 (40 ref.)

gamma-Aminobutyric acid metabolism and behavioral effects after intraventricular injection of spermine in chicks. Di Giorgio RM, et al. **J Neurochem** 1985 Sep;45(3):739–43

Cholecystokinin potentiates dopamine-mediated behaviors: evidence for modulation specific to a site of coexistence. Crawley JN, et al. **J Neurosci** 1985 Aug;5(8):1972–83

Rapid induction of supersensitivity to muscarinic antagonists-induced motor excitation by continuous stimulation of cholinergic receptors. Fernando JC, et al. **Life Sci** 1985 Sep 2;37(9):883–92

Quantification of dopaminergic supersensitization using apomorphine-induced behavior in the mouse. Randall PK. **Life Sci** 1985 Oct 14;37(15):1419–23

Sensitization to stress: the enduring effects of prior stress on amphetamine-induced rotational behavior. Robinson TE, et al. **Life Sci** 1985 Sep 16;37(11):1039–42

Animal models of behavioral pathology and violent aggression. Valzelli L. **Methods Find Exp Clin Pharmacol** 1985 Apr;7(4):189–93

The role of central dopaminergic systems in the behavioral effects of H-Phe-Ile-Tyr-His-Ser-Tyr-Lys-OH. Vécsei L, et al. **Neuropeptides** 1985 Jun;6(3):183–90

Intracerebroventricular administration of cholecystokinin inhibits the activity of the dopaminergic and serotoninergic systems of the brain. Vasar EE, et al. **Neurosci Behav Physiol** 1985 May–Jun;15(3):232–6

Acute and chronic behavioral interactions between phencyclidine (PCP) and amphetamine: evidence for a dopaminergic role in some PCP-induced behaviors. Greenberg BD, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):99–105

Behaviorally equivalent stressors differentially modify the monoamine altering property of d-amphetamine. Klauenberg BJ, et al. **Pharmacol Biochem Behav** 1985 Sep;23(3):417–23

A rapid and simple behavioural screening method for simultaneous assessment of limbic and striatal blocking effects of neuroleptic drugs. Ljungberg T, et al. **Pharmacol Biochem Behav** 1985 Sep; 23(3):479–85

Cathinone, cocaine and methamphetamine: similarity of behavioral effects. Schechter MD, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):913–6

Sexual excitement and stretching and yawning induced by B-HT 920. Ferrari F. **Pharmacol Res Commun** 1985 Jun;17(6):557–64

The 5-HT syndrome and the drug discrimination paradigm in rats: application in behavioral studies on the central 5-HT system. Ortmann R. **Pharmacopsychiatry** 1985 Mar;18(2):198–201

Influence of early beta-endorphin treatment on the behavior and reaction to beta-endorphin in the adult male rat. Meyerson BJ. **Psychoneuroendocrinology** 1985;10(2):135–47

Cholecystokinin potentiates dopamine-mediated behaviors in the nucleus accumbens, a site of CCK-DA co-existence. Crawley JN. **Psychopharmacol Bull** 1985;21(3):523–7

Serotonin-behavior interactions in vervet monkeys. McGuire MT, et al. **Psychopharmacol Bull** 1985;21(3):458–63

Stimulus control induced by benzodiazepine antagonist Ro 15-1788 in the rat. De Vry J, et al. **Psychopharmacology (Berlin)** 1985; 85(4):483–5

Circadian variation in behavioural responses to central 5-HT receptor stimulation in the mouse. Moser PC, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):223–7

Effects of d,l-propranolol on open field behavior of rats. Poli A, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):153–5

Comparison between the effects of propranolol and chlordiazepoxide on timing behaviour in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1985;87(2):219–24

[Effects of prolonged methamphetamine treatment and its withdrawal on behavior and brain monoamine metabolism in mice] Odo S, et al. **Seishin Shinkeigaku Zasshi** 1985;87(3):155–75 (Eng. Abstr.) **(Jpn)**

[Effect of stress-inducing factors on the behavior of monkeys. I. The behavior of monkeys under acute emotional stress] Butovskaia ML, et al. **Biol Nauki** 1985;(6):67–74 (Eng. Abstr.) **(Rus)**

[Effect of the antioxidant dibunol and its combination with phenazepam on the behavior of rats in a conflict situation] Molodavkin GM, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):36–8 (Eng. Abstr.) **(Rus)**

[Behavior disorder in rats induced by Madopar and its pharmacological correction] Bondarenko NA, et al. **Farmakol Toksikol** 1985 Jul–Aug; 48(4):31–4 (Eng. Abstr.) **(Rus)**

[Emotional stress-induced changes in catecholamines in the nuclei of the brains of rats differing in 'open-field' behavior] Belova TI, et al. **Fiziol Zh SSSR** 1985 Jul;71(7):813–22 (Eng. Abstr.) **(Rus)**

[Effect of a derivative of GABA, phenibut, on behavior and the activity of visual cortex neurons of the rabbit during elaboration of a defensive reflex and internal inhibition] Shul'gina GI, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):695–702 (Eng. Abstr.)**(Rus)**

BENZAZEPINES

Blockade of renal effects of dopamine in the dog by the DA1 antagonist SCH 23390. Frederickson ED, et al. **Am J Physiol** 1985 Aug; 249(2 Pt 2):F236–40

Arylazide photoaffinity probe for alpha 2-adrenoceptors. Regan JW, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3667–72

Interactions between diltiazem and isoflurane. An in vitro investigation in isolated guinea pig atria. Broadbent MP, et al. **Br J Anaesth** 1985 Oct;57(10):1018–21

Effect of verapamil and diltiazem on calcium-dependent electrical activity in cardiac Purkinje fibres. Amerini S, et al. **Br J Pharmacol** 1985 May; 85(1):89–96

Vasomotor responses of cerebral arterioles in situ to putative dopamine receptor agonists. Edvinsson L, et al. **Br J Pharmacol** 1985 Jun; 85(2):403–10

The effect of diltiazem on noradrenaline release. Wolchinsky C, et al. **Br J Pharmacol** 1985 Jun;85(2):387–93

SCH 23390, a selective D1 dopamine receptor blocker, enhances the firing rate of nigral dopaminergic neurons but fails to activate striatal tyrosine hydroxylase. Onali P, et al. **Brain Res** 1985 Aug 5;340(1):1–7

Chemical transformation of protoberberines. VII. Efficient conversion of protoberberines into benzindenoazepines via 8,14-cycloberbines. Hanaoka M, et al. **Chem Pharm Bull (Tokyo)** 1985 Apr; 33(4):1434–43

Interaction of SCH 23390, a D-1-selective antagonist, with the anterior pituitary D-2 receptors and prolactin secretion in the rat. Apud JA, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):187–93

SCH-23390 antagonism of a D-2 dopamine agonist depends upon catecholaminergic neurons. Breese GR, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):109–14

Benzodiazepine receptor binding with a new ligand, Ro 22-8515. Goeders NE, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):147–8

SCH 23390, a selective dopamine D1 antagonist, activates dopamine neurons but fails to prevent their inhibition by apomorphine. Mereu G, et al. **Eur J Pharmacol** 1985 May 20;111(3):393–6

The effects of several ion channel blockers and calmodulin antagonists on fertilization-induced acid release and 45Ca2+ uptake in sea urchin eggs. Komukai M, et al. **Exp Cell Res** 1985 Aug;159(2):463–72

Improved recovery of cardiac function after 24 h of hypothermic arrest in the isolated rat heart: comparison of a prostacyclin analogue (ZK 36 374) and a calcium entry blocker (diltiazem). van Gilst WH, et al. **J Cardiovasc Pharmacol** 1985 May–Jun;7(3):520–4

Blocking effect of diltiazem on thiopentone-induced vasoconstriction in isolated canine internal carotid arteries. Tsuji T, et al. **J Cereb Blood Flow Metab** 1985 Sep;5(3):446–50

Diltiazem and desacetyldiltiazem analysis in human plasma using high-performance liquid chromatography: improved sensitivity without derivation. Abernethy DR, et al. **J Chromatogr** 1985 Jul 12; 342(1):216–20

Lack of effects of diltiazem on digoxin pharmacokinetics. Beltrami TR, et al. **J Clin Pharmacol** 1985 Jul–Aug;25(5):390–2

Binding of [3H]SCH23390 in rat brain: regional distribution and effects of assay conditions and GTP suggest interactions at a D1-like dopamine receptor. Schulz DW, et al. **J Neurochem** 1985 Nov;45(5):1601–11

Pharmacological analysis of the actions of SKF 82526 on cardiovascular dopamine receptors. Lokhandwala MF, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):337–44

Hyperactivity induced by stimulation of separate dopamine D-1 and D-2 receptors in rats with bilateral 6-OHDA lesions. Arnt J. **Life Sci** 1985 Aug 26;37(8):717–23

Effect of diltiazem on in vitro rabbit bladder function. Malkowicz SB, et al. **Pharmacology** 1985;31(1):24–33

[The antiaggregation effect of diltiazem] Alušík S, et al. **Vnitr Lek** 1985 Sep;31(9):877–81 (Eng. Abstr.) **(Cze)**

[Effect of calcium antagonists on physical fitness and metabolism] Kindermann W, et al. **Dtsch Med Wochenschr** 1985 Oct 25; 110(43):1657–61 (Eng. Abstr.) **(Ger)**

[Effect of intravenous administration of diltiazem on cerebral blood flow and brain function] Konishi T, et al. **No To Shinkei** 1985 Jun; 37(6):567–73 (Eng. Abstr.) **(Jpn)**

BENZODIAZEPINE TRANQUILIZERS

Psychomotor effects of alprazolam and diazepam during acute and subacute treatment, and during the follow-up phase. Aranko K, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):364-72

Benzodiazepine dependence: clinical and neurobiological aspects. Böning J. **Adv Biochem Psychopharmacol** 1985;40:185-92 (37 ref.)

Metabolism of ethyl loflazepate in the rat, the dog, the baboon and in man. Davi H, et al. **Arzneimittelforschung** 1985;35(7):1061-5

Topographic EEG changes with benzodiazepine administration in generalized anxiety disorder. Buchsbaum MS, et al. **Biol Psychiatry** 1985 Aug;20(8):832-42

Central effects during the continuous osmotic infusion of a benzodiazepine (triazolam). Breimer DD, et al. **Br J Clin Pharmacol** 1985 Jun; 19(6):807-15

Effects of end stage renal disease and aluminium hydroxide on triazolam pharmacokinetics. Kroboth PD, et al. **Br J Clin Pharmacol** 1985 Jun; 19(6):839-42

Effect on postural sway of various benzodiazepine tranquillizers. Patat A, et al. **Br J Clin Pharmacol** 1985 Jul;20(1):9-16

Single dose pharmacokinetics and pharmacodynamics of oral loprazolam in the elderly. Swift CG, et al. **Br J Clin Pharmacol** 1985 Aug; 20(2):119-28

Anxiety, performance and anti-anxiety drugs. Hindmarch I. **Br J Clin Pract [Symp Suppl]** 1985 May;38:53-8

An evaluation of alprazolam in the treatment of reactive or neurotic (secondary) depression. Imlah NW. **Br J Psychiatry** 1985 May; 146:515-9

Temazepam and the perceptual-motor performance of professional footballers. Golby J, et al. **Br J Sports Med** 1985 Jun;19(2):115-8

Clinical management of benzodiazepine dependence. Higgitt AC, et al. **Br Med J [Clin Res]** 1985 Sep 14;291(6497):688-90

A multi-centre, double-blind parallel trial of bromazepam ('Lexotan') and lorazepam to compare the acute benefit-risk ratio in the treatment of patients with anxiety. Cordingley GJ, et al. **Curr Med Res Opin** 1985; 9(7):505-10

The influence of H2 receptor antagonists on the plasma concentrations of midazolam and temazepam. Elliott P, et al. **Eur J Anaesthesiol** 1984 Sep;1(3):245-51

Inhibition of diazepam metabolism in microsomal- and perfused liver preparations of the rat by desmethyldiazepam, N-methyloxazepam and oxazepam. Savenije-Chapel EM, et al. **Eur J Drug Metab Pharmacokinet** 1985 Jan-Mar;10(1):15-20

Triazolam addiction [letter] Lynn EJ. **Hosp Community Psychiatry** 1985 Jul;36(7):779-80

Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. Pourbaix S, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Aug;23(8):447-51

Capillary gas-liquid chromatographic determination of the benzodiazepine triazolam in plasma using a retention gap. Baktir G, et al. **J Chromatogr** 1985 Apr 12;339(1):192-7

Determination of circulating ethyl loflazepate metabolites in the baboon by radio-high-performance liquid chromatography with injection of crude plasma samples: comparison with solvent extraction and thin-layer chromatography. Davi H, et al. **J Chromatogr** 1985 Jul 12; 342(1):159-65

Benzodiazepine dependence potential: current studies and trends. Smith DE. **J Subst Abuse Treat** 1984;1(3):163-7

Evaluation of the induction of hepatic drug-metabolizing enzymes in the rat and mouse treated with temazepam using trimethadione as the indicator. Kitagawa YF, et al. **J Toxicol Sci** 1985 Feb;10(1):21-8

Tolerance to the anticonvulsant action of benzodiazepines. Relationship to decreased receptor density. Rosenberg HC, et al. **Neuropharmacology** 1985 Jul;24(7):639-44

Experimental comparison of low doses of 1.5 mg fluspirilene and bromazepam in out-patients with psychovegetative disturbances. Hassel P. **Pharmacopsychiatry** 1985 Sep;18(5):297-302

5-Carboxylic derivatives of some 1,5-benzodiazepines. Nawojski A, et al. **Pol J Pharmacol Pharm** 1985 Jan-Feb;37(1):69-72

Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. Ellinwood EH Jr, et al. **Psychopharmacology (Berlin)** 1985;86(4):392-9

Benzodiazepines reduce the tolerance to reward delay in rats. Thiébot MH, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):147-52

Kinetic and pharmacological studies on estazolam in mice and man. Mancinelli A, et al. **Xenobiotica** 1985 Mar;15(3):257-65

[Clinical experience with bromazepam in endogenous depression] Náhunek K, et al. **Cesk Psychiatr** 1985 Aug;81(4):235-41 (Eng. Abstr.) **(Cze)**

[Treatment of masked depressions using bromazepam] Vencovský E, et al. **Cesk Psychiatr** 1985 Apr;81(2):75-8 (Eng. Abstr.) **(Cze)**

[Panic attacks treated with alprazolam (letter)] Andersen T. **Ugeskr Laeger** 1985 Jun 17;147(25):2014-5 **(Dan)**

[Validation of a method for detecting benzodiazepines in the urine by acid extraction of their benzophenones and thin layer chromatography] Vu Duc T, et al. **Ann Biol Clin (Paris)** 1985;43(3):261-5 (Eng. Abstr.) **(Fre)**

[Screening and detection of tetrazepam and its major metabolites] Schütz H, et al. **Arzneimittelforschung** 1985;35(7):1015-24 (Eng. Abstr.) **(Ger)**

[Clinical experiences with the new-generation anxiolytic agent cloxazolam--a double-blind study] Zmorski T, et al. **Schweiz Rundsch Med Prax** 1985 Jul 2;74(27):728-34 (Eng. Abstr.) **(Ger)**

BENZODIAZEPINONES

Mianserin is better tolerated and more effective in depression than a nomifensine-clobazam combination: a double-blind study. Levin A, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:75-80

Effects of single and repeated application of clonazepam and diazepam combined with cyproheptadine on apomorphine stereotypy in rats. Georgiev VP, et al. **Agressologie** 1985 Jan;26(1):57-60

Metabolism of ethyl loflazepate in the rat, the dog, the baboon and in man. Davi H, et al. **Arzneimittelforschung** 1985;35(7):1061-5

Carbachol stimulation of phosphatidic acid synthesis: competitive inhibition by pirenzepine in synaptosomes from rat cerebral cortex. Smith TL, et al. **Biochem Biophys Res Commun** 1985 Jul 16; 130(1):282-5

Single dose pharmacokinetics and pharmacodynamics of oral loprazolam in the elderly. Swift CG, et al. **Br J Clin Pharmacol** 1985 Aug; 20(2):119-28

A placebo controlled comparison of the effects of pirenzepine and amitriptyline on the tyramine pressor test in healthy volunteers. Wilkins MR, et al. **Br J Clin Pharmacol** 1985 Jun;19(6):829-31

The behavior of 1,4-benzodiazepine drugs in acidic media. II. Kinetics and mechanism of the acid-base equilibrium reaction of oxazolam. Kurono Y, et al. **Chem Pharm Bull (Tokyo)** 1985 Apr;33(4):1633-40

Effects of a new benzodiazepine derivative, ethyl loflazepate (CM6912), on the arousal level of normal humans assessed by the averaged photopalpebral reflex. Tanaka M, et al. **Clin Neuropharmacol** 1985; 8(3):271-9

Chlordiazepoxide-induced hyperphagia in non-food-deprived rats: effects of Ro15-1788, CGS 8216 and ZK 93 426. Cooper SJ, et al. **Eur J Pharmacol** 1985 May 28;112(1):39-45

Simple approach to assess potentiated drug combinations in clinical trials: studies with pirenzepine plus H2-receptor antagonists. Pöch G, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Jun;23(6):283-7

Determination of circulating ethyl loflazepate metabolites in the baboon by radio-high-performance liquid chromatography with injection of crude plasma samples: comparison with solvent extraction and thin-layer chromatography. Davi H, et al. **J Chromatogr** 1985 Jul 12; 342(1):159-65

Liquid chromatographic analysis of clonazepam in human serum with solid-phase (Bond-Elut) extraction. Kabra PM, et al. **J Chromatogr** 1985 Jun 14;341(2):383-90

Pro- and anti-convulsant drug effects in combination with the convulsant benzodiazepine Ro 5-4864. Pellow S, et al. **J Pharm Pharmacol** 1985 Aug;37(8):560-3

Reversal of slow-wave sleep by benzodiazepine antagonist Ro 15-1788 [letter] Ziegler G, et al. **Lancet** 1985 Aug 31;2(8453):510

Differences between the tolerance characteristics of two anticonvulsant benzodiazepines. Gent JP, et al. **Life Sci** 1985 Sep 2;37(9):849-56

Effects of the 1,5-benzodiazepine clobazam on pituitary hormones in the male rat. Valli M, et al. **Methods Find Exp Clin Pharmacol** 1985 Apr; 7(4):179-81

Molecular structure of Ro15-1788 and a model for the binding of benzodiazepine receptor ligands. Structural identification of common features in antagonists. Codding PW, et al. **Mol Pharmacol** 1985 Aug; 28(2):178-84

Pirenzepine indicates heterogeneity of muscarinic receptors linked to cerebral inositol phospholipid metabolism. Lazareno S, et al. **Neuropharmacology** 1985 Jun;24(6):593-5

Selective blockade of benzodiazepine receptors by Ro 15-1788 prevents foot shock-induced decrease of low affinity gamma-aminobutyric acid receptors. Corda MG, et al. **Neurosci Lett** 1985 May 23;56(3):265-9

Reduction of inhibition by a benzodiazepine antagonist, Ro15-1788, in the rat hippocampal slice. King GL, et al. **Neuroscience** 1985 Jun; 15(2):371-8

Benzodiazepine-receptor mediated inhibition of isolation-induced aggression in mice. Skolnick P, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):17-20

Initial study of methylclonazepam in generalized anxiety disorder. Evidence for greater power in the cross-over design. Ansseau M, et al. **Psychopharmacology (Berlin)** 1985;87(2):130-5

Stimulus control induced by benzodiazepine antagonist Ro 15-1788 in the rat. De Vry J, et al. **Psychopharmacology (Berlin)** 1985; 85(4):483-5

Effects of valproate on hyponeophagia in rats: competitive antagonism with picrotoxin and non-competitive antagonism with RO 15-1788. Shephard RA, et al. **Psychopharmacology (Berlin)** 1985;86(3):313-7

Characterization of pirenzepine interaction with cytochrome P-450. Rendić S, et al. **Xenobiotica** 1985 May;15(5):399-405

Correlation of the clinical pharmacodynamics of loprazolam with serum concentration. Stevens LA, et al. **Xenobiotica** 1985 Jul;15(7):623–31

[Screening and detection of tetrazepam and its major metabolites] Schütz H, et al. **Arzneimittelforschung** 1985;35(7):1015–24 (Eng. Abstr.) **(Ger)**

[Clinical experiences with the new-generation anxiolytic agent cloxazolam—a double-blind study] Zmorski T, et al. **Schweiz Rundsch Med Prax** 1985 Jul 2;74(27):728–34 (Eng. Abstr.) **(Ger)**

[Effect of the antioxidant dibunol and its combination with phenazepam on the behavior of rats in a conflict situation] Molodavkin GM, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):36–8 (Eng. Abstr.) **(Rus)**

[The role of changes in the antioxidative activity and phospholipid composition of the rat liver in the mechanism of phenazepam action on the liver and the protective effect of talamonal] Molochkina EM, et al. **Vopr Med Khim** 1985 May–Jun;31(3):17–21 (Eng. Abstr.) **(Rus)**

BIOGENIC AMINES

Effects of amiflamine and related compounds on the accumulation of biogenic monoamines in rat brain slices in vitro and ex vivo in relation to their behavioural effects. Rényi L, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):416–26

Ontogenetic development of the monoamine oxidase activity and of the metabolism of biogenic monoamines in rat brain. Stancheva S, et al. **Acta Physiol Pharmacol Bulg** 1985;11(1):3–9

Effect of tocainide on the concentrations of norepinephrine dopamine, serotonin and histamine in rat brain and its binding affinity to neuroceptors. Przuntek H, et al. **Arzneimittelforschung** 1985; 35(5):787–9

Late changes in cerebral monoamine metabolism following focal ventrolateral cerebrocortical lesions in rats. Finklestein S, et al. **Brain Res** 1985 Oct 7;344(2):205–10

Monoamine-induced responses in lateral septal neurons: influence of iontophoretically applied vasopressin. Joëls M, et al. **Brain Res** 1985 Sep 30;344(1):120–6

Epinephrine accumulation in rat brain after chronic administration of pargyline and LY 51641—comparison with other brain amines. Mefford IN, et al. **Brain Res** 1985 Jul 29;339(2):342–5

Long-term effects of repeated methylamphetamine administration on monoamine neurons in the rhesus monkey brain. Preston KL, et al. **Brain Res** 1985 Jul 15;338(2):243–8

Monoamine release from dopamine-depleted rat caudate nucleus reinnervated by substantia nigra transplants: an in vivo electrochemical study. Rose G, et al. **Brain Res** 1985 Aug 19;341(1):92–100

Monoamine, amino acid and cholinergic interactions in slices of rat cerebral cortex. Flint RS, et al. **Brain Res Bull** 1985 Aug; 15(2):197–202

Three dimensional analysis of retinal neuropeptides and amine in the chick. Kiyama H, et al. **Brain Res Bull** 1985 Aug;15(2):155–65

The effect of tryptophan on biogenic amines in the hepatic portal circulation of the dog. Hussain MN, et al. **Can J Physiol Pharmacol** 1985 Jul;63(7):863–6

The effect of growth hormone on biogenic amines in the hepatic portal circulation of the dog. Hussain MN, et al. **Can J Physiol Pharmacol** 1985 May;63(5):463–7

Modification of the effects of repetitive restraint stress on brain biogenic amines by L-tyrosine. Quirce CM, et al. **Chung Kuo Yao Li Hsueh Pao** 1984 Dec;5(4):226–8

Repetitive measurement of monoamine metabolite levels in cerebrospinal fluid of conscious rats: effects of reserpine and haloperidol. Scheinin H, et al. **Eur J Pharmacol** 1985 Jul 31;113(3):345–51

Electrochemical detection of biogenic amines following acylation by N-hydroxysuccinimide esters. Jacobson KA, et al. **FEBS Lett** 1985 Sep 2;188(2):307–11

Peptidergic and aminergic innervation of the facial nucleus of the rat with special reference to ontogenetic development. Senba E, et al. **J Comp Neurol** 1985 Aug 22;238(4):429–39

Effects of rolipram, a novel antidepressant, on monoamine metabolism in rat brain. Kehr W, et al. **J Neural Transm** 1985;63(1):1–12

Monoamine distribution on the ventral surface of the rat medulla oblongata. Smialowska M, et al. **J Neural Transm** 1985;63(1):13–29

Postmortem changes in catecholamines, indoleamines, and their metabolites in rat brain regions: prevention with 10-kW microwave irradiation. Ikarashi Y, et al. **J Neurochem** 1985 Sep;45(3):935–9

Sulfate conjugation of monoamines in human brain: purification and some properties of an arylamine sulfotransferase from cerebral cortex. Yu PH, et al. **J Neurochem** 1985 Sep;45(3):836–43

The sensitivity of GABA-receptor is increased by biogenic amines. Koketsu K, et al. **Kurume Med J** 1984;31(4):331–4

Effects of intracerebroventricular administration of ovine corticotropin-releasing factor (CRF 1-41) on passive avoidance behaviour: lack of influence on monoamine contents of limbic brain areas. Fekete M, et al. **Neuropeptides** 1985 Jul;6(4):283–292

Sensation seeking, mania, and monoamines. Zuckerman M. **Neuropsychobiology** 1985;13(3):121–8

Behaviorally equivalent stressors differentially modify the monoamine altering property of d-amphetamine. Klauenberg BJ, et al. **Pharmacol Biochem Behav** 1985 Sep;23(3):417–23

Somatostatin mediates the effect of growth hormone surges on splanchnic biogenic amines. Hussain MN, et al. **Proc Soc Exp Biol Med** 1985 Sep; 179(4):517–21

Rhesus monkey cerebrospinal fluid amine metabolite changes following treatment with the reversible monoamine oxidase type-A inhibitor cimoxatone. Garrick NA, et al. **Psychopharmacology (Berlin)** 1985; 86(3):265–9

Effect of repeated dietary exposure of aflatoxin B1 on brain biogenic amines and metabolites in the rat. Coulombe RA Jr, et al. **Toxicol Appl Pharmacol** 1985 Sep 30;80(3):496–501

Prenatal carbon monoxide exposure differentially affects postnatal weight and monoamine concentration of rat brain regions. Storm JE, et al. **Toxicol Appl Pharmacol** 1985 Oct;81(1):139–46

[Changes in the CSF levels of monoamine metabolites in 102 chronic schizophrenic patients following probenecid before and after neuroleptic medication] Chen YF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Oct; 17(5):273–7 (Eng. Abstr.) **(Chi)**

[Differential voltametry: a new method for studying the cerebral metabolism of monoamines] Pujol JF. **J Pharmacol** 1985; 16 Suppl 1:33–50 (Eng. Abstr.) **(Fre)**

[Effects of prolonged methamphetamine treatment and its withdrawal on behavior and brain monoamine metabolism in mice] Odo S, et al. **Seishin Shinkeigaku Zasshi** 1985;87(3):155–75 (Eng. Abstr.) **(Jpn)**

[Anticonvulsant action of a thyrotropin-releasing hormone analog (DN-1417) and changes in brain monoamines] Sato M, et al. **Seishin Shinkeigaku Zasshi** 1985;87(3):176–85 **(Jpn)**

[Localization of biogenic monoamines in the dura mater of the rat brain] Motavkin PA, et al. **Arkh Anat Gistol Embriol** 1985 May;88(5):11–6 (Eng. Abstr.) **(Rus)**

[Effect of 7-hydroxygluacine on brain biogenic monoamines] Petkov VD, et al. **Farmakol Toksikol** 1985 May–Jun;48(3):19–22 (Eng. Abstr.) **(Rus)**

[Effect of 24-hour sleep deprivation on the metabolism of biogenic amines] Bol'shkova TD, et al. **Fiziol Cheloveka** 1985 Jul–Aug;11(4):652–6 **(Rus)**

[Concentration of biogenic amines in different brain structures of the rat adapted to chronic emotional stress] Anokhina IP, et al. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):348–53 (Eng. Abstr.) **(Rus)**

[Change in certain forms of aggressive behavior and the concentration of monoamines in the brain during selection of wild rats for taming] Nikulina EM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):703–9 (Eng. Abstr.) **(Rus)**

BIPOLAR DISORDER

Clinical and laboratory effects of discontinuation of lithium prophylaxis. Goodnick PJ. **Acta Psychiatr Scand** 1985 Jun;71(6):608–14

Depression and anxiety: mianserin and nomifensine compared in a double-blind multicentre trial. Granier F, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:67–74

Hematological effects of carbamazepine in patients with affective illness. Joffe RT, et al. **Am J Psychiatry** 1985 Oct;142(10):1196–9

CSF substance P immunoreactivity in affective disorders. Berrettini WH, et al. **Biol Psychiatry** 1985 Sep;20(9):965–70

Rapid antidepressant activity of destyr gamma endorphin: correlation with urinary melatonin. Chazot G, et al. **Biol Psychiatry** 1985 Sep; 20(9):1026–30

An open clinical trial of carbamazepine in treatment-resistant bipolar and schizo-affective psychotics. Elphick M. **Br J Psychiatry** 1985 Aug; 147:198–200

Treatment of rapid cycling affective illness [letter] Lowe MR. **Br J Psychiatry** 1985 May;146:558

Carbamazepine in manic depressive psychosis. Arap Mengech HN. **East Afr Med J** 1985 Mar;62(3):172–4

Spontaneous afternoon plasma cortisol in depression. Christensen P, et al. **J Affective Disord** 1985 May–Jun;8(3):271–8

The use of sodium valproate, carbamazepine and oxcarbazepine in patients with affective disorders. Emrich HM, et al. **J Affective Disord** 1985 May–Jun;8(3):243–50

Lithium prophylaxis of recurrent affective disorders. Glen AI. **J Affective Disord** 1985 May–Jun;8(3):259–65

Lithium dosage in the elderly. A study with matched age groups. Greil W, et al. **J Affective Disord** 1985 Jul;9(1):1–4

Dopamine in manic depressive illness. A pharmacological synthesis. Silverstone T. **J Affective Disord** 1985 May–Jun;8(3):225–31

Alternative therapies for bipolar disorder. Lerer B. **J Clin Psychiatry** 1985 Aug;46(8):309–16 (93 ref.)

Developmental manifestations in a boy with prepubertal bipolar disorder. Reiss AL. **J Clin Psychiatry** 1985 Oct;46(10):441–3

L-phenylalanine [letter] Simonson M. **J Clin Psychiatry** 1985 Aug; 46(8):355

Treatment of bulimia and rapid-cycling bipolar disorder with sodium valproate: a case report. Herridge PL, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):229–30

Factors associated with response to lithium prophylaxis in DSM III major depression and bipolar disorder. Maj M, et al. **Pharmacopsychiatry** 1985 Sep;18(5):309-13

A controlled study of cellular immune function in affective disorders before and during somatic therapy. Albrecht J, et al. **Psychiatry Res** 1985 Jul;15(3):185-93

Illness behaviour and rehospitalization in bipolar affective disorder. Joyce PR. **Psychol Med** 1985 Aug;15(3):521-5

Side-effects of lithium at lower therapeutic levels: the significance of thirst. King JR, et al. **Psychol Med** 1985 May;15(2):355-61

Investigating renal function during lithium treatment. Waller DG, et al. **Psychol Med** 1985 May;15(2):369-75

Dopamine receptor binding of C-11-3-N-methylspiperone in the caudate in schizophrenia and bipolar disorder: a preliminary report. Wong DF, et al. **Psychopharmacol Bull** 1985;21(3):595-8

[Clinical study of 86 cases of manic-depressive psychosis] Cai JB. **Chung Hua I Hsueh Tsa Chih** 1985 Jun;65(6):325-8 (Eng. Abstr.) **(Chi)**

[A clinical study of 456 cases of manic-depressive disorder] Sun JW. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Aug; 17(4):236-8 (Eng. Abstr.) **(Chi)**

[Lithium levels in biological media and treatment surveillance] Greffe J, et al. **Encephale** 1985 Mar-Apr;11(2):79-83 (Eng. Abstr.) **(Fre)**

[Therapy of depressive and manic diseases] Seige D. **Psychiatr Neurol Med Psychol Beih** 1966;4-5:186-92 **(Ger)**

[Family interactions and adherence to lithium pharmacotherapy] de León OA, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):7-16 (Eng. Abstr.) **(Spa)**

BLOOD-BRAIN BARRIER

Enhanced cerebrovascular permeability by Metrazol: significance for brain metastases. Greig N, et al. **Clin Exp Metastasis** 1983 Jan-Mar; 1(1):83-95

BRADYKININ

Control of sodium and potassium transport in the cortical collecting duct of the rat. Effects of bradykinin, vasopressin, and deoxycorticosterone. Tomita K, et al. **J Clin Invest** 1985 Jul;76(1):132-6

In vivo and in vitro effects of bradykinin on the release of beta-endorphin-like immunoreactivity. Matsumura M, et al. **Neuroendocrinology** 1985 Aug;41(2):101-6

[The effect of bradykinin on free nitrogen compounds and energy production in the rat brain] Hashimoto Y, et al. **Shikwa Gakuho** 1985 Mar;85(3):371-9 (Eng. Abstr.) **(Jpn)**

BUTYLAMINES

Biotransformation of terodiline. II. Disposition in the male rat. Identification of metabolites in rat urine and rat liver microsomes by mass spectrometry. Norén B, et al. **Acta Pharm Suec** 1985; 22(3):131-46

Comparison of the calcium-antagonistic effects of terodiline, nifedipine and verapamil. Larsson-Backström C, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Jul;57(1):8-17

Biotransformation of terodiline I. Identification of metabolites in dog urine by mass spectrometry. Norén B, et al. **Biomed Mass Spectrom** 1985 Aug;12(8):367-79

Determination of diprobutine in human plasma using gas-liquid chromatography with nitrogen-selective detection. Davies CL, et al. **J Chromatogr** 1985 Apr 12;339(1):186-91

BUTYROPHENONE TRANQUILIZERS

Treatment of rapid cycling affective illness [letter] Lowe MR. **Br J Psychiatry** 1985 May;146:558

Sensitive analysis of butyrophenone neuroleptics by high-performance liquid chromatography with ultraviolet detection at 254 am. Parkinson D. **J Chromatogr** 1985 Jun 14;341(2):465-72

[Evaluation of the efficacy of haloperidol decanoate in the treatment of chronic psychotic hospital patients] Marchant N, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):37-41 (Eng. Abstr.) **(Spa)**

BUTYROPHENONES

Effects of phospholipids on the specific binding of [3H]spiroperidol to the cholate extract of rat brain synaptic membranes. Moroi K, et al. **Int J Biochem** 1985;17(5):637-44

Changes of the striatal 3H-spiperone binding 3-6 weeks after nigrostriatal denervation and after two years. Guerin B, et al. **Life Sci** 1985 Sep 9;37(10):953-61

Dopamine receptor binding of C-11-3-N-methylspiperone in the caudate in schizophrenia and bipolar disorder: a preliminary report. Wong DF, et al. **Psychopharmacol Bull** 1985;21(3):595-8

Prolonged antidopaminergic actions of single doses of butyrophenones in the rat. Campbell A, et al. **Psychopharmacology (Berlin)** 1985; 87(2):161-6

[The affinity of aromatic fluoride derivatives of phenothiazine neuroleptics to spiroperidol binding sites of dopamine receptors by the radioligand technic in vitro] Oelssner W Jr, et al. **Pharmazie** 1985 May; 40(5):341-2 (Eng. Abstr.) **(Ger)**

CARBAMAZEPINE

Hematological effects of carbamazepine in patients with affective illness. Joffe RT, et al. **Am J Psychiatry** 1985 Oct;142(10):1196-9

An open clinical trial of carbamazepine in treatment-resistant bipolar and schizo-affective psychotics. Elphick M. **Br J Psychiatry** 1985 Aug; 147:198-200

Use of carbamazepine in psychiatric disorders. Birkhimer LJ, et al. **Clin Pharm** 1985 Jul-Aug;4(4):425-34

Plasma concentrations of carbamazepine and carbamazepine 10,11-epoxide during pregnancy and after delivery. Battino D, et al. **Clin Pharmacokinet** 1985 May-Jun;10(3):279-84

Carbamazepine in manic depressive psychosis. Arap Mengech HN. **East Afr Med J** 1985 Mar;62(3):172-4

Practical therapeutics: the use of carbamazepine in affective disorders. Ouel AO, et al. **East Afr Med J** 1985 Mar;62(3):224-8

Relative bioavailability of rectally administered carbamazepine suspension in humans. Graves NM, et al. **Epilepsia** 1985 Sep-Oct;26(5):429-33

Chronic carbamazepine treatment increases brain adenosine receptors. Marangos PJ, et al. **Epilepsia** 1985 Sep-Oct;26(5):493-8

Antinociceptive effect of intracisternal carbamazepine evidenced by the bradykinin-induced biting-like response in rats. Foong FW, et al. **Exp Neurol** 1985 Oct;90(1):264-7

The use of sodium valproate, carbamazepine and oxcarbazepine in patients with affective disorders. Emrich HM, et al. **J Affective Disord** 1985 May-Jun;8(3):243-50

Successful treatment of psychotic depression with carbamazepine. Schaffer CB, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):233-5

Bioequivalence of carbamazepine chewable and conventional tablets: single-dose and steady-state studies. Chan KK, et al. **J Pharm Sci** 1985 Aug;74(8):866-70

Overflow urinary incontinence due to carbamazepine. Anders RJ, et al. **J Urol** 1985 Oct;134(4):758-9

Side-effects induced by carbamazepine-10,11-epoxide [letter] Patsalos PN, et al. **Lancet** 1985 Aug 31;2(8453):496

Neuronal sensitivity to substance P is increased after repeated treatment with tranylcypromine, carbamazepine or oxaprotaline, but decreased after repeated electroconvulsive shock. Jones RS, et al. **Neuropharmacology** 1985 Jul;24(7):627-33

The central action of carbamazepine as a potential antidepressant drug. Maj J, et al. **Pol J Pharmacol Pharm** 1985 Jan-Feb;37(1):47-56

Therapeutic indications in carbamazepine overdose. Kossoy AF, et al. **South Med J** 1985 Aug;78(8):999-1000

Carbamazepine and carbamazepine-epoxide serum protein binding in newborn infants. Groce JB 3d, et al. **Ther Drug Monit** 1985; 7(3):274-6

Carbamazepine protein binding and disposition in pregnancy. Yerby MS, et al. **Ther Drug Monit** 1985;7(3):269-73

Carbamazepine and psychotherapy in the treatment of schizoaffective psychosis. Cegalis JA, et al. **Yale J Biol Med** 1985 Jul-Aug; 58(4):327-36

CARBIDOPA

Metabolism of carbidopa to alpha-methyldopamine and alpha-methylnorepinephrine in rats. Shelton RC, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3623-6

Peripheral carbidopa affects striatal monoamine oxidase activity [letter] LeWitt PA, et al. **Neurology** 1985 Aug;35(8):1258-9

CATALEPSY

[Changes in the serotonin system of the brains of rats genetically predisposed to catalepsy] Popova NK, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):742-6 (Eng. Abstr.) **(Rus)**

CATECHOL ESTROGENS

Effect of intraventricular administration of catechol estrogens on catecholamine content in various brain regions. Panek DU, et al. **Brain Res** 1985 Aug 5;340(1):87-90

Catechol oestradiol control of FSH-stimulated granulosa cell steroidogenesis. Hudson KE, et al. **J Endocrinol** 1985 Jul; 106(1):R1-4

HPLC-ECD procedure for the measurement of O-methylation of catechol estrogens by vascular tissue. Reid JJ, et al. **J Pharmacol Methods** 1985 Aug;14(1):25-39

CATECHOLAMINES

Urinary catecholamines in iron-deficient rats at rest and following surgical stress. Groeneveld D, et al. **Am J Clin Nutr** 1985 Aug;42(2):263-9

Application of the dual-cell coulometric detector: a method for assaying monoamines and their metabolites. Achilli G, et al. **Anal Biochem** 1985 Jul;148(1):1–9

Plasma catecholamine concentrations in acute states of stress and trauma [letter] Little RA, et al. **Arch Emerg Med** 1985 Mar;2(1):46–7

Enhancement of acetylcholine–evoked catecholamine release from perfused dog adrenals by elevating cyclic AMP levels. Morita K, et al. **Arch Int Pharmacodyn Ther** 1985 Jun;275(2):208–16

Inhibitory effect of hyperosmolality on catecholamine secretion from the bovine adrenal medulla. Pinto JE, et al. **Arch Int Pharmacodyn Ther** 1985 Aug;276(2):236–46

Catecholamine regulation of neocortical spindling in DBA/2 mice. Ryan LJ. **Behav Brain Res** 1985 Aug;16(2–3):103–15

Effects of debrisoquin on the excretion of catecholamine and octopamine metabolites in the rat and guinea pig. Edwards DJ, et al. **Biochem Pharmacol** 1985 Aug 15;34(16):2911–6

Conjugated catecholamines and pressor responses to angiotensin, luteinizing hormone–releasing hormone and prazosin in conscious toads. Wilson JX. **Br J Pharmacol** 1985 Jul;85(3):647–53

Regional distribution of catecholaminergic terminals in the pigeon visual system. Bagnoli P, et al. **Brain Res** 1985 Jul 1;337(2):277–86

Unilateral odor deprivation: effects on the development of olfactory bulb catecholamines and behavior. Brunjes PC, et al. **Brain Res** 1985 Sep; 354(1):1–6

Effect of intraventricular administration of catechol estrogens on catecholamine content in various brain regions. Panek DU, et al. **Brain Res** 1985 Aug 5;340(1):87–90

Catecholaminergic fiber sprouting in granuloprival coeruleo–cerebellar cultures. Seil FJ, et al. **Brain Res** 1985 Aug;353(2):251–5

Catecholaminergic innervation of the rat adrenal cortex. Kleitman N, et al. **Cell Tissue Res** 1985;241(1):139–47

Interference of labetalol metabolites in the determination of plasma catecholamines by HPLC with electrochemical detection. Bouloux PM, et al. **Clin Chim Acta** 1985 Aug 15;150(2):111–7

The effects of piretanide on catecholamine metabolism, plasma renin activity and plasma aldosterone: a double–blind study versus furosemide in healthy volunteers. Verho M, et al. **Curr Med Res Opin** 1985; 9(7):461–74

Genetic variation in catecholamine responsive metabolic pathways—a hypothesis for a common regulatory mechanism in BALB/c sublines. Kozak LP. **Curr Top Microbiol Immunol** 1985;122:66–70

Partial expression of catecholaminergic traits in cholinergic chick ciliary ganglia: studies in vivo and in vitro. Iacovitti L, et al. **Dev Biol** 1985 Aug;110(2):402–12

Biochemical and behavioral changes in rats during and after chronic d–amphetamine exposure. Vogel WH, et al. **Drug Alcohol Depend** 1985 Jun;15(3):245–53

Circadian variations of free and sulfoconjugated catecholamines in normal subjects. Kuchel O, et al. **Endocr Res** 1985;11(1–2):17–25

Angiotensin II restoration of reflex adrenal medullary secretion to anephric dogs is physiologically dose dependent. Badder EM, et al. **Endocrinology** 1985 Nov;117(5):1920–9

Effects of TRH and a rat TSH preparation on discrete hypothalamic and forebrain catecholamine nerve terminal networks in the hypophysectomized male rat. Andersson K, et al. **Eur J Pharmacol** 1985 May 20;111(3):295–307

Involvement of amygdaloid catecholaminergic mechanism in suppressive effects of desipramine and imipramine on duration of immobility in rats forced to swim. Araki H, et al. **Eur J Pharmacol** 1985 Jul 31; 113(3):313–8

The importance of the alpha–adrenoceptor agonist activity of dobutamine to inotropic selectivity in the anaesthetized cat. Kenakin TP, et al. **Eur J Pharmacol** 1985 May 20;111(3):347–54

Effects of catecholamines, monophenolamines and phenylamines on identifiable giant neurons of an African giant snail (Achatina fulica Férussac). Ku BS, et al. **Eur J Pharmacol** 1985 Aug 7;114(1):1–8

Sources of the catecholaminergic innervation of the trigeminal nucleus caudalis in cat. Stevens RT, et al. **Exp Neurol** 1985 Oct; 90(1):215–23

Phorbol ester stimulates catecholamine synthesis in isolated bovine adrenal medullary cells. Houchi H, et al. **FEBS Lett** 1985 Sep 2; 188(2):205–8

Catecholamine effects on blood pressure and heart rate in warm– and cold–acclimated American bullfrogs (Rana catesbeiana). Herman CA, et al. **Gen Comp Endocrinol** 1985 Sep;59(3):434–41

Quantitation and immunohistochemistry of catecholamines in the posterior segment of the eye. Ehinger B, et al. **Histochemistry** 1985; 82(5):435–9

The neurochemistry of mania. The effect of lithium on catecholamines, indoleamines and calcium mobilization. Wood K. **J Affective Disord** 1985 May–Jun;8(3):215–23

Free, glucuronide, and sulfate catecholamines in the rat: effect of hypoxia. Claustre J, et al. **J Appl Physiol** 1985 Jul;59(1):12–7

Modification of dobutamine– and terbutaline–induced calcium and fluid secretion from rat salivary glands by atenolol and butoxamine. Schneyer CA, et al. **J Auton Nerv Syst** 1985 Aug;13(4):275–85

Determination of adult sheep plasma catecholamines using [3H]norepinephrine as the internal standard. Boylan JM, et al. **J Chromatogr** 1985 Feb 27;338(1):192–4

Ventricular myocardial catecholamines in primates. Pierpont GL, et al. **J Lab Clin Med** 1985 Aug;106(2):205–10

CSF sulfoconjugated catecholamines in man: their relationship with plasma catecholamines. Kuchel O, et al. **J Neural Transm** 1985; 62(1–2):91–7

Postmortem changes in catecholamines, indoleamines, and their metabolites in rat brain regions: prevention with 10–kW microwave irradiation. Ikarashi Y, et al. **J Neurochem** 1985 Sep;45(3):935–9

Metabolic aspects of spinal cord injuries. Northrup BE. **J Neurosurg Sci** 1984 Jul–Dec;28(3–4):121–5

Spectrophotometric determination of catecholamines. Basyoni Salem F. **J Pharm Belg** 1985 May–Jun;40(3):185–90

Effect of 6–hydroxydopamine on the metabolism of endogenous octopamines and catecholamines. Ibrahim KE, et al. **J Pharm Pharmacol** 1985 Jul;37(7):496–7

The affinity and efficacy of naturally occurring catecholamines at beta–adrenoceptor subtypes. McPherson GA, et al. **J Pharm Pharmacol** 1985 Jul;37(7):499–501

Effect of epidural morphine on urinary catecholamine excretion during postoperative period. Yasuda S, et al. **Keio J Med** 1985 Mar; 34(1):25–9

Comparison of the effects of neuropeptide Y and adrenergic transmitters on LH release and food intake in male rats. Allen LG, et al. **Life Sci** 1985 Aug 19;37(7):617–23

Catecholamine metabolism in the attention deficit disorder: implications for the use of amino acid precursor therapy. McConnell H. **Med Hypotheses** 1985 Aug;17(4):305–11

Interactions of microtubule–active agents with nicotinic acetylcholine receptors. Relationship to their inhibition of catecholamine secretion by adrenal chromaffin cells. McKay DB, et al. **Mol Pharmacol** 1985 Jul;28(1):10–6

Adrenergic stimulation of pepsinogen release from rabbit isolated gastric glands. Skoubo–Kristensen E, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jul;330(1):37–41

Electrophysiological interactions between haloperidol and reduced haloperidol, and dopamine, norepinephrine and phencyclidine in rat brain. Kirch DG, et al. **Neuropharmacology** 1985 May;24(5):375–9

Effect of catecholamines on the activity of rat brain dipeptidyl aminopeptidase. Imai K, et al. **Neurosci Res** 1984 Oct;1(5):353–6

New dopaminergic terminal fields in the motor, visual (area 18b) and retrosplenial cortex in the young and adult rat. Immunocytochemical and catecholamine histochemical analyses. Berger B, et al. **Neuroscience** 1985 Aug;15(4):983–98

Dietary carbohydrate intake and catecholamine secretion in man. **Nutr Rev** 1985 May;43(5):138–40 (12 ref.)

The chromaffin vesicle: a model secretory organelle. Njus D, et al. **Physiologist** 1985 Aug;28(4):235–41 (53 ref.)

Changes in plasma proenkephalin peptide F and catecholamine levels during graded exercise in men. Kraemer WJ, et al. **Proc Natl Acad Sci USA** 1985 Sep;82(18):6349–51

Effect of various catecholamine antagonists on prolactin secretion in conscious male rabbits. Kaji H, et al. **Proc Soc Exp Biol Med** 1985 Oct;180(1):144–8

Peptide–catecholamine interaction: feeding and satiety. Myers RD. **Psychopharmacol Bull** 1985;21(3):406–11

Amphetamine–induced enhancement of ethanol consumption: role of central catecholamines. Levy AD, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):233–6

Association between learning and cortical catecholamines in non–drug–treated rats. Sahakian BJ, et al. **Psychopharmacology (Berlin)** 1985;86(3):339–43

Cardiotonic agents: a simple HPLC procedure for the quantitation of dobutamine and a new congener in plasma. Dixon R, et al. **Res Commun Chem Pathol Pharmacol** 1985 May;48(2):313–6

Effects of hypoxia on catecholamine and cardiorespiratory responses in exercising dogs. Favier RJ, et al. **Respir Physiol** 1985 Aug; 61(2):167–77

The adrenal chromaffin cell. Carmichael SW, et al. **Sci Am** 1985 Aug; 253(2):40–9

[Stress and the excretion of catecholamines in patients after kidney transplantation] Honzák R, et al. **Cas Lek Cesk** 1985 Jul 19; 124(29):912–3 (Eng. Abstr.) **(Cze)**

[Catecholaminergic receptors of the blood cells of schizophrenics] Ackenheil M, et al. **Encephale** 1985 May–Jun;11(3):95–100 (Eng. Abstr.) **(Fre)**

[Levels of free and conjugated catecholamines in amniotic fluid and in umbilical and maternal blood in patients undergoing cesarean section] Bardazzi N, et al. **Quad Sclavo Diagn** 1984 Dec;20(4):364–71 (Eng. Abstr.) **(Ita)**

[Effects of amrinone on hemodynamics, oxygen consumption and plasma catecholamine levels in anesthetized dogs] Kosugi I, et al. **Masui** 1985 Apr;34(4):429–33 (Eng. Abstr.) **(Jpn)**

[A comparative study on the effect of vagotomy and splanchnicectomy on the catecholamine content of the stomach, duodenum and pancreas]

Hamaji M, et al. **Nippon Shokakibyo Gakkai Zasshi** 1985 Apr; 82(4):587–91 (Eng. Abstr.) **(Jpn)**

[Changes in the adrenal medulla of the rat during immobilization stress] Shvalev VN, et al. **Arkh Anat Gistol Embriol** 1985 Aug; 89(8):97–102 (Eng. Abstr.) **(Rus)**

[Radioprotective action of catecholamines on a Chinese hamster fibroblast culture] Chirkov IuIu, et al. **Biol Nauki** 1985;(5):38–41 (Eng. Abstr.) **(Rus)**

[State of the peripheral catecholaminergic systems during pharmacologic correction of immobilization stress using sodium oxybutyrate] Khaisman EB, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):317–9 (Eng. Abstr.) **(Rus)**

[Effects of fasting and satiation monoamine levels in the brain] Kravets SV. **Fiziol Zh** 1985 Jul–Aug;31(4):468–72 (Eng. Abstr.) **(Rus)**

[Emotional stress–induced changes in catecholamines in the nuclei of the brains of rats differing in 'open–field' behavior] Belova TI, et al. **Fiziol Zh SSSR** 1985 Jul;71(7):813–22 (Eng. Abstr.) **(Rus)**

[Catecholamines in nuclei of the brains of the August strain rat during immobilization stress] Ivanova TM, et al. **Fiziol Zh SSSR** 1985 Jul; 71(7):823–8 (Eng. Abstr.) **(Rus)**

[Effect of sympathetic denervation on the outflow of intraocular fluid and the concentration of pyrocatechins in the fluids and tissues of the eye] Razumovskiĭ MI, et al. **Fiziol Zh SSSR** 1985 Jun;71(6).719–23 (Eng. Abstr.) **(Rus)**

[Monoaminergic structures of the hypothalamus in chronic stress] Konstantinova MS, et al. **Probl Endokrinol (Mosk)** 1985 Jul–Aug; 31(4):49–51 (Eng. Abstr.) **(Rus)**

[Catecholamines and regulation of the activity of the cellular genome] Bozhkog Kh. **Usp Fiziol Nauk** 1985 Jul–Sep;16(3):73–88 **(Rus)**

[The effect of dexasone and metyrapone on the level of catecholamines in the adrenal glands of guinea pigs and rats] Lončar–Stevanović H, et al. **Srp Arh Celok Lek** 1983 Nov–Dec;111(11–12):1475–83 (Eng. Abstr.) **(Scc)**

[Levels of catecholamines in the hypothalamus, hypophysis and in the adrenal in sheep after whole–body exposure to gamma rays] Pástorová B, et al. **Vet Med (Praha)** 1985 Aug;30(8):485–92 (Eng. Abstr.) **(Slo)**

[Distribution of catecholamines and monoamine oxidase activity in the system controlling sexual function in sheep] Pástorová B, et al. **Vet Med (Praha)** 1985 Sep;30(9):563–70 (Eng. Abstr.) **(Slo)**

[Correlation between clinical and laboratory data in depression. Therapeutic orientation by means of vitamins and amino acids] Mesones HL, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):25–36 (Eng. Abstr.) **(Spa)**

CENTRAL NERVOUS SYSTEM AGENTS

Different effects of centrally acting drugs on rabbit platelet aggregation: with special reference to selective inhibitory effects of antipsychotics and antidepressants. Ishigooka J, et al. **Biol Psychiatry** 1985 Aug; 20(8):866–73

CHILD BEHAVIOR

Attention deficit disorder children with or without hyperactivity. Which behaviors are helped by stimulants? Ullmann RK, et al. **Clin Pediatr (Phila)** 1985 Oct;24(10):547–51

CHILD BEHAVIOR DISORDERS

Developmental manifestations in a boy with prepubertal bipolar disorder. Reiss AL. **J Clin Psychiatry** 1985 Oct;46(10):441–3

Successful nicotinamide treatment in an autosomal dominant behavioral and psychiatric disorder. Blom W, et al. **J Inherited Metab Dis** 1985; 8 Suppl 2:107–8

CHILD PSYCHIATRY

Evaluating attitudes of child psychiatry residents to psychotropic medication: implications for training. Schachar RJ. **Can J Psychiatry** 1985 Aug;30(5):348–52

CHLORAMINES

Removal of sodium channel inactivation in squid axon by the oxidant chloramine–T. Wang GK, et al. **J Gen Physiol** 1985 Aug; 86(2):289–302

[Comparative sensitivity of microorganisms to monochloramine B] Krucheniuk TB. **Gig Sanit** 1985 Jun;(6):75–7 **(Rus)**

[Gram–negative conditionally pathogenic microflora in hospitals and its resistance to chloramine] Trukhina GM, et al. **Gig Sanit** 1985 May; (5):82–4 **(Rus)**

CHLORDIAZEPOXIDE

No cross–tolerance between the stimulatory and depressant actions of benzodiazepines in mice. File SE, et al. **Behav Brain Res** 1985 Sep; 17(1):1–7

Correlation of [3H]diazepam binding density with anxiolytic locus in the amygdaloid complex of the rat. Thomas SR, et al. **Brain Res** 1985 Sep 2;342(1):85–90

Chlordiazepoxide–induced hyperphagia in non–food–deprived rats: effects of Ro15–1788, CGS 8216 and ZK 93 426. Cooper SJ, et al. **Eur J Pharmacol** 1985 May 28;112(1):39–45

Chlordiazepoxide and successive discrimination: different effects on acquisition and performance. McNaughton N. **Pharmacol Biochem Behav** 1985 Sep;23(3):487–94

Associative control of tolerance to the sedative and hypothermic effects of chlordiazepoxide. Greeley J, et al. **Psychopharmacology (Berlin)** 1985; 86(4):487–93

Maternal aggression in rats: effects of chlordiazepoxide and fluprazine. Olivier B, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):68–76

Comparison between the effects of propranolol and chlordiazepoxide on timing behaviour in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1985;87(2):219–24

[Pharmacology in automobile driving and medical practice. II. Euhypnotic effect of Elenium and psychomotor efficiency in humans] Gałuszko P, et al. **Psychiatr Pol** 1984 Nov–Dec;18(6):555–60 (Eng. Abstr.) **(Pol)**

P-CHLOROPHENYLALANINE

Maternal aggression in mice: effects of treatments with PCPA, 5-HTP and 5–HT receptor antagonists. Ieni JR, et al. **Eur J Pharmacol** 1985 May 8;111(2):211–20

Pharmacological studies on the serotoninergic and nonserotonin–mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pretreatment with fluoxetine, indalpine, PCPA, and L–tryptophan. Van de Kar LD, et al. **Neuroendocrinology** 1985 Oct; 41(4):283–8

Evidence of norepinephrine–mediated suppression of para–chlorophenylalanine–induced muricidal behavior. Pucilowski O, et al. **Pharmacol Res Commun** 1985 May;17(5):457–62

CHLORPROMAZINE

The susceptibility of Plasmodium falciparum in vitro to chlorpromazine and the stereo–isomeric compounds cis(Z)– and trans(E)–clopenthixol. Kristiansen JE, et al. **Acta Pathol Microbiol Immunol Scand [B]** 1985 Jun;93(3):249–51

Plasma protein binding of salicylic acid, phenytoin, chlorpromazine, propranolol and pethidine using equilibrium dialysis and ultracentrifugation. Verbeeck RK, et al. **Arzneimittelforschung** 1985; 35(6):903–6

Generation of electronically excited species during enzymatic oxidation of chlorpromazine and related compound. Nakano M, et al. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):952–6

Chlorpromazine—a specific effect on breathlessness? O'Neill PA, et al. **Br J Clin Pharmacol** 1985 Jun;19(6):793–7

Cross–tolerance to the hypothermic effect of delta 8–tetrahydrocannabinol 11–hydroxy–delta 8–tetrahydrocannabinol and chlorpromazine in the mouse. Yamamoto I, et al. **Eur J Pharmacol** 1985 May 8; 111(2):159–66

The effects of chlorpromazine and imipramine on rate and stimulus control of matching to sample. Newland MC, et al. **J Exp Anal Behav** 1985 Jul;44(1):49–68

The effect of sample storage on the stability of chlorpromazine in plasma and whole blood. McKay G, et al. **J Pharmacol Methods** 1984 Oct; 12(3):221–3

Effects of triethyltin and its interaction with d–amphetamine and chlorpromazine on responding under a multiple schedule of food presentation in rats. Rastogi SK, et al. **Neurobehav Toxicol Teratol** 1985 May–Jun;7(3):239–42

Ultrastructure of nerve tissue on experimental brain injuries in animals with increased immunobiological reactivity of the body on action of some desensitizing preparations. Sukhorukova LI. **Neurosci Behav Physiol** 1985 Mar–Apr;15(2):93–7

A conveyor belt task for assessing visuo–motor coordination in the marmoset (Callithrix jacchus): effects of diazepam, chlorpromazine, pentobarbital and d–amphetamine. D'Mello GD, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):125–31

Influence of housing conditions and state of partner on conditioning and extinction of taste aversion to lithium and chlorpromazine. Giardini V. **Psychopharmacology (Berlin)** 1985;86(1–2):96–101

Therapeutic monitoring of chlorpromazine I: Pitfalls in plasma analysis. Hubbard JW, et al. **Ther Drug Monit** 1985;7(2):222–8

CHLORPROTHIXENE

Phenolic metabolites of chlorprothixene in man and dog. Breyer–Pfaff U, et al. **Drug Metab Dispos** 1985 Jul–Aug;13(4):479–89

CHOICE BEHAVIOR

Benzodiazepines reduce the tolerance to reward delay in rats. Thiébot MH, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):147–52

CLOMIPRAMINE

A double-blind group comparison of mianserin and clomipramine in the treatment of mildly depressed psychiatric out-patients. Dunbar GC, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:60–6

Clomipramine treatment of childhood obsessive-compulsive disorder. A double-blind controlled study. Flament MF, et al. **Arch Gen Psychiatry** 1985 Oct;42(10):977–83

Superfusion of clomipramine within the ventromedial hypothalamus selectively suppresses paradoxical sleep in freely moving rats. Danguir J, et al. **Brain Res Bull** 1985 Jul;15(1):1–4

Severe depression treatment: experience using maprotiline (Ludiomil) in combination with clomipramine (Anafranil). Ovuga E. **East Afr Med J** 1985 Feb;62(2):79–81

Determination of citalopram, amitriptyline and clomipramine in plasma by reversed-phase high-performance liquid chromatography. Rop PP, et al. **J Chromatogr** 1985 Feb 27;338(1):171–8

Efficacy and tolerability of sustained-release clomipramine (Anafranil SR) in the treatment of phobias: a comparison with the conventional formulation of clomipramine (Anafranil). Allsopp LF, et al. **J Int Med Res** 1985;13(4):203–8

Changes in human platelet 5 HT level after 1 week of chlorimipramine treatment. Poirier MF, et al. **Psychopharmacology (Berlin)** 1985; 86(1–2):194–6

[Measurement of basal plasma levels of 3 anterior pituitary hormones during acute or chronic treatment with tricyclic antidepressants] Goyot C, et al. **Encephale** 1985 Mar–Apr;11(2):45–51 (Eng. Abstr.) **(Fre)**

COCAINE

Effect of cocaine dependence on plasma phenylalanine and tyrosine levels and on urinary MHPG excretion. Tennant FS Jr. **Am J Psychiatry** 1985 Oct;142(10):1200–1

Propranolol-induced hypertension in treatment of cocaine intoxication. Ramoska E, et al. **Ann Emerg Med** 1985 Nov;14(11):1112–3

Electrochemistry of norcocaine nitroxide and related compounds: implications for cocaine hepatotoxicity. Charkoudian JC, et al. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):1044–51

Sodium-independent binding of [3H]cocaine in mouse striatum is serotonin related. Reith ME, et al. **Brain Res** 1985 Sep 2;342(1):145–8

The rising popularity of cocaine: how serious a problem? Katz S. **Can Med Assoc J** 1985 Oct 1;133(7):682–5

Kinetics of cocaine distribution, elimination, and chronotropic effects. Chow MJ, et al. **Clin Pharmacol Ther** 1985 Sep;38(3):318–24

Treatment of chronic cocaine abuse and attention deficit disorder, residual type, with magnesium pemoline. Weiss RD, et al. **Drug Alcohol Depend** 1985 May;15(1–2):69–72

Comparison of fixed-ratio and progressive-ratio schedules of maintenance of stimulant drug-reinforced responding. Winger G, et al. **Drug Alcohol Depend** 1985 May;15(1–2):123–30

Histopathology of the spinal cord after intrathecal cocaine, bupivacaine, lignocaine and adrenaline in the rat. Bahar M, et al. **Eur J Anaesthesiol** 1984 Sep;1(3):293–7

Factors which differentiate cocaine users in treatment from nontreatment users. Chitwood DD, et al. **Int J Addict** 1985 Mar;20(3):449–59

Classics revisited. Uber Coca. By Sigmund Freud. **J Subst Abuse Treat** 1984;1(3):206–17

The Fair Oaks Hospital cocaine treatment program. Annitto WJ, et al. **J Subst Abuse Treat** 1984;1(3):223–6

Status of cocaine abuse 1984. Dougherty RJ. **J Subst Abuse Treat** 1984; 1(3):157–61

Methylphenidate (Ritalin) treatment of cocaine dependence--a preliminary report. Khantzian EJ, et al. **J Subst Abuse Treat** 1984; 1(2):107–12

Involvement of dopamine in the aversive stimulus properties of cocaine in rats. Hunt T, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):945–8

Cathinone, cocaine and methamphetamine: similarity of behavioral effects. Schechter MD, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):913–6

Cocaine: excitatory effects on sensorimotor reactivity measured with acoustic startle. Davis M. **Psychopharmacology (Berlin)** 1985; 86(1–2):31–6

Information processing components of the auditory event related potential are reduced by cocaine. Herning RI, et al. **Psychopharmacology (Berlin)** 1985;87(2):178–85

Self-administration of low-dose cocaine by rats at reduced and recovered body weight. Papasava M, et al. **Psychopharmacology (Berlin)** 1985; 85(4):419–25

Cocaine blocks the dopamine depletion induced by MPTP. Mayer RA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jul;49(1):145–8

COGNITION

Hyperactive children treated with stimulants. Is cognitive training a useful adjunct? Abikoff H, et al. **Arch Gen Psychiatry** 1985 Oct; 42(10):953–61

Delineation of pharmacopsychological effects by means of endogenous event-related brain potentials: an exemplification with flupentixol. Rösler F, et al. **Neuropsychobiology** 1985;13(1–2):81–92

Information processing components of the auditory event related potential are reduced by cocaine. Herning RI, et al. **Psychopharmacology (Berlin)** 1985;87(2):178–85

Cognitive effects of lithium treatment in normal volunteers. Weingartner H, et al. **Psychopharmacology (Berlin)** 1985;86(4):472–4

COGNITION DISORDERS

[Effect of diazepam on interference processes] Vinitskiĭ IM, et al. **Farmakol Toksikol** 1985 Jul–Aug;48(4):38–41 (Eng. Abstr.) **(Rus)**

CONDITIONING (PSYCHOLOGY)

Effects of phenobarbital, clonazepam, valproic acid, ethosuximide, and phenytoin on the delayed matching-to-sample performance of pigeons. Picker M, et al. **Psychopharmacology (Berlin)** 1985;86(4):494–8

CONDITIONING, CLASSICAL

Relationship between the release and uptake of noradrenaline by rat brain synaptosomes in the formation of defensive conditioned reflex. Bazyan AS, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(1–2):37–46

Role of ethanol in conditioning aversion to alcoholic beverages in rats. Franchina JJ, et al. **Behav Res Ther** 1985;23(5):521–9

The conditioned place preference is affected by two independent reinforcement processes. White NM, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):37–42

Influence of housing conditions and state of partner on conditioning and extinction of taste aversion to lithium and chlorpromazine. Giardini V. **Psychopharmacology (Berlin)** 1985;86(1–2):96–101

[Effect of insulin and its polymeric analogs on learning and memory processes in the rabbit] Bakharev VD, et al. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):314–21 (Eng. Abstr.) **(Rus)**

[Effect of a cyclic analog of enkephalin on learning and memory in the mouse] Getsova VM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug; 35(4):710–7 (Eng. Abstr.) **(Rus)**

[Effect of noradrenaline, microapplied to the dorsal hippocampus of the rat, on conditioned reflex memory] Melikov EM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):780–2 **(Rus)**

[Formation and extinction of drinking conditioned reflexes after unilateral intercollicular sectioning of the brain in the rat] Shabanov PD, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):777–9 **(Rus)**

CONDITIONING, OPERANT

The effects of chlorpromazine and imipramine on rate and stimulus control of matching to sample. Newland MC, et al. **J Exp Anal Behav** 1985 Jul;44(1):49–68

Comparisons between discrete lever-press and shuttle avoidance responses in mice: acquisition processes and effects of psychoactive drugs. Kuribara H, et al. **Jpn J Pharmacol** 1985 Jun;38(2):141–51

Comparative effects of cathinone and amphetamine on fixed-interval operant responding: a rate-dependency analysis. Goudie AJ. **Pharmacol Biochem Behav** 1985 Sep;23(3):355–65

Involvement of dopamine in the aversive stimulus properties of cocaine in rats. Hunt T, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):945–8

Asymmetrical effect of unilateral cortical lesions and amphetamine on DRL-20: a time-loss analysis. Kubos KL, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):1001–6

Norepinephrine-facilitated eating: reduction in saccharin preference and conditioned flavor preferences with increase in quinine aversion. Matthews JW, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):1045–52

Rate-dependency and hyperactivity: methylphenidate effects on operant responding. Rapport MD, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):77–83

Opposing acute and chronic behavioural effects of a beta-blocker, propranolol, in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1985;86(4):480–6

[Development of passivity in the rat: effect of tranquilizers and antidepressants] Khonicheva NM, et al. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):339–47 (Eng. Abstr.) **(Rus)**

[Functional differentiation of the theta-rhythm of the hippocampus in the cat] Melikov EM. **Zh Vyssh Nerv Deiat** 1985 May–Jun; 35(3):457–64 (Eng. Abstr.) **(Rus)**

CONFLICT (PSYCHOLOGY)

Mechanisms of the initial treatment phenomenon to diazepam in the rat. Mokler DJ, et al. **Psychopharmacology (Berlin)** 1985;87(2):242–6

[Effect of the antioxidant dibunol and its combination with phenazepam on the behavior of rats in a conflict situation] Molodavkin GM, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):36–8 (Eng. Abstr.) **(Rus)**

CORTICOSTERONE

Monoamines and the effect of ethanol on corticosterone and non-esterified fatty acids. Brick J, et al. **Alcohol** 1985 Mar-Apr;2(2):261-5

Effect of exogenous ACTH on serum corticosterone and cortisol concentrations in the Moluccan cockatoo (Cacatua moluccensis). Walsh MT, et al. **Am J Vet Res** 1985 Jul;46(7):1584-8

Down-regulation of neural corticosterone receptors by corticosterone and dexamethasone. Sapolsky RM, et al. **Brain Res** 1985 Jul 22; 339(1):161-5

Sexual dimorphism of glucocorticoid binding in rat brain. Turner BB, et al. **Brain Res** 1985 Sep 16;343(1):16-23

Increased serum corticosterone levels in triorthotolyl phosphate-treated chickens. Foil L, et al. **Bull Environ Contam Toxicol** 1985 Jun; 34(6):780-6

The effect of chronic saline exposure on the electrolyte balance, nitrogen metabolism, and corticosterone titer in the American alligator, Alligator mississippiensis. Laurén DJ. **Comp Biochem Physiol** [A] 1985; 81(2):217-23

Plasma concentrations of arginine vasotocin, prolactin, aldosterone and corticosterone in relation to oviposition and dietary NaCl in the domestic fowl. Rice GE, et al. **Comp Biochem Physiol** [A] 1985; 81(4):769-77

Effect of hypophysectomy on plasma electrolytes and adrenal mineralocorticoid secretion in the terrestrial chelonian Testudo hermanni. Vallarino M, et al. **Comp Biochem Physiol** [A] 1985; 81(2):283-6

Changes in plasma levels of cortisol and corticosterone after acute ACTH stimulation in rusa deer (Cervus rusa timorensis). van Mourik S, et al. **Comp Biochem Physiol** [A] 1985;81(3):545-9

Adrenergic stimulation of adrenocortical secretion in immature fowl. Rees A, et al. **Comp Biochem Physiol** [C] 1985;81(2):387-9

Properties of binding of partially purified glucocorticoid receptor from rat liver with glucocorticoids of different biopotencies. Izawa M, et al. **Endocrinol Jpn** 1985 Jun;32(3):385-97

Protein utilization in growth: effect of lysine deficiency on serum growth hormone, somatomedins, insulin, total thyroxine (T4) and triiodothyronine, free T4 index, and total corticosterone. Cree TC, et al. **Endocrinology** 1985 Aug;117(2):667-73

The central vs. peripheral effects of clonidine on ACTH, corticosterone and glucose release. Smythe GA, et al. **Eur J Pharmacol** 1985 May 20;111(3):401-3

The lack of effect of electrochemical stimulation of the hypothalamus and median eminence on the plasma corticosterone level after lesion of the paraventricular nuclei. Lengvári I, et al. **Exp Clin Endocrinol** 1985 Jun;85(3):314-8

Adrenocortical hormones and brain growth: reversibility and differential sensitivity during development. Devenport LD, et al. **Exp Neurol** 1985 Oct;90(1):44-52

Adrenocortical metabolism and plasma corticosterone in soman intoxicated rabbits. Doebler JA, et al. **Experientia** 1985 Sep 15; 41(9):1145-7

Effects of continuous treatment with synthetic ACTH1-24 or corticosterone on immature Gallus domesticus. Davison TF, et al. **Gen Comp Endocrinol** 1985 Sep;59(3):416-23

Factors affecting the secretory dynamics of 1 alpha-hydroxycorticosterone in the dogfish, Scyliorhinus canicula. Hazon N, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):50-5

Corticosterone and aldosterone dose-dependent responses to ACTH and angiotensin II in the duck (Anas platyrnynchos). Klingbeil CK. **Gen Comp Endocrinol** 1985 Sep;59(3):382-90

Transitory corticosterone responses of ducks (Anas platyrhynchos) to exercise. Rees A, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):100-4

Effects of corticosterone and 5 alpha-dihydrocorticosterone on brain excitability in the rat. Dubrovsky B, et al. **J Neurosci Res** 1985; 14(1):117-28

Effect of calcium on corticosteroid secretion by isolated frog interrenal gland. Lihrmann I, et al. **J Steroid Biochem** 1985 Aug;23(2):169-75

Effect of somatostatin on the zona glomerulosa of rats treated with angiotensin II or captopril: stereology and plasma hormone concentrations. Mazzocchi G, et al. **J Steroid Biochem** 1985 Sep; 23(3):353-6

Plasma cortisol and corticosterone concentrations in the golden hamster, (Mesocricetus auratus). Ottenweller JE, et al. **Life Sci** 1985 Oct 21; 37(16):1551-8

Delta-sleep-inducing peptide reduces CRF-induced corticosterone release. Graf MV, et al. **Neuroendocrinology** 1985 Oct;41(4):353-6

Simultaneous determination of blood levels of corticosterone and growth hormone in the male rat: relation to sleep-wakefulness cycle. Mitsugi N, et al. **Neuroendocrinology** 1985 Aug;41(2):125-30

Pharmacological studies on the serotoninergic and nonserotonin-mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pretreatment with fluoxetine, indalpine, PCPA, and L-tryptophan. Van de Kar LD, et al. **Neuroendocrinology** 1985 Oct; 41(4):283-8

Modifications of adrenocortical responses following frontal cortex simulation in rats with hypothalamic deafferentations and medial forebrain bundle lesions. Feldman S, et al. **Neuroscience** 1985 Aug; 15(4):1045-7

Extraction of corticosterone from cell homogenates and subcellular fractions of the rat adrenal cortex. II. ACTH-induced changes in subcellular corticosterone. Mathew JK, et al. **Steroids** 1984 Aug; 44(2):105-22

[Effects of different acute and chronic stresses on general growth and adrenal cortex activity in rats] el Feki A, et al. **Ann Endocrinol (Paris)** 1985;46(2):107-12 (Eng. Abstr.) **(Fre)**

[The effect of bradykinin on free nitrogen compounds and energy production in the rat brain] Hashimoto Y, et al. **Shikwa Gakuho** 1985 Mar;85(3):371-9 (Eng. Abstr.) **(Jpn)**

[ACTH, corticosterone and beta-endorphin in the blood plasma of rats under prolonged immobilization stress] Kiiatkin EA, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):157-60 (Eng. Abstr.) **(Rus)**

[Receptor binding of corticosterone in various structures of the rat brain after neonatal blockade of the hypophyseal-adrenal system] Garina IA, et al. **Probl Endokrinol (Mosk)** 1985 Jul-Aug;31(4):46-9 (Eng. Abstr.) **(Rus)**

[Plasma lipoprotein absorption by steroid-producing organs in the rat] Poliakov LM, et al. **Probl Endokrinol (Mosk)** 1985 Jul-Aug; 31(4):72-5 (Eng. Abstr.) **(Rus)**

CORTICOTROPIN

Cell types of the pars distalis of the hedgehog (Erinaceus europaeus L.) adenohypophysis: cytological, immunocytochemical and ultrastructural studies. 3. Opiocorticomelanotropic cells. Girod C, et al. **Acta Anat (Basel)** 1985;123(1):67-71

Propranolol inhibits the maturational effect of adrenocorticotropin in the fetal sheep lung. Vilos GA, et al. **Am J Obstet Gynecol** 1985 Oct 15; 153(4):472-7

Diurnal-stimulated and stress-induced ACTH release in rats is mediated by ventral noradrenergic bundle. Szafarczyk A, et al. **Am J Physiol** 1985 Aug;249(2 Pt 1):E219-26

Effect of exogenous ACTH on serum corticosterone and cortisol concentrations in the Moluccan cockatoo (Cacatua moluccensis). Walsh MT, et al. **Am J Vet Res** 1985 Jul;46(7):1584-8

Proopiomelanocortin-derived peptides in the immune system. Blalock JE. **Clin Endocrinol** (Oxf) 1985 Jun;22(6):823-7 (15 ref.)

Augmentation of the response to CRF in man: relative contributions of endogenous angiotensin and vasopressin. Milsom SR, et al. **Clin Endocrinol (Oxf)** 1985 May;22(5):623-9

Changes in plasma levels of cortisol and corticosterone after acute ACTH stimulation in rusa deer (Cervus rusa timorensis). van Mourik S, et al. **Comp Biochem Physiol** [A] 1985;81(3):545-9

Corticotrope response to removal of releasing factors and corticosteroids in vivo. Dallman MF, et al. **Endocrinology** 1985 Nov;117(5):2190-7

The effect of various corticotropin-releasing factor trains on the release of adrenocorticotropin, beta-endorphin, and beta-lipotropin from perifused ovine pituitary cells. Evans MJ, et al. **Endocrinology** 1985 Sep;117(3):893-9

Direct effects of adrenocorticotropic hormone on bovine adrenomedullary cells: adenosine 3',5'-monophosphate-dependent phosphorylation of tyrosine hydroxylase. Michener ML, et al. **Endocrinology** 1985 Aug; 117(2):730-7

The effects of growth hormone, prolactin, corticotropin, and thyrotropin on the production and secretion of somatostatin by hypothalamic cells in vitro. Robbins RJ, et al. **Endocrinology** 1985 Aug;117(2):538-43

The central vs. peripheral effects of clonidine on ACTH, corticosterone and glucose release. Smythe GA, et al. **Eur J Pharmacol** 1985 May 20;111(3):401-3

beta-Endorphin and ACTH related peptides in primary cultures of rat anterior pituitary cells: evidence for different intracellular pools. Ham J, et al. **FEBS Lett** 1985 Oct 14;190(2):253-8

Effects of continuous treatment with synthetic ACTH1-24 or corticosterone on immature Gallus domesticus. Davison TF, et al. **Gen Comp Endocrinol** 1985 Sep;59(3):416-23

Corticosterone and aldosterone dose-dependent responses to ACTH and angiotensin II in the duck (Anas platyrhynchos). Klingbeil CK. **Gen Comp Endocrinol** 1985 Sep;59(3):382-90

Thyroid function in adult rough-skinned newts (Taricha granulosa): effects of hypophysectomy and hormone replacement. Specker JL, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):326-31

Investigation of beta-endorphin and adrenocorticotropic hormone in placenta, amniotic membrane and umbilical cord using an immunoperoxidase technique. Reinthaller A, et al. **Gynecol Obstet Invest** 1985;19(3):135-8

Plasma ACTH, cortisol and aldosterone concentrations in chronically cannulated ovine fetuses and in lambs injected with ovine corticotropin releasing factor. Pradier P, et al. **J Dev Physiol** 1985 Aug; 7(4):259-68

Salmonid melanin-concentrating hormone inhibits corticotrophin release. Baker BI, et al. **J Endocrinol** 1985 Aug;106(2):R5-8

Effect of imipramine and adrenocorticotropin administration on the rat brain norepinephrine-coupled cyclic nucleotide generating system:

alterations in alpha and beta adrenergic components. Duman RS, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):409–14

Calmodulin inhibitors decrease the CRF–and AVP–induced ACTH release in vitro: interaction of calcium–calmodulin and the cyclic AMP system. Murakami K, et al. **Neuroendocrinology** 1985 Jul;41(1):7–12

Early visual information processing in depressive patients treated with ORG 2766 (an ACTH 4–9 analogue). d'Elia G, et al. **Neuropsychobiology** 1985;13(1–2):63–8

Regulation of adrenocorticotropin release from the anterior pituitary. Reisine T. **Psychopharmacol Bull** 1985;21(3):438–42

Extraction of corticosterone from cell homogenates and subcellular fractions of the rat adrenal cortex. II. ACTH–induced changes in subcellular corticosterone. Mathew JK, et al. **Steroids** 1984 Aug; 44(2):105–22

[ACTH, corticosterone and beta–endorphin in the blood plasma of rats under prolonged immobilization stress] Kiiatkin EA, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):157–60 (Eng. Abstr.) **(Rus)**

[Effect of ACTH on the corticosteroid and progesterone levels in female hamadryas baboons in relation to the menstrual cycle phase] Todua TN, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):135–7 (Eng. Abstr.) **(Rus)**

CORTICOTROPIN RELEASING HORMONE

The distribution of immunoreactive corticotrophin–releasing factor in the human pituitary stalk. Coates PJ. **Acta Endocrinol (Copenh)** 1985 Aug; 109(4):433–9

Stability of rat (human) corticotropin–releasing factor in serum, urine and tissue incubation medium. Hashimoto K, et al. **Acta Med Okayama** 1985 Jun;39(3):199–206

Cholecystokinin in the medial parvocellular subdivision of the paraventricular nucleus. Co–existence with corticotropin–releasing hormone. Mezey E, et al. **Ann NY Acad Sci** 1985;448:152–6

CRF–containing neurons of the rat hypothalamus. Daikoku S, et al. **Cell Tissue Res** 1985;240(3):575–84

Augmentation of the response to CRF in man: relative contributions of endogenous angiotensin and vasopressin. Milsom SR, et al. **Clin Endocrinol (Oxf)** 1985 May;22(5):623–9

Conspectus. Corticotropin–releasing factor. DeSouza EB. **Compr Ther** 1985 Jun;11(6):3–5

Corticotropin–releasing factor: its action on the islets of Langerhans. Moltz JH, et al. **Endocr Res** 1985;11(1–2):87–93

Corticotrope response to removal of releasing factors and corticosteroids in vivo. Dallman MF, et al. **Endocrinology** 1985 Nov;117(5):2190–7

The effect of various corticotropin–releasing factor trains on the release of adrenocorticotropin, beta–endorphin, and beta–lipotropin from perifused ovine pituitary cells. Evans MJ, et al. **Endocrinology** 1985 Sep;117(3):893–9

Effects of adrenalectomy and dexamethasone administration on the level of prepro–corticotropin–releasing factor messenger ribonucleic acid (mRNA) in the hypothalamus and adrenocorticotropin/beta–lipotropin precursor mRNA in the pituitary in rats. Jingami H, et al. **Endocrinology** 1985 Oct;117(4):1314–20

Evidence for local corticotropin releasing factor (CRF)–immunoreactive neuronal circuits in the paraventricular nucleus of the rat hypothalamus. An electron microscopic immunohistochemical analysis. Liposits Z, et al. **Histochemistry** 1985;83(1):5–16 (59 ref.)

Plasma ACTH, cortisol and aldosterone concentrations in chronically cannulated ovine fetuses and in lambs injected with ovine corticotropin releasing factor. Pradier P, et al. **J Dev Physiol** 1985 Aug; 7(4):259–68

Gastrointestinal secretory, motor and circulatory effects of corticotropin releasing factor (CRF). Konturek SJ, et al. **Life Sci** 1985 Sep 30; 37(13):1231–40

In vitro study of immunoreactive corticotropin–releasing factor release from the rat hypothalamus. Suda T, et al. **Life Sci** 1985 Oct 21; 37(16):1499–505

Co–localization of corticotropin–releasing factor and vasopressin in median eminence neurosecretory vesicles. Whitnall MH, et al. **Nature** 1985 Sep 19–25;317(6034):248–50

Delta–sleep–inducing peptide reduces CRF–induced corticosterone release. Graf MV, et al. **Neuroendocrinology** 1985 Oct;41(4):353–6

Calmodulin inhibitors decrease the CRF–and AVP–induced ACTH release in vitro: interaction of calcium–calmodulin and the cyclic AMP system. Murakami K, et al. **Neuroendocrinology** 1985 Jul;41(1):7–12

Effects of intracerebroventricular administration of ovine corticotropin–releasing factor (CRF 1–41) on passive avoidance behaviour: lack of influence on monoamine contents of limbic brain areas. Fekete M, et al. **Neuropeptides** 1985 Jul;6(4):283–292

Corticotropin releasing factor–like immunoreactivity in sensory ganglia and capsaicin sensitive neurons of the rat central nervous system: colocalization with other neuropeptides. Skofitsch G, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):307–18

Distribution of corticotropin releasing factor–like immunoreactivity in the rat brain by immunohistochemistry and radioimmunoassay: comparison and characterization of ovine and rat/human CRF antisera. Skofitsch G, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):319–36

CULTURE

Cultural phenomenology and residency training revisited: a personal account. Zimmer B. **Int J Soc Psychiatry** 1985 Autumn;31(3):188–93

DANSYL COMPOUNDS

Internalization of cycloheptaamylose–dansyl chloride complex during labelling of surface membrane in living Paramecium aurelia cells. Giordano PA, et al. **Basic Appl Histochem** 1985;29(2):121–33

Introduction of the dansyl group into histidine and tyrosine residues in peptides and proteins. Buchta R, et al. **Biochem Biophys Res Commun** 1985 Jul 16;130(1):350–7

Cellular uptake and localization of fluorescent derivatives of phorbol ester tumor promoters. Liskamp RM, et al. **Biochem Biophys Res Commun** 1985 Sep 16;131(2):920–7

Lactose repressor protein modified with dansyl chloride: activity effects and fluorescence properties. Hsieh WT, et al. **Biochemistry** 1985 Jun 4;24(12):3043–9

DELUSIONS

A 'gratuitous' conclusion on ECT [letter] Fink M. **Am J Psychiatry** 1985 Sep;142(9):1129–30

Nortriptyline in the treatment of a monosymptomatic delusion [letter] Pylko T, et al. **Am J Psychiatry** 1985 Oct;142(10):1223

Dysmorphophobia and monosymptomatic hypochondriasis [letter] Thomas CS. **Am J Psychiatry** 1985 Sep;142(9):1121

Higher CSF levels of HVA and 5–HIAA in delusional compared to nondelusional depression [letter] Aberg–Wistedt A, et al. **Arch Gen Psychiatry** 1985 Sep;42(9):925–6

DEMENTIA

Involutional dementias: new perspectives. Borromei A, et al. **Ital J Neurol Sci** 1985 Jun;6(2):167–71

DEPRESSION

Separate and combined anxiolytic and anti–depressant treatment of mixed anxiety/depression. A double–blind, placebo controlled comparison. Sussex Clinical Trials Group. **Acta Psychiatr Scand** 1985 Jul; 72(1):81–8

A double–blind group comparison of mianserin and clomipramine in the treatment of mildly depressed psychiatric out–patients. Dunbar GC, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:60–6

The present status of monoamine oxidase inhibitors. Pare CM. **Br J Psychiatry** 1985 Jun;146:576–84 (88 ref.)

A monoamine oxidase inhibitor reverses the 'separation syndrome' in a new hamster separation model of depression. Crawley JN. **Eur J Pharmacol** 1985 May 28;112(1):129–33

Electro–acupuncture vs. amitriptyline in the treatment of depressive states. Luo HC, et al. **J Tradit Chin Med** 1985 Mar;5(1):3–8

[Questionnaires for anxiety and depression] Harlay A. **Infirm Fr** 1985 Apr; (264):15–22 **(Fre)**

[Clinical experiences with the new–generation anxiolytic agent cloxazolam—a double–blind study] Zmorski T, et al. **Schweiz Rundsch Med Prax** 1985 Jul 2;74(27):728–34 (Eng. Abstr.) **(Ger)**

DEPRESSIVE DISORDER

Long–term lithium prophylaxis in recurrent unipolar depression. A controversial indication? Lepkifker E, et al. **Acta Psychiatr Belg** 1985 May–Jun;85(3):434–43

Citalopram versus mianserin. A controlled, double–blind trial in depressed patients. de Wilde J, et al. **Acta Psychiatr Scand** 1985 Jul; 72(1):89–96

Double–blind comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressed outpatients. Clinical aspects. Nyström C, et al. **Acta Psychiatr Scand** 1985 Jul;72(1):6–15

Relationship of free nortriptyline levels to therapeutic response. Perry PJ, et al. **Acta Psychiatr Scand** 1985 Aug;72(2):120–5

New implications of antidepressant therapy in neuropsychopharmacology: focus on mianserin. 14th Congress of the Collegium Internationale Neuro–Psychopharmacologicum. Florence, Italy, 19–23 June 1984. **Acta Psychiatr Scand [Suppl]** 1985;320:1–105

Interaction of biologic and psychologic factors in the origin of depressive disorders. Akiskal HS. **Acta Psychiatr Scand [Suppl]** 1985;319:131–9

Treatment of childhood and adolescent depression with mianserin. Dugas M, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:48–53

Depression and anxiety: mianserin and nomifensine compared in a double–blind multicentre trial. Granier F, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:67–74

Mianserin is better tolerated and more effective in depression than a nomifensine–clobazam combination: a double–blind study. Levin A, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:75–80

Changes in sleep EEG architecture during the treatment of depressed patients with mianserin. Mendlewicz J, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:26-9

Profiles of antidepressant activity with the Montgomery-Asberg Depression Rating Scale. Montgomery SA, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:38-42

Approach to chronic and treatment-resistant depressions. Akiskal HS. **Adv Biochem Psychopharmacol** 1985;40:159-63

Maintenance treatment of recurrent unipolar depression: pharmacology and psychotherapy. Frank E, et al. **Adv Biochem Psychopharmacol** 1985; 40:139-51

Research overview of drug therapy in recurrent and chronic depression. Prien RF. **Adv Biochem Psychopharmacol** 1985;40:121-30

Practical problems of lithium maintenance treatment. Schou M. **Adv Biochem Psychopharmacol** 1985;40:131-8

Recognition of pseudodementia. McAllister TW. **Am Fam Physician** 1985 Oct;32(4):175-81

A 'gratuitous' conclusion on ECT [letter] Fink M. **Am J Psychiatry** 1985 Sep;142(9):1129-30

Serial ECG measurements at controlled plasma levels of nortriptyline in depressed children. Geller B, et al. **Am J Psychiatry** 1985 Sep; 142(9):1095-7

A lithium-tricyclic combination for treatment of depression [letter] Pande AD, et al. **Am J Psychiatry** 1985 Oct;142(10):1228-9

Subjective memory complaints in geriatric depression. Plotkin DA, et al. **Am J Psychiatry** 1985 Sep;142(9):1103-5

Overview: toward a dysregulation hypothesis of depression. Siever LJ, et al. **Am J Psychiatry** 1985 Sep;142(9):1017-31 (134 ref.)

Higher CSF levels of HVA and 5-HIAA in delusional compared to nondelusional depression [letter] Aberg-Wistedt A, et al. **Arch Gen Psychiatry** 1985 Sep;42(9):925-6

Alprazolam as an antidepressant [letter] Empson P. **Aust NZ J Psychiatry** 1985 Jun;19(2):197

CSF substance P immunoreactivity in affective disorders. Berrettini WH, et al. **Biol Psychiatry** 1985 Sep;20(9):965-70

Rapid antidepressant activity of destyr gamma endorphin: correlation with urinary melatonin. Chazot G, et al. **Biol Psychiatry** 1985 Sep; 20(9):1026-30

MHPG, ECT, and depression [letter] McDougle CJ, et al. **Biol Psychiatry** 1985 Aug;20(8):927

A comparison of the acute effects of dextroamphetamine and fenfluramine in depression. Ward NG, et al. **Biol Psychiatry** 1985 Oct; 20(10):1090-7

Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients--relationship to the debrisoquine hydroxylation metabolic ratio. Nordin C, et al. **Br J Clin Pharmacol** 1985 Jun; 19(6):832-5

An evaluation of alprazolam in the treatment of reactive or neurotic (secondary) depression. Imlah NW. **Br J Psychiatry** 1985 May; 146:515-9

The present status of monoamine oxidase inhibitors. Pare CM. **Br J Psychiatry** 1985 Jun;146:576-84 (88 ref.)

Depression in general practice: case thresholds and diagnosis. Sireling LI, et al. **Br J Psychiatry** 1985 Aug;147:113-9

Depression in general practice: clinical features and comparison with out-patients. Sireling LI, et al. **Br J Psychiatry** 1985 Aug; 147:119-26

Decision making in the treatment of depression by family medicine physicians. Zung WW, et al. **Compr Ther** 1985 Jul;11(7):19-23

Guidelines for the pharmacological management of depression. Creelman W, et al. **Conn Med** 1985 Sep;49(9):565-9

Severe depression treatment: experience using maprotiline (Ludiomil) in combination with clomipramine (Anafranil). Ovuga E. **East Afr Med J** 1985 Feb;62(2):79-81

Heterogeneity of major affective disorders. Biological and clinical evidence. Vita A, et al. **Encephale** 1985 Mar-Apr;11(2):71-7

Relationship between clinical effects, serum drug concentration and serotonin uptake inhibition in depressed patients treated with citalopram. A double-blind comparison of three dose levels. Bjerkenstedt L, et al. **Eur J Clin Pharmacol** 1985;28(5):553-7

Simultaneous measurement of various antidepressants in the plasma of depressed patients by high performance liquid chromatography. Yufu N, et al. **Folia Psychiatr Neurol Jpn** 1984;38(1):57-64

Long-term amitriptyline in chronic depression. Giller E Jr, et al. **Hillside J Clin Psychiatry** 1985;7(1):16-33

Neurochemical aspects of depression: the past and the future? Jesberger JA, et al. **Int J Neurosci** 1985 Jul;27(1-2):19-47 (240 ref.)

Tricyclic antidepressive treatment reinforced by reserpine. Moscovich D, et al. **Isr J Psychiatry Relat Sci** 1984;21(4):283-9

Spontaneous afternoon plasma cortisol in depression. Christensen P, et al. **J Affective Disord** 1985 May-Jun;8(3):271-8

Cerebrospinal fluid levels of amitriptyline, nortriptyline, imipramine and desmethylimipramine. Relationship to plasma levels and treatment outcome. Hanin I, et al. **J Affective Disord** 1985 Jul;9(1):69-78

The clinical interview for depression. Development, reliability and validity. Paykel ES. **J Affective Disord** 1985 Jul;9(1):85-96

A video analysis of the non-verbal behaviour of depressed patients before and after treatment. Ulrich G, et al. **J Affective Disord** 1985 Jul; 9(1):63-7

A proposed clinical approach to chronic and 'resistant' depressions: evaluation and treatment. Akiskal HS. **J Clin Psychiatry** 1985 Oct; 46(10 Pt 2):32-7

Patterns of attrition for psychosocial and pharmacologic treatments of depression. Last CG, et al. **J Clin Psychiatry** 1985 Sep;46(9):361-6

Tricyclic-resistant depression: treatment resistance or inadequate treatment? Lydiard RB. **J Clin Psychiatry** 1985 Oct;46(10):412-7 (93 ref.)

Nortriptyline pharmacokinetics and plasma levels: implications for clinical practice. Rubin EH, et al. **J Clin Psychiatry** 1985 Oct;46(10):418-24 (56 ref.)

Depression and serotonin metabolism: rationale for neurotransmitter precursor treatment. Byerley WF, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):191-206 (188 ref.)

Serial monitoring and achievement of steady state nortriptyline plasma levels in depressed children and adolescents: preliminary data. Geller B, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):213-6

Desipramine plasma levels and response in elderly melancholic patients. Nelson JC, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):217-20

Successful treatment of psychotic depression with carbamazepine. Schaffer CB, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):233-5

Effect of L-tryptophan on electroconvulsive therapy seizure time. Price WA, et al. **J Nerv Ment Dis** 1985 Oct;173(10):636-8

Early visual information processing in depressive patients treated with ORG 2766 (an ACTH 4-9 analogue). d'Elia G, et al. **Neuropsychobiology** 1985;13(1-2):63-8

Periodic sleep deprivation in drug-refractory depression. Dessauer M, et al. **Neuropsychobiology** 1985;13(3):111-6

Effect of bilateral olfactory bulbectomy in the rat, alone or in combination with antidepressants, on the learned immobility model of depression. Górka Z, et al. **Neuropsychobiology** 1985;13(1-2):26-30

Biochemical and diagnostic classification and serum drug levels: relation to antidepressive effect of imipramine. Møller SE, et al. **Neuropsychobiology** 1985;13(4):160-6

Antidepressant treatment of children: clinical relapse is unrelated to tricyclic plasma concentrations. Olig RM, et al. **Percept Mot Skills** 1985 Jun;60(3):879-89

Factors associated with response to lithium prophylaxis in DSM III major depression and bipolar disorder. Maj M, et al. **Pharmacopsychiatry** 1985 Sep;18(5):309-13

Oxaprotiline in the treatment of endogenous depressed inpatients an early clinical trial. Schmauss M, et al. **Pharmacopsychiatry** 1985 Jul; 18(4):282-5

Neurochemical and cognitive aspects of depression. Kidman A. **Prog Neurobiol** 1985;24(3):187-97

A controlled study of cellular immune function in affective disorders before and during somatic therapy. Albrecht J, et al. **Psychiatry Res** 1985 Jul;15(3):185-93

The GABA hypothesis of depression and antidepressant drug action. Bartholini G, et al. **Psychopharmacol Bull** 1985;21(3):385-8

Nocturnal serum melatonin in major depressive disorder before and after desmethylimipramine treatment. Brown RP, et al. **Psychopharmacol Bull** 1985;21(3):579-81

Melancholia in rodents: neurobiology and pharmacology. Henn FA, et al. **Psychopharmacol Bull** 1985;21(3):443-6

Imipramine for treatment of chronic depression. Kocsis JH, et al. **Psychopharmacol Bull** 1985;21(3):698-700

Effect of panic attacks on the treatment of atypical depressives. Liebowitz MR, et al. **Psychopharmacol Bull** 1985;21(3):558-61

Panic attacks in outpatients with depression: response to antidepressant treatment. Robinson DS, et al. **Psychopharmacol Bull** 1985; 21(3):562-7

Delayed biochemical changes following antidepressant treatment. Sugrue MF. **Psychopharmacol Bull** 1985;21(3):619-22

Addition of estrogen to imipramine in female-resistant depressives. Zohar J, et al. **Psychopharmacol Bull** 1985;21(3):705-6

Cardiovascular effects of amitriptyline in the treatment of elderly depressed patients. Christensen P, et al. **Psychopharmacology (Berlin)** 1985;87(2):212-5

Cianopramine and amitriptyline in the treatment of depressed patients--a placebo-controlled study. Hormazabal L, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):205-8

Informed consent in psychiatric research: preliminary findings from an ongoing investigation. Benson PR, et al. **Soc Sci Med** 1985; 20(12):1331-41

[Clinical experience with bromazepam in endogenous depression] Náhunek K, et al. **Cesk Psychiatr** 1985 Aug;81(4):235-41 (Eng. Abstr.) **(Cze)**

[Treatment of masked depressions using bromazepam] Vencovský E, et al. **Cesk Psychiatr** 1985 Apr;81(2):75-8 (Eng. Abstr.) **(Cze)**

[Are monoamine oxidase inhibitors coming back?] Nolen WA. **Ned Tijdschr Geneeskd** 1985 Aug 17;129(33):1571-6 **(Dut)**

[Measurement of basal plasma levels of 3 anterior pituitary hormones

during acute or chronic treatment with tricyclic antidepressants] Goyot C, et al. **Encephale** 1985 Mar-Apr;11(2):45-51 (Eng. Abstr.) **(Fre)**

[Action of clovoxamine on the sleep of depressed patients. 'Polygraphic recordings'] Minot R, et al. **Encephale** 1985 Mar-Apr;11(2):65-70 (Eng. Abstr.) **(Fre)**

[Study of the metabolism of cerebral noradrenaline in depressed patients by the assay of plasma dihydroxyphenylethylene glycol] Loo H, et al. **Presse Med** 1985 Jun 22;14(25):1363-6 (Eng. Abstr.) **(Fre)**

[Therapy of depressive and manic diseases] Seige D. **Psychiatr Neurol Med Psychol Beih** 1966;4-5:186-92 **(Ger)**

[Treatment of anxious-depressive syndromes with Mianserin hydrochloride. Statistical evaluation of the data by Student's 't test'] Spinetti G, et al. **Minerva Psichiatr** 1985 Jan-Mar;26(1):79-86 (Eng. Abstr.) **(Ita)**

[Vascular activator of fibrinolysis in patients treated with antidepressive drugs] Olajossy M, et al. **Psychiatr Pol** 1984 Nov-Dec;18(6):543-8 (Eng. Abstr.) **(Pol)**

[Modern approach to the therapy of depression] Borišev I. **Med Pregl** 1985;38(3-4):193-5 (Eng. Abstr.) **(Ser)**

[Correlation between clinical and laboratory data in depression. Therapeutic orientation by means of vitamins and amino acids] Mesones HL, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):25-36 (Eng. Abstr.) **(Spa)**

DESIPRAMINE

Monoamine uptake inhibitors attenuate ethanol intake in alcohol-preferring (P) rats. Murphy JM, et al. **Alcohol** 1985 Mar-Apr; 2(2):349-52

Plasma melatonin during desmethylimipramine treatment: evidence for changes in noradrenergic transmission. Cowen PJ, et al. **Br J Clin Pharmacol** 1985 Jun;19(6):799-805

Involvement of amygdaloid catecholaminergic mechanism in suppressive effects of desipramine and imipramine on duration of immobility in rats forced to swim. Araki H, et al. **Eur J Pharmacol** 1985 Jul 31; 113(3):313-8

Cerebrospinal fluid levels of amitriptyline, nortriptyline, imipramine and desmethylimipramine. Relationship to plasma levels and treatment outcome. Hanin I, et al. **J Affective Disord** 1985 Jul;9(1):69-78

Desipramine plasma levels and response in elderly melancholic patients. Nelson JC, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):217-20

The hypothalamic and neurohypophysial oxytocin content as influenced by desmethylimipramine in normal and pinealectomized white male rats. Guzek JW, et al. **J Neural Transm** 1985;62(1-2):125-36

Behavioral responses of high and low active male rats to the chronic ingestion of desipramine. Echandia EL, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):917-20

Nocturnal serum melatonin in major depressive disorder before and after desmethylimipramine treatment. Brown RP, et al. **Psychopharmacol Bull** 1985;21(3):579-81

Desmethylimipramine overdose: nonlinear kinetics in a slow hydroxylator. Spina E, et al. **Ther Drug Monit** 1985;7(2):239-41

DESOXYCORTICOSTERONE

Renal interstitial pressure in mineralocorticoid escape. Burnett JC Jr, et al. **Am J Physiol** 1985 Sep;249(3 Pt 2):F396-9

Deoxycorticosterone-stimulated bicarbonate secretion in rabbit cortical collecting ducts: effects of luminal chloride removal and in vivo acid loading. Garcia-Austt J, et al. **Am J Physiol** 1985 Aug; 249(2 Pt 2):F205-12

Adrenocortical hormones and brain growth: reversibility and differential sensitivity during development. Devenport LD, et al. **Exp Neurol** 1985 Oct;90(1):44-52

Control of sodium and potassium transport in the cortical collecting duct of the rat. Effects of bradykinin, vasopressin, and deoxycorticosterone. Tomita K, et al. **J Clin Invest** 1985 Jul;76(1):132-6

Hydrolysis of deoxycorticosterone-21-yl sulphate and dehydroepiandrosterone sulphate by microsomal preparations of human placentae: evidence for a common enzyme. Egyed J, et al. **J Endocrinol** 1985 Sep;106(3):295-301

Effects of corticosterone and 5 alpha-dihydrocorticosterone on brain excitability in the rat. Dubrovsky B, et al. **J Neurosci Res** 1985; 14(1):117-28

The dependence of the salt appetite of the rat on the hormonal consequences of sodium deficiency. Epstein AN. **J Physiol (Paris)** 1984; 79(6):496-8

DEXTROAMPHETAMINE

A comparison of the acute effects of dextroamphetamine and fenfluramine in depression. Ward NG, et al. **Biol Psychiatry** 1985 Oct; 20(10):1090-7

Biochemical and behavioral changes in rats during and after chronic d-amphetamine exposure. Vogel WH, et al. **Drug Alcohol Depend** 1985 Jun;15(3):245-53

Antagonism of the amphetamine cue by both classical and atypical antipsychotic drugs. Nielsen EB, et al. **Eur J Pharmacol** 1985 May 8; 111(2):167-76

Demonstration of reduced levels of zinc in rat brain after treatment with d-amphetamine, but not after treatment with reserpine. Szerdahelyi P, et al. **Histochemistry** 1985;83(2):181-7

Psychostimulant plasma concentration and learning performance. Kupietz SS, et al. **J Clin Psychopharmacol** 1985 Oct;5(5):293-5

Repeated treatment with imipramine or amitriptyline increases the locomotor response of rats to (+)-amphetamine given into the nucleus accumbens. Maj J, et al. **J Pharm Pharmacol** 1985 May;37(5):362-4

Cardiovascular effects of two potential beta-hydroxylase inhibitors. Venugopalan CS, et al. **J Pharm Sci** 1985 Jun;74(6):681-4

Tolerance pattern to amphetamine anorexia after selective lesions in the hypothalamic dopaminergic projection. Bhakthavatsalam P, et al. **Life Sci** 1985 Aug 19;37(7):635-43

Effects of triethyltin and its interaction with d-amphetamine and chlorpromazine on responding under a multiple schedule of food presentation in rats. Rastogi SK, et al. **Neurobehav Toxicol Teratol** 1985 May-Jun;7(3):239-42

Altered central monoamine response to D-amphetamine in rats chronically exposed to inorganic lead. Lasley SM, et al. **Neurochem Res** 1985 Jul;10(7):933-44

The effects of MIF-I, beta-endorphin and alpha-MSH on d-amphetamine induced paradoxical behavioral thermoregulation: possible involvement of the dopaminergic system. Yehuda S, et al. **Peptides (Fayetteville)** 1985 Mar-Apr;6(2):189-92

Acute and chronic behavioral interactions between phencyclidine (PCP) and amphetamine: evidence for a dopaminergic role in some PCP-induced behaviors. Greenberg BD, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):99-105

Behaviorally equivalent stressors differentially modify the monoamine altering property of d-amphetamine. Klauenberg BJ, et al. **Pharmacol Biochem Behav** 1985 Sep;23(3):417-23

The discriminative stimulus and subjective effects of d-amphetamine in humans. Chait LD, et al. **Psychopharmacology (Berlin)** 1985; 86(3):307-12

A conveyor belt task for assessing visuo-motor coordination in the marmoset (Callithrix jacchus): effects of diazepam, chlorpromazine, pentobarbital and d-amphetamine. D'Mello GD, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):125-31

Amphetamine-induced enhancement of ethanol consumption: role of central catecholamines. Levy AD, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):233-6

Comparison between locomotor activity changes produced by phencyclidine and D-amphetamine in CD-1 male mice. Stavchansky S, et al. **Res Commun Chem Pathol Pharmacol** 1985 May; 48(2):189-202

DIAZEPAM

Psychomotor effects of alprazolam and diazepam during acute and subacute treatment, and during the follow-up phase. Aranko K, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):364-72

Indications and contraindications for chronic anxiolytic treatment: is there tolerance to the anxiolytic effect? Rickels K, et al. **Adv Biochem Psychopharmacol** 1985;40:193-204

Comparative bioavailability studies on brands of diazepam tablets. Ogunbona FA, et al. **Afr J Med Med Sci** 1985 Mar-Jun; 14(1-2):21-5

Effects of single and repeated application of clonazepam and diazepam combined with cyproheptadine on apomorphine stereotypy in rats. Georgiev VP, et al. **Agressologie** 1985 Jan;26(1):57-60

No cross-tolerance between the stimulatory and depressant actions of benzodiazepines in mice. File SE, et al. **Behav Brain Res** 1985 Sep; 17(1):1-7

The genetic architecture of hyponeophagia and the action of diazepam in rats. Shephard RA, et al. **Behav Genet** 1985 May;15(3):265-86

The effect of nonsedating doses of diazepam on regional cerebral blood flow. Mathew RJ, et al. **Biol Psychiatry** 1985 Oct;20(10):1109-16

Responsiveness to oral diazepam in the elderly: relationship to total and free plasma concentrations. Swift CG, et al. **Br J Clin Pharmacol** 1985 Aug;20(2):111-8

Correlation of [3H]diazepam binding density with anxiolytic locus in the amygdaloid complex of the rat. Thomas SR, et al. **Brain Res** 1985 Sep 2;342(1):85-90

Liquid-chromatographic assay of diazepam and its major metabolites in serum, and application to pharmacokinetic study of high doses of diazepam in schizophrenics. Tada K, et al. **Clin Chem** 1985 Oct; 31(10):1712-5

A comparison of diazepam and midazolam as sedatives for minor oral surgery. Skelly AM, et al. **Eur J Anaesthesiol** 1984 Sep;1(3):253-67

Interactions between smectite, a mucus stabilizer, and acidic and basic drugs. In vitro and in vivo studies. Albengres E, et al. **Eur J Clin Pharmacol** 1985;28(5):601-5

Diazepam: kinetic profiles in various brain areas, plasma and erythrocytes after chronic administration in the rat. Hariton C, et al. **Eur J Drug Metab Pharmacokinet** 1985 Apr-Jun;10(2):105-11

Inhibition of diazepam metabolism in microsomal- and perfused liver preparations of the rat by desmethyldiazepam, N-methyloxazepam and oxazepam. Savenije-Chapel EM, et al. **Eur J Drug Metab Pharmacokinet** 1985 Jan-Mar;10(1):15-20

Liquid chromatographic determination of diazepam in tablets: collaborative study. Tsougros M. **J Assoc Off Anal Chem** 1985 May-Jun; 68(3):545-6

The pH dependence of the thermodynamics of the interaction of diazepam with human serum albumin. Janssen LH, et al. **J Biol Chem** 1985 Sep 25;260(21):11442-5

Comparison of models describing the sorption of nitroglycerin and diazepam by plastic infusion systems: diffusion and compartment models. Kowaluk EA, et al. **J Pharm Sci** 1985 Jun;74(6):625-33

Thymidine transport and metabolism in choroid plexus: effect of diazepam and thiopental. Spector R. **J Pharmacol Exp Ther** 1985 Oct; 235(1):16-9

Valproate increases diazepam impregnation selectively in CNS of the rat after subchronic administration. Hariton C, et al. **Life Sci** 1985 Oct 7;37(14):1343-9

Pharmacokinetics of diazepam after intravenous, intramuscular and oral administration to humans. Wichliński LM, et al. **Mater Med Pol** 1985 Jan-Mar;17(1):44-6

The interdiction of diazepam provision. Mason JC. **Milit Med** 1985 Jul; 150(7):376-7

Benzodiazepine-receptor mediated inhibition of isolation-induced aggression in mice. Skolnick P, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):17-20

The reinforcing properties of diazepam under several conditions in the rhesus monkey. Bergman J, et al. **Psychopharmacology (Berlin)** 1985; 86(1-2):108-13

Drug preference in normal volunteers: effects of age and time of day. de Wit H, et al. **Psychopharmacology (Berlin)** 1985;87(2):186-93

A conveyor belt task for assessing visuo-motor coordination in the marmoset (Callithrix jacchus): effects of diazepam, chlorpromazine, pentobarbital and d-amphetamine. D'Mello GD, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):125-31

Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. Ellinwood EH Jr, et al. **Psychopharmacology (Berlin)** 1985;86(4):392-9

Diazepam administration to mice prevents some of the changes in monoamine-mediated behaviour produced by repeated electroconvulsive shock treatment. Green AR, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):190-3

Effects of diazepam and triazolam on auditory and visual thresholds and reaction times in the baboon. Lukas SE, et al. **Psychopharmacology (Berlin)** 1985;87(2):167-72

Evaluation of signal detection theory on the effects of psychotropic drugs on critical flicker-fusion frequency in normal subjects. MacNab MW, et al. **Psychopharmacology (Berlin)** 1985;85(4):431-5

Mechanisms of the initial treatment phenomenon to diazepam in the rat. Mokler DJ, et al. **Psychopharmacology (Berlin)** 1985;87(2):242-6

A beta-carboline antagonizes benzodiazepine actions but does not precipitate the abstinence syndrome in cats. Ongini E, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):132-6

Effects of alprazolam and diazepam on the daytime sleepiness of non-anxious subjects. Seidel WF, et al. **Psychopharmacology (Berlin)** 1985;87(2):194-7

[Effect of diazepam on interference processes] Vinitskil IM, et al. **Farmakol Toksikol** 1985 Jul-Aug;48(4):38-41 (Eng. Abstr.) **(Rus)**

[Importance of protein binding of lorazepam in its clinical management] Aguilera Celorrio L, et al. **Rev Esp Anestesiol Reanim** 1985 May-Jun; 32(3):115-8 (Eng. Abstr.) **(Spa)**

DIBENZAZEPINES

Citalopram versus mianserin. A controlled, double-blind trial in depressed patients. de Wilde J, et al. **Acta Psychiatr Scand** 1985 Jul; 72(1):89-96

New implications of antidepressant therapy in neuropsychopharmacology: focus on mianserin. 14th Congress of the Collegium Internationale Neuro-Psychopharmacologicum. Florence, Italy, 19-23 June 1984. **Acta Psychiatr Scand [Suppl]** 1985;320:1-105

Treatment of childhood and adolescent depression with mianserin. Dugas M, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:48-53

A double-blind group comparison of mianserin and clomipramine in the treatment of mildly depressed psychiatric out-patients. Dunbar GC, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:60-6

Depression and anxiety: mianserin and nomifensine compared in a double-blind multicentre trial. Granier F, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:67-74

Mianserin is better tolerated and more effective in depression than a nomifensine-clobazam combination: a double-blind study. Levin A, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:75-80

Changes in sleep EEG architecture during the treatment of depressed patients with mianserin. Mendlewicz J, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:26-9

Profiles of antidepressant activity with the Montgomery-Asberg Depression Rating Scale. Montgomery SA, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:38-42

Adrenoreceptor interactions of the enantiomers and metabolites of mianserin: are they responsible for the antidepressant effect? Pinder RM. **Acta Psychiatr Scand [Suppl]** 1985;320:1-9 (29 ref.)

Oxidation in H2O and D2O of 6-ethyl-5H-dibenz(c,e)azepine and 1-methylnicotinamide by aldehyde oxidase from rabbit liver. Thomas HG, et al. **Arch Biochem Biophys** 1985 Sep;241(2):649-55

Trimipramine, a tricyclic antidepressant exerting atypical actions on the central noradrenergic system. Hauser K, et al. **Eur J Pharmacol** 1985 Apr 23;111(1):23-30

Cardiovascular effects of single doses of the antidepressants amitriptyline and lofepramine in healthy subjects. Stern H, et al. **Pharmacopsychiatry** 1985 Jul;18(4):272-7

Early relapse after sudden withdrawal or dose reduction of clozapine [letter] Perényi A, et al. **Psychopharmacology (Berlin)** 1985; 86(1-2):244

Carpipramine metabolism in the rat, rabbit and dog and in man after oral administration. Bieder A, et al. **Xenobiotica** 1985 May;15(5):421-35

[Clozapine and agranulocytosis] Xu SH. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Oct; 17(5):271-2 (Eng. Abstr.) **(Chi)**

[An analysis of 106 cases of schizophrenia treated with clozapine] Yang JS. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Aug; 17(4):242-4 (Eng. Abstr.) **(Chi)**

[Schizophrenically disordered time perception and its modification by neuroleptics] Heim M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Jul;37(7):410-5 (Eng. Abstr.) **(Ger)**

[Treatment of anxious-depressive syndromes with Mianserin hydrochloride. Statistical evaluation of the data by Student's 't test'] Spinetti G, et al. **Minerva Psichiatr** 1985 Jan-Mar;26(1):79-86 (Eng. Abstr.) **(Ita)**

[Effect of leponex on the ultrastructure of the brain] Uranova NA. **Zh Nevropatol Psikhiatr** 1985;85(7):1006-11 (Eng. Abstr.) **(Rus)**

DIBENZOTHIEPINS

High-performance liquid chromatographic determination of 3-hydroxymethyl-dibenzo[b,f]thiepin 5,5-dioxide and its acid metabolite in human plasma and urine. Slobodzian DK, et al. **J Chromatogr** 1985 Feb 27;338(1):253-8

Reduced head-twitch response to quipazine of rats previously treated with methiothepin: possible involvement of dopaminergic system. Dall'Olio R, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):43-8

[Clinical effectiveness of isofloxythepin--an open study] Zapletálek M, et al. **Cesk Psychiatr** 1985 Aug;81(4):242-6 (Eng. Abstr.) **(Cze)**

DIBENZOXAZEPINES

Determination of amoxapine and metabolites in plasma by liquid chromatography with electrochemical detection. Suckow RF, et al. **J Chromatogr** 1985 Feb 27;338(1):225-9

Acute renal failure secondary to non-traumatic rhabdomyolysis following amoxapine overdose. Frendin TJ, et al. **NZ Med J** 1985 Aug 28; 98(785):690-1

DISCRIMINATION (PSYCHOLOGY)

Chlordiazepoxide and successive discrimination: different effects on acquisition and performance. McNaughton N. **Pharmacol Biochem Behav** 1985 Sep;23(3):487-94

Discriminative stimulus properties and schedule effects of fencamfamine in rats. Risner ME, et al. **Pharmacol Biochem Behav** 1985 Sep; 23(3):449-56

Trends in drug discrimination research analysed with a cross-indexed bibliography, 1982-1983. Stolerman IP, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):1-11 (191 ref.)

DISCRIMINATION LEARNING

Psychopharmacological profile of cholecystokinin using the self-stimulation and the drug discrimination paradigms. De Witte P, et al. **Ann NY Acad Sci** 1985;448:470-87

The effects of chlorpromazine and imipramine on rate and stimulus control of matching to sample. Newland MC, et al. **J Exp Anal Behav** 1985 Jul;44(1):49-68

The non-sedating anxiolytic CGS 9896 produces discriminative stimuli that may be related to an anxioselective effect. Bennett DA. **Life Sci** 1985 Aug 26;37(8):703-9

Chlordiazepoxide and successive discrimination: different effects on acquisition and performance. McNaughton N. **Pharmacol Biochem Behav** 1985 Sep;23(3):487-94

The 5-HT syndrome and the drug discrimination paradigm in rats: application in behavioral studies on the central 5-HT system. Ortmann R. **Pharmacopsychiatry** 1985 Mar;18(2):198-201

The discriminative stimulus and subjective effects of d-amphetamine in humans. Chait LD, et al. **Psychopharmacology (Berlin)** 1985;

86(3):307-12

Drug discrimination training with a single choice trial per session. Tomie A, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):217-22

DOPA

Melanocyte metabolites in the urine of people of different skin colour. Wirestrand LE, et al. **Acta Derm Venereol (Stockh)** 1985;65(4):345-8

The effect of ring-fluorination on the rate of O-methylation of dihydroxyphenylalanine (DOPA) by catechol-O-methyltransferase: significance in the development of 18F-PETT scanning agents. Creveling CR, et al. **Biochem Biophys Res Commun** 1985 Aug 15; 130(3):1123-31

Regulation of galactokinase gene expression in Tetrahymena thermophila. II. Identification of 3,4-dihydroxyphenylalanine as a primary effector of adrenergic control of galactokinase expression. Ness JC, et al. **J Biol Chem** 1985 Aug 25;260(18):10013-8

Inhibition of tyrosine hydroxylation in rat striatal tissue slices by 1-methyl-4-phenylpyridinium ion. Hirata Y, et al. **Neurosci Lett** 1985 Jun 24;57(3):301-5

[Synthesis of tyrosine and 3,4-dihydroxyphenylalanine by Citrobacter freundii bacteria from lactic acid] Kupletskaia MB. **Prikl Biokhim Mikrobiol** 1985 May-Jun;21(3):342-8 (Eng. Abstr.) **(Rus)**

DOPAMINE

Influence of beta-receptor stimulation on catecholamine and phospholipid concentrations in lungs of fetal rabbits. Urban J, et al. **Acta Paediatr Hung** 1985;26(2):127-32

Effects of lesions and ganglioside GM1 treatment on striatal polyamine levels and nigral DA neurons. A role of putrescine in the neurotropic activity of gangliosides. Agnati LF, et al. **Acta Physiol Scand** 1985 Aug; 124(4):499-506

Calcium, cAMP, and dopamine affect single mammotrophs assayed by hemolytic plaques. Anderson JM, et al. **Am J Physiol** 1985 Oct; 249(4 Pt 1):E337-44

Blockade of renal effects of dopamine in the dog by the DA1 antagonist SCH 23390. Frederickson ED, et al. **Am J Physiol** 1985 Aug; 249(2 Pt 2):F236-40

Blinking frequency and dopamine availability [letter] Ostow M. **Am J Psychiatry** 1985 Aug;142(8):994

In vitro measurement of dopamine concentration with carbon fiber electrode. Akiyama A, et al. **Anal Chem** 1985 Jul;57(8):1518-22

Fast in vivo monitoring of dopamine release in the rat brain with differential pulse amperometry. Marcenac F, et al. **Anal Chem** 1985 Jul; 57(8):1778-9

Flow injection amperometric determination of ascorbic acid and dopamine at a sessile mercury drop electrode without deoxygenation. Fogg AG, et al. **Analyst** 1985 Apr;110(4):341-3

The influence of verapamil on dopamine's ability to augment cardiac output. Sturm JT. **Ann Emerg Med** 1985 Oct;14(10):945-7

Cholecystokinin potentiation of dopamine-mediated behaviors in the nucleus accumbens. Crawley JN. **Ann NY Acad Sci** 1985;448:283-92

Interactions of cholecystokinin and dopamine in the nucleus accumbens. Wang RY, et al. **Ann NY Acad Sci** 1985;448:352-60

The effect of dopamine, apomorphine and piribedil on the mesenterial blood flow of the cat. György L, et al. **Arch Int Pharmacodyn Ther** 1985 May;275(1):22-32

Change of catecholamine turnover in ovary during the rat estrous cycle. Nagahara Y, et al. **Asia Oceania J Obstet Gynaecol** 1985 Jun; 11(2):261-4

Differential effects of intrafrontocortical microinjections of dopamine agonists and antagonists on circling behavior of rats. Stewart RJ, et al. **Behav Brain Res** 1985 Sep;17(1):67-72

Dopamine-mediated increases in nigral substance P-like immunoreactivity. Ritter JK, et al. **Biochem Pharmacol** 1985 Sep 1; 34(17):3161-6

Metabolism of carbidopa to alpha-methyldopamine and alpha-methylnorepinephrine in rats. Shelton RC, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3623-6

Purification and kinetic characterization of a dopamine-sulfating form of phenol sulfotransferase from human brain. Whittemore RM, et al. **Biochemistry** 1985 May 7;24(10):2477-82

Dopamine stimulated fucosylation of rat hippocampal proteins in vitro. A histoautoradiographic study. Pohle W, et al. **Biomed Biochim Acta** 1985;44(4):527-35

The effects of dopexamine on the cardiovascular system of the dog. Brown RA, et al. **Br J Pharmacol** 1985 Jul;85(3):609-19

In vitro dopamine biosynthesis in the median eminence of rat hypothalamic slices: possible involvement of a Na+-Ca2+ exchange mechanism. Arita J, et al. **Brain Res** 1985 Jul 15;338(2):384-6

Postnatal ontogenesis of the dopaminergic innervation in the rat anterior cingulate cortex (area 24). Immunocytochemical and catecholamine fluorescence histochemical analysis. Berger B, et al. **Brain Res** 1985 Jul;353(1):31-47

Regional depletion of central nervous system catecholamines: effects on blood pressure and drinking behavior. Gordon FJ, et al. **Brain Res** 1985 Oct 21;345(2):285-97

Primary cultures from defined brain areas; effects of seeding time on the development of beta-adrenergic- and dopamine-stimulated cAMP-activity during cultivation. Hansson E. **Brain Res** 1985 Aug; 353(2):187-92

Dopamine D-2 receptors in rat caudate-putamen: the lateral to medial gradient does not correspond to dopaminergic innervation. Joyce JN, et al. **Brain Res** 1985 Jul 15;338(2):209-18

Coexistence of immunoreactivities for glutamate decarboxylase and tyrosine hydroxylase in some neurons in the periglomerular region of the rat main olfactory bulb: possible coexistence of gamma-aminobutyric acid (GABA) and dopamine. Kosaka T, et al. **Brain Res** 1985 Sep 16; 343(1):166-71

In vivo voltammetric and behavioural evidence for somatodendritic autoreceptor control of mesolimbic dopamine neurones. Maidment NT, et al. **Brain Res** 1985 Jul 15;338(2):317-25

Suppression of MPTP-induced dopaminergic neurotoxicity in mice by nomifensine and L-DOPA. Melamed E, et al. **Brain Res** 1985 Sep 9; 342(2):401-4

Tyrosine hydroxylase immunohistochemistry fails to demonstrate dopaminergic interplexiform cells in the turtle retina. Nguyen-Legros J, et al. **Brain Res** 1985 Jul 29;339(2):323-8

Effects on the caudate spindle in rats of taurine and gamma-aminobutyric acid (GABA) microinjected into the substantia nigra: involvement of the dopaminergic system. Okuyama S, et al. **Brain Res** 1985 Sep 9; 342(2):366-8

SCH 23390, a selective D1 dopamine receptor blocker, enhances the firing rate of nigral dopaminergic neurons but fails to activate striatal tyrosine hydroxylase. Onali P, et al. **Brain Res** 1985 Aug 5;340(1):1-7

Neurotensin depolarizes substantia nigra dopamine neurones. Pinnock RD. **Brain Res** 1985 Jul 8;338(1):151-4

Dopamine changes the shape of action potentials in hippocampal pyramidal cells. Pockett S. **Brain Res** 1985 Sep 9;342(2):386-90

Sodium-independent binding of [3H]cocaine in mouse striatum is serotonin related. Reith ME, et al. **Brain Res** 1985 Sep 2;342(1):145-8

Simultaneous voltammetric and chemical monitoring of dopamine release in situ. Rice ME, et al. **Brain Res** 1985 Aug 5;340(1):151-5

Monoamine release from dopamine-depleted rat caudate nucleus reinnervated by substantia nigra transplants: an in vivo electrochemical study. Rose G, et al. **Brain Res** 1985 Aug 19;341(1):92-100

In vivo analysis of dopamine and its metabolites in the caudate nucleus during euthermia and hibernation. Salzman SK, et al. **Brain Res** 1985 Sep 16;343(1):95-103

Calmodulin-dependent adenylate cyclase in rat retina and the response to dopamine. Sano M. **Brain Res** 1985 Oct 21;345(2):337-40

The effect of water-deprivation on locomotor activity in rats treated with 6-hydroxydopamine. Seiden LS, et al. **Brain Res** 1985 Jul 1; 337(2):225-32

Organization of diencephalic dopamine neurones projecting to the spinal cord in the rat. Skagerberg G, et al. **Brain Res** 1985 Sep 9; 342(2):340-51

Behavioral study after local injection of 6-hydroxydopamine into the nucleus accumbens in the rat. Taghzouti K, et al. **Brain Res** 1985 Sep 30;344(1):9-20

Interaction of vasopressin with the nigro-striatal dopamine system: site and mechanism of action. van Heuven-Nolsen D, et al. **Brain Res** 1985 Jul 1;337(2):269-76

Effects of mazindol on rat lateral hypothalamic neurons. Sikdar SK, et al. **Brain Res Bull** 1985 Jul;15(1):33-8

Identification of dopamine-containing cell bodies in the dorsal and median raphe nuclei of the rat brain using tyrosine hydroxylase immunochemistry. Trulson ME, et al. **Brain Res Bull** 1985 Aug; 15(2):229-34

Simultaneous recording of substantia nigra neurons and voltammetric release of dopamine in the caudate of behaving cats. Trulson ME. **Brain Res Bull** 1985 Aug;15(2):221-3

Vagal afferent activity and renal nerve release of dopamine. Morgunov N, et al. **Can J Physiol Pharmacol** 1985 Jun;63(6):636-41

Schizophrenia: an amotivational syndrome in men. Lewine R. **Can J Psychiatry** 1985 Aug;30(5):316-8 (17 ref.)

The interaction of trh and dopaminergic mechanisms in the regulation of stimulated prolactin release in man. Ho KY, et al. **Clin Endocrinol (Oxf)** 1985 Jul;23(1):7-16

Amine-containing neurons in the brain of Lymnaea stagnalis: distribution and effects of precursors. Audesirk G. **Comp Biochem Physiol** [A] 1985; 81(2):359-65

Effect of gonadectomy on brain catecholamines during the postnatal period. Leret ML, et al. **Comp Biochem Physiol** [C] 1985; 81(2):405-9

Effect of microelectrophoretically applied acetylcholine, noradrenaline, dopamine and serotonin on the discharge of paraventricular oxytocinergic neurones in the rat. Honda K, et al. **Endocrinol Jpn** 1985 Feb;32(1):127-33

Stimulation of somatostatin release in vitro by synthetic human growth hormone-releasing factor by a nondopaminergic mechanism. Aguila

MC, et al. **Endocrinology** 1985 Aug;117(2):762–5

Stimulation of the adenosine 3',5'–monophosphate and the Ca2+ messenger systems together reverse dopaminergic inhibition of prolactin release. Delbeke D, et al. **Endocrinology** 1985 Aug;117(2):439–46

Examination of the effects of epinephrine, norepinephrine, and dopamine on aldosterone production in bovine glomerulosa cells in vitro. Sequeira SJ, et al. **Endocrinology** 1985 Nov;117(5):1947–52

Effect of dopamine agonists and antagonists on the binding of [3H]estradiol to its receptors in the anterior pituitary gland of male rats. Szijan I, et al. **Endocrinology** 1985 Nov;117(5):1742–8

Effects of GABA receptor agonists on [3H]dopamine release from median eminence and pituitary neurointermediate lobe. Anderson R, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):109–12

The dynamics of dopamine metabolism in the rat superior cervical, coeliac and mesenteric ganglia. Dalmaz Y, et al. **Eur J Pharmacol** 1985 Aug 15;114(2):209–17

Mesolimbic dopaminergic neurons are not spared by MPTP neurotoxicity in mice. Melamed E, et al. **Eur J Pharmacol** 1985 Aug 7; 114(1):97–100

Inhibition of protein carboxylmethylation and dopamine autoreceptor functioning. Saller CF, et al. **Eur J Pharmacol** 1985 Apr 23; 111(1):17–22

Lack of evidence supporting a role for dopamine in 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine neurotoxicity. Schmidt CJ, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):149–50

Effect of N–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) on age–related changes in dopamine turnover and transporter function in the mouse striatum. Sershen H, et al. **Eur J Pharmacol** 1985 Jul 11; 113(1):135–6

Morphine increases the activity of midbrain dopamine neurons in vitro. Trulson ME, et al. **Eur J Pharmacol** 1985 Aug 7;114(1):105–9

Spatial distribution of visual pigment and dopamine in the bullfrog retina. Makino–Tasaka M, et al. **Exp Eye Res** 1985 Jun;40(6):767–78

Striatal dopamine after cortical injury. Boyeson MG, et al. **Exp Neurol** 1985 Aug;89(2):479–83

Serotonergic conversion of MPTP and dopaminergic accumulation of MPP+. Shen RS, et al. **FEBS Lett** 1985 Sep 23;189(2):225–30

Dopamine in manic depressive illness. A pharmacological synthesis. Silverstone T. **J Affective Disord** 1985 May–Jun;8(3):225–31

Regulation of pro–opiomelanocortin synthesis by dopamine and cAMP in the amphibian pituitary intermediate lobe. Loh YP, et al. **J Biol Chem** 1985 Jul 25;260(15):8956–63

Patterns of muscarinic cholinergic binding in the striatum and their relation to dopamine islands and striosomes. Nastuk MA, et al. **J Comp Neurol** 1985 Jul 8;237(2):176–94

Time–dependent effects of oestradiol and progesterone on hypothalamic catecholamine turnover in ovariectomized rats. Hiemke C, et al. **J Endocrinol** 1985 Sep;106(3):303–9

Effects of dopamine and morphine on immunoreactive somatostatin and LH–releasing hormone secretion from hypothalamic fragments in vitro. Lengyel AM, et al. **J Endocrinol** 1985 Sep;106(3):317–22

Guinea pig striatum as a model of human dopamine deamination: the role of monoamine oxidase isozyme ratio, localization, and affinity for substrate in synaptic dopamine metabolism. Azzaro AJ, et al. **J Neurochem** 1985 Sep;45(3):949–56

1–Methyl–4–phenyl–1,2,3,6–tetrahydropyridine: correspondence of its binding sites to monoamine oxidase in rat brain, and inhibition of dopamine oxidative deamination in vivo and in vitro. Bocchetta A, et al. **J Neurochem** 1985 Sep;45(3):673–6

Relationship between catechol–O–methyltransferase and phenolsulfotransferase in the metabolism of dopamine in the rat brain. Buu NT. **J Neurochem** 1985 Nov;45(5):1612–9

Study of dopamine turnover by monitoring the decline of dopamine metabolites in rat CSF after alpha–methyl–p–tyrosine. Mignot E, et al. **J Neurochem** 1985 Nov;45(5):1527–33

Binding of [3H]SCH23390 in rat brain: regional distribution and effects of assay conditions and GTP suggest interactions at a D1–like dopamine receptor. Schulz DW, et al. **J Neurochem** 1985 Nov;45(5):1601–11

[3H]Threo–(+/–)–methylphenidate binding to 3,4–dihydroxyphenylethylamine uptake sites in corpus striatum: correlation with the stimulant properties of ritalinic acid esters. Schweri MM, et al. **J Neurochem** 1985 Oct;45(4):1062–70

Serotonin agonists reduce dopamine synthesis in the striatum only when the impulse flow of nigro–striatal neurons is intact. Spampinato U, et al. **J Neurochem** 1985 Sep;45(3):980–2

Cholecystokinin potentiates dopamine–mediated behaviors: evidence for modulation specific to a site of coexistence. Crawley JN, et al. **J Neurosci** 1985 Aug;5(8):1972–83

Two different mechanisms of calcium spike modulation by dopamine. Paupardin–Tritsch D, et al. **J Neurosci** 1985 Sep;5(9):2522–32

The release of endogenous dopamine from rat striatum during incubation in vitro. Snape BM, et al. **J Neurosci Methods** 1985 Jun;14(1):53–64

Dopaminergic modulation of neuromuscular transmission in the prawn. Miller MW, et al. **J Physiol (Lond)** 1985 Jun;363:363–75

Modification of antinociceptive action of morphine by dopamine agonist and antagonist in mice. Kamata K, et al. **Jpn J Pharmacol** 1985 May; 38(1):113–5

Dopaminergic modulation of the renal effect of arginine–vasopressin in water–loaded rats. Koyama S, et al. **Jpn J Pharmacol** 1985 May; 38(1):25–30

Tolerance pattern to amphetamine anorexia after selective lesions in the hypothalamic dopaminergic projection. Bhakthavatsalam P, et al. **Life Sci** 1985 Aug 19;37(7):635–43

Influence of selective, reversible inhibitors of monoamine oxidase on the prolonged depletion of striatal dopamine by 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine in mice. Fuller RW, et al. **Life Sci** 1985 Sep 23;37(12):1089–96

Free and conjugated catecholamines in digestive tissues of rats. Gaudin C, et al. **Life Sci** 1985 Oct 21;37(16):1469–74

Lack of functional evidence for the involvement of sigma opiate receptors in the actions of the 3–PPP enantiomers on central dopaminergic systems: discrepancies between in vitro and in vivo observations. Hjorth S, et al. **Life Sci** 1985 Aug 19;37(7):673–84

Dopamine–beta–hydroxylase inhibition acutely stimulates rats hypothalamic noradrenaline and dopamine neuronal activity as assessed from metabolic ratios and circulating glucose and ACTH responses. Smythe GA, et al. **Life Sci** 1985 Sep 2;37(9):841–7

Very rapid turnover of dopamine in noradrenaline cell body regions. Andén NE, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 May; 329(3):258–63

An electrophysiological analysis of the actions of the 3–PPP enantiomers on the nigrostriatal dopamine system. Clark D, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun;329(4):344–54

Cyclic AMP facilitates the electrically evoked release of radiolabelled noradrenaline, dopamine and 5–hydroxytryptamine from rat brain slices. Schoffelmeer AN, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jul;330(1):74–6

Altered central monoamine response to D–amphetamine in rats chronically exposed to inorganic lead. Lasley SM, et al. **Neurochem Res** 1985 Jul;10(7):933–44

In vitro dopamine release from the rat striatum: diurnal rhythm and its modification by the estrous cycle. Dluzen D, et al. **Neuroendocrinology** 1985 Aug;41(2):97–100

Hypothalamic monoaminergic activity and pituitary function in male rats with estrogen–induced pituitary hyperplasia. Terry LC, et al. **Neuroendocrinology** 1985 Oct;41(4):269–75

The role of central dopaminergic systems in the behavioral effects of H–Phe–Ile–Tyr–His–Ser–Tyr–Lys–OH. Vécsei L, et al. **Neuropeptides** 1985 Jun;6(3):183–90

S(+)Apomorphines. Selective inhibition of excitatory effects of dopamine injected into the limbic system of the rat. Campbell A, et al. **Neuropharmacology** 1985 May;24(5):391–9

Intracerebroventricular administration of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) and its metabolite 1–methyl–4–phenylpyridinium ion (MPP+) decrease dopamine and increase acetylcholine in the mouse neostriatum. Cavalla D, et al. **Neuropharmacology** 1985 Jun;24(6):585–6

Oxytocin and a C–terminal derivative (Z–prolyl–D–leucine) attenuate tolerance to and dependence on morphine and interact with dopaminergic neurotransmission in the mouse brain. Kovács GL, et al. **Neuropharmacology** 1985 May;24(5):413–9

Intracerebroventricular administration of cholecystokinin inhibits the activity of the dopaminergic and serotoninergic systems of the brain. Vasar EE, et al. **Neurosci Behav Physiol** 1985 May–Jun;15(3):232–6

Dopamine–sensitive adenylate cyclase in rabbit portal vein. Amenta F. **Neurosci Lett** 1985 May 23;56(3):279–82

Electrophysiological properties of single units in dopamine–rich mesencephalic transplants in rat brain. Arbuthnott G, et al. **Neurosci Lett** 1985 Jun 12;57(2):205–10

Dopaminergic agents differentially alter beta–endorphin processing patterns in the rat pituitary neurointermediate lobe. Autelitano DJ, et al. **Neurosci Lett** 1985 Aug 16;59(1):141–6

Dopaminergic toxicity after the stereotaxic administration of the 1–methyl–4–phenylpyridinium ion (MPP+) to rats. Heikkila RE, et al. **Neurosci Lett** 1985 Aug 16;59(1):135–40

Effects of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) and several of its analogues on the dopaminergic nigrostriatal pathway in mice. Heikkila RE, et al. **Neurosci Lett** 1985 Jul 4;58(1):133–7

Muscarine–binding sites localized to cortical dopamine terminals. Liskowsky DR, et al. **Neurosci Lett** 1985 Jul 31;58(2):229–33

In vivo voltammetric determination of the kinetics of dopamine metabolism in the rat. Michael AC, et al. **Neurosci Lett** 1985 May 23; 56(3):365–9

1–Methyl–4–phenylpyridine (MPP+) is toxic to mesencephalic dopamine neurons in culture. Mytilineou C, et al. **Neurosci Lett** 1985 Jun 4; 57(1):19–24

Effects on the caudate spindle in rats of dopamine microinjected into the caudate nucleus. Okuyama S, et al. **Neurosci Lett** 1985 Aug 16; 59(1):27–32

Effects of N–methyl–4–phenyl–1,2,3,6–tetrahydropyridine and its metabolite, N–methyl–4–phenylpyridinium ion, on dopaminergic nigrostriatal neurons in the mouse. Perry TL, et al. **Neurosci Lett** 1985

Aug 5;58(3):321-6

Sodium-dependent, calmodulin-dependent transmitter release from synaptosomes. Sandoval ME, et al. **Neurosci Lett** 1985 May 23; 56(3):271-7

In vitro demonstration of dopamine uptake by neostriatal serotonergic neurons of the rat. Schmidt CJ, et al. **Neurosci Lett** 1985 Aug 16; 59(1):9-14

Suckling decreases dopamine turnover in both medial and lateral aspects of the median eminence in the rat. Selmanoff M, et al. **Neurosci Lett** 1985 Jun 4;57(1):25-30

Opposite effects of monosodium glutamate on the dopaminergic and GABAergic innervations of the median eminence and the intermediate lobe in the mouse. Stoeckel ME, et al. **Neurosci Lett** 1985 May 23; 56(3):249-55

Laminar distributions of neurons sensitive to acetylcholine, noradrenaline and dopamine in the dorsolateral prefrontal cortex of the monkey. Sawaguchi T, et al. **Neurosci Res** 1985 Apr;2(4):255-73

Selective neonatal depletion of dopamine has no effect on medial prefrontal cortex self-stimulation in the rat. Umemoto M, et al. **Neurosci Res** 1984 Oct;1(5):295-307

New dopaminergic terminal fields in the motor, visual (area 18b) and retrosplenial cortex in the young and adult rat. Immunocytochemical and catecholamine histochemical analyses. Berger B, et al. **Neuroscience** 1985 Aug;15(4):983-98

The effects of MIF-I, beta-endorphin and alpha-MSH on d-amphetamine induced paradoxical behavioral thermoregulation: possible involvement of the dopaminergic system. Yehuda S, et al. **Peptides (Fayetteville)** 1985 Mar-Apr;6(2):189-92

Involvement of dopamine in the aversive stimulus properties of cocaine in rats. Hunt T, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):945-8

Central serotonin neurones in avoidance learning: interactions with noradrenaline and dopamine neurones. Ogren SO. **Pharmacol Biochem Behav** 1985 Jul;23(1):107-23

Cholecystokinin potentiates dopamine-mediated behaviors in the nucleus accumbens, a site of CCK-DA co-existence. Crawley JN. **Psychopharmacol Bull** 1985;21(3):523-7

Persistent effects of amphetamine, p-chloroamphetamine, and related compounds on central dopamine and serotonin neurons in rodents. Fuller RW. **Psychopharmacol Bull** 1985;21(3):528-32

Prolonged antidopaminergic actions of single doses of butyrophenones in the rat. Campbell A, et al. **Psychopharmacology (Berlin)** 1985; 87(2):161-6

Dopamine agonist action in mesolimbic, cortical and extrapyramidal areas to modify spontaneous climbing behaviour of the mouse. Costall B, et al. **Psychopharmacology (Berlin)** 1985;86(4):452-7

Production and excretion of dopamine by the isolated perfused rat kidney. Adam WR, et al. **Renal Physiol** 1985;8(3):150-8

Cocaine blocks the dopamine depletion induced by MPTP. Mayer RA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jul;49(1):145-8

Responsiveness and receptive field size of carp horizontal cells are reduced by prolonged darkness and dopamine. Mangel SC, et al. **Science** 1985 Sep 13;229(4718):1107-9

Effects of dopamine and substance P infusion on gastric acid secretion in Pavlov and Heidenhain pouched dogs. Ogoshi K, et al. **Tokai J Exp Clin Med** 1984 Aug;9(3):183-90

[Effect of dopaminergic pharmacological agents on thyrotropic hormone secretion by the hypophysis when stimulated with thyrotropin-releasing hormone] Boiadzhieva N, et al. **Eksp Med Morfol** 1985;24(1):29-32 (Eng. Abstr.) **(Bul)**

[Lack of effect of aging on dopaminergic inhibition of aldosterone and prolactin increase] Preis P, et al. **Z Gerontol** 1985 Jul-Aug; 18(4):241-3 (Eng. Abstr.) **(Ger)**

[Regulation of dopamine release through the system of presynaptic receptors] Nowak JZ. **Folia Med Cracov** 1984;25(3-4):287-96 (22 ref.) (Eng. Abstr.) **(Pol)**

[Identification of dopaminergic vesicles in the electron-microscopic picture of the compact layer of the substantia nigra in the rat] Dydyk L, et al. **Neuropatol Pol** 1985;23(1):145-65 (Eng. Abstr.) **(Pol)**

[Dopaminergic receptor activity and the evolution of schizophrenia] Fodoreanu L. **Rev Med Interna [Neurol Psihiatr]** 1985 Apr-Jun; 30(2):131-4 (15 ref.) **(Rum)**

[Role of the kallikrein-kinin system and prostaglandins in the action of dopamine on blood flow and sodium transport in the rat kidney] Kuz'min OB, et al. **Fiziol Zh SSSR** 1985 May;71(5):619-24 (Eng. Abstr.) **(Rus)**

[Action of noradrenaline and dopamine on the pacemaker cells of the normal rat sinus node and in pharmacological sympathectomy] Sutiagin PV, et al. **Kardiologiia** 1985 May;25(5):88-93 (Eng. Abstr.) **(Rus)**

[Level of dopamine in structures of the nigro-striatal and mesolimbic systems of the brain in experimental pathology of higher nervous activity in the rat] Saul'skaia NB. **Zh Vyssh Nerv Deiat** 1985 May-Jun; 35(3):561-4 (Eng. Abstr.) **(Rus)**

[Brain levels of dopamine during the estrous cycle in the rat] Lerdo de Tejada A, et al. **Gac Med Mex** 1985 May-Jun;121(5-6):185-7 (Eng. Abstr.) **(Spa)**

DOPAMINE BETA-HYDROXYLASE

Genes for neurotransmitter synthesis, storage, and uptake. Joh TH, et al. **Fed Proc** 1985 Sep;44(12):2773-9

Dopamine-beta-hydroxylase-like immunoreactive neurons in two insect species, Calliphora erythrocephala and Periplaneta americana. Klemm N, et al. **Histochemistry** 1985;83(2):159-64

1-DOPA decarboxylase and dopamine-beta-hydroxylase isolated from sympathetic splenic nerves estimated by sodium dodecyl sulphate polyacrylamide gel electrophoresis with and without mercaptoethanol. Husseini HS, et al. **J Chromatogr** 1985 Jul 19;329(2):300-6

Characterization of the subunit structure of dopamine beta-hydroxylase by anion-exchange high-performance liquid chromatography. Speedie MK, et al. **J Chromatogr** 1985 Jun 26;327:351-7

Dopamine-beta-hydroxylase inhibition acutely stimulates rats hypothalamic noradrenaline and dopamine neuronal activity as assessed from metabolic ratios and circulating glucose and ACTH responses. Smythe GA, et al. **Life Sci** 1985 Sep 2;37(9):841-7

[Dopamine beta-hydroxylase activity in the plasma of women as an indicator of perioperative stress] Zrubek H, et al. **Ginekol Pol** 1984 Nov;55(11):859-62 (Eng. Abstr.) **(Pol)**

DOXEPIN

Doxepin plasma concentrations in clinical practice. Could there be a pharmacokinetic explanation for low concentrations? Joyce PR, et al. **Clin Pharmacokinet** 1985 Jul-Aug;10(4):365-70

Cimetidine-doxepin interaction. Brown MA, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):245-7

[Effect of antidepressive drugs and histamine H1 receptor blockaders on histamine level in rat brain] Zawilska J, et al. **Folia Med Cracov** 1984; 25(3-4):297-306 (Eng. Abstr.) **(Pol)**

ELECTROCONVULSIVE THERAPY

A 'gratuitous' conclusion on ECT [letter] Fink M. **Am J Psychiatry** 1985 Sep;142(9):1129-30

MHPG, ECT, and depression [letter] McDougle CJ, et al. **Biol Psychiatry** 1985 Aug;20(8):927

Effect of L-tryptophan on electroconvulsive therapy seizure time. Price WA, et al. **J Nerv Ment Dis** 1985 Oct;173(10):636-8

Electroconvulsive therapy in 1985--a review. Varghese FT, et al. **Med J Aust** 1985 Sep 2;143(5):192-6 (40 ref.)

A controlled study of cellular immune function in affective disorders before and during somatic therapy. Albrecht J, et al. **Psychiatry Res** 1985 Jul;15(3):185-93

ELECTROENCEPHALOGRAPHY

Electroencephalographic studies of psychopharmaca in Czechoslovakia. An overview. Mrňa B. **Acta Univ Palacki Olomuc Fac Med** 1985; 108:289-94

Effects of intracerebral morphine and enkephalins on the caudate-EEG spindle burst. Kamata K, et al. **Arch Int Pharmacodyn Ther** 1985 May; 275(1):68-77

Catecholamine regulation of neocortical spindling in DBA/2 mice. Ryan LJ. **Behav Brain Res** 1985 Aug;16(2-3):103-15

Topographic EEG changes with benzodiazepine administration in generalized anxiety disorder. Buchsbaum MS, et al. **Biol Psychiatry** 1985 Aug;20(8):832-42

Behavioral and eegraphic changes induced by dopaminergic antidepressants in rabbits. Bo P, et al. **Farmaco [Sci]** 1985 Aug; 40(8):608-16

Delineation of pharmacopsychological effects by means of endogenous event-related brain potentials: an exemplification with flupentixol. Rösler F, et al. **Neuropsychobiology** 1985;13(1-2):81-92

Information processing components of the auditory event related potential are reduced by cocaine. Herning RI, et al. **Psychopharmacology (Berlin)** 1985;87(2):178-85

The effect of methylphenidate on information processing. Naylor H, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):90-5

[The effect of nootropic substances on fluctuations in vigilance tonus in postinjury pseudoneurasthenia. EEG study] Strnad P, et al. **Cesk Neurol Neurochir** 1985 Jul;48(4):235-9 (Eng. Abstr.) **(Cze)**

[The effect of propranolol on the pentetrazole-induced spindle activity in the EEG of the rat] Lasek R. **Pharmazie** 1985 May;40(5):364 **(Ger)**

[Functional differentiation of the theta-rhythm of the hippocampus in the cat] Melikov EM. **Zh Vyssh Nerv Deiat** 1985 May-Jun; 35(3):457-64 (Eng. Abstr.) **(Rus)**

ELECTROLYTES

[Adaptation of distal tubular segments to changes in electrolyte metabolism] Kaissling B, et al. **Acta Histochem [Suppl] (Jena)** 1985; 31:185-91 **(Ger)**

ELECTROSHOCK

Involvement of benzodiazepine recognition sites in the foot shock-induced decrease of low affinity GABA receptors in the rat cerebral cortex. Concas A, et al. **Brain Res** 1985 Aug 19;341(1):50-6

DSP-4 lesioning prevents the enhancement of dopamine and 5-hydroxytryptamine mediated behavioural changes by repeated electroconvulsive shock. Heal DJ, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):117-21

Upregulation of gamma-aminobutyric acid (GABA) B binding sites in rat frontal cortex: a common action of repeated administration of different classes of antidepressants and electroshock. Lloyd KG, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):191-9

Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Goodwin GM, et al. **Nature** 1985 Oct 10-16;317(6037):531-3

The role of central noradrenergic neurons in electroconvulsive shock-induced muricide inhibition in olfactory bulbectomized rats. Liou SY, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):65-70

[The anticonvulsant effect of propranolol in maximal electroshock in sub chronic applications] Lasek R. **Pharmazie** 1985 Jun;40(6):430 (Ger)

EMOTIONS

The participation of serotoninergic system in the regulation of emotional-defensive behavior evoked by intrahypothalamic carbachol injections in the cat. Gołebiewski H, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(1-2):25-36

A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. Leff J, et al. **Br J Psychiatry** 1985 Jun; 146:594-600

The discriminative stimulus and subjective effects of d-amphetamine in humans. Chait LD, et al. **Psychopharmacology (Berlin)** 1985; 86(3):307-12

ENDORPHINS

Cell types of the pars distalis of the hedgehog (Erinaceus europaeus L.) adenohypophysis: cytological, immunocytochemical and ultrastructural studies. 3. Opiocorticomelanotropic cells. Girod C, et al. **Acta Anat (Basel)** 1985;123(1):67-71

Effects of extracorporeal circulation on plasma beta-endorphin-like-immunoreactivity in children. Yamashita M, et al. **Agressologie** 1985 Mar;26(3):267-9

Conversion and inactivation of opioid peptides by rabbit brain endo-oligopeptidase A. Camargo AC, et al. **Biochem Biophys Res Commun** 1985 Jul 31;130(2):932-8

Neuropeptide processing by single-step cleavage: conversion of leumorphin (dynorphin B-29) to dynorphin B. Devi L, et al. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):1168-76

Radioimmunoassay for beta-endorphin (1-18), a novel pituitary peptide derived from proopiomelanocortin. Vuolteenaho O. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):1226-32

Rapid antidepressant activity of destyr gamma endorphin: correlation with urinary melatonin. Chazot G, et al. **Biol Psychiatry** 1985 Sep; 20(9):1026-30

Characterization of proenkephalin B-derived opioid peptides in the human hypothalamo-neurohypophyseal axis. Arendt RM, et al. **Brain Res** 1985 Oct 21;345(2):230-7

Light and electron microscopic immunocytochemistry of beta-endorphin/beta-LPH-like immunoreactive neurons in the arcuate nucleus and surrounding areas of the rat hypothalamus. Ibata Y, et al. **Brain Res** 1985 Aug 26;341(2):233-42

Release of immunoreactive Met-enkephalin from the spinal cord by intraventricular beta-endorphin but not morphine in anesthetized rats. Tseng LF, et al. **Brain Res** 1985 Sep 16;343(1):60-9

Proopiomelanocortin-derived peptides in the immune system. Blalock JE. **Clin Endocrinol (Oxf)** 1985 Jun;22(6):823-7 (15 ref.)

In vivo and in vitro effects of angiotensin II on the release of beta-endorphin-like immunoreactivity. Matsumura M, et al. **Endocrinol Jpn** 1985 Apr;32(2):233-40

Evidence that beta-endorphin binds to specific receptors in rat peripheral tissues and stimulates the adenylate cyclase-adenosine 3',5'-monophosphate system. Dave JR, et al. **Endocrinology** 1985 Oct; 117(4):1389-96

The effect of various corticotropin-releasing factor trains on the release of adrenocorticotropin, beta-endorphin, and beta-lipotropin from perifused ovine pituitary cells. Evans MJ, et al. **Endocrinology** 1985 Sep;117(3):893-9

Evidence that a benzodiazepine receptor mechanism regulates the secretion of pituitary beta-endorphin in rats. Maiewski SF, et al. **Endocrinology** 1985 Aug;117(2):474-80

Opioid peptides rapidly stimulate superoxide production by human polymorphonuclear leukocytes and macrophages. Sharp BM, et al. **Endocrinology** 1985 Aug;117(2):793-5

Novel opioid peptides derived from mitochondrial cytochrome b: cytochrophins. Brantl V, et al. **Eur J Pharmacol** 1985 May 8; 111(2):293-4

beta-Endorphin and ACTH related peptides in primary cultures of rat anterior pituitary cells: evidence for different intracellular pools. Ham J, et al. **FEBS Lett** 1985 Oct 14;190(2):253-8

Plasma beta-endorphin and the menstrual cycle. Laatikainen T, et al. **Fertil Steril** 1985 Aug;44(2):206-9

Stress-induced elevation of plasma alpha-MSH and endorphin in brown trout, Salmo trutta L. Sumpter JP, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):257-65

Lack of beta-endorphin plasma level rise in oxytocin-induced labor. Genazzani AR, et al. **Gynecol Obstet Invest** 1985;19(3):130-4

Investigation of beta-endorphin and adrenocorticotropic hormone in placenta, amniotic membrane and umbilical cord using an immunoperoxidase technique. Reinthaller A, et al. **Gynecol Obstet Invest** 1985;19(3):135-8

Localization of dynorphin B-like and alpha-neoendorphin-like immunoreactivities in the guinea pig organ of Corti. Altschuler RA, et al. **Hear Res** 1985 Mar;17(3):249-58

Beta-endorphin. Synthesis and biological activity of analogs with disulfide bridges. Blake J, et al. **Int J Pept Protein Res** 1985 Jun;25(6):575-9

Beta-endorphin does not protect alkylation of opiate receptor by N-ethylmaleimide. Westphal M, et al. **Int J Pept Protein Res** 1985 Apr; 25(4):403-7

Isolation of a specific mu-opiate receptor peptide, morphiceptin, from an enzymatic digest of milk proteins. Chang KJ, et al. **J Biol Chem** 1985 Aug 15;260(17):9706-12

Covalent labeling of opioid receptors with radioiodinated human beta-endorphin. Identification of binding site subunit. Howard AD, et al. **J Biol Chem** 1985 Sep 5;260(19):10833-9

Opioid peptides in human adrenal: partial characterization and presence of adrenal peptide E. Boarder MR, et al. **J Clin Endocrinol Metab** 1985 Oct;61(4):658-65

Inhibition by prostaglandin E2 of the release of vasopressin and beta-endorphin from rat pituitary neurointermediate lobe or medial basal hypothalamus in vitro. Knepel W, et al. **J Endocrinol** 1985 Aug; 106(2):189-95

Novel opioid peptide amidorphin: characterization and distribution of amidorphin-like immunoreactivity in bovine, ovine, and porcine brain, pituitary, and adrenal medulla. Liebisch DC, et al. **J Neurochem** 1985 Nov;45(5):1495-503

Isolation and characterization of an endogenous C-terminal fragment of the alpha-neo-endorphin/dynorphin precursor from bovine caudate nucleus. Evans CJ, et al. **J Neurosci** 1985 Jul;5(7):1803-7

Diuresis and suppression of vasopressin by kappa opioids: comparison with mu and delta opioids and clonidine. Leander JD, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):463-9

On the potassium conductance increased by opioids in rat locus coeruleus neurones. North RA, et al. **J Physiol (Lond)** 1985 Jul;364:265-80

Binding of radioiodinated human beta-endorphin to serum proteins from rats and humans, determined by several methods. Sato H, et al. **Life Sci** 1985 Oct 7;37(14):1309-18

Release of immunoreactive beta-endorphin in vitro from pituitaries of young and old male rats. Forman LJ, et al. **Neurobiol Aging** 1985 Summer;6(2):101-5

Effects of endogenous opioid peptides and opiates on luteinizing hormone and prolactin secretion in ovariectomized rats. Leadem CA, et al. **Neuroendocrinology** 1985 Oct;41(4):342-52

In vivo and in vitro effects of bradykinin on the release of beta-endorphin-like immunoreactivity. Matsumura M, et al. **Neuroendocrinology** 1985 Aug;41(2):101-6

Pituitary secretion of growth hormone in response to opioid peptides and opiates is mediated through growth hormone-releasing factor. Wehrenberg WB, et al. **Neuroendocrinology** 1985 Jul;41(1):13-6

Beta-endorphin suppression of acute morphine abstinence in morphine dependent monkeys: effective given intraventricularly but ineffective given intravenously. Domino EF, et al. **Neuropeptides** 1985 Jul; 6(4):343-50

Long-term haloperidol treatment elevates beta-endorphin levels in the intermediate pituitary but not in rat brain. Millington WR, et al. **Neuropeptides** 1985 Jul;6(4):365-72

Dopaminergic agents differentially alter beta-endorphin processing patterns in the rat pituitary neurointermediate lobe. Autelitano DJ, et al. **Neurosci Lett** 1985 Aug 16;59(1):141-6

Effects of branched-chain amino acids on beta-endorphin in the pituitary of the rat. Cobert BJ, et al. **Neurosci Lett** 1985 Aug 5;58(3):339-42

Presence of immunoreactive alpha-melanotropin and beta-endorphin in spinal motoneurones of the dystrophic mouse. Haynes LW, et al. **Neurosci Lett** 1985 Jul 4;58(1):13-8

Prodynorphin opioid peptides in small somatosensory primary afferents of guinea pig. Weihe E, et al. **Neurosci Lett** 1985 Aug 5; 58(3):347-52

Causal links between plasma and CSF endorphin levels in stress: vector-ARMA analysis. Carr DB, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 1:5-10

The effects of MIF-I, beta-endorphin and alpha-MSH on d-amphetamine induced paradoxical behavioral thermoregulation: possible involvement of the dopaminergic system. Yehuda S, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):189–92

Diclofenac and pirprofen modify pituitary and hypothalamic beta–endorphin concentrations. Sacerdote P, et al. **Pharmacol Res Commun** 1985 Aug;17(8):679–84

Beta–casomorphin affects fast and slow action potentials in ventricular myocardium. Nilius B, et al. **Pharmazie** 1985 Jun;40(6):428–9

Morphine and other opiates from beef brain and adrenal. Goldstein A, et al. **Proc Natl Acad Sci USA** 1985 Aug;82(15):5203–7

The Wellcome Foundation lecture, 1982. Opioid Peptides and their Receptors. Kosterlitz HW. **Proc R Soc Lond [Biol]** 1985 Jul 22; 225(1238):27–40 (48 ref.)

Dexamethasone suppresses beta–endorphin in humans. Krantz DE, et al. **Psychoneuroendocrinology** 1985;10(2):211–4

Influence of early beta–endorphin treatment on the behavior and reaction to beta–endorphin in the adult male rat. Meyerson BJ. **Psychoneuroendocrinology** 1985;10(2):135–47

Opioid peptides in the adrenal pituitary axis. Evans CJ, et al. **Psychopharmacol Bull** 1985;21(3):466–71

The Ying–Yang hypothesis of opioid peptide immunomodulation. Plotnikoff NP. **Psychopharmacol Bull** 1985;21(3):489

Current concepts in premenstrual syndrome. Ullman LE. **RI Med J** 1985 Jun;68(6):269–72

Effects of some opiates and vasoactive intestinal peptide (VIP) on duodenal surface epithelial bicarbonate secretion in the rat. Flemström G, et al. **Scand J Gastroenterol [Suppl]** 1985;110:49–53

[Effect of hypoxia on the content of endogenous opioid peptides and cyclic nucleotides in the rat brain] Fujita S, et al. **Masui** 1985 Jun; 34(6):767–72 (Eng. Abstr.) **(Jpn)**

[Distribution of alpha–, beta– and gamma–endorphins in the forebrain and diencephalon of the rat brain (immunohistochemical study)] Makarenko IG, et al. **Arkh Anat Gistol Embriol** 1985 Jul;89(7):10–8 (Eng. Abstr.) **(Rus)**

[ACTH, corticosterone and beta–endorphin in the blood plasma of rats under prolonged immobilization stress] Kiiatkin EA, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):157–60 (Eng. Abstr.) **(Rus)**

[Biosynthesis of pro–opiomelanocortin and secretion of its fragments by cultured bone marrow cells of mice] Dmitriev AD, et al. **Dokl Akad Nauk SSSR** 1985 May–Jun;282(1):199–202 **(Rus)**

[Effect of opioid peptides on nervous tissue in vitro] Il'inskii OB, et al. **Neirofiziologiia** 1985;17(4):550–7 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, LEUCINE

Hemorrhagic shock and the central vasopressin and opioid peptide system of rats. Feuerstein G, et al. **Am J Physiol** 1985 Sep; 249(3 Pt 1):E244–50

Localization of substance P–like, leucine–enkephalin–like, methionine–enkephalin–like, and FMRFamide–like immunoreactivity in the eyestalk of the fiddler crab, Uca pugilator. Fingerman M, et al. **Cell Tissue Res** 1985;241(3):473–7

On the origin of Leu–enkephalin and Met–enkephalin in the rat neurohypophysis. Zamir N. **Endocrinology** 1985 Oct;117(4):1687–92

Cyanogen bromide cleavage of methionine residues as a control method for enkephalin immunocytochemistry. Jirikowski G. **Histochemistry** 1985;83(1):93–5

Reduced mechanical activity of perfused rat heart following morphine or enkephalin peptides administration. Clò C, et al. **Life Sci** 1985 Oct 7;37(14):1327–33

Sulfonic acid enkephalin: binding specificity to rat brain opiate receptors. Martin JL, et al. **Neuropeptides** 1985 Jul;6(4):293–302

Enkephalin pseudopeptides: resistance to in vitro proteolytic degradation afforded by amide bond replacements extends to remote sites. Benovitz DE, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):257–61

Central effects of mu, delta, and kappa receptor agonists in hemorrhagic shock. Feuerstein G, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 1:11–3

[Synthesis of leucine– and methionine–enkephalin using papain] Zapevalova NP, et al. **Bioorg Khim** 1985 Jun;11(6):733–7 (Eng. Abstr.) **(Rus)**

[Mechanism of the antistressor effect of D–Ala(2)–Leu(5)–Arg(6)–enkephalin] Lishmanov IuB, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):268–70 (Eng. Abstr.) **(Rus)**

[Effect of leu–enkephalin and the delta–sleep–inducing peptide, M (DSIP), on endogenous noradrenaline release by brain synaptosomes in the rat] Rozhanets VV, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):199–201 (Eng. Abstr.) **(Rus)**

[Differential method of analyzing ligand complex formation with binding centers. The detection of the superhigh–affinity binding centers of opiate ligands] Zaitsev SV, et al. **Dokl Akad Nauk SSSR** 1985; 281(3):727–31 **(Rus)**

[Effect of enkephalins on the plasticity of pond snail] Verbnyi IaI. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):306–13 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, METHIONINE

Pharmacological analysis of the mechanism of action for colonic contraction induced by neurotensin, substance P and methionine–enkephalin. Hellström PM. **Acta Physiol Scand** 1985 Sep; 125(1):13–24

ATP–dependent [3H]Met–enkephalin uptake by bovine adrenal chromaffin granule membrane. Takeda F, et al. **Brain Res** 1985 Oct 7;344(2):220–6

Release of immunoreactive Met–enkephalin from the spinal cord by intraventricular beta–endorphin but not morphine in anesthetized rats. Tseng LF, et al. **Brain Res** 1985 Sep 16;343(1):60–9

Localization of substance P–like, leucine–enkephalin–like, methionine–enkephalin–like, and FMRFamide–like immunoreactivity in the eyestalk of the fiddler crab, Uca pugilator. Fingerman M, et al. **Cell Tissue Res** 1985;241(3):473–7

On the origin of Leu–enkephalin and Met–enkephalin in the rat neurohypophysis. Zamir N. **Endocrinology** 1985 Oct;117(4):1687–92

Cyanogen bromide cleavage of methionine residues as a control method for enkephalin immunocytochemistry. Jirikowski G. **Histochemistry** 1985;83(1):93–5

Immunocytochemical localization of a methionine–enkephalin–resembling neuropeptide in the central nervous system of the American cockroach, Periplaneta americana L. Verhaert P, et al. **J Comp Neurol** 1985 Sep 1;239(1):54–61

Intragranular colocalization of immunoreactive methionine–enkephalin and oxytocin within the nerve terminals in the posterior pituitary. Adachi T, et al. **J Histochem Cytochem** 1985 Sep;33(9):891–9

Localization of Met–enkephalin–Arg6–Gly7–Leu8–like immunoreactivity in the gastrointestinal tract of rat and pig. Nihei K, et al. **J Histochem Cytochem** 1985 Oct;33(10):1001–6

A potentiometric and spectroscopic study of the proton and copper(II) complexes of methionine enkephalin and some related ligands. Formicka–Kozlowska G, et al. **J Inorg Biochem** 1985 Aug; 24(4):299–307

Ventilatory response to intravenous methionine enkephalin in awake dogs. Evanich MJ, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):677–80

Cyclooxygenase inhibitors affect Met–enkephalin– and acetylcholine–stimulated motility of the isolated rat colon. Scheurer U, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):742–6

Reduced mechanical activity of perfused rat heart following morphine or enkephalin peptides administration. Clò C, et al. **Life Sci** 1985 Oct 7;37(14):1327–33

Mechanism of methionine–enkephalin modulation of glutamatergic transmission in the rat striatum. Kuznetsov VI, et al. **Neurosci Lett** 1985 Jun 12;57(2):143–6

Methionine–enkephalin–Arg6–Gly7–Leu8–immunoreactive nerve fibers and cell bodies in lumbar paravertebral ganglia and the celiac–superior mesenteric ganglion complex of the rat: an immunohistochemical study. Shimosegawa T, et al. **Neurosci Lett** 1985 Jun 12;57(2):169–74

The proenkephalin A fragment metorphamide shows supraspinal and spinal opioid activity in vivo. Dray A, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):217–21

Pro–enkephalin peptides possessing Met–enkephalin–Arg6–Gly7–Leu8–immunoreactivity in rat CSF, striatum and adrenal gland. Jackson S, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):169–78

[Met–enkephalin–Arg–Gly–Leu–like immunoreactivity–containing nerve fibers and cell bodies in the abdominal sympathetic ganglia of the rat—an immunohistochemical study] Shimosegawa T, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 May 20;61(5):581–91 (Eng. Abstr.) **(Jpn)**

[Synthesis of leucine– and methionine–enkephalin using papain] Zapevalova NP, et al. **Bioorg Khim** 1985 Jun;11(6):733–7 (Eng. Abstr.) **(Rus)**

[Mechanism of the modulating effect of met–enkephalin on glutamatergic synaptic transmission] Kuznetsov VI, et al. **Dokl Akad Nauk SSSR** 1985; 282(2):456–9 **(Rus)**

[Effect of enkephalins on the plasticity of pond snail] Verbnyi IaI. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):306–13 (Eng. Abstr.) **(Rus)**

ENKEPHALINS

Sodium–induced release of enkephalins from bovine chromaffin granules in vitro. Uvnäs B, et al. **Acta Physiol Scand** 1985 Aug;124(4):629–30

Myenteric enkephalin neurons around the laser–photocoagulation necrosis: an immunocytochemical investigation in the guinea pig jejunum and proximal colon. Kobayashi S, et al. **Arch Histol Jpn** 1985 Apr;48(2):239–54

Effects of intracerebral morphine and enkephalins on the caudate–EEG spindle burst. Kamata K, et al. **Arch Int Pharmacodyn Ther** 1985 May; 275(1):68–77

Neuropeptide processing by single–step cleavage: conversion of leumorphin (dynorphin B–29) to dynorphin B. Devi L, et al. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):1168–76

Endopeptidase in human cerebrospinal fluid which cleaves proenkephalin B opioid peptides at consecutive basic amino acids. Nyberg F, et al. **Biochem Biophys Res Commun** 1985 Sep 30;131(3):1069–74

Conformation of cyclic analogs of enkephalin. III. Effect of varying ring size. Hall D, et al. **Biopolymers** 1985 Jun;24(6):935–45

Prediction of the native conformation of a polypeptide by a statistical-mechanical procedure. I. Backbone structure of enkephalin. Paine GH, et al. **Biopolymers** 1985 Aug;24(8):1391–436

Use of buildup and energy-minimization procedures to compute low-energy structures of the backbone of enkephalin. Vásquez M, et al. **Biopolymers** 1985 Aug;24(8):1437–47

Ontogenesis of proenkephalin products in rat striatum and the inhibitory effects of low-level lead exposure. Bailey C, et al. **Brain Res** 1985 Sep; 354(1):75–9

Opposing effects of oxytocin and of a mu-receptor agonistic opioid peptide on the same class of non-pyramidal neurones in rat hippocampus. Raggenbass M, et al. **Brain Res** 1985 Oct 7; 344(2):392–6

The effect of some enkephalins on calcitonin secretion. Gozariu L, et al. **Endocrinologie** 1985 Jul–Sep;23(3):201–4

The proenkephalin A fragment, peptide E: central processing and CNS activity in vivo. Davis TP, et al. **Eur J Pharmacol** 1985 May 8; 111(2):177–83

Chronic antidepressant treatment increases enkephalin levels in n. accumbens and striatum of the rat. De Felipe MC, et al. **Eur J Pharmacol** 1985 May 28;112(1):119–22

Increased affinity and selectivity of enkephalin tripeptide (Tyr–D–Ala–Gly) dimers. Lutz RA, et al. **Eur J Pharmacol** 1985 May 8;111(2):257–61

Detection of the tripeptide Tyr–Gly–Gly, a putative enkephalin metabolite in brain, using a sensitive radioimmunoassay. Llorens-Cortes C, et al. **FEBS Lett** 1985 Sep 23;189(2):325–8

Synthesis and biological activity of linear and cyclic enkephalins modified at the Gly3–Phe4 amide bond. Richman SJ, et al. **Int J Pept Protein Res** 1985 Jun;25(6):648–62

Synthesis and biological evaluation of phosphonamidate peptide inhibitors of enkephalinase and angiotensin-converting enzyme. Elliott RL, et al. **J Med Chem** 1985 Sep;28(9):1208–16

Presence and ontogeny of enkephalin and substance P in the chick ciliary ganglion. White JD, et al. **J Neurochem** 1985 Oct;45(4):1319–22

Isolation and characterization of an endogenous C-terminal fragment of the alpha-neo-endorphin/dynorphin precursor from bovine caudate nucleus. Evans CJ, et al. **J Neurosci** 1985 Jul;5(7):1803–7

Peptidases that terminate the action of enkephalins. Consideration of physiological importance for amino-, carboxy-, endo-, and pseudoenkephalinase. Dua AK, et al. **Life Sci** 1985 Sep 16; 37(11):985–92 (70 ref.)

Use of mRNA hybridization and radioimmunoassay to study mechanisms of drug-induced accumulation of enkephalins in rat brain structures. Mocchetti I, et al. **Mol Pharmacol** 1985 Jul;28(1):86–91

Effects of endogenous opioid peptides and opiates on luteinizing hormone and prolactin secretion in ovariectomized rats. Leadem CA, et al. **Neuroendocrinology** 1985 Oct;41(4):342–52

Release of proenkephalin-derived opioid peptides from rat striatum in vitro and their rapid degradation. Patey G, et al. **Neuroscience** 1985 Aug;15(4):1035–44

Ontogeny and regional distribution of proenkephalin- and prodynorphin-derived peptides and opioid receptors in rat hippocampus. Zamir N, et al. **Neuroscience** 1985 Aug;15(4):1025–34

Central effects of mu, delta, and kappa receptor agonists in hemorrhagic shock. Feuerstein G, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 1:11–3

Changes in plasma proenkephalin peptide F and catecholamine levels during graded exercise in men. Kraemer WJ, et al. **Proc Natl Acad Sci USA** 1985 Sep;82(18):6349–51

Proenkephalin and enkephalin metabolism by rat brain cathepsin B: conversion, inactivation, and suppression by an endogenous inhibitor. Marks N, et al. **Prog Clin Biol Res** 1985;180:247–9

[The spinal enkephalinergic and serotoninergic systems in the control of transmission of nociceptive messages] Cesselin F, et al. **J Pharmacol** 1985;16 Suppl 1:119–37 (70 ref.) (Eng. Abstr.) **(Fre)**

[Effect of gamma irradiation on brain enkephalin hydrolase activity in the rat] Gengin MT, et al. **Radiobiologiia** 1985 May–Jun;25(3):394–7 (Eng. Abstr.) **(Rus)**

[Effect of a cyclic analog of enkephalin on learning and memory in the mouse] Getsova VM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug; 35(4):710–7 (Eng. Abstr.) **(Rus)**

EPINEPHRINE

Beta receptors in peripheral mononuclear cells increase acutely during exercise. Burman KD, et al. **Acta Endocrinol (Copenh)** 1985 Aug; 109(4):563–8

Central hyperglycaemic effect of adrenaline and carbachol. Iguchi A, et al. **Acta Endocrinol (Copenh)** 1985 Aug;109(4):440–5

Effect of the rate of blood loss on the plasma catecholamine response. Tárnoky K, et al. **Acta Physiol Hung** 1985;66(2):143–53

Central nervous system actions of somatostatin-related peptides. Brown MR, et al. **Adv Exp Med Biol** 1985;188:217–28

Blood flow in the renal portal circulation of the turkey: effect of epinephrine. Palmore WP, et al. **Am J Vet Res** 1985 Jul; 46(7):1589–92

Beneficial effect of epinephrine infusion on cerebral and myocardial blood flows during CPR. Koehler RC, et al. **Ann Emerg Med** 1985 Aug; 14(8):744–9

Effects of prolonged intravenous infusions of adrenaline on glucose utilization, plasma metabolites, hormones and milk production in lactating sheep. Leenanuruksa D, et al. **Aust J Biol Sci** 1985; 38(2):197–208

Stress, catecholamines, and sleep. Harrison GA. **Aviat Space Environ Med** 1985 Jul;56(7):651–3

Adrenergic-agonist-induced Ca2+ fluxes in rat parotid cells are not Na+-dependent. Helman J, et al. **Biochem J** 1985 Sep 1; 230(2):313–20

Release of endogenous brain epinephrine by the calcium ionophores X537A and A23187. Liang NY, et al. **Brain Res** 1985 Aug 26; 341(2):297–302

Increased plasma noradrenaline during low dose adrenaline infusion in resting man and during sympathetic stimulation. Musgrave IF, et al. **Clin Exp Pharmacol Physiol** 1985 May–Jun;12(3):285–9

Beta-adrenoceptor responsiveness and plasma catecholamines as determinants of cardiovascular reactivity to mental stress. Eisenhofer G, et al. **Clin Sci** 1985 Oct;69(4):483–92

The development of a homologous teleost insulin radioimmunoassay and its use in the study of adrenaline on insulin secretion from isolated pancreatic islet tissue of the rainbow trout, Salmo gairdinerii (R.). Tilzey JF, et al. **Comp Biochem Physiol** [A] 1985;81(4):821–5

Adrenergic stimulation of adrenocortical secretion in immature fowl. Rees A, et al. **Comp Biochem Physiol** [C] 1985;81(2):387–9

Pretreatment with detergents modulates the effects of epinephrine on uveal flow and intraocular pressure. van Pinxteren PC, et al. **Curr Eye Res** 1985 Jul;4(7):783–8

Thyroid hormones in rats during long-term cold exposure and hypometabolic effect of reverse triiodothyronine on adrenaline induced thermogenesis. Vybíral S, et al. **Endocrinol Exp (Bratisl)** 1985 Sep; 19(3):179–85

Elevated catecholamines in porcine follicular fluid before ovulation. Bahr JM, et al. **Endocrinology** 1985 Aug;117(2):620–3

Examination of the effects of epinephrine, norepinephrine, and dopamine on aldosterone production in bovine glomerulosa cells in vitro. Sequeira SJ, et al. **Endocrinology** 1985 Nov;117(5):1947–52

Histopathology of the spinal cord after intrathecal cocaine, bupivacaine, lignocaine and adrenaline in the rat. Bahar M, et al. **Eur J Anaesthesiol** 1984 Sep;1(3):293–7

Plasma testosterone and catecholamine responses to physical exercise of different intensities in men. Ježová D, et al. **Eur J Appl Physiol** 1985; 54(1):62–6

Decrease in adrenaline content of various organs of the rat after 6-hydroxydopamine. Sudo A. **Eur J Pharmacol** 1985 Aug 7; 114(1):79–83

A role for adrenaline and calmodulin in modulating cyclic AMP levels during the lactogenic cycle. Muñoz A, et al. **FEBS Lett** 1985 Jul 22; 187(1):173–6

Epinephrine effect on carbohydrate metabolism in isolated and perfused catfish liver. Ottolenghi C, et al. **Gen Comp Endocrinol** 1985 Aug; 59(2):219–29

Effect of slow calcium channel blockers on the electromechanical activity of frog myocardium in the presence of epinephrine. Gendvilienė V, et al. **Gen Physiol Biophys** 1985 Aug;4(4):349–58

Iontophoresis of epinephrine isomers to rabbit eyes induced HSV-1 ocular shedding. Hill JM, et al. **Invest Ophthalmol Vis Sci** 1985 Sep; 26(9):1299–303

Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep. Topper JE, et al. **Invest Ophthalmol Vis Sci** 1985 Oct; 26(10):1315–9

Vascular responses to intravenous catecholamines in hands and forearms with normal and with increased skin blood flow. Allen JA, et al. **Ir J Med Sci** 1985 May;154(5):178–86

The hemodynamic and plasma catecholamine responses to routine restorative dental care. Cioffi GA, et al. **J Am Dent Assoc** 1985 Jul; 111(1):67–70

Stimulation by epinephrine of the membrane transport of long chain fatty acid in the adipocyte. Abumrad NA, et al. **J Biol Chem** 1985 Aug 25; 260(18):9969–71

Haemodynamic and catecholamine responses to hypothermia in the fetal sheep in utero. Gunn TR, et al. **J Dev Physiol** 1985 Aug;7(4):241–9

Do catecholamines directly modulate the delayed plateau potassium current in frog atrium? Hume JR. **J Mol Cell Cardiol** 1985 Aug; 17(8):813–6

Autoregulation of endogenous epinephrine release via presynaptic adrenoceptors in the rat hypothalamic slice. Goshima Y, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):248–53

Free and conjugated catecholamines in digestive tissues of rats. Gaudin C, et al. **Life Sci** 1985 Oct 21;37(16):1469–74

Adrenaline and anaphylaxis [letter] Ford RM. **Med J Aust** 1985 Sep 30; 143(7):319

In support of a model bill allowing the use of insect sting kits by trained laymen. Frazier CA. **NC Med J** 1985 Jun;46(6):571–2

Serotonin coexists with epinephrine in rat adrenal medullary cells. Holzwarth MA, et al. **Neuroendocrinology** 1985 Sep;41(3):230–6

Biochemical, physical and psychological findings in patients suffering from cardiac neurosis. Gasic S, et al. **Neuropsychobiology** 1985; 13(1–2):12–6

Neuroendocrine differences between violent and non–violent parasuicides. Prasad AJ. **Neuropsychobiology** 1985;13(4):157–9

Substance P given intrathecally at the spinal T9 level increases adrenal output of adrenaline and noradrenaline in the rat. Yashpal K, et al. **Neuroscience** 1985 Jun;15(2):529–36

Mechanisms involved in the adrenaline–induced blockade of milk ejection in dairy cattle. Gorewit RC, et al. **Proc Soc Exp Biol Med** 1985 Nov; 180(2):340–7

Role of brain epinephrine neurons in the regulation of serum prolactin and luteinizing hormone release in female rats. Liang NY, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jun;48(3):459–62

Plasma adrenaline and noradrenaline during mental stress and isometric exercise in man. The role of arterial sampling. Jörgensen LS, et al. **Scand J Clin Lab Invest** 1985 Sep;45(5):447–52

Epinephrine–induced aggregation of rabbit platelets refractory to ADP. Lalau Keraly C, et al. **Thromb Haemost** 1985 Jun 24;53(3):366–71

[The effect of water structure on cyclodextrin inclusion and light sensitivity of epinephrine] Hüttenrauch R, et al. **Pharmazie** 1985 Mar; 40(3):199–200 **(Ger)**

[Individual differences in circadian response to a schedule with a 12–hour time shift––a laboratory study of oral temperature, and adrenaline and 17–OHCS excretion] Okada A, et al. **Ann Physiol Anthropol** 1984 Oct; 3(4):275–82 (Eng. Abstr.) **(Jpn)**

[Effects of epinephrine on plasma potassium; their relations with the liver] Saito Y, et al. **Masui** 1985 Apr;34(4):458–62 (Eng. Abstr.) **(Jpn)**

[Psychoneurotic disorders in puberty and the activity of the adrenergic system] Szewczyk L. **Pediatr Pol** 1985 Apr;60(4):306–11 (Eng. Abstr.) **(Pol)**

[Effect of Na+, K+ and Ca++ ions on catecholamine release in the caudal mesenteric ganglion] Reprintseva VM. **Fiziol Zh SSSR** 1985 May; 71(5):561–8 (Eng. Abstr.) **(Rus)**

[Effect of carbon dioxide baths on the content of catecholamines in the brain and processes of their inactivation] Mirzoian SA, et al. **Vopr Kurortol Fizioter Lech Fiz Kult** 1985 May–Jun;(3):16–9 (Eng. Abstr.) **(Rus)**

[Urinary excretion of epinephrine in patients on short–term and long–term corticosteroid therapy] Ješić S, et al. **Srp Arh Celok Lek** 1985 Jan; 113(1):29–40 (Eng. Abstr.) **(Scc)**

ESCAPE REACTION

[Substance P in the central mechanisms of the escape reaction] Zilov VG, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):6–8 (Eng. Abstr.) **(Rus)**

[Endogenous peptides in the organization of somato–vegetative responses to hypothalamic stimulation] Badikov VI, et al. **Fiziol Zh SSSR** 1985 Jul;71(7):840–7 (Eng. Abstr.) **(Rus)**

ESTRADIOL

Systemic and uterine responsiveness to angiotensin II and norepinephrine in estrogen–treated nonpregnant sheep. Naden RP, et al. **Am J Obstet Gynecol** 1985 Oct 15;153(4):417–25

LH response to LH–RH neonatally estrogenized male rats. Pinilla L, et al. **Andrologia** 1985 May–Jun;17(3):254–6

Pulsatile administration of gonadotropin–releasing hormone to anestrous sows: endocrine changes associated with GnRH–induced and spontaneous estrus. Armstrong JD, et al. **Biol Reprod** 1985 Sep; 33(2):375–80

Elevated catecholamines in porcine follicular fluid before ovulation. Bahr JM, et al. **Endocrinology** 1985 Aug;117(2):620–3

Effects of ovarian hormones on the concentrations of immunoreactive neuropeptide Y in discrete brain regions of the female rat: correlation with serum luteinizing hormone (LH) and median eminence LH–releasing hormone. Crowley WR, et al. **Endocrinology** 1985 Sep; 117(3):1151–5

In vivo gonadotropin–releasing hormone release and serum luteinizing hormone measurements in ovariectomized, estrogen–treated rhesus macaques. Levine JE, et al. **Endocrinology** 1985 Aug;117(2):711–21

Secretion of ovine luteinizing hormone in vitro: differential positive control by 17 beta–estradiol and a preparation of porcine ovarian inhibin. Miller WL, et al. **Endocrinology** 1985 Sep;117(3):907–11

Effect of dopamine agonists and antagonists on the binding of [3H]estradiol to its receptors in the anterior pituitary gland of male rats. Szijan I, et al. **Endocrinology** 1985 Nov;117(5):1742–8

Effect of local GABA administration on rat ovarian blood flow, and on progesterone and estradiol secretion. Erdő S, et al. **Eur J Pharmacol** 1985 May 20;111(3):397–400

Sex–specific effects of estradiol on hypothalamic noradrenaline turnover in gonadectomized rats. Hiemke C, et al. **Exp Brain Res** 1985; 59(1):68–72

Estradiol and melatonin effects on adrenal cortex of ovariectomized and pinealectomized rats. Malendowicz LK, et al. **Exp Clin Endocrinol** 1985 Jun;85(3):276–82

Clomiphene citrate can mimic the augmentative (positive) but not the depressing (negative) effect of estradiol on the LHRH–stimulated release of LH and FSH by the pituitary gland of the long–term ovariectomized rat. Schuiling GA, et al. **Experientia** 1985 Aug 15;41(8):1060–3

Antioestrogen inhibition of oestradiol–induced alterations in hypothalamic noradrenaline turnover. Hiemke C, et al. **J Endocrinol** 1985 Jul; 106(1):37–42

Time–dependent effects of oestradiol and progesterone on hypothalamic catecholamine turnover in ovariectomized rats. Hiemke C, et al. **J Endocrinol** 1985 Sep;106(3):303–9

Catechol oestradiol control of FSH–stimulated granulosa cell steroidogenesis. Hudson KE, et al. **J Endocrinol** 1985 Jul; 106(1):R1–4

Estradiol increases growth hormone secretion in rats exposed to swimming stress or reserpine treatment. Eriksson E, et al. **Life Sci** 1985 Sep 30; 37(13):1241–8

Preoptic catecholamine, GABA, and glutamate release in ovariectomized and ovariectomized estrogen–primed rats utilizing a push–pull cannula technique. Demling J, et al. **Neuroendocrinology** 1985 Sep; 41(3):212–8

Ovarian steroid regulation of pulsatile luteinizing hormone release during the interval between the mornings of diestrus 2 and proestrus in the rat. Leipheimer RE, et al. **Neuroendocrinology** 1985 Sep;41(3):252–7

Estradiol–induced LH release in juvenile female rats: nembutal blocks both the decline and the exposure of nonavailable pituitary LHRH receptor sites. Smith SS, et al. **Neuroendocrinology** 1985 Sep; 41(3):246–51

Hypothalamic monoaminergic activity and pituitary function in male rats with estrogen–induced pituitary hyperplasia. Terry LC, et al. **Neuroendocrinology** 1985 Oct;41(4):269–75

Effects of pimozide and domperidone administration on prolactin levels in neonatally estrogenized female rats. Aguilar E, et al. **Rev Esp Fisiol** 1985 Jun;41(2):183–6

[Correlation between the thyroxine, 17–beta–estradiol and luteinizing hormones in the systemic circulation and the rectal and vaginal temperature in heifers and cows after administration of cloprostenol] Elečko J, et al. **Vet Med (Praha)** 1985 May;30(5):257–66 (Eng. Abstr.) **(Slo)**

ETHOLOGY

[Discrete and continuous mathematical models of intraspecific behavior in the pharmacoethology of the mouse] Poshivalov VP, et al. **Zh Vyssh Nerv Deiat** 1985 May–Jun;35(3):487–96 (Eng. Abstr.) **(Rus)**

EXPLORATORY BEHAVIOR

A genetically controlled hippocampal transmitter system regulating exploratory behavior in mice. van Abeelen JH, et al. **J Neurogenet** 1984 Apr;1(2):153–8

The effects of compounds related to gamma–aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: choice behaviour in the T–maze. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;86(3):328–33

EXTINCTION (PSYCHOLOGY)

The abolition of the partial reinforcement extinction effect (PREE) by amphetamine. Weiner I, et al. **Psychopharmacology (Berlin)** 1985; 86(3):318–23

FACTITIOUS DISORDERS

Recognition of pseudodementia. McAllister TW. **Am Fam Physician** 1985 Oct;32(4):175–81

FEAR

Lactate–induced panic attacks: possible involvement of serotonin reuptake stimulation. Lingjaerde O. **Acta Psychiatr Scand** 1985 Aug; 72(2):206–8

Platelet monoamine oxidase activity in patients with panic disorder. Gorman J, et al. **Biol Psychiatry** 1985 Aug;20(8):852–7

Thyroid indices in panic disorder. Fishman SM, et al. **J Clin Psychiatry** 1985 Oct;46(10):432–3

Suppressant effect of REM sleep deprivation on neophobia in normal rats and in rats with selective DSP–4 induced damage of locus coeruleus neurons. Mogilnicka E, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):93–7

Effect of panic attacks on the treatment of atypical depressives. Liebowitz MR, et al. **Psychopharmacol Bull** 1985;21(3):558–61

Panic attacks in outpatients with depression: response to antidepressant treatment. Robinson DS, et al. **Psychopharmacol Bull** 1985; 21(3):562–7

Neuroendocrine abnormalities in panic disorder. Roy–Byrne PP, et al. **Psychopharmacol Bull** 1985;21(3):546–50

[Panic attacks treated with alprazolam (letter)] Andersen T. **Ugeskr Laeger** 1985 Jun 17;147(25):2014–5 **(Dan)**

FENFLURAMINE

Experimental neurotoxicity of the anorectic fenfluramine. I. A fine structural model for cerebral lysosomal storage and neuroglial reaction. Dastur DK, et al. **Acta Neuropathol (Berl)** 1985;67(1–2):142–54

Pilot study on the effects of fenfluramine on negative symptoms in twelve schizophrenic inpatients. Stahl SM, et al. **Biol Psychiatry** 1985 Oct; 20(10):1098–102

A comparison of the acute effects of dextroamphetamine and fenfluramine in depression. Ward NG, et al. **Biol Psychiatry** 1985 Oct; 20(10):1090–7

Use of mRNA hybridization and radioimmunoassay to study mechanisms of drug-induced accumulation of enkephalins in rat brain structures. Mocchetti I, et al. **Mol Pharmacol** 1985 Jul;28(1):86–91

Pharmacological studies on the serotoninergic and nonserotonin-mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pretreatment with fluoxetine, indalpine, PCPA, and L-tryptophan. Van de Kar LD, et al. **Neuroendocrinology** 1985 Oct; 41(4):283–8

Serotonin and norepinephrine-dependent effects of fenfluramine on plasma renin activity in conscious male rats. Van de Kar LD, et al. **Neuropharmacology** 1985 Jun;24(6):487–94

FK 33–824

Influence of methionine-enkephalin analogue (FK-33-824) on the secretion of pancreatic hormones. Sekiya K, et al. **Gastroenterol Jpn** 1985 Jun;20(3):252–9

Blockade of alpha 2-adrenoceptors prevents the growth hormone releasing effect of FK 33-824 in the dog. Cella SG, et al. **Horm Metab Res** 1985 Jul;17(7):379–80

Gonadal steroids deficiency and prolactin response to a met-enkephalin analog in man. Foresta C, et al. **Horm Metab Res** 1985 Jun; 17(6):319–20

FLICKER FUSION

Temazepam and the perceptual-motor performance of professional footballers. Golby J, et al. **Br J Sports Med** 1985 Jun;19(2):115–8

Evaluation of signal detection theory on the effects of psychotropic drugs on critical flicker-fusion frequency in normal subjects. MacNab MW, et al. **Psychopharmacology (Berlin)** 1985;85(4):431–5

FLUPHENAZINE

Separate and combined anxiolytic and anti-depressant treatment of mixed anxiety/depression. A double-blind, placebo controlled comparison. Sussex Clinical Trials Group. **Acta Psychiatr Scand** 1985 Jul; 72(1):81–8

Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial. III. Relapse postponement or relapse prevention? The implications for long-term outcome. Curson DA, et al. **Br J Psychiatry** 1985 May;146:474–80

Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial I. Course of illness, stability of diagnosis, and the role of a special maintenance clinic. Curson DA, et al. **Br J Psychiatry** 1985 May;146:464–9

Neuroleptic serum levels measured by radioreceptor assay in patients receiving intramuscular depot neuroleptics. Some preliminary findings. Turbott J, et al. **Br J Psychiatry** 1985 Apr;146:439–42

FOOD DEPRIVATION

Effects of cadmium ingestion and food restriction on energy metabolism and tissue metal concentrations in mallard ducks (Anas platyrhynchos). Di Giulio RT, et al. **Environ Res** 1985 Aug;37(2):433–44

Norepinephrine turnover in the hypothalamus of adult male rats: alteration of circadian patterns by semistarvation. Schweiger U, et al. **J Neurochem** 1985 Sep;45(3):706–9

Effects of withholding food for 0–72 h on mating, pregnancy rate and pituitary function in female rats. McClure TJ, et al. **J Reprod Fertil** 1985 May;74(1):57–64

FSH

Effect of pretreatment of long-term ovariectomized (OVX) rats with a competitive LRH antagonist on FSH release in vitro. van Dieten JA, et al. **Acta Endocrinol (Copenh)** 1985 Aug;109(4):481–4

Selective and/or overlapping effect of pituitary hormones (thyrotropin, gonadotropin) on serum thyroxin and testosterone level in newly hatched cockerels. Dobozy O, et al. **Acta Physiol Hung** 1985; 66(2):177–81

Plasma FSH and LH in prepubertal Booroola ewe lambs. Bindon BM, et al. **Aust J Biol Sci** 1985;38(2):215–20

A suppression of gonadotropin secretion by cortisol in castrated male rhesus monkeys (Macaca mulatta) mediated by the interruption of hypothalamic gonadotropin-releasing hormone release. Dubey AK, et al. **Biol Reprod** 1985 Sep;33(2):423–31

The effects of cycloheximide on in vitro response of Rana pipiens pituitaries to continuously superfused gonadotropin-releasing hormone. Porter DA. **Biol Reprod** 1985 Sep;33(2):393–400

Thyrotropin and gonadotropin releasing hormones (TRH and GnRH) do not alter levels of oxytocin and oxytocin does not change the response of luteinizing or follicle stimulating hormones to GnRH in humans. Amico JA, et al. **Endocr Res** 1985;11(1–2):75–85

Differential regulation of pulsatile luteinizing hormone (LH) and follicle-stimulating hormone secretion in ovariectomized rats disclosed by treatment with a LH-releasing hormone antagonist and phenobarbital. De Paolo LV. **Endocrinology** 1985 Nov; 117(5):1826–33

Identification of subpopulations of rat granulosa cells: sedimentation properties and hormonal responsiveness. Kasson BG, et al. **Endocrinology** 1985 Sep;117(3):1027–34

Corelease of dynorphin-like immunoreactivity, luteinizing hormone, and follicle-stimulating hormone from rat adenohypophysis in vitro. Knepel W, et al. **Endocrinology** 1985 Aug;117(2):481–7

Effects of glucocorticoids on responsiveness of luteinizing hormone and follicle-stimulating hormone to gonadotropin-releasing hormone by male rat pituitary cells in vitro. Suter DE, et al. **Endocrinology** 1985 Sep;117(3):855–9

Effects of glucocorticoids on secretion of luteinizing hormone and follicle-stimulating hormone by female rat pituitary cells in vitro. Suter DE, et al. **Endocrinology** 1985 Sep;117(3):849–54

Clomiphene citrate can mimic the augmentative (positive) but not the depressing (negative) effect of estradiol on the LHRH-stimulated release of LH and FSH by the pituitary gland of the long-term ovariectomized rat. Schuiling GA, et al. **Experientia** 1985 Aug 15;41(8):1060–3

Serum luteinizing hormone-releasing hormone (LH-RH) and gonadotropic hormones in men after a bolus dose of LH-RH: comparison of different doses and routes of administration. Fauser BC, et al. **Fertil Steril** 1985 Sep;44(3):384–9

Effects of chicken (Gln8)- and mammalian (Arg8)-luteinizing hormone-releasing hormones on the release of gonadotrophins in vitro and in vivo from the adenohypophysis of Japanese quail. Hattori A, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):155–61

Seasonal cycles in testicular activity, gonadotropin, and thyroxine in the painted turtle, Chrysemys picta, under natural conditions. Licht P, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):130–9

Pituitary responsiveness to superfused GnRH in two species of ranid frogs. Porter DA, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):308–15

Effects of dihydrotestosterone benzoate administration on gonadotropin secretion in ovariectomized pony mares. Garza F Jr, et al. **J Anim Sci** 1985 Jul;61(1):240–4

Catechol oestradiol control of FSH-stimulated granulosa cell steroidogenesis. Hudson KE, et al. **J Endocrinol** 1985 Jul; 106(1):R1–4

Effects of LH-releasing hormone antagonist or lesions of the medial basal hypothalamus on periovulatory gonadotrophin release in female rats. Rush ME. **J Endocrinol** 1985 Sep;106(3):361–6

Time series analysis of plasma LH and FSH concentrations as a method of assessing episodic secretion. McLeod BJ, et al. **J Reprod Fertil** 1985 Jul;74(2):575–87

Plasma LH and FSH responses and ovarian activity in prepubertal heifers treated with repeated injections of low doses of GnRH for 72 h. McLeod BJ, et al. **J Reprod Fertil** 1985 Jul;74(2):589–96

Twin pregnancy after pituitary desensitisation with LHRH agonist and pure FSH [letter] Shaw RW, et al. **Lancet** 1985 Aug 31; 2(8453):506–7

Effects of the 1,5-benzodiazepine clobazam on pituitary hormones in the male rat. Valli M, et al. **Methods Find Exp Clin Pharmacol** 1985 Apr; 7(4):179–81

Electrofocusing fractionation of follicle stimulating hormone in pituitary cell culture extracts from male and female rats. Foulds LM, et al. **Mol Cell Endocrinol** 1985 Jul;41(2–3):129–36

A prolactin-inhibiting factor within the precursor for human gonadotropin-releasing hormone. Nikolics K, et al. **Nature** 1985 Aug 8–14;316(6028):511–7

[Gonadotropin stimulation during LH/RH analog-induced inhibition of pituitary function] Bettendorf G, et al. **Geburtshilfe Frauenheilkd** 1985 Jul;45(7):431–7 (Eng. Abstr.) **(Ger)**

GABA

Memory effects of GABA-ergic antagonists in rats trained with two-way active avoidance tasks. Yonkov DI, et al. **Acta Physiol Pharmacol Bulg** 1985;11(2):44–9

gamma-Aminobutyric acid concentrations are maintained in anoxic turtle brain. Lutz PL, et al. **Am J Physiol** 1985 Sep;249(3 Pt 2):R372–4

Uptake and release of gamma-aminobutyric acid in guinea pig gallbladder. Saito N, et al. **Am J Physiol** 1985 Aug;249(2 Pt 1):G192–6

Modulation of a GABA-ergic inhibitory circuit in the in vitro hippocampus by etomidate isomers. Ashton D, et al. **Anesth Analg** 1985 Oct;64(10):975–80

An inhibitory protein of intestinal fluid secretion reverses neuronal GABA transport. Lange S, et al. **Biochem Biophys Res Commun** 1985 Aug 15; 130(3):1032–6

A gamma-aminobutyric acid-specific transport mechanism in mammalian kidney. Goodyer PR, et al. **Biochim Biophys Acta** 1985 Aug 8; 818(1):45–54

An unusual effect of gamma-aminobutyric acid on synaptic transmission of frog tectal neurones in vitro. Nistri A, et al. **Br J Pharmacol** 1985 Aug;85(4):917–21

Circannual variations of GABA content in cytosolic and crude synaptosomal fractions in some brain areas of the European hamster. Ciesielski L, et al. **Brain Res** 1985 Sep 30;344(1):146–9

A calculation method for evaluating the time course of GABA removal from a synaptic cleft by presynaptic uptake systems. Cupello A, et al. **Brain Res** 1985 Sep 2;342(1):176–8

Coexistence of immunoreactivities for glutamate decarboxylase and tyrosine hydroxylase in some neurons in the periglomerular region of the rat main olfactory bulb: possible coexistence of gamma-aminobutyric acid (GABA) and dopamine. Kosaka T, et al. **Brain Res** 1985 Sep 16; 343(1):166–71

Growth cones isolated from developing rat forebrain: uptake and release of GABA and noradrenaline. Lockerbie RO, et al. **Brain Res** 1985 Aug; 353(2):265–75

Evidence for impaired GABAergic activity in the substantia nigra of amygdaloid kindled rats. Löscher W, et al. **Brain Res** 1985 Jul 22; 339(1):146–50

Evidence for GABA mediation of sympathetic inhibition evoked from midline medullary depressor sites. McCall RB, et al. **Brain Res** 1985 Jul 29;339(2):356–60

Development of sensitivity to GABA and glycine in cultured cerebellar neurons. Mori-Okamoto J, et al. **Brain Res** 1985 Jun;352(2):249–58

Effects on the caudate spindle in rats of taurine and gamma-aminobutyric acid (GABA) microinjected into the substantia nigra: involvement of the dopaminergic system. Okuyama S, et al. **Brain Res** 1985 Sep 9; 342(2):366–8

Newly identified GABAergic neurons in regions of the ventrolateral medulla which regulate blood pressure. Ruggiero DA, et al. **Brain Res** 1985 Jul 22;339(1):171–7

Effects of 4-aminopyridine, GABA and bicuculline on cutaneous receptive fields of cat dorsal horn neurons. Saadé N, et al. **Brain Res** 1985 Oct 7;344(2):356–9

GABA mimetics decrease extracellular concentrations of 5-HIAA (as measured by in vivo voltammetry) in the dorsal raphe of the rat. Scatton B, et al. **Brain Res** 1985 Aug 26;341(2):372–6

Some factors that influence the decrement in the response to GABA during its continuous iontophoretic application to hippocampal neurons. Thalmann RH, et al. **Brain Res** 1985 Sep 9;342(2):219–33

Localization of GABA immunoreactivity in the auditory brainstem of guinea pigs. Thompson GC, et al. **Brain Res** 1985 Jul 22; 339(1):119–22

GABA activates different types of chloride-conducting receptor-ionophore complexes in a dose-dependent manner. Yasui S, et al. **Brain Res** 1985 Sep 30;344(1):176–80

Stimulated release of endogenous GABA and glycine from the goldfish retina. Yazulla S, et al. **Brain Res** 1985 Oct 21;345(2):384–8

Involvement of growth hormone-releasing factor in growth hormone secretion induced by gamma-aminobutyric acid in conscious rats. Murakami Y, et al. **Endocrinology** 1985 Aug;117(2):787–9

Evidence for a GABAergic control of the exercise-induced rise in GH in man. Steardo L, et al. **Eur J Clin Pharmacol** 1985;28(5):607–9

GABAergic drugs and sexual behaviour in the male rat. Agmo A, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):371–8

Effect of local GABA administration on rat ovarian blood flow, and on progesterone and estradiol secretion. Erdö S, et al. **Eur J Pharmacol** 1985 May 20;111(3):397–400

Inhibition by yohimbine of the calcium-dependent evoked release of [3H]GABA in rat and mouse brain slices in vitro. Maurin Y, et al. **Eur J Pharmacol** 1985 Apr 23;111(1):37–48

Progabide reverses the nigral substance P reduction induced by chronic impairment of dopaminergic transmission. Zivkovic B, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):253–5

The non-GABAergic nature of 3H-baclofen binding in rat peripheral tissues. Kato K, et al. **Gen Pharmacol** 1985;16(4):327–33

Insulin and glucagon secretion by the dog pancreas during intravenous and oral administration of gamma aminobutyric acid (GABA). Minuk GY, et al. **Horm Metab Res** 1985 Jun;17(6):313–4

Lateral differences in the GABAergic system of the rat striatum. Guarneri P, et al. **Ital J Neurol Sci** 1985 Jun;6(2):173–6

Reconstitution and purification of the sodium- and chloride-coupled gamma-aminobutyric acid transporter from rat brain. Radian R, et al. **J Biol Chem** 1985 Sep 25;260(21):11859–65

GABAergic neurons containing CCK-8-like and/or VIP-like immunoreactivities in the rat hippocampus and dentate gyrus. Kosaka T, et al. **J Comp Neurol** 1985 Sep 22;239(4):420–30

Prolactin in cerebrospinal fluid increases the synthesis and release of hypothalamic gamma-aminobutyric acid. Locatelli V, et al. **J Endocrinol** 1985 Sep;106(3):323–8

In vivo effects of anticonvulsant drugs on nerve terminal (synaptosomal) GABA levels in 11 brain regions of the rat. Löscher W, et al. **J Neural Transm** 1985;63(2):157–67

1-Piperideine as an in vivo precursor of the gamma-aminobutyric acid homologue 5-aminopentanoic acid. Callery PS, et al. **J Neurochem** 1985 Sep;45(3):946–8

gamma-Aminobutyric acid metabolism and behavioral effects after intraventricular injection of spermine in chicks. Di Giorgio RM, et al. **J Neurochem** 1985 Sep;45(3):739–43

Improved method for isolating synaptosomes from 11 regions of one rat brain: electron microscopic and biochemical characterization and use in the study of drug effects on nerve terminal gamma-aminobutyric acid in vivo. Löscher W, et al. **J Neurochem** 1985 Sep;45(3):879–89

Uptake and release of gamma-aminobutyric acid in the guinea pig cochlear nucleus after axotomy of cochlear and centrifugal fibers. Potashner SJ, et al. **J Neurochem** 1985 Nov;45(5):1558–66

Binding of lanthanum ions and ruthenium red to synaptosomes and its effects on neurotransmitter release. Tapia R, et al. **J Neurochem** 1985 Nov;45(5):1464–70

Succinic semialdehyde as a substrate for the formation of gamma-aminobutyric acid. van Bemmelen FJ, et al. **J Neurochem** 1985 Nov;45(5):1471–4

Conversion of gamma-hydroxybutyrate to gamma-aminobutyrate in vitro. Vayer P, et al. **J Neurochem** 1985 Sep;45(3):810–4

Methionine-induced changes in glutamate, aspartate, glutamine, and gamma-aminobutyrate levels in brain tissue. Wood JD, et al. **J Neurochem** 1985 Sep;45(3):777–83

Properties of succinic semialdehyde dehydrogenase in cultured human lymphoblasts. Gibson KM, et al. **J Neurogenet** 1985 Apr;2(2):111–22

Rectification of single GABA-gated chloride channels in adult hippocampal neurons. Gray R, et al. **J Neurophysiol** 1985 Jul; 54(1):134–42

Characterization of GABAergic neurons in cerebellar primary cultures and selective neurotoxic effects of a serum fraction. Aloisi F, et al. **J Neurosci** 1985 Aug;5(8):2001–8

Modulation of neurotransmitter action: control of the gamma-aminobutyric acid response through the benzodiazepine receptor. Chan CY, et al. **J Neurosci** 1985 Sep;5(9):2365–73

The morphology of physiologically identified GABAergic neurons in the somatic sensory part of the thalamic reticular nucleus in the cat. Yen CT, et al. **J Neurosci** 1985 Aug;5(8):2254–68

GABA inhibits excitatory neurotransmission in rat pelvic ganglia. Maggi CA, et al. **J Pharm Pharmacol** 1985 May;37(5):349–51

Upregulation of gamma-aminobutyric acid (GABA) B binding sites in rat frontal cortex: a common action of repeated administration of different classes of antidepressants and electroshock. Lloyd KG, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):191–9

An intracellular analysis of gamma-aminobutyric-acid-associated ion movements in rat sympathetic neurones. Ballanyi K, et al. **J Physiol (Lond)** 1985 Aug;365:41–58

Action and localization of gamma-aminobutyric acid in the cat retina. Bolz J, et al. **J Physiol (Lond)** 1985 May;362:369–93

Effect of excitatory amino acids on gamma-aminobutyric acid release from frog horizontal cells. Cunningham JR, et al. **J Physiol (Lond)** 1985 May;362:51–67

Substance P provoked gamma-aminobutyric acid release from the myenteric plexus of the guinea-pig small intestine. Tanaka C, et al. **J Physiol (Lond)** 1985 May;362:319–29

Elevated levels of gamma amino butyric acid (GABA) in the thymus gland during the immune response. Hall NR, et al. **Lymphokine Res** 1985 Fall;4(4):339–41

Uptake of GABA by bovine adrenal medulla slices. Oset Gasque MJ, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun;329(4):372–5

Lack of effect of GABA on [3H]leucine incorporation into a rat oviduct ribosomal system. Orensanz LM, et al. **Neurochem Res** 1985 Jun; 10(6):789–96

Effects of bath-applied GABA on the firing pattern of cells in an in vitro preparation of mammalian cerebral cortex. Bagust J, et al. **Neuropharmacology** 1985 Jun;24(6):551–4

Effect of aminooxyacetic acid on gamma-aminobutyric acid release from frog retina. Bedwani JR, et al. **Neuropharmacology** 1985 Jun; 24(6):495–7

Effects of a depressant/convulsant pair of glutarimides on neuronal activity in the isolated spinal cord of the immature rat. Nicholson GM, et al. **Neuropharmacology** 1985 Jun;24(6):461–4

Stability of the amino acid content of nerve endings after administration of gamma-aminobutyrate agonists and antagonists. Wood JD, et al. **Neuropharmacology** 1985 Jul;24(7):685–7

Spontaneous inhibitory postsynaptic potentials in guinea pig neocortex and olfactory cortex neurones. Galvan M, et al. **Neurosci Lett** 1985 Jun 12;57(2):131–5

The gamma-aminobutyric acid-mimetic action of omega-aminocaprylic

acid in rat cortex. Hicks TP, et al. **Neurosci Lett** 1985 Jun 24; 57(3):295–9

On the binding of gamma-[3H]aminobutyric acid to the rat oviduct [letter] Orensanz LM, et al. **Neurosci Lett** 1985 Jun 24;57(3):213–4

Sodium-dependent, calmodulin-dependent transmitter release from synaptosomes. Sandoval ME, et al. **Neurosci Lett** 1985 May 23; 56(3):271–7

Opposite effects of monosodium glutamate on the dopaminergic and GABAergic innervations of the median eminence and the intermediate lobe in the mouse. Stoeckel ME, et al. **Neurosci Lett** 1985 May 23; 56(3):249–55

GABAergic intrinsic interneurons in the red nucleus of the cat demonstrated with combined immunocytochemistry and anterograde degeneration methods. Katsumaru H, et al. **Neurosci Res** 1984 Feb; 1(1):35–44

Patch-clamp studies of chloride channels activated by gamma-aminobutyric acid in cultured hippocampal neurones of the rat. Ozawa S, et al. **Neurosci Res** 1984 Oct;1(5):275–93

Angiotensin II-induced depression of Purkinje cell firing and possible modulatory action on GABA responses. Tongroach P, et al. **Neurosci Res** 1984 Oct;1(5):369–72

Reduction of inhibition by a benzodiazepine antagonist, Ro15-1788, in the rat hippocampal slice. King GL, et al. **Neuroscience** 1985 Jun; 15(2):371–8

The role of the gamma-aminobutyrate system in the interactions of cortical evoked potentials. Toldi J, et al. **Neuroscience** 1985 Aug; 15(4):977–81

Effect of valproate on brain GABA: comparison with various medium chain fatty acids. Keane PE, et al. **Pharmacol Res Commun** 1985 Jun; 17(6):547–55

Ion channels activated by L-glutamate and GABA in cultured cerebellar neurons of the rat. Cull-Candy SG, et al. **Proc R Soc Lond [Biol]** 1985 May 22;224(1236):367–73

The GABA hypothesis of depression and antidepressant drug action. Bartholini G, et al. **Psychopharmacol Bull** 1985;21(3):385–8

GABAergic effects of reserpine following chronic treatment. Suzdak PD, et al. **Psychopharmacology (Berlin)** 1985;87(2):157–60

Actions and interactions of GABA and benzodiazepines in the mouse hippocampal slice. Biscoe TJ, et al. **Q J Exp Physiol** 1985 Jul; 70(3):313–28

The anion selectivity of GABA-mediated post-synaptic potentials in mouse hippocampal cells. Biscoe TJ, et al. **Q J Exp Physiol** 1985 Jul; 70(3):305–12

Inhibition of gamma-[3H]aminobutyric acid uptake by organotin compounds in vitro. Costa LG. **Toxicol Appl Pharmacol** 1985 Jul; 79(3):471–9

Probicyclophosphates: monocyclophosphates as potential prodrugs for bicyclophosphate GABA antagonists. Toia RF, et al. **Toxicol Appl Pharmacol** 1985 Oct;81(1):50–7

Inhibition of 4-aminobutyric acid (GABA) turnover by chlordane. Fishman BE, et al. **Toxicol Lett** 1985 Aug;26(2-3):219–23

GABAergic inhibition and orientation selectivity of neurons in the kitten visual cortex at the time of eye opening. Tsumoto T, et al. **Vision Res** 1985;25(3):383–8

[Effect of 2 new GABA-ergic agents on apomorphine stereotypy in the rat] Vamvakidès A. **Agressologie** 1985 Jan;26(1):63–5 (Eng. Abstr.) **(Fre)**

[3 new GABA-ergics: research on their possible site of action] Vamvakidès A. **Agressologie** 1985 Jun;26(7):591–4 (Eng. Abstr.) **(Fre)**

[GABAergic control of hypophyseal gonadotropic function and prolactin. Demonstration by valproic acid] Giroud M, et al. **J Gynecol Obstet Biol Reprod (Paris)** 1985;14(2):163–9 (Eng. Abstr.) **(Fre)**

[Effects of calcium hopantenate on GABA receptors in the aged rat brain cortex] Ogawa N, et al. **Nippon Ronen Igakkai Zasshi** 1985 May; 22(3):264–5 **(Jpn)**

[GABAergic neurons in the mammalian intestine] Taniyama K. **Nippon Yakurigaku Zasshi** 1985 May;85(5):305–13 (313 ref.) (Eng. Abstr.) **(Jpn)**

[Effect of manganese chloride poisoning during pregnancy and lactation on the levels and synthesis of gamma-aminobutyric acid (GABA) in the rat brain] Kosicka B, et al. **Neuropatol Pol** 1985;23(2):201–9 (Eng. Abstr.) **(Pol)**

[Effect of fenibut on the GABA B receptors of the spinal motor neurons] Abramets II, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):698–700 (Eng. Abstr.) **(Rus)**

[Nature of a mediator participating in reflex inhibition of the activity of the lymphatic center of the frog] Serbeniuk TsV, et al. **Fiziol Zh SSSR** 1985 Jul;71(7):889–95 (Eng. Abstr.) **(Rus)**

[Early changes in GABA and glutamate levels and aminotransferase activity in parts of the rat brain following whole-body gamma irradiation at an absolutely lethal dose] Rozanov VA, et al. **Radiobiologiia** 1985 May–Jun;25(3):384–8 (Eng. Abstr.) **(Rus)**

[Effect of a derivative of GABA, phenibut, on behavior and the activity of visual cortex neurons of the rabbit during elaboration of a defensive reflex and internal inhibition] Shul'gina GI, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):695–702 (Eng. Abstr.)**(Rus)**

GALVANIC SKIN RESPONSE

Two types of changes in skin conductance activity after intraventricular administration of 6-hydroxydopamine in rats. Yamamoto K, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(3):245–50

GENERALIZATION, STIMULUS

Midazolam cue in rats: generalization tests with anxiolytic and other drugs. Garcha HS, et al. **Psychopharmacology (Berlin)** 1985;87(2):233–7

GENETICS, BEHAVIORAL

The genetic architecture of hyponeophagia and the action of diazepam in rats. Shephard RA, et al. **Behav Genet** 1985 May;15(3):265–86

GLUCURONIDASE

Circadian and seasonal rhythm of beta-glucuronidase in rat liver. Bhattacharya RD. **Cell Mol Biol** 1985;31(4):305–7

Diurnal variations in the transferases and hydrolases involved in glucuronide and sulfate conjugation of rat liver. Bélanger PM, et al. **Drug Metab Dispos** 1985 May–Jun;13(3):386–9

Fibroblasts acquire beta-glucuronidase by direct and indirect transfer during co-culture with macrophages. McNamara A, et al. **Exp Cell Res** 1985 Sep;160(1):150–7

Genetic variation for enzyme structure and systemic regulation in two new haplotypes of the beta-glucuronidase gene of Mus musculus castaneus. Pfister K, et al. **J Biol Chem** 1985 Sep 25; 260(21):11588–94

Weak androgen reduces the rate constant of beta-glucuronidase induction. Bullock LP, et al. **Mol Cell Endocrinol** 1985 Jul;41(2-3):179–85

GONADOTROPINS, PITUITARY

Desensitization of testicular ornithine decarboxylase to gonadotropin releasing hormone and gonadotropic hormones. Madhubala R, et al. **Biochem Int** 1985 Aug;11(2):225–32

The corpus luteum of the primate menstrual cycle is capable of recovering from a transient withdrawal of pituitary gonadotropin support. Hutchison JS, et al. **Endocrinology** 1985 Sep;117(3):1043–9

Role of GnRH in the maturation of pituitary gonadotroph function. Clayton RN. **J Reprod Fertil** 1985 Sep;75(1):307–15 (62 ref.)

The effects of thymus-derived peptides on hypothalamic LRF and pituitary gonadotropin content in prepubertal congenitally athymic nude mice and their normal heterozygous littermates. Strich G, et al. **J Reprod Immunol** 1985 Jun;7(4):351–9

[Pulsed administration of gonadoliberine (GnRH) in the treatment of anovulation] Jaffiol C, et al. **Bull Acad Natl Med (Paris)** 1985 Jan; 169(1):95–8 (Eng. Abstr.) **(Fre)**

[GABAergic control of hypophyseal gonadotropic function and prolactin. Demonstration by valproic acid] Giroud M, et al. **J Gynecol Obstet Biol Reprod (Paris)** 1985;14(2):163–9 (Eng. Abstr.) **(Fre)**

GUANETHIDINE

Protection from guanethidine-induced neuronal destruction by nerve growth factor: effect of NGF on immune function. Manning PT, et al. **Brain Res** 1985 Aug 5;340(1):61–9

Reproductive physiology and behavior in the male rat following acute and chronic peripheral adrenergic depletion by guanethidine. Stefanick ML, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):55–63

HALOPERIDOL

Lipid peroxidation as a possible mechanism for the neurotoxic and nephrotoxic effects of a combination of lithium carbonate and haloperidol. Sawas AH, et al. **Arch Int Pharmacodyn Ther** 1985 Aug; 276(2):301–12

Interconversions of haloperidol and reduced haloperidol in guinea pig and rat liver microsomes. Korpi ER, et al. **Biochem Pharmacol** 1985 Aug 15;34(16):2923–7

Plasma cortisol levels in mania: associated clinical ratings and changes during treatment with haloperidol. Cookson JC, et al. **Br J Psychiatry** 1985 May;146:498–502

Treatment of rapid cycling affective illness [letter] Lowe MR. **Br J Psychiatry** 1985 May;146:558

In vivo voltammetric and behavioural evidence for somatodendritic autoreceptor control of mesolimbic dopamine neurones. Maidment NT, et al. **Brain Res** 1985 Jul 15;338(2):317–25

Effect of transition or heavy metals on [3H]haloperidol binding in rat striatal membranes in vitro. Komulainen H, et al. **Eur J Pharmacol** 1985 Aug 15;114(2):113–9

Chronic haloperidol causes increase in salivary response and alpha 1-adrenoceptors in submandibular gland of the rat. Pazo JH, et al.

Eur J Pharmacol 1985 Jul 11;113(1):121–4

Repetitive measurement of monoamine metabolite levels in cerebrospinal fluid of conscious rats: effects of reserpine and haloperidol. Scheinin H, et al. **Eur J Pharmacol** 1985 Jul 31;113(3):345–51

Comparison of injectable molindone and haloperidol followed by oral dosage forms in acutely ill schizophrenics. Escobar JI, et al. **J Clin Psychiatry** 1985 Aug;46(8 Pt 2):15–9

Quantification of reduced haloperidol and haloperidol by radioimmunoassay. Browning JL, et al. **J Immunoassay** 1985; 6(1–2):45–66

Synthesis of high specific activity [75Br]- and [77Br]bromperidol and tissue distribution studies in the rat. Moerlein SM, et al. **J Med Chem** 1985 Sep;28(9):1319–24

Quantification of dopaminergic supersensitization using apomorphine–induced behavior in the mouse. Randall PK. **Life Sci** 1985 Oct 14;37(15):1419–23

Use of mRNA hybridization and radioimmunoassay to study mechanisms of drug–induced accumulation of enkephalins in rat brain structures. Mocchetti I, et al. **Mol Pharmacol** 1985 Jul;28(1):86–91

Long–term haloperidol treatment elevates beta–endorphin levels in the intermediate pituitary but not in rat brain. Millington WR, et al. **Neuropeptides** 1985 Jul;6(4):365–72

Electrophysiological interactions between haloperidol and reduced haloperidol, and dopamine, norepinephrine and phencyclidine in rat brain. Kirch DG, et al. **Neuropharmacology** 1985 May;24(5):375–9

Comparative efficacy of red cell and plasma haloperidol as predictors of clinical response in schizophrenia. Smith RC, et al. **Psychopharmacology (Berlin)** 1985;85(4):449–55

Neuroleptic–induced priapism. Gomez EA. **Tex Med** 1985 Sep; 81(9):47–8

[Schizophrenically disordered time perception and its modification by neuroleptics] Heim M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Jul;37(7):410–5 (Eng. Abstr.) **(Ger)**

[Evaluation of the efficacy of haloperidol decanoate in the treatment of chronic psychotic hospital patients] Marchant N, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):37–41 (Eng. Abstr.) **(Spa)**

[Malignant hyperthermia caused by neuroleptics] Escolano Villén F, et al. **Rev Esp Anestesiol Reanim** 1985 Jul–Aug;32(4):189–91 (Eng. Abstr.) **(Spa)**

HEXOBARBITAL

Route– and dose–dependent pharmacokinetics of hexobarbitone in the rat: a re–evaluation of the use of sleeping times in metabolic studies. Van der Graaff M, et al. **J Pharm Pharmacol** 1985 Aug;37(8):550–4

The inhibition of bacterial bioluminescence by xenobiotics. Danilov VS, et al. **Xenobiotica** 1985 Apr;15(4):271–6

HISTAMINE

Effects of histamine and cimetidine on the levels of serotonin and 5–hydroxyindoleacetic acid in various parts of the digestive tract and in the blood and brain of rats. Kleinrok Z, et al. **Acta Physiol Pol** 1984 Mar–Apr;35(2):125–30

Effects of histamine and H1 and H2–receptor antagonists on the wet–dog–shaking episodes in rats induced with lithium chloride. Rajtar G, et al. **Acta Physiol Pol** 1984 Mar–Apr;35(2):131–5

Effect of gastrin, histamine, serotonin, and adrenergic amines on gastroesophageal sphincter pressure in the dog. Strombeck DR, et al. **Am J Vet Res** 1985 Aug;46(8):1684–90

Histamine is an antagonist of the acetylcholine receptor at the frog endplate. Ariyoshi M, et al. **Br J Pharmacol** 1985 May;85(1):65–73

Histamine–immunoreactive endocrine cells in the adrenal medulla of the rat. Häppölä O, et al. **Brain Res** 1985 Jul 29;339(2):393–6

Decrease in histamine turnover in the brain of spontaneously hypertensive rats. Oishi R, et al. **Brain Res** 1985 Sep 16;343(1):180–3

Histamine–mediated acetylcholine release in the guinea–pig ileum. Rubinstein R, et al. **Eur J Pharmacol** 1985 May 8;111(2):245–50

Effect of histamine on basal and TRH/LH–RH–stimulated PRL and LH secretion during different phases of the menstrual cycle in normal women. Knigge U, et al. **Neuroendocrinology** 1985 Oct;41(4):337–41

Positive interaction between leukotriene C4 and histamine and other mediators on vascular tissues. Omini C, et al. **Prostaglandins** 1985 Jun; 29(6):1009–20

Antramine (antral histamine) antagonizes somatostatin inhibition on endogenous gastrin–induced gastric secretion. A new hypothesis for the role of histamine in gastric secretion regulation. Vatier J, et al. **Scand J Gastroenterol** 1985 Aug;20(6):671–6

[Effect of antidepressive drugs and histamine H1 receptor blockaders on histamine level in rat brain] Zawilska J, et al. **Folia Med Cracov** 1984; 25(3–4):297–306 (Eng. Abstr.) **(Pol)**

HOMOVANILLIC ACID

Oral dosing of rats with polychlorinated biphenyls increases urinary homovanillic acid production. Seegal RF, et al. **J Toxicol Environ Health** 1985;15(5):575–86

Correlations between aminergic metabolites simultaneously obtained from human CSF and brain. Stanley M, et al. **Life Sci** 1985 Oct 7; 37(14):1279–86

HYDANTOINS

Interaction of prostaglandin D2 with prostacyclin, carbacyclin and the hydantoin prostaglandin, BW245C, in guinea–pig platelets. Hamid S, et al. **Br J Pharmacol** 1985 May;85(1):285–90

Stereoselective mephobarbital hydroxylation cosegregates with mephenytoin hydroxylation. Küpfer A, et al. **Clin Pharmacol Ther** 1985 Oct;38(4):414–8

Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. Nakamura K, et al. **Clin Pharmacol Ther** 1985 Oct; 38(4):402–8

Reversed–phase high–performance liquid chromatographic separation and quantitation of phenylthiohydantoin derivatives of 25 amino acids, including those of cysteic acid, 4–hydroxyproline, methionine sulfone, S–carboxymethylcysteine and S–methylcysteine. Kolbe HV, et al. **J Chromatogr** 1985 Jun 26;327:1–7

Phenotypic differences in mephenytoin pharmacokinetics in normal subjects. Wedlund PJ, et al. **J Pharmacol Exp Ther** 1985 Sep; 234(3):662–9

Participation of a rat liver cytochrome P–450 induced by pregnenolone 16 alpha–carbonitrile and other compounds in the 4–hydroxylation of mephenytoin. Shimada T, et al. **Mol Pharmacol** 1985 Aug; 28(2):215–9

HYDRAZINES

Determination of isoniazid, acetylisoniazid, acetylhydrazine and diacetylhydrazine in biological fluids by high–performance liquid chromatography. von Sassen W, et al. **J Chromatogr** 1985 Feb 27; 338(1):113–22

Pharmacological actions of SQ 29,548, a novel selective thromboxane antagonist. Ogletree ML, et al. **J Pharmacol Exp Ther** 1985 Aug; 234(2):435–41

[Cyclic hydrazides of mucobromic acid. (II)] Dorneanu M, et al. **Rev Med Chir Soc Med Nat Iasi** 1984 Oct–Dec;88(4):712–4 (Eng. Abstr.) **(Rum)**

[Behavior disorder in rats induced by Madopar and its pharmacological correction] Bondarenko NA, et al. **Farmakol Toksikol** 1985 Jul–Aug; 48(4):31–4 (Eng. Abstr.) **(Rus)**

HYDRAZONES

Synthesis and hypoglycemic activity of N–alkylated hydrazonopropionic acids. Wolff HP, et al. **J Med Chem** 1985 Oct;28(10):1436–40

HYDROXYBUTYRATES

The phosphonomethyl analogue of 3–phosphoglycerate is a potent competitive inhibitor of phosphoglycerate mutases. McAleese SM, et al. **Biochem J** 1985 Sep 1;230(2):535–42

Endogenous sugar acid control of hypothalamic neuron activity and gastric acid secretion in rats. Shiraishi T, et al. **Brain Res Bull** 1985 May;14(5):431–8

Effects of insulin on net hepatic metabolism of acetate and beta–hydroxybutyrate in sheep (Ovis aries). Brockman RP, et al. **Comp Biochem Physiol** [A] 1985;81(2):255–7

Stimulation by 3–hydroxybutyrate of pyruvate carboxylation in mitochondria from rat liver. Siess EA. **Eur J Biochem** 1985 Oct 1; 152(1):131–6

Evidence for a role of high Km aldehyde reductase in the degradation of endogenous gamma–hydroxybutyrate from rat brain. Vayer P, et al. **FEBS Lett** 1985 Oct 7;190(1):55–60

Conversion of gamma–hydroxybutyrate to gamma–aminobutyrate in vitro. Vayer P, et al. **J Neurochem** 1985 Sep;45(3):810–4

Properties of succinic semialdehyde dehydrogenase in cultured human lymphoblasts. Gibson KM, et al. **J Neurogenet** 1985 Apr;2(2):111–22

[Use of Gamma–OH by the oral route in children] Lansade A, et al. **Agressologie** 1985 Mar;26(3):277–8 (Eng. Abstr.) **(Fre)**

[State of the peripheral catecholaminergic systems during pharmacologic correction of immobilization stress using sodium oxybutyrate] Khalsman EB, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):317–9 (Eng. Abstr.) **(Rus)**

[Combined action of lithium salts and serotonin on the caudate nucleus] Zamoshchina TA, et al. **Biull Eksp Biol Med** 1985 Aug; 100(8):191–3 (Eng. Abstr.) **(Rus)**

HYDROXYDOPAMINES

Facilitation of spontaneous and learned spatial behaviours following 6–hydroxydopamine lesions of the lateral septum: a cholinergic hypothesis. Galey D, et al. **Brain Res** 1985 Aug 5;340(1):171–4

The effect of water–deprivation on locomotor activity in rats treated with

6-hydroxydopamine. Seiden LS, et al. **Brain Res** 1985 Jul 1; 337(2):225-32

Behavioral study after local injection of 6-hydroxydopamine into the nucleus accumbens in the rat. Taghzouti K, et al. **Brain Res** 1985 Sep 30;344(1):9-20

Localisation of neuropeptide Y in nerves of the rat cardiovascular system and the effect of 6-hydroxydopamine. Allen JM, et al. **Cardiovasc Res** 1985 Sep;19(9):570-7

Decrease in adrenaline content of various organs of the rat after 6-hydroxydopamine. Sudo A. **Eur J Pharmacol** 1985 Aug 7; 114(1):79-83

Substantial reduction of noradrenaline in kitten visual cortex by intraventricular injections of 6-hydroxydopamine does not always prevent ocular dominance shifts after monocular deprivation. Daw NW, et al. **Exp Brain Res** 1985;59(1):30-5

Effect of 6-hydroxydopamine on the metabolism of endogenous octopamines and catecholamines. Ibrahim KE, et al. **J Pharm Pharmacol** 1985 Jul;37(7):496-7

Dopamine agonist-induced locomotor activity in rats treated with 6-hydroxydopamine at differing ages: functional supersensitivity of D-1 dopamine receptors in neonatally lesioned rats. Breese GR, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):447-55

Hyperactivity induced by stimulation of separate dopamine D-1 and D-2 receptors in rats with bilateral 6-OHDA lesions. Arnt J. **Life Sci** 1985 Aug 26;37(8):717-23

Inactivation by 6-hydroxydopamine of the cerebral factor(s) responsible for the inhibition of the autoxidation of norepinephrine in vitro. Kovachich GB. **Neurosci Lett** 1985 Jul 31;58(2):245-50

6-Hydroxydopamine induces degenerative changes in innervation of the rat pituitary gland. Saland LC, et al. **Neurosci Lett** 1985 Jun 4; 57(1):49-55

Neonatal 6-hydroxydopamine potentiates clonidine's locomotor effects throughout maturation in the rat. Smythe JW, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):1075-8

Two types of changes in skin conductance activity after intraventricular administration of 6-hydroxydopamine in rats. Yamamoto K, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(3):245-50

HYDROXYINDOLEACETIC ACID

Effects of histamine and cimetidine on the levels of serotonin and 5-hydroxyindoleacetic acid in various parts of the digestive tract and in the blood and brain of rats. Kleinrok Z, et al. **Acta Physiol Pol** 1984 Mar-Apr;35(2):125-30

Serotonin content of foods: effect on urinary excretion of 5-hydroxyindoleacetic acid. Feldman JM, et al. **Am J Clin Nutr** 1985 Oct;42(4):639-43

Higher CSF levels of HVA and 5-HIAA in delusional compared to nondelusional depression [letter] Aberg-Wistedt A, et al. **Arch Gen Psychiatry** 1985 Sep;42(9):925-6

Effects of benzene and pyridine on the concentration of mouse striatal tryptamine and 5-hydroxytryptamine. Juorio AV, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3774-6

GABA mimetics decrease extracellular concentrations of 5-HIAA (as measured by in vivo voltammetry) in the dorsal raphe of the rat. Scatton B, et al. **Brain Res** 1985 Aug 26;341(2):372-6

Measurement of 5-HIAA levels in ventricular CSF (by LCEC) and in striatum (by in vivo voltammetry) during pharmacological modifications of serotonin metabolism in the rat. Mignot E, et al. **J Neural Transm** 1985;62(1-2):117-24

Correlations between aminergic metabolites simultaneously obtained from human CSF and brain. Stanley M, et al. **Life Sci** 1985 Oct 7; 37(14):1279-86

Increase in levels and ex vivo release of thyrotrophin-releasing hormone (TRH) in specific regions of the CNS of the rat by chronic treatment with antidepressants. Lighton C, et al. **Neuropharmacology** 1985 May; 24(5):401-6

Low HVA and normal 5HIAA CSF levels in drug-free schizophrenic patients compared to healthy volunteers: correlations to symptomatology and family history. Lindström LH. **Psychiatry Res** 1985 Apr;14(4):265-73

CSF monoamine metabolites in chronic schizophrenic patients who attempt suicide. Roy A, et al. **Psychol Med** 1985 May;15(2):335-40

HYDROXYTRYPTOPHAN

Sexual differences in the effect of serotonin on LH secretion in rats. Moguilevsky JA, et al. **Acta Endocrinol (Copenh)** 1985 Jul; 109(3):320-5

Effect of passive immunization with antisera to vasoactive intestinal polypeptide and peptide histidine isoleucine amide on 5-hydroxy-L-tryptophan-induced prolactin release in rats. Kaji H, et al. **Endocrinology** 1985 Nov;117(5):1914-9

Maternal aggression in mice: effects of treatments with PCPA, 5-HTP and 5-HT receptor antagonists. Ieni JR, et al. **Eur J Pharmacol** 1985 May 8;111(2):211-20

Specific antagonism of enteric neural serotonin receptors by dipeptides of 5-hydroxytryptophan: evidence that serotonin is a mediator of slow synaptic excitation in the myenteric plexus. Takaki M, et al. **J Neurosci** 1985 Jul;5(7):1769-80

The influence of pharmacological manipulation of serotonin on serum growth hormone and luteinizing hormone levels in young turkeys (Meleagris gallopavo). Fehrer SC, et al. **Poult Sci** 1985 Jul; 64(7):1356-62

Circadian variation in behavioural responses to central 5-HT receptor stimulation in the mouse. Moser PC, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):223-7

[Correlation between the number of serotonin type 2 receptors in the frontal cortex of the mouse brain and the expressivity of serotonin-dependent head twitches] Popova NK, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):322-4 (Eng. Abstr.) **(Rus)**

HYPOCHONDRIASIS

Dysmorphophobia and monosymptomatic hypochondriasis [letter] Thomas CS. **Am J Psychiatry** 1985 Sep;142(9):1121

IMIPRAMINE

Maintenance treatment of recurrent unipolar depression: pharmacology and psychotherapy. Frank E, et al. **Adv Biochem Psychopharmacol** 1985; 40:139-51

Research overview of drug therapy in recurrent and chronic depression. Prien RF. **Adv Biochem Psychopharmacol** 1985;40:121-30

Imipramine in the treatment of agoraphobia: dose-response relationships. Mavissakalian M, et al. **Am J Psychiatry** 1985 Sep;142(9):1032-6

A lithium-tricyclic combination for treatment of depression [letter] Pande AD, et al. **Am J Psychiatry** 1985 Oct;142(10):1228-9

Opposite effects of chronic imipramine treatment on brain and urine MHPG levels in the rat. Sedlock ML, et al. **Biol Psychiatry** 1985 Aug; 20(8):858-65

Lack of effect of oral activated charcoal on imipramine clearance. Goldberg MJ, et al. **Clin Pharmacol Ther** 1985 Sep;38(3):350-3

Pharmacokinetics of imipramine and its major metabolites in pregnant rats and their fetuses following a single dose. DeVane CL, et al. **Drug Metab Dispos** 1985 Jul-Aug;13(4):438-42

2-Nitroimipramine: a photoaffinity probe for the serotonin uptake/tricyclic binding site complex. Wennogle LP, et al. **EMBO J** 1985 Apr;4(4):971-7

Involvement of amygdaloid catecholaminergic mechanism in suppressive effects of desipramine and imipramine on duration of immobility in rats forced to swim. Araki H, et al. **Eur J Pharmacol** 1985 Jul 31; 113(3):313-8

Effects of imipramine on behavior and brain norepinephrine metabolism in tetrabenazine treated rats: comparative study of a single administration with repeated administrations of imipramine. Hori A, et al. **Folia Psychiatr Neurol Jpn** 1983;37(4):465-74

Cerebrospinal fluid levels of amitriptyline, nortriptyline, imipramine and desmethylimipramine. Relationship to plasma levels and treatment outcome. Hanin I, et al. **J Affective Disord** 1985 Jul;9(1):69-78

Determination of cianopramine in human plasma by high-performance liquid chromatography and gas-liquid chromatography with ultraviolet, fluorescence and electron-capture detection. Hojabri H, et al. **J Chromatogr** 1985 Jul 12;342(1):97-103

The effects of chlorpromazine and imipramine on rate and stimulus control of matching to sample. Newland MC, et al. **J Exp Anal Behav** 1985 Jul;44(1):49-68

Elevated density of [3H]imipramine binding in aged human brain. Severson JA, et al. **J Neurochem** 1985 Nov;45(5):1382-9

Repeated treatment with imipramine or amitriptyline increases the locomotor response of rats to (+)-amphetamine given into the nucleus accumbens. Maj J, et al. **J Pharm Pharmacol** 1985 May;37(5):362-4

Effect of imipramine and adrenocorticotropin administration on the rat brain norepinephrine-coupled cyclic nucleotide generating system: alterations in alpha and beta adrenergic components. Duman RS, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):409-14

Biochemical and diagnostic classification and serum drug levels: relation to antidepressive effect of imipramine. Møller SE, et al. **Neuropsychobiology** 1985;13(4):160-6

Antidepressant treatment of children: clinical relapse is unrelated to tricyclic plasma concentrations. Olig RM, et al. **Percept Mot Skills** 1985 Jun;60(3):879-89

Serotonin uptake and imipramine binding in rat platelets after chronic dexamethasone and amitriptyline treatment. Chan MY, et al. **Pharmacol Res Commun** 1985 Jul;17(7):619-32

The acute and the chronic effects of imipramine on the spontaneous motility in chick embryos. Sedláček J. **Physiol Bohemoslov** 1985; 34(3):225-34

Imipramine for treatment of chronic depression. Kocsis JH, et al. **Psychopharmacol Bull** 1985;21(3):698-700

Addition of estrogen to imipramine in female-resistant depressives. Zohar J, et al. **Psychopharmacol Bull** 1985;21(3):705-6

Cianopramine and amitriptyline in the treatment of depressed patients—a placebo-controlled study. Hormazabal L, et al.

Psychopharmacology (Berlin) 1985;86(1-2):205-8

Ro 11-2465 (cyan-imipramine), citalopram and their N-desmethyl metabolites: effects on the uptake of 5-hydroxytryptamine and noradrenaline in vivo and related pharmacological activities. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):156-63

Repeated treatment with imipramine potentiates the locomotor effect of apomorphine administered into the hippocampus in rats. Smialowski A, et al. **Psychopharmacology (Berlin)** 1985;86(4):468-71

[Effect of antidepressive drugs and histamine H1 receptor blockaders on histamine level in rat brain] Zawilska J, et al. **Folia Med Cracov** 1984; 25(3-4):297-306 (Eng. Abstr.) **(Pol)**

[Inhibitors of reverse serotonin uptake and of specific imipramine binding in human blood plasma] Brusov OS, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):26-8 (Eng. Abstr.) **(Rus)**

[Isolation of substances inhibiting the specific binding of imipramine and serotonin uptake from the brain of the bull] Mukhin AG, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):197-9 (Eng. Abstr.) **(Rus)**

[Autoradiographic study of the ontogeny of the imipramine receptors in the cerebral cortex of rats] Pirogova MV, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):752-4 (Eng. Abstr.) **(Rus)**

INHIBITION (PSYCHOLOGY)

[Effect of a derivative of GABA, phenibut, on behavior and the activity of visual cortex neurons of the rabbit during elaboration of a defensive reflex and internal inhibition] Shul'gina GI, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):695-702 (Eng. Abstr.)**(Rus)**

INTERVIEW, PSYCHOLOGICAL

The clinical interview for depression. Development, reliability and validity. Paykel ES. **J Affective Disord** 1985 Jul;9(1):85-96

ISOCARBOXAZID

Monoamine oxidase inhibitor therapy for anorexia nervosa and bulimia: a preliminary trial of isocarboxazid. Kennedy SH, et al. **J Clin Psychopharmacol** 1985 Oct;5(5):279-85

LACTATES

Further studies on reflectometric monitoring of cerebrocortical microcirculation. Importance of lactate anions in coupling between cerebral blood flow and metabolism. Dóra E. **Acta Physiol Hung** 1985; 66(2):199-211

Lactate-induced panic attacks: possible involvement of serotonin reuptake stimulation. Lingjaerde O. **Acta Psychiatr Scand** 1985 Aug; 72(2):206-8

[Synthesis of tyrosine and 3,4-dihydroxyphenylalanine by Citrobacter freundii bacteria from lactic acid] Kupletskaia MB. **Prikl Biokhim Mikrobiol** 1985 May-Jun;21(3):342-8 (Eng. Abstr.) **(Rus)**

LEARNING

Amygdala norepinephrine involved in two separate long-term memory retrieval processes. Ellis ME. **Brain Res** 1985 Sep 2;342(1):191-5

Genetic dissection of Drosophila adenylate cyclase. Livingstone MS. **Proc Natl Acad Sci USA** 1985 Sep;82(17):5992-6

Association between learning and cortical catecholamines in non-drug-treated rats. Sahakian BJ, et al. **Psychopharmacology (Berlin)** 1985;86(3):339-43

[Effect of a derivative of GABA, phenibut, on behavior and the activity of visual cortex neurons of the rabbit during elaboration of a defensive reflex and internal inhibition] Shul'gina GI, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):695-702 (Eng. Abstr.)**(Rus)**

LEVODOPA

Suppression of MPTP-induced dopaminergic neurotoxicity in mice by nomifensine and L-DOPA. Melamed E, et al. **Brain Res** 1985 Sep 9; 342(2):401-4

[Behavior disorder in rats induced by Madopar and its pharmacological correction] Bondarenko NA, et al. **Farmakol Toksikol** 1985 Jul-Aug; 48(4):31-4 (Eng. Abstr.) **(Rus)**

LH

Sexual differences in the effect of serotonin on LH secretion in rats. Moguilevsky JA, et al. **Acta Endocrinol (Copenh)** 1985 Jul; 109(3):320-5

Effect of pretreatment of long-term ovariectomized (OVX) rats with a competitive LRH antagonist on FSH release in vitro. van Dieten JA, et al. **Acta Endocrinol (Copenh)** 1985 Aug;109(4):481-4

Differential effects of forskolin on LH and GH release. Evans WS, et al. **Am J Physiol** 1985 Oct;249(4 Pt 1):E392-7

LH response to LH-RH neonatally estrogenized male rats. Pinilla L, et al. **Andrologia** 1985 May-Jun;17(3):254-6

Plasma FSH and LH in prepubertal Booroola ewe lambs. Bindon BM, et al. **Aust J Biol Sci** 1985;38(2):215-20

Pulsatile administration of gonadotropin-releasing hormone to anestrous sows: endocrine changes associated with GnRH-induced and spontaneous estrus. Armstrong JD, et al. **Biol Reprod** 1985 Sep; 33(2):375-80

A suppression of gonadotropin secretion by cortisol in castrated male rhesus monkeys (Macaca mulatta) mediated by the interruption of hypothalamic gonadotropin-releasing hormone release. Dubey AK, et al. **Biol Reprod** 1985 Sep;33(2):423-31

The effects of cycloheximide on in vitro response of Rana pipiens pituitaries to continuously superfused gonadotropin-releasing hormone. Porter DA. **Biol Reprod** 1985 Sep;33(2):393-400

Thyrotropin and gonadotropin releasing hormones (TRH and GnRH) do not alter levels of oxytocin and oxytocin does not change the response of luteinizing or follicle stimulating hormones to GnRH in humans. Amico JA, et al. **Endocr Res** 1985;11(1-2):75-85

Vasoactive intestinal polypeptide effects a central inhibition of pulsatile luteinizing hormone secretion in ovariectomized rats. Alexander MJ, et al. **Endocrinology** 1985 Nov;117(5):2134-9

Differential secretion of O-glycosylated gonadotropin alpha-subunit and luteinizing hormone (LH) in the presence of LH-releasing hormone. Corless CL, et al. **Endocrinology** 1985 Oct;117(4):1699-706

Effects of ovarian hormones on the concentrations of immunoreactive neuropeptide Y in discrete brain regions of the female rat: correlation with serum luteinizing hormone (LH) and median eminence LH-releasing hormone. Crowley WR, et al. **Endocrinology** 1985 Sep; 117(3):1151-5

Differential regulation of pulsatile luteinizing hormone (LH) and follicle-stimulating hormone secretion in ovariectomized rats disclosed by treatment with a LH-releasing hormone antagonist and phenobarbital. De Paolo LV. **Endocrinology** 1985 Nov; 117(5):1826-33

Corelease of dynorphin-like immunoreactivity, luteinizing hormone, and follicle-stimulating hormone from rat adenohypophysis in vitro. Knepel W, et al. **Endocrinology** 1985 Aug;117(2):481-7

In vivo gonadotropin-releasing hormone release and serum luteinizing hormone measurements in ovariectomized, estrogen-treated rhesus macaques. Levine JE, et al. **Endocrinology** 1985 Aug;117(2):711-21

Synthesis and release of luteinizing hormone in vitro by rat anterior pituitary cells: effects of gallopamil hydrochloride (D600) and pimozide. Liu TC, et al. **Endocrinology** 1985 Oct;117(4):1608-14

Secretion of ovine luteinizing hormone in vitro: differential positive control by 17 beta-estradiol and a preparation of porcine ovarian inhibin. Miller WL, et al. **Endocrinology** 1985 Sep;117(3):907-11

Effects of glucocorticoids on responsiveness of luteinizing hormone and follicle-stimulating hormone to gonadotropin-releasing hormone by male rat pituitary cells in vitro. Suter DE, et al. **Endocrinology** 1985 Sep;117(3):855-9

Effects of glucocorticoids on secretion of luteinizing hormone and follicle-stimulating hormone by female rat pituitary cells in vitro. Suter DE, et al. **Endocrinology** 1985 Sep;117(3):849-54

Gonadotropin-releasing hormone pulses in third ventricular cerebrospinal fluid of ovariectomized rhesus monkeys: correlation with luteinizing hormone pulses. Van Vugt DA, et al. **Endocrinology** 1985 Oct; 117(4):1550-8

Sex-specific effects of estradiol on hypothalamic noradrenaline turnover in gonadectomized rats. Hiemke C, et al. **Exp Brain Res** 1985; 59(1):68-72

Quinolinic acid stimulates luteinizing hormone secretion through a serotonin-dependent mechanism. Johnson MD, et al. **Exp Brain Res** 1985;59(1):62-7

The effect of delta 1tetrahydrocannabinol on luteinizing hormone release in castrated and hypothalamic deafferented male rats. Puder M, et al. **Exp Brain Res** 1985;59(2):213-6

Clomiphene citrate can mimic the augmentative (positive) but not the depressing (negative) effect of estradiol on the LHRH-stimulated release of LH and FSH by the pituitary gland of the long-term ovariectomized rat. Schuiling GA, et al. **Experientia** 1985 Aug 15;41(8):1060-3

Serum luteinizing hormone-releasing hormone (LH-RH) and gonadotropic hormones in men after a bolus dose of LH-RH: comparison of different doses and routes of administration. Fauser BC, et al. **Fertil Steril** 1985 Sep;44(3):384-9

The influence of thyrotropin releasing hormone on in vivo prolactin release and in vitro prolactin, luteinizing hormone, and growth hormone release from dispersed pituitary cells of the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Gen Comp Endocrinol** 1985 Jul; 59(1):64-72

Hypothalamic and serum factors influence on prolactin and luteinizing hormone release by the pituitary gland of the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Gen Comp Endocrinol** 1985 Jul; 59(1):73-81

Effects of chicken (Gln8)- and mammalian (Arg8)-luteinizing hormone-releasing hormones on the release of gonadotrophins in vitro and in vivo from the adenohypophysis of Japanese quail. Hattori A, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):155-61

LH secretion in response to gonadotropin releasing hormone (GnRH) by superfused pituitaries from two species of turtles. Licht P, et al. **Gen Comp Endocrinol** 1985 Sep;59(3):442-8

Pituitary responsiveness to superfused GnRH in two species of ranid frogs. Porter DA, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):308-15

Relationship between release of LH and incorporation of tritiated thymidine in the anterior pituitary gland of the castrated female rat. Machiavelli GA, et al. **Horm Metab Res** 1985 Jun;17(6):298-300

Effects of dihydrotestosterone benzoate administration on gonadotropin secretion in ovariectomized pony mares. Garza F Jr, et al. **J Anim Sci** 1985 Jul;61(1):240-4

Changes of luteinizing hormone and progesterone for dairy cows after gonadotropin-releasing hormone at first postpartum breeding. Lee CN, et al. **J Dairy Sci** 1985 Jun;68(6):1463-70

Changes in pituitary responsiveness to LH-releasing hormone after acute buserelin treatment: a time-course and dose-response study. Heather JD, et al. **J Endocrinol** 1985 Jul;106(1):27-30

The role of microfilaments in the priming effect of LH-releasing hormone: an ultrastructural study using cytochalasin B. Lewis CE, et al. **J Endocrinol** 1985 Aug;106(2):211-8

Differential effects of melatonin on the stimulated release of LH from dispersed pituitary cells of the prepubertal female rat. Symons AM, et al. **J Endocrinol** 1985 Oct;107(1):107-12

LH bioactivity in male puberty and senescence. Montanini V, et al. **J Endocrinol Invest** 1984;7 Suppl 3:43-52

The effect of ovine pineal compounds prepared under red or green light on the activity of male rat anterior pituitaries in vitro. Slama-Scemama A, et al. **J Neural Transm** 1985;62(1-2):155-67

Time series analysis of plasma LH and FSH concentrations as a method of assessing episodic secretion. McLeod BJ, et al. **J Reprod Fertil** 1985 Jul;74(2):575-87

Plasma LH and FSH responses and ovarian activity in prepubertal heifers treated with repeated injections of low doses of GnRH for 72 h. McLeod BJ, et al. **J Reprod Fertil** 1985 Jul;74(2):589-96

Comparison of the effects of neuropeptide Y and adrenergic transmitters on LH release and food intake in male rats. Allen LG, et al. **Life Sci** 1985 Aug 19;37(7):617-23

Effects of the 1,5-benzodiazepine clobazam on pituitary hormones in the male rat. Valli M, et al. **Methods Find Exp Clin Pharmacol** 1985 Apr;7(4):179-81

A prolactin-inhibiting factor within the precursor for human gonadotropin-releasing hormone. Nikolics K, et al. **Nature** 1985 Aug 8-14;316(6028):511-7

Further studies on the effects of testosterone on hypothalamic LH-RH and serum LH levels: castration-induced delayed response. Kalra PS. **Neuroendocrinology** 1985 Sep;41(3):219-23

Effect of histamine on basal and TRH/LH-RH-stimulated PRL and LH secretion during different phases of the menstrual cycle in normal women. Knigge U, et al. **Neuroendocrinology** 1985 Oct;41(4):337-41

Effects of endogenous opioid peptides and opiates on luteinizing hormone and prolactin secretion in ovariectomized rats. Leadem CA, et al. **Neuroendocrinology** 1985 Oct;41(4):342-52

Ovarian steroid regulation of pulsatile luteinizing hormone release during the interval between the mornings of diestrus 2 and proestrus in the rat. Leipheimer RE, et al. **Neuroendocrinology** 1985 Sep;41(3):252-7

Estradiol-induced LH release in juvenile female rats: nembutal blocks both the decline and the exposure of nonavailable pituitary LHRH receptor sites. Smith SS, et al. **Neuroendocrinology** 1985 Sep;41(3):246-51

Interaction between the posterior pituitary and LHRH in the control of LH secretion. Froehlich JC, et al. **Peptides (Fayetteville)** 1985;6 Suppl 1:127-31

The influence of pharmacological manipulation of serotonin on serum growth hormone and luteinizing hormone levels in young turkeys (Meleagris gallopavo). Fehrer SC, et al. **Poult Sci** 1985 Jul;64(7):1356-62

LH-RH antagonists--mechanisms of action. van Rees GP. **Prog Clin Biol Res** 1985;185A:155-9

Role of brain epinephrine neurons in the regulation of serum prolactin and luteinizing hormone release in female rats. Liang NY, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jun;48(3):459-62

[Gonadotropin stimulation during LH/RH analog-induced inhibition of pituitary function] Bettendorf G, et al. **Geburtshilfe Frauenheilkd** 1985 Jul;45(7):431-7 (Eng. Abstr.) **(Ger)**

[Effect of gonadectomy and luliberin on the gonadotropic function of the hypophysis in Papio hamadryas] Katsiia GV, et al. **Probl Endokrinol (Mosk)** 1985 Jul-Aug;31(4):55-8 (Eng. Abstr.)**(Rus)**

[Correlation between the thyroxine, 17-beta-estradiol and luteinizing hormones in the systemic circulation and the rectal and vaginal temperature in heifers and cows after administration of cloprostenol] Elečko J, et al. **Vet Med (Praha)** 1985 May;30(5):257-66 (Eng. Abstr.) **(Slo)**

LH-FSH RELEASING HORMONE

Effect of pretreatment of long-term ovariectomized (OVX) rats with a competitive LRH antagonist on FSH release in vitro. van Dieten JA, et al. **Acta Endocrinol (Copenh)** 1985 Aug;109(4):481-4

LH response to LH-RH neonatally estrogenized male rats. Pinilla L, et al. **Andrologia** 1985 May-Jun;17(3):254-6

LHRH self-priming in the male: effect of multiple priming injections in the immature rat. Nazian SJ. **Arch Androl** 1984;13(2-3):241-4

Pregnancy rate of cows given synthetic gonadotrophin-releasing hormone at the time of service. Anderson GA, et al. **Aust Vet J** 1985 Jul;62(7):222-4

Luteinizing hormone-releasing hormone enhances polyphosphoinositide breakdown in rat granulosa cells. Ma F, et al. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):1201-8

Identification and partial characterization of gonadotropin-releasing hormone-like factors in human seminal plasma. Sokol RZ, et al. **Biol Reprod** 1985 Sep;33(2):370-4

Conjugated catecholamines and pressor responses to angiotensin, luteinizing hormone-releasing hormone and prazosin in conscious toads. Wilson JX. **Br J Pharmacol** 1985 Jul;85(3):647-53

Combined electrophysiological, immunocytochemical and peptide release measurements in the hypothalamic slice. Kelly MJ, et al. **Brain Res** 1985 Oct 21;345(2):264-70

Dibutyryl cyclic adenosine monophosphate stimulates in vitro luteinizing hormone-releasing hormone release only from median eminence derived from ovariectomized, estradiol-primed rats. Kim K, et al. **Brain Res** 1985 Sep 2;342(1):154-7

The LH-RH-containing neuronal network in the preoptic area of the rat: demonstration of LH-RH-containing nerve terminals in synaptic contact with LH-RH neurons. Leranth C, et al. **Brain Res** 1985 Oct 21;345(2):332-6

LH-RH analogue acts as substance P antagonist by inhibiting spinal cord vasomotor responses. Takano Y, et al. **Brain Res** 1985 Jul 1;337(2):357-61

Gonadotropin-releasing hormone-immunoreactive neuronal structures in the brain and pituitary of the African catfish, Clarias gariepinus (Burchell). Goos HJ, et al. **Cell Tissue Res** 1985;241(3):593-6

Thyrotropin and gonadotropin releasing hormones (TRH and GnRH) do not alter levels of oxytocin and oxytocin does not change the response of luteinizing or follicle stimulating hormones to GnRH in humans. Amico JA, et al. **Endocr Res** 1985;11(1-2):75-85

Gonadotropin-releasing hormone induces classical meiotic maturation in subpopulations of atretic preantral follicles. Banka CL, et al. **Endocrinology** 1985 Oct;117(4):1500-7

Progesterone decreases the responsiveness of ovine pituitary cultures to luteinizing hormone-releasing hormone. Batra SK, et al. **Endocrinology** 1985 Oct;117(4):1436-40

Differential secretion of O-glycosylated gonadotropin alpha-subunit and luteinizing hormone (LH) in the presence of LH-releasing hormone. Corless CL, et al. **Endocrinology** 1985 Oct;117(4):1699-706

Effects of ovarian hormones on the concentrations of immunoreactive neuropeptide Y in discrete brain regions of the female rat: correlation with serum luteinizing hormone (LH) and median eminence LH-releasing hormone. Crowley WR, et al. **Endocrinology** 1985 Sep;117(3):1151-5

Differential regulation of pulsatile luteinizing hormone (LH) and follicle-stimulating hormone secretion in ovariectomized rats disclosed by treatment with a LH-releasing hormone antagonist and phenobarbital. De Paolo LV. **Endocrinology** 1985 Nov;117(5):1826-33

Hyperprolactinemia inhibits gonadotropin-releasing hormone (GnRH) stimulation of the number of pituitary GnRH receptors. Garcia A, et al. **Endocrinology** 1985 Sep;117(3):954-9

Photoaffinity labeling of pituitary and gonadal receptors for gonadotropin-releasing hormone. Iwashita M, et al. **Endocrinology** 1985 Aug;117(2):738-46

In vivo gonadotropin-releasing hormone release and serum luteinizing hormone measurements in ovariectomized, estrogen-treated rhesus macaques. Levine JE, et al. **Endocrinology** 1985 Aug;117(2):711-21

Luteinizing hormone-releasing hormone stimulates arachidonic acid release in rat granulosa cells. Minegishi T, et al. **Endocrinology** 1985 Nov;117(5):2001-7

Stimulation of cyclic adenosine 3',5'-monophosphate production enhances hypothalamic luteinizing hormone-releasing hormone release without increasing prostaglandin E2 synthesis: studies in prepubertal female rats. Ojeda SR, et al. **Endocrinology** 1985 Sep;117(3):1175-8

Gonadotropin-releasing hormone pulses in third ventricular cerebrospinal fluid of ovariectomized rhesus monkeys: correlation with luteinizing hormone pulses. Van Vugt DA, et al. **Endocrinology** 1985 Oct;117(4):1550-8

Immunoreactive substance P and LH-RH content in median eminence and pituitary gland during proestrus, oestrus, lactation and after anterior hypothalamic deafferentation. Jakubowska-Naziemblo B, et al. **Exp Clin Endocrinol** 1985 Apr;85(2):155-66

Serum luteinizing hormone-releasing hormone (LH-RH) and gonadotropic hormones in men after a bolus dose of LH-RH: comparison of different doses and routes of administration. Fauser BC, et al. **Fertil Steril** 1985 Sep;44(3):384-9

Immunocytochemistry of luteinizing hormone-releasing hormone and sexual maturation of the frog brain: comparisons of juvenile and adult bullfrogs (Rana catesbeiana). Crim JW. **Gen Comp Endocrinol** 1985 Sep; 59(3):424–33

Effects of chicken (Gln8)- and mammalian (Arg8)-luteinizing hormone-releasing hormones on the release of gonadotrophins in vitro and in vivo from the adenohypophysis of Japanese quail. Hattori A, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):155–61

An immunohistochemical study of seasonal changes in luteinizing hormone-releasing hormone and vasotocin in the forebrain and the neurohypophysis of the toad, Bufo japonicus. Jokura Y, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):238–45

Pituitary responsiveness to superfused GnRH in two species of ranid frogs. Porter DA, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):308–15

Direct effect of the luteinizing hormone releasing hormone analog D-Trp6-Pro9-Net-LHRH on rat ovarian steroidogenesis. Malozowski S, et al. **Horm Metab Res** 1985 Jun;17(6):321–2

Specific binding of gonadotrophin-releasing hormone and an agonist to human corpus luteum homogenates: characterization, properties, and luteal phase levels. Bramley TA, et al. **J Clin Endocrinol Metab** 1985 Nov;61(5):834–41

Pulsatile gonadotropin secretion in women with hypothalamic amenorrhea: evidence that reduced frequency of gonadotropin-releasing hormone secretion is the mechanism of persistent anovulation. Reame NE, et al. **J Clin Endocrinol Metab** 1985 Nov;61(5):851–8

Ontogenesis of neurons producing luteinizing hormone-releasing hormone (LHRH) in the nervus terminalis of the rat. Schwanzel-Fukuda M, et al. **J Comp Neurol** 1985 Aug 15;238(3):348–64

Changes in pituitary responsiveness to LH-releasing hormone after acute buserelin treatment: a time-course and dose-response study. Heather JD, et al. **J Endocrinol** 1985 Jul;106(1):27–30

Pituitary receptors for LH-releasing hormone (LHRH) and responsiveness to LHRH in adult female rats after neonatal monosodium L-glutamate treatment. Inkster SE, et al. **J Endocrinol** 1985 Oct; 107(1):9–13

Effects of dopamine and morphine on immunoreactive somatostatin and LH-releasing hormone secretion from hypothalamic fragments in vitro. Lengyel AM, et al. **J Endocrinol** 1985 Sep;106(3):317–22

The role of microfilaments in the priming effect of LH-releasing hormone: an ultrastructural study using cytochalasin B. Lewis CE, et al. **J Endocrinol** 1985 Aug;106(2):211–8

Effects of LH-releasing hormone antagonist or lesions of the medial basal hypothalamus on periovulatory gonadotrophin release in female rats. Rush ME. **J Endocrinol** 1985 Sep;106(3):361–6

Pituitary gonadotrophin-releasing hormone receptor up-regulation in vitro: dependence on calcium and microtubule function. Young LS, et al. **J Endocrinol** 1985 Oct;107(1):49–56

The effect of ovine pineal compounds prepared under red or green light on the activity of male rat anterior pituitaries in vitro. Slama-Scemama A, et al. **J Neural Transm** 1985;62(1–2):155–67

Release of LHRH in vitro and anterior pituitary responsiveness to LHRH in vivo during sexual maturation in pullets (Gallus domesticus). Knight PG, et al. **J Reprod Fertil** 1985 May;74(1):145–51

Long-term reversible suppression of oestrus in bitches with nafarelin acetate, a potent LHRH agonist. McRae GI, et al. **J Reprod Fertil** 1985 Jul;74(2):389–97

The effects of thymus-derived peptides on hypothalamic LRF and pituitary gonadotropin content in prepubertal congenitally athymic nude mice and their normal heterozygous littermates. Strich G, et al. **J Reprod Immunol** 1985 Jun;7(4):351–9

Reproductive/endocrine and anaphylactoid properties of an LHRH-antagonist, ORF 18260 [Ac-DNAL1(2), 4FDPhe2,D-Trp3,D-Arg6]-GnRH. Hahn DW, et al. **Life Sci** 1985 Aug 12;37(6):505–14

Stimulation and inhibition of Leydig cell steroidogenesis by the phorbol ester 12-O-tetradecanoylphorbol 13-acetate: similarity to the effects of gonadotropin-releasing hormone. Moger WH. **Life Sci** 1985 Sep 2; 37(9):869–73

Enzymatic tracer damage during the gonadotropin releasing hormone radioimmunoassay: analytical and immunological assessment. O'Conner JL, et al. **Life Sci** 1985 Sep 23;37(12):1155–65

Effect of an intranasal LHRH agonist on gonadotrophins and hot flushes in post-menopausal women. Shaw RW, et al. **Maturitas** 1985 Jul; 7(2):161–7

The mechanisms of LHRH agonist action in gonadal tissues. Cooke BA, et al. **Mol Cell Endocrinol** 1985 Jul;41(2–3):115–22 (68 ref.)

Has the prolactin inhibiting peptide at last been found? [news] Fink G. **Nature** 1985 Aug 8–14;316(6028):487–8

A prolactin-inhibiting factor within the precursor for human gonadotropin-releasing hormone. Nikolics K, et al. **Nature** 1985 Aug 8–14;316(6028):511–7

Immunocytochemical localization in rat brain of a prolactin release-inhibiting sequence of gonadotropin-releasing hormone prohormone. Phillips HS, et al. **Nature** 1985 Aug 8–14; 316(6028):542–5

Effects of advancing age on hypothalamic neurotransmitter content and on basal and norepinephrine-stimulated LHRH release. Steger RW, et al. **Neurobiol Aging** 1985 Summer;6(2):113–6

Castration of male rats reduces the capacity of granules isolated from the median eminence to secrete luteinizing hormone-releasing hormone in response to copper. Barnea A, et al. **Neuroendocrinology** 1985 Aug; 41(2):149–55

Hormonal modulation of the responsiveness of midbrain central gray neurons to LH-RH. Chan A, et al. **Neuroendocrinology** 1985 Aug; 41(2):163–8

Further studies on the effects of testosterone on hypothalamic LH-RH and serum LH levels: castration-induced delayed response. Kalra PS. **Neuroendocrinology** 1985 Sep;41(3):219–23

Effect of histamine on basal and TRH/LH-RH-stimulated PRL and LH secretion during different phases of the menstrual cycle in normal women. Knigge U, et al. **Neuroendocrinology** 1985 Oct;41(4):337–41

Ovarian LHRH receptors increase following lesions of the major LHRH structures in the rat brain: involvement of a direct neural pathway. Marchetti B, et al. **Neuroendocrinology** 1985 Oct;41(4):321–31

Progesterone and the control of functional luteolysis, of secretion of prolactin and of pituitary LHRH responsiveness. A study with pseudopregnant rats kept in alternating and constant lighting conditions. Schuiling GA, et al. **Neuroendocrinology** 1985 Jul;41(1):52–9

Estradiol-induced LH release in juvenile female rats: nembutal blocks both the decline and the exposure of nonavailable pituitary LHRH receptor sites. Smith SS, et al. **Neuroendocrinology** 1985 Sep; 41(3):246–51

Interaction between the posterior pituitary and LHRH in the control of LH secretion. Froehlich JC, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 1:127–31

Methods for the isolation of viable gonadotropin-releasing hormone (LRF) neurons. Melrose PA, et al. **Peptides (Fayetteville)** 1985 Mar–Apr; 6(2):347–51

[Trp7,Leu8]LH-RH in reptilian brain. Powell RC, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):223–7

Synaptology of luteinizing hormone-releasing hormone neurons in rat preoptic area. Witkin JW, et al. **Peptides (Fayetteville)** 1985 Mar–Apr; 6(2):263–71

LHRH and mating behavior: sexual receptivity versus sexual preference. Dudley CA, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):967–72

LH-RH antagonists--mechanisms of action. van Rees GP. **Prog Clin Biol Res** 1985;185A:155–9

Hypothalamic pulse generators. Lincoln DW, et al. **Recent Prog Horm Res** 1985;41:369–419 (154 ref.)

Progesterone action on the LHRH and the nigrostriatal dopamine neuronal systems: in vitro and in vivo studies. Ramirez VD, et al. **Recent Prog Horm Res** 1985;41:421–72 (110 ref.)

[The undescended testis] Westphal O, et al. **Monatsschr Kinderheilkd** 1985 Jun;133(6):352–4 **(Ger)**

[Early oviposition in Serinus canaria after endonasal administration of Gn-RH. (Preliminary research)] Costantini V, et al. **Boll Soc Ital Biol Sper** 1985 Apr 30;61(4):633–8 (Eng. Abstr.) **(Ita)**

[Effect of gonadectomy and luliberin on the gonadotropic function of the hypophysis in Papio hamadryas] Katsiia GV, et al. **Probl Endokrinol (Mosk)** 1985 Jul–Aug;31(4):55–8 (Eng. Abstr.)**(Rus)**

[Effect of a cyclic luliberin analog on ovulation] Korkhov VV, et al. **Probl Endokrinol (Mosk)** 1985 Jul–Aug;31(4):52–5 (Eng. Abstr.)**(Rus)**

LIPOTROPIN

Light and electron microscopic immunocytochemistry of beta-endorphin/beta-LPH-like immunoreactive neurons in the arcuate nucleus and surrounding areas of the rat hypothalamus. Ibata Y, et al. **Brain Res** 1985 Aug 26;341(2):233–42

The effect of various corticotropin-releasing factor trains on the release of adrenocorticotropin, beta-endorphin, and beta-lipotropin from perifused ovine pituitary cells. Evans MJ, et al. **Endocrinology** 1985 Sep;117(3):893–9

[Biosynthesis of pro-opiomelanocortin and secretion of its fragments by cultured bone marrow cells of mice] Dmitriev AD, et al. **Dokl Akad Nauk SSSR** 1985 May–Jun;282(1):199–202 **(Rus)**

LITHIUM

Ocular effects of oral lithium in humans. Kaufman PL, et al. **Acta Ophthalmol (Copenh)** 1985 Jun;63(3):327–32

Effects of acute and short-time antibiotic treatment on renal lithium elimination and serum lithium levels in the rat. Lassen E. **Acta Pharmacol Toxicol (Copenh)** 1985 Apr;56(4):273–7

Effects of histamine and H1 and H2-receptor antagonists on the wet-dog-shaking episodes in rats induced with lithium chloride. Rajtar G, et al. **Acta Physiol Pol** 1984 Mar–Apr;35(2):131–5

Long-term lithium prophylaxis in recurrent unipolar depression. A controversial indication? Lepkifker E, et al. **Acta Psychiatr Belg** 1985 May–Jun;85(3):434–43

Clinical and laboratory effects of discontinuation of lithium prophylaxis. Goodnick PJ. **Acta Psychiatr Scand** 1985 Jun;71(6):608–14

Lithium effects on ophthalmological-electrophysiological parameters in young healthy volunteers. Ullrich A, et al. **Acta Psychiatr Scand** 1985

Aug;72(2):113-9

Response to lithium prophylaxis in schizoaffective psychoses. Kemali D, et al. **Adv Biochem Psychopharmacol** 1985;40:153-8

Research overview of drug therapy in recurrent and chronic depression. Prien RF. **Adv Biochem Psychopharmacol** 1985;40:121-30

Practical problems of lithium maintenance treatment. Schou M. **Adv Biochem Psychopharmacol** 1985;40:131-8

Modification of urinary potassium secretion following lithium in rats of different ages. Kersten L, et al. **Agressologie** 1985 Mar;26(3):253-6

Nonspecific stomatitis due to lithium therapy [letter] Bar Nathan EA, et al. **Am J Psychiatry** 1985 Sep;142(9):1126-7

A lithium-tricyclic combination for treatment of depression [letter] Pande AD, et al. **Am J Psychiatry** 1985 Oct;142(10):1228-9

Matrix modifiers in graphite furnace atomic absorption analysis of trace lithium in biological fluids. Trapp GA. **Anal Biochem** 1985 Jul; 148(1):127-32

Determination of lithium, rubidium and strontium in foodstuffs. Evans WH, et al. **Analyst** 1985 Jun;110(6):619-23

Effect of lithium treatment on blood pressure and angiotensin-converting enzyme activity in normotensive Wistar-Kyoto and spontaneously hypertensive rats. Das S, et al. **Arch Int Pharmacodyn Ther** 1985 Jul; 276(1):82-91

Lipid peroxidation as a possible mechanism for the neurotoxic and nephrotoxic effects of a combination of lithium carbonate and haloperidol. Sawas AH, et al. **Arch Int Pharmacodyn Ther** 1985 Aug; 276(2):301-12

Salt-dependent structural changes of neurohormones: lithium ions induce conformational rearrangements of ocytocin to a vasopressin-like structure. Rholam M, et al. **Biochemistry** 1985 Jun 18;24(13):3345-9

Changes in the diagnoses of the functional psychoses associated with the introduction of lithium. Parker G, et al. **Br J Psychiatry** 1985 Apr; 146:377-82

Neuroleptics, lithium and renal function. Waller DG, et al. **Br J Psychiatry** 1985 May;146:510-4

The role of lithium carbonate in the management of hemolymphoblastosis: estimation of plasmatic and erythrocyte lithium levels. Fanci R, et al. **Chemioterapia** 1985 Jun;4(3):260-4

Short-term lithium administration enhances serotonergic neurotransmission: electrophysiological evidence in the rat CNS. Blier P, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):69-77

Energy response of LiF (TLD-100) and CaSO4:Dy TL dosimeters to different diagnostic spectra. Servomaa AJ. **Eur J Radiol** 1985 Aug; 5(3):236-9

Lithium intolerance disproved by blind clinical trial. Kellner CH, et al. **Hillside J Clin Psychiatry** 1985;7(1):82-7

Slow-release lithium in treatment of schizoaffective syndromes. Romeo R, et al. **Int J Clin Pharmacol Res** 1985;5(3):205-11

Variation in the relationship between serum and saliva lithium levels. Sankaranarayanan A, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Jul;23(7):365-6

Lithium prophylaxis of recurrent affective disorders. Glen AI. **J Affective Disord** 1985 May-Jun;8(3):259-65

Lithium dosage in the elderly. A study with matched age groups. Greil W, et al. **J Affective Disord** 1985 Jul;9(1):1-4

Lithium in the treatment of mania. Tyrer SP. **J Affective Disord** 1985 May-Jun;8(3):251-7

The neurochemistry of mania. The effect of lithium on catecholamines, indoleamines and calcium mobilization. Wood K. **J Affective Disord** 1985 May-Jun;8(3):215-23

Lichenoid stomatitis associated with lithium carbonate. Hogan DJ, et al. **J Am Acad Dermatol** 1985 Aug;13(2 Pt 1):243-6

Interrelationships among quinidine, amiloride, and lithium as inhibitors of the renal Na+-H+ exchanger. Mahnensmith RL, et al. **J Biol Chem** 1985 Oct 15;260(23):12586-92

Lithium ion inhibits nerve growth factor-induced neurite outgrowth and phosphorylation of nerve growth factor-modulated microtubule-associated proteins. Burstein DE, et al. **J Cell Biol** 1985 Sep;101(3):862-70

Lithium Information Center: The Lithium Library revisited. Greist JH, et al. **J Clin Psychiatry** 1985 Aug;46(8):327-31

Selective transport of Li+ across lipid bilayer membranes mediated by an ionophore of novel design (ETH1644). Zeevi A, et al. **J Membr Biol** 1985;86(1):61-7

Differential effects of lithium on muscarinic receptor stimulation of inositol phosphates in rat cerebral cortex slices. Batty I, et al. **J Neurochem** 1985 Nov;45(5):1514-21

Intrinsic dissolution of lithium carbonate in aqueous solutions. Wall BP, et al. **J Pharm Pharmacol** 1985 May;37(5):338-40

Evidence for in vivo effect of lithium on p-aminohippurate transport in rat kidney, preliminary study. Sugihara K, et al. **Jpn J Pharmacol** 1985 Jun;38(2):127-32

Low dose lithium carbonate in the treatment of post traumatic stress disorder: brief communication. Kitchner I, et al. **Milit Med** 1985 Jul; 150(7):378-81

Effect of chronic lithium administration on neurotransmitter metabolism in synaptosomes from rat brain. Rafałowska U, et al. **Neuropatol Pol** 1985;23(2):211-8

Erythrocyte differentiation of naturally occurring isotopic lithium abundances. Lieberman KW, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):145-6

Factors associated with response to lithium prophylaxis in DSM III major depression and bipolar disorder. Maj M, et al. **Pharmacopsychiatry** 1985 Sep;18(5):309-13

Renal function and enzymatic studies of the urine in patients on a long-term lithium therapy. Astrug A, et al. **Przegl Lek** 1985; 42(3):361-3

A controlled study of cellular immune function in affective disorders before and during somatic therapy. Albrecht J, et al. **Psychiatry Res** 1985 Jul;15(3):185-93

Serum lithium minimum and diuresis. Mellerup ET, et al. **Psychiatry Res** 1985 Apr;14(4):309-13

Mood-independent aberrancies in associative processes in bipolar affective disorder: an apparent stabilizing effect of lithium. Pons L, et al. **Psychiatry Res** 1985 Apr;14(4):315-22

Side-effects of lithium at lower therapeutic levels: the significance of thirst. King JR, et al. **Psychol Med** 1985 May;15(2):355-61

Investigating renal function during lithium treatment. Waller DG, et al. **Psychol Med** 1985 May;15(2):369-75

Influence of housing conditions and state of partner on conditioning and extinction of taste aversion to lithium and chlorpromazine. Giardini V. **Psychopharmacology (Berlin)** 1985;86(1-2):96-101

Cognitive effects of lithium treatment in normal volunteers. Weingartner H, et al. **Psychopharmacology (Berlin)** 1985;86(4):472-4

Inhibitory effect on lithium on p-aminohippurate transport in rat kidney cortex in vitro. Gemba M, et al. **Renal Physiol** 1985;8(3):179-88

Li+-induced release of the folate binding protein from human granulocytes. Holm J, et al. **Scand J Haematol** 1985 Jul; 35(1):109-14

[The prediction of therapeutic dosage of lithium] Zhang MY. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Aug; 17(4):239-41 (Eng. Abstr.) **(Chi)**

[Lithium levels in biological media and treatment surveillance] Greffe J, et al. **Encephale** 1985 Mar-Apr;11(2):79-83 (Eng. Abstr.) **(Fre)**

[Changes in cerebral calcium, sodium and potassium after single or repeated administration of lithium in the rat] Scotto di Tella AM, et al. **Encephale** 1985 Mar-Apr;11(2):53-6 (Eng. Abstr.) **(Fre)**

[Effect of lithium chloride on thyroid structural elements in the rat and on the balance of calcitropic hormones] Petrov NM, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):711-3 (Eng. Abstr.) **(Rus)**

[Combined action of lithium salts and serotonin on the caudate nucleus] Zamoshchina TA, et al. **Biull Eksp Biol Med** 1985 Aug; 100(8):191-3 (Eng. Abstr.) **(Rus)**

[Effectiveness of combined administration of lithium carbonate and prednisolone in neutropenias] Iavorkovskiĭ LL, et al. **Ter Arkh** 1985; 57(7):84-8 (Eng. Abstr.) **(Rus)**

[Family interactions and adherence to lithium pharmacotherapy] de León OA, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):7-16 (Eng. Abstr.) **(Spa)**

[Poisoning caused by lithium salts (letter)] Pérez Martínez JM, et al. **Med Clin (Barc)** 1985 Mar 30;84(12):500 **(Spa)**

[Nephrotic syndrome associated with lithium therapy (letter)] Rodríguez Jornet A, et al. **Med Clin (Barc)** 1985 Jun 15;85(3):125 **(Spa)**

LORAZEPAM

Task-dependent development of cross-tolerance to psychomotor effects of lorazepam in man. Aranko K. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):373-81

Parenteral premedication with lorazepam--a dose/response study. Odugbesan CO, et al. **Afr J Med Med Sci** 1985 Mar-Jun; 14(1-2):65-9

Lorazepam dependence and chronic psychosis [letter] Fraser AA, et al. **Br J Psychiatry** 1985 Aug;147:211

A multi-centre, double-blind parallel trial of bromazepam ('Lexotan') and lorazepam to compare the acute benefit-risk ratio in the treatment of patients with anxiety. Cordingley GJ, et al. **Curr Med Res Opin** 1985; 9(7):505-10

Sleep and wake after benzodiazepine hypnotics: a 20-hour EEG comparison of lormetazepam and flunitrazepam. Timsit-Berthier M, et al. **Curr Med Res Opin** 1985;9(8):552-9

Lorazepam--a benzodiazepine to choose or avoid? **Drug Ther Bull** 1985 Aug 12;23(16):61-2

Temporal variations of lorazepam pharmacokinetics. Bruguerolle B, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Jul;23(7):352-4

Probenecid impairment of acetaminophen and lorazepam clearance: direct inhibition of ether glucuronide formation. Abernethy DR, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):345-9

The influence of ritanserin, a serotonin antagonist, in anxiety disorders: a double-blind placebo-controlled study versus lorazepam. Ceulemans DL, et al. **Pharmacopsychiatry** 1985 Sep;18(5):303-5

Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. Ellinwood EH Jr, et al. **Psychopharmacology (Berlin)** 1985;86(4):392-9

[Temesta] Scottez B, et al. **Soins Psychiatr** 1985 May;(55):I-II **(Fre)**

[Importance of protein binding of lorazepam in its clinical management] Aguilera Celorrio L, et al. **Rev Esp Anestesiol Reanim** 1985 May-Jun; 32(3):115-8 (Eng. Abstr.) **(Spa)**

MANIC DISORDER

Plasma cortisol levels in mania: associated clinical ratings and changes during treatment with haloperidol. Cookson JC, et al. **Br J Psychiatry** 1985 May;146:498-502

The use of sodium valproate, carbamazepine and oxcarbazepine in patients with affective disorders. Emrich HM, et al. **J Affective Disord** 1985 May-Jun;8(3):243-50

Lithium prophylaxis of recurrent affective disorders. Glen AI. **J Affective Disord** 1985 May-Jun;8(3):259-65

Lithium in the treatment of mania. Tyrer SP. **J Affective Disord** 1985 May-Jun;8(3):251-7

The neurochemistry of mania. The effect of lithium on catecholamines, indoleamines and calcium mobilization. Wood K. **J Affective Disord** 1985 May-Jun;8(3):215-23

Sensation seeking, mania, and monoamines. Zuckerman M. **Neuropsychobiology** 1985;13(3):121-8

Erythrocyte differentiation of naturally occurring isotopic lithium abundances. Lieberman KW, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):145-6

[Manic decompensation] Lavoie JG. **Can J Psychiatry** 1985 Jun; 30(4):270-3 (Eng. Abstr.) **(Fre)**

[Therapy of depressive and manic diseases] Seige D. **Psychiatr Neurol Med Psychol Beih** 1966;4-5:186-92 **(Ger)**

[Parenteral form of pipothiazine in the treatment of endogenous psychoses] Matkowski K, et al. **Psychiatr Pol** 1984 Nov-Dec;18(6):567-70 (Eng. Abstr.) **(Pol)**

MATERNAL BEHAVIOR

Maternal aggression in mice: effects of treatments with PCPA, 5-HTP and 5-HT receptor antagonists. Ieni JR, et al. **Eur J Pharmacol** 1985 May 8;111(2):211-20

Maternal aggression in rats: effects of chlordiazepoxide and fluprazine. Olivier B, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):68-76

MEMORY

Memory effects of GABA-ergic antagonists in rats trained with two-way active avoidance tasks. Yonkov DI, et al. **Acta Physiol Pharmacol Bulg** 1985;11(2):44-9

Neocortical involvement in the acquisition and retention of learned alcohol aversions in rats. Kiefer SW, et al. **Alcohol** 1985 Jul-Aug; 2(4):597-601

Amygdala norepinephrine involved in two separate long-term memory retrieval processes. Ellis ME. **Brain Res** 1985 Sep 2;342(1):191-5

Converging sectors of psychoanalysis and neurobiology: mutual challenge and opportunity. Reiser MF. **J Am Psychoanal Assoc** 1985; 33(1):11-34

Blockade of peripheral beta-adrenergic receptors fails to suppress the cerebral spread of an engram in mice. Church AC, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):27-31

The conditioned place preference is affected by two independent reinforcement processes. White NM, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):37-42

Posterior hypothalamic deafferentation abolishes the amnestic effect of electroconvulsive shock in rats. Netto CA, et al. **Psychoneuroendocrinology** 1985;10(2):159-63

Memory enhancement: supra-additive effect of subcutaneous cholinergic drug combinations in mice. Flood JF, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):61-7

Effects of phenobarbital, clonazepam, valproic acid, ethosuximide, and phenytoin on the delayed matching-to-sample performance of pigeons. Picker M, et al. **Psychopharmacology (Berlin)** 1985;86(4):494-8

The effect of stimulus preexposure upon the context effect in taste-aversion learning in noradrenaline-depleted rats. Archer T, et al. **Scand J Psychol** 1985;26(2):158-69

[Effect of a cyclic analog of enkephalin on learning and memory in the mouse] Getsova VM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug; 35(4):710-7 (Eng. Abstr.) **(Rus)**

[Effect of noradrenaline, microapplied to the dorsal hippocampus of the rat, on conditioned reflex memory] Melikov EM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):780-2 **(Rus)**

MEMORY DISORDERS

Subjective memory complaints in geriatric depression. Plotkin DA, et al. **Am J Psychiatry** 1985 Sep;142(9):1103-5

MENTAL DISORDERS

Patient attitudes in short-term psychiatric care. Relations to social and psychiatric background, clinical symptoms, and treatment model. Hansson L, et al. **Acta Psychiatr Scand** 1985 Aug;72(2):193-201

Hair analysis for detection of phencyclidine in newly admitted psychiatric patients. Sramek JJ, et al. **Am J Psychiatry** 1985 Aug;142(8):950-3

Daily patterns of serotonin uptake in platelets from psychiatric patients and control volunteers. Humphries LL, et al. **Biol Psychiatry** 1985 Oct; 20(10):1073-81

Use of carbamazepine in psychiatric disorders. Birkhimer LJ, et al. **Clin Pharm** 1985 Jul-Aug;4(4):425-34

Service and patient predictors of continuation in clinic-based treatment. Atwood N, et al. **Hosp Community Psychiatry** 1985 Aug;36(8):865-9

An empirical view of patients exercising their right to refuse treatment. Bloom JD, et al. **Int J Law Psychiatry** 1984;7(3-4):315-28

Psychiatric treatment refusal, patient competence, and informed consent. Brown P. **Int J Law Psychiatry** 1986;8(1):83-94

The combination of psychiatric treatment and yoga. Nešpor K. **Int J Psychosom** 1985;32(2):24-7

Psychotropic drug use in older people: a review. Greene JA. **J Tenn Med Assoc** 1985 Jul;78(7):431-5

The pharmacokinetics of some psychoactive drugs and relationships to clinical response. Gottschalk LA. **Methods Find Exp Clin Pharmacol** 1985 May;7(5):275-82 (33 ref.)

The effect of milenperone on the aggressive behavior of psychogeriatric patients. A double-blind placebo-controlled study. De Cuyper H, et al. **Neuropsychobiology** 1985;13(1-2):1-6

Discussing issue of cost of drugs for the long term mentally ill. Roberts S. **Nurs Stand** 1985 Jul 4;(404):5

Planned change: an innovative nursing rehabilitation model. Bevvino CA, et al. **Perspect Psychiatr Care** 1984 Oct-Dec;22(4):149-58

A common single binding site for many psychotropic drugs on human alpha 1-acid glycoprotein. Therapeutically relevant observation? Müller WE. **Pharmacopsychiatry** 1985 Jul;18(4):257-8

Use of psychotropics in patients with kidney failure. Levy NB. **Psychosomatics** 1985 Sep;26(9):699-701, 705, 709

[Modern pharmacotherapy in psychiatry] Vinař O. **Psychiatr Neurol Med Psychol Beih** 1966;4-5:155-71 **(Ger)**

[Chemotherapy and psychotherapy--therapeutic approaches in psychiatric diseases resistant to treatment] Nishizono M. **Seishin Shinkeigaku Zasshi** 1984;86(12):939-50 **(Jpn)**

[Has psychopharmacotherapy had any effect on the chronicity of mental patients? (apropos of the article by A.B. Smulevich and G.P. Panteleev) (letter)] Krasik ED, et al. **Zh Nevropatol Psikhiatr** 1985;85(7):1077-9 **(Rus)**

[Level of dopamine in structures of the nigro-striatal and mesolimbic systems of the brain in experimental pathology of higher nervous activity in the rat] Saul'skaia NB. **Zh Vyssh Nerv Deiat** 1985 May-Jun; 35(3):561-4 (Eng. Abstr.) **(Rus)**

MENTAL PROCESSES

Early visual information processing in depressive patients treated with ORG 2766 (an ACTH 4-9 analogue). d'Elia G, et al. **Neuropsychobiology** 1985;13(1-2):63-8

Effect of neuroleptic treatments on attention, information processing, and thought disorder. Spohn HE, et al. **Psychopharmacol Bull** 1985; 21(3):582-7

The effect of methylphenidate on information processing. Naylor H, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):90-5

MEPROBAMATE

Determination of meprobamate as an n-butylboronate ester derivative in serum by gas-liquid chromatography. Johansson B, et al. **J Chromatogr** 1985 Jun 14;341(2):462-4

METHOTRIMEPRAZINE

[Malignant hyperthermia caused by neuroleptics] Escolano Villén F, et al. **Rev Esp Anestesiol Reanim** 1985 Jul-Aug;32(4):189-91 (Eng. Abstr.) **(Spa)**

METHYLPHENIDATE

Methylphenidate and children with attention deficit disorder. Dose effects on classroom academic and social behavior. Pelham WE, et al. **Arch Gen Psychiatry** 1985 Oct;42(10):948-52

Attention deficit disorder children with or without hyperactivity. Which behaviors are helped by stimulants? Ullmann RK, et al. **Clin Pediatr (Phila)** 1985 Oct;24(10):547-51

Developmental changes in the mother-child interactions of hyperactive boys: effects of two dose levels of Ritalin. Barkley RA, et al. **J Child Psychol Psychiatry** 1985 Sep;26(5):705-15

[3H]Threo-(+/-)-methylphenidate binding to 3,4-dihydroxyphenylethylamine uptake sites in corpus striatum: correlation with the stimulant properties of ritalinic acid esters. Schweri MM, et al. **J Neurochem** 1985 Oct;45(4):1062-70

Methylphenidate (Ritalin) treatment of cocaine dependence--a preliminary report. Khantzian EJ, et al. **J Subst Abuse Treat** 1984;

1(2):107-12

Ten years of experience with 1,000 hyperactive children in a private practice. Eichlseder W. **Pediatrics** 1985 Aug;76(2):176-84

Rate-dependency and hyperactivity: methylphenidate effects on operant responding. Rapport MD, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):77-83

The effect of methylphenidate on information processing. Naylor H, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):90-5

MOTIVATION

Schizophrenia: an amotivational syndrome in men. Lewine R. **Can J Psychiatry** 1985 Aug;30(5):316-8 (17 ref.)

MOTOR ACTIVITY

Side effects of drugs stimulating prolactin secretion on the behavior of male rats. Drago F, et al. **Arch Int Pharmacodyn Ther** 1985 Aug; 276(2):271-8

Differential effects of intrafrontocortical microinjections of dopamine agonists and antagonists on circling behavior of rats. Stewart RJ, et al. **Behav Brain Res** 1985 Sep;17(1):67-72

Increased total activity in the rat after L-tryptophan plus the monoamine oxidase-A inhibitor amiflamine but not after L-tryptophan plus clorgyline. Archer T, et al. **Br J Pharmacol** 1985 Jul;85(3):581-90

The effect of water-deprivation on locomotor activity in rats treated with 6-hydroxydopamine. Seiden LS, et al. **Brain Res** 1985 Jul 1; 337(2):225-32

Behavioural effects in the rat after acute unilateral intranigral infusions of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Sirinathsinghji DJ. **Brain Res** 1985 Jul 29;339(2):366-70

Involvement of amygdaloid catecholaminergic mechanism in suppressive effects of desipramine and imipramine on duration of immobility in rats forced to swim. Araki H, et al. **Eur J Pharmacol** 1985 Jul 31; 113(3):313-8

Neuronal mechanisms involved in drug-induced jumping behavior in mice. Ushijima I, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):225-9

Repeated treatment with imipramine or amitriptyline increases the locomotor response of rats to (+)-amphetamine given into the nucleus accumbens. Maj J, et al. **J Pharm Pharmacol** 1985 May;37(5):362-4

Dopamine agonist-induced locomotor activity in rats treated with 6-hydroxydopamine at differing ages: functional supersensitivity of D-1 dopamine receptors in neonatally lesioned rats. Breese GR, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):447-55

Hyperactivity induced by stimulation of separate dopamine D-1 and D-2 receptors in rats with bilateral 6-OHDA lesions. Arnt J. **Life Sci** 1985 Aug 26;37(8):717-23

Brain NADH and jumping behavior in the rat. Shen Z, et al. **Life Sci** 1985 Aug 26;37(8):731-8

Unilateral lesion of the intrinsic cells in the medial forebrain bundle depresses self-stimulation but not stimulus-bound locomotor activity. Velley L. **Neurosci Lett** 1985 Jun 12;57(2):199-204

Central nervous system effect of 2,5-hexane diol. Agrawal AK, et al. **Neurotoxicology** 1985 Fall;6(3):53-9

The effects of MIF-I, beta-endorphin and alpha-MSH on d-amphetamine induced paradoxical behavioral thermoregulation: possible involvement of the dopaminergic system. Yehuda S, et al. **Peptides (Fayetteville)** 1985 Mar-Apr;6(2):189-92

Behavioral responses of high and low active male rats to the chronic ingestion of desipramine. Echandia EL, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):917-20

Effect of DL-erythro-dihydroxyphenylserine on the locomotor activity of the mouse. Mori T, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):979-83

Neonatal 6-hydroxydopamine potentiates clonidine's locomotor effects throughout maturation in the rat. Smythe JW, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):1075-8

Dopamine agonist action in mesolimbic, cortical and extrapyramidal areas to modify spontaneous climbing behaviour of the mouse. Costall B, et al. **Psychopharmacology (Berlin)** 1985;86(4):452-7

Effects of d,l-propranolol on open field behavior of rats. Poli A, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):153-5

Repeated treatment with imipramine potentiates the locomotor effect of apomorphine administered into the hippocampus in rats. Smialowski A, et al. **Psychopharmacology (Berlin)** 1985;86(4):468-71

The comparative long-term effects of ciladopa (AY-27,110), a chemically novel dopaminergic agonist, in 6-OHDA-lesioned and intact rats. Voith K. **Psychopharmacology (Berlin)** 1985;85(4):405-9

Comparison between locomotor activity changes produced by phencyclidine and D-amphetamine in CD-1 male mice. Stavchansky S, et al. **Res Commun Chem Pathol Pharmacol** 1985 May; 48(2):189-202

[Effect of l-stepholidine on rotational behavior in rats] Shi WX, et al. **Chung Kuo Yao Li Hsueh Pao** 1984 Dec;5(4):222-5 (Eng. Abstr.) **(Chi)**

[A simply designed apparatus and its use for measuring vertical and horizontal motor activities in methamphetamine-treated mice] Itoh T, et al. **Yakubutsu Seishin Kodo** 1985 May;5(1):19-23 (Eng. Abstr.) **(Jpn)**

MOTOR SKILLS

Temazepam and the perceptual-motor performance of professional footballers. Golby J, et al. **Br J Sports Med** 1985 Jun;19(2):115-8

MSH

Cell types of the pars distalis of the hedgehog (Erinaceus europaeus L.) adenohypophysis: cytological, immunocytochemical and ultrastructural studies. 3. Opiocorticomelanotropic cells. Girod C, et al. **Acta Anat (Basel)** 1985;123(1):67-71

Dynorphin-A(1-8) and gamma-melanotropin exist within different myenteric plexus neurons of rat duodenum. Wolter HJ. **Biochem Biophys Res Commun** 1985 Sep 16;131(2):821-6

Stress-induced elevation of plasma alpha-MSH and endorphin in brown trout, Salmo trutta L. Sumpter JP, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):257-65

Presence of immunoreactive alpha-melanotropin and beta-endorphin in spinal motoneurones of the dystrophic mouse. Haynes LW, et al. **Neurosci Lett** 1985 Jul 4;58(1):13-8

The effects of MIF-I, beta-endorphin and alpha-MSH on d-amphetamine induced paradoxical behavioral thermoregulation: possible involvement of the dopaminergic system. Yehuda S, et al. **Peptides (Fayetteville)** 1985 Mar-Apr;6(2):189-92

Current concepts in premenstrual syndrome. Ullman LE. **RI Med J** 1985 Jun;68(6):269-72

NEUROREGULATORS

Dose-related effects of cysteamine treatment on hypothalamic and striatal dopamine, noradrenaline and serotonin neurotransmission. Vécsei L, et al. **Acta Physiol Hung** 1985;66(2):213-7

Immunocytochemical studies of somatostatin neurons in brain. Elde R, et al. **Adv Exp Med Biol** 1985;188:167-81

Monoamines and the effect of ethanol on corticosterone and non-esterified fatty acids. Brick J, et al. **Alcohol** 1985 Mar-Apr;2(2):261-5

Proctolin induces rhythmic contractions and spikes in Limulus heart muscle. Watson WH 3d, et al. **Am J Physiol** 1985 Oct; 249(4 Pt 2):R490-5

Overview: toward a dysregulation hypothesis of depression. Siever LJ, et al. **Am J Psychiatry** 1985 Sep;142(9):1017-31 (134 ref.)

Distribution of cholecystokinin-like immunoreactivity in the nervous system. Co-existence with classical neurotransmitters and other neuropeptides. Hökfelt T, et al. **Ann NY Acad Sci** 1985;448:255-74

Developmental study on the regulation of neurotransmitter-sensitive adenylate cyclase systems in primary cerebral cell cultures from embryonic mice. Shanker G, et al. **Biosci Rep** 1985 Jul;5(7):601-8

Neurotransmitter-related markers in the normal and experimentally lesioned telencephalon of the goldfish. Bissoli R, et al. **Brain Res** 1985 Oct 7;344(2):397-401

An antiserum to locust adipokinetic hormone reveals a novel peptidergic system in the rat central nervous system. Sasek CA, et al. **Brain Res** 1985 Sep 16;343(1):172-5

Monoamine, amino acid and cholinergic interactions in slices of rat cerebral cortex. Flint RS, et al. **Brain Res Bull** 1985 Aug; 15(2):197-202

Integrative peptides. Hoebel BG. **Brain Res Bull** 1985 Jun;14(6):525-8 (54 ref.)

Peptides as central regulators of feeding. Morley JE, et al. **Brain Res Bull** 1985 Jun;14(6):511-9 (108 ref.)

Measurements of transmitter action: the problem of voltage dependence. MacDonald JF. **Can J Physiol Pharmacol** 1985 Jul;63(7):825-30

Non-vascular central nervous system effects of calcium entry blockers. Govoni S, et al. **Cephalalgia** 1985 May;5 Suppl 2:115-8

Calmodulin, synchronous and asynchronous release of neurotransmitter. Publicover SJ. **Comp Biochem Physiol [A]** 1985;82(1):7-11 (45 ref.)

Distribution and localization of regulatory peptides. Ballesta J, et al. **CRC Crit Rev Clin Lab Sci** 1985;22(3):185-218 (250 ref.)

Inhibition of quantal transmitter release by the polycationic ligand cationized ferritin. Publicover SJ. **Exp Brain Res** 1985;59(3):629-32

Genes for neurotransmitter synthesis, storage, and uptake. Joh TH, et al. **Fed Proc** 1985 Sep;44(12):2773-9

The hyperglycemic factor of the CNS of the freshwater snail Lymnaea stagnalis: interaction with glucose stimulation of glycogen synthesis and evidence for its release during anaerobiosis. Hemminga MA, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):301-7

Circadian variations of neurotransmitter binding in three age groups of rats. Jenni-Eiermann S, et al. **Gerontology** 1985;31(3):138-49

Biochemical and immunochemical approaches to the study of the auditory system. Wenthold RJ. **J Acoust Soc Am** 1985 Jul;78(1 Pt 2):334-9

Depression and serotonin metabolism: rationale for neurotransmitter precursor treatment. Byerley WF, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):191-206 (188 ref.)

In vitro differentiation of neuronal precursor cells from amphibian late gastrulae; morphological, immunocytochemical studies, biosynthesis, accumulation and uptake of neurotransmitters. Duprat AM, et al. **J Embryol Exp Morphol** 1985 Apr;86:71–87

Binding of lanthanum ions and ruthenium red to synaptosomes and its effects on neurotransmitter release. Tapia R, et al. **J Neurochem** 1985 Nov;45(5):1464–70

A genetically controlled hippocampal transmitter system regulating exploratory behavior in mice. van Abeelen JH, et al. **J Neurogenet** 1984 Apr;1(2):153–8

Actions of neurotransmitters on pontine medical reticular formation neurons of the cat. Greene RW, et al. **J Neurophysiol** 1985 Sep; 54(3):520–31

Modulation of neurotransmitter action: control of the gamma–aminobutyric acid response through the benzodiazepine receptor. Chan CY, et al. **J Neurosci** 1985 Sep;5(9):2365–73

Properties of choroid and ciliary neurons in the avian ciliary ganglion and evidence for substance P as a neurotransmitter. Dryer SE, et al. **J Neurosci** 1985 Oct;5(10):2654–61

Effects of changes in motor unit size on transmitter release at the frog neuromuscular junction. Herrera AA, et al. **J Neurosci** 1985 Jul; 5(7):1896–900

Excitatory effect of amino acids on identified neuron R14 of Aplysia. II. Neutral amino acids and structure–activity relationships. Ichinose M, et al. **J Neurosci Res** 1985;14(1):145–58

Evidence against VIP or substance P being the transmitter in non–cholinergic excitatory nerves supplying the guinea–pig bladder. Meldrum LA, et al. **J Pharm Pharmacol** 1985 Jun;37(6):432–4

Effects of K+–channel blockers on transmitter release in bullfrog sympathetic ganglia. Kumamoto E, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):241–7

Non–uniform effects of neurohumoral agents on the internal diameter in parallel and series arranged small arteries in rabbit hindlimb. Sada K, et al. **Jpn J Physiol** 1985;35(2):321–34

Effects of advancing age on hypothalamic neurotransmitter content and on basal and norepinephrine–stimulated LHRH release. Steger RW, et al. **Neurobiol Aging** 1985 Summer;6(2):113–6

Preoptic catecholamine, GABA, and glutamate release in ovariectomized and ovariectomized estrogen–primed rats utilizing a push–pull cannula technique. Demling J, et al. **Neuroendocrinology** 1985 Sep; 41(3):212–8

Effect of chronic lithium administration on neurotransmitter metabolism in synaptosomes from rat brain. Rafałowska U, et al. **Neuropatol Pol** 1985;23(2):211–8

Models for transmitter activation process in retinal rod outer segments to flash stimuli. Ichikawa K. **Neurosci Res** 1985 Jun;2(5):349–64

Neurotransmitters of the hypothalamic suprachiasmatic nucleus: immunocytochemical analysis of 25 neuronal antigens. van den Pol AN, et al. **Neuroscience** 1985 Aug;15(4):1049–86

Ginseng saponins: influence on neurotransmitter uptake in rat brain synaptosomes. Tsang D, et al. **Planta Med** 1985 Jun;(3):221–4

Brain neurotransmitters and appetite regulation. Leibowitz SF. **Psychopharmacol Bull** 1985;21(3):412–8

Peripheral models for the study of neurotransmitter receptors in man. Stahl SM. **Psychopharmacol Bull** 1985;21(3):663–71

[Localization of biogenic monoamines in the dura mater of the rat brain] Motavkin PA, et al. **Arkh Anat Gistol Embriol** 1985 May;88(5):11–6 (Eng. Abstr.) **(Rus)**

[Effect of fenibut on the GABA B receptors of the spinal motor neurons] Abramets II, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):698–700 (Eng. Abstr.) **(Rus)**

[Periodic changes in evoked mediator secretion at the neuromuscular synapse] Zefirov AL. **Fiziol Zh SSSR** 1985 Jun;71(6):737–43 (Eng. Abstr.) **(Rus)**

[Age aspects of receptor–effector reactions and the regulation of adenylate cyclase activity] Burchinskii SG, et al. **Ukr Biokhim Zh** 1985 Jul–Aug; 57(4):86–98 (101 ref.) (Eng. Abstr.) **(Rus)**

[Analysis of the significance of irregular spike activity in response to mediator action on Helix pomatia neurons] Vagin IuE, et al. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):322–9 (Eng. Abstr.) **(Rus)**

[Conformation study, using an empirical atom–atom potential, of biologically active amino acids as neurotransmitters] Jáuregui EA, et al. **Acta Cient Venez** 1984;35(5–6):337–41 (Eng. Abstr.) **(Spa)**

[Correlation between clinical and laboratory data in depression. Therapeutic orientation by means of vitamins and amino acids] Mesones HL, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):25–36 (Eng. Abstr.) **(Spa)**

NEUROTENSIN

Pharmacological analysis of the mechanism of action for colonic contraction induced by neurotensin, substance P and methionine–enkephalin. Hellström PM. **Acta Physiol Scand** 1985 Sep; 125(1):13–24

Neurotensin–like immunoreactivity in some preparations of secretin and cholecystokinin. Feurle GE. **Agents Actions** 1985 Jul;16(5):411–4

Structure–activity studies with carboxy– and amino–terminal fragments of neurotensin on hypothalamic neurons in vitro. Baldino F Jr, et al. **Brain Res** 1985 Sep 9;342(2):266–72

The comparative distribution of [Lys8–Asn9]–neurotensin8–13–like immunoreactivity in chicken and rat tissues. Goedert M, et al. **Brain Res** 1985 Sep 9;342(2):259–65

Neurotensin depolarizes substantia nigra dopamine neurones. Pinnock RD. **Brain Res** 1985 Jul 8;338(1):151–4

Phylogenetic conservatism in the presence of a neurotensin–related hexapeptide in neurons of globus pallidus. Reiner A, et al. **Brain Res** 1985 Aug 26;341(2):365–71

Effect of vagal blockade on food– and hormone–stimulated release of pancreatic polypeptide and motilin in dogs. Greenberg GR, et al. **Dig Dis Sci** 1985 Oct;30(10):946–53

Effect of truncal vagotomy on neurotensin–like immunoreactivity release in dogs. Yoshiya K, et al. **Gastroenterol Jpn** 1985 Jun;20(3):197–200

Inactivation of neurotensin by rat brain synaptic membranes partly occurs through cleavage at the Arg8–Arg9 peptide bond by a metalloendopeptidase. Checler F, et al. **J Neurochem** 1985 Nov; 45(5):1509–13

The application of enzyme–linked immunosorbent assays (ELISA) to neuropeptides. Davis LG, et al. **J Neurosci Methods** 1985 Jun; 14(1):15–23

Effects of intraventricular neurotensin on blood pressure and heat balance in rats. Shido O, et al. **Jpn J Physiol** 1985;35(2):311–20

Neurotensin stimulates polyphosphoinositide breakdown and prolactin release in anterior pituitary cells in culture. Canonico PL, et al. **Mol Cell Endocrinol** 1985 Oct;42(3):215–20

Primary explants as a model of the hypothalamus in situ. Baldino F Jr, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):249–56

Distribution of neurotensin–like immunoreactivity in rat and cat area postrema. Newton BW, et al. **Peptides (Fayetteville)** 1985 Mar–Apr; 6(2):301–6

Emetic effects of centrally administered angiotensin II, arginine vasopressin and neurotensin in the dog. Wu M, et al. **Peptides (Fayetteville)** 1985;6 Suppl 1:173–5

Importance of the ileum in neurotensin released by fat. Walker JP, et al. **Surgery** 1985 Aug;98(2):224–9

NEUROTIC DISORDERS

Chronic treatments in neuropsychiatry. **Adv Biochem Psychopharmacol** 1985;40:1–219

[Psychoneurotic disorders in puberty and the activity of the adrenergic system] Szewczyk L. **Pediatr Pol** 1985 Apr;60(4):306–11 (Eng. Abstr.) **(Pol)**

[Selected elements of complex therapy in the opinion of former patients of the neurosis ward of the Psychiatric Clinic in Bydgoszcz] Brzeziński R. **Psychiatr Pol** 1984 Sep–Oct;18(5):457–63 (Eng. Abstr.) **(Pol)**

[Effect of insulin and its polymeric analogs on learning and memory processes in the rabbit] Bakharev VD, et al. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):314–21 (Eng. Abstr.) **(Rus)**

NITRAZEPAM

Determination of nitrazepam and its main metabolites in urine by thin–layer chromatography and direct densitometry. Inoue T, et al. **J Chromatogr** 1985 Apr 12;339(1):163–9

NOMIFENSINE

Depression and anxiety: mianserin and nomifensine compared in a double–blind multicentre trial. Granier F, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:67–74

Mianserin is better tolerated and more effective in depression than a nomifensine–clobazam combination: a double–blind study. Levin A, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:75–80

Fatal immune haemolysis associated with nomifensine [letter] Ross JR. **Br Med J [Clin Res]** 1985 Aug 31;291(6495):606

Suppression of MPTP–induced dopaminergic neurotoxicity in mice by nomifensine and L–DOPA. Melamed E, et al. **Brain Res** 1985 Sep 9; 342(2):401–4

Psychopharmacological effects of nomifensine enantiomers. Poncelet M, et al. **Eur J Pharmacol** 1985 Jul 17;113(2):271–4

NOREPINEPHRINE

Beta receptors in peripheral mononuclear cells increase acutely during exercise. Burman KD, et al. **Acta Endocrinol (Copenh)** 1985 Aug; 109(4):563–8

The vasopressin response to microinjections of norepinephrine into the brain of the conscious pig. Forsling ML, et al. **Acta Endocrinol (Copenh)** 1985 Jul;109(3):330–4

Relationship between the release and uptake of noradrenaline by rat brain synaptosomes in the formation of defensive conditioned reflex. Bazyan AS, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(1–2):37–46

Influence of beta–receptor stimulation on catecholamine and phospholipid concentrations in lungs of fetal rabbits. Urban J, et al. **Acta Paediatr Hung** 1985;26(2):127–32

Effect of the rate of blood loss on the plasma catecholamine response. Tárnoky K, et al. **Acta Physiol Hung** 1985;66(2):143–53

Subcellular storage and axonal transport of neuropeptide Y (NPY) in relation to catecholamines in the cat. Fried G, et al. **Acta Physiol Scand** 1985 Sep;125(1):145–54

The relation between in vitro efflux of noradrenaline from platelets and vas deferens in man. Mattiasson I, et al. **Acta Physiol Scand** 1985 Sep;125(1):155–8

Indirect adrenergic effect of compound 48/80 in cat cerebral arteries. Marco EJ, et al. **Agents Actions** 1985 Jul;16(5):310–2

Systemic and uterine responsiveness to angiotensin II and norepinephrine in estrogen-treated nonpregnant sheep. Naden RP, et al. **Am J Obstet Gynecol** 1985 Oct 15;153(4):417–25

Effect of norepinephrine on gluconeogenesis in perfused livers of cold-exposed rats. Shiota M, et al. **Am J Physiol** 1985 Sep;249(3 Pt 1):E281–6

Diurnal-stimulated and stress-induced ACTH release in rats is mediated by ventral noradrenergic bundle. Szafarczyk A, et al. **Am J Physiol** 1985 Aug;249(2 Pt 1):E219–26

Spermatogenesis of rat: effect of central norepinephrine synthesis inhibition by diethyldithiocarbamate. Mazumder R, et al. **Andrologia** 1985 Jul–Aug;17(4):400–5

Effect of norepinephrine and vasopressin on renal kallikrein excretion in rats. Martinez Seeber A, et al. **Arch Int Physiol Biochim** 1985 Jun;93(2):83–8

Change of catecholamine turnover in ovary during the rat estrous cycle. Nagahara Y, et al. **Asia Oceania J Obstet Gynaecol** 1985 Jun;11(2):261–4

Stress, catecholamines, and sleep. Harrison GA. **Aviat Space Environ Med** 1985 Jul;56(7):651–3

Evidence that noradrenaline increases pyruvate dehydrogenase activity and decreases acetyl-CoA carboxylase activity in rat interscapular brown adipose tissue in vivo. Gibbins JM, et al. **Biochem J** 1985 Jun 15;228(3):751–5

Alpha-adrenergic stimulation of glutamine metabolism in isolated rat hepatocytes. Verhoeven AJ, et al. **Biochem J** 1985 Sep 1;230(2):457–63

Metabolism of carbidopa to alpha-methyldopamine and alpha-methylnorepinephrine in rats. Shelton RC, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3623–6

Control of oxygen uptake, microcirculation and glucose release by circulating noradrenaline in perfused rat liver. Beckh K, et al. **Biol Chem Hoppe Seyler** 1985 Jul;366(7):671–8

Plasma melatonin during desmethylimipramine treatment: evidence for changes in noradrenergic transmission. Cowen PJ, et al. **Br J Clin Pharmacol** 1985 Jun;19(6):799–805

Comparison of the antagonistic effects of phentolamine on vasoconstrictor responses to exogenous and neurally released noradrenaline in vivo. Bell C. **Br J Pharmacol** 1985 May;85(1):249–53

Effect of the dihydropyridine Bay K 8644 on the release of [3H]-noradrenaline from the rat isolated vas deferens. Ceña V, et al. **Br J Pharmacol** 1985 Jul;85(3):691–6

Bay K 8644, a dihydropyridine calcium agonist, augments vasoconstrictor responses to endogenous and exogenous noradrenaline in the peripheral vasculature of the dog. Goto T, et al. **Br J Pharmacol** 1985 Aug;85(4):913–6

The effect of diltiazem on noradrenaline release. Wolchinsky C, et al. **Br J Pharmacol** 1985 Jun;85(2):387–93

Coexistence of vasopressin, neurophysin and noradrenaline immunoreactivity in medium-sized cells of the locus coeruleus and subcoeruleus in the rat. Caffé AR, et al. **Brain Res** 1985 Jul 8;338(1):160–4

Amygdala norepinephrine involved in two separate long-term memory retrieval processes. Ellis ME. **Brain Res** 1985 Sep 2;342(1):191–5

Desensitization of beta-receptors on primary astrocyte cultures by norepinephrine but not by tricyclic antidepressants. Frangakis MV, et al. **Brain Res** 1985 Jul 22;339(1):49–56

Regional depletion of central nervous system catecholamines: effects on blood pressure and drinking behavior. Gordon FJ, et al. **Brain Res** 1985 Oct 21;345(2):285–97

Water deprivation increases anterior hypothalamic norepinephrine metabolism in the rat. Klemfuss H, et al. **Brain Res** 1985 Aug 26;341(2):222–7

Exogenous monoamines affect the segregation of retinogeniculate fibers in developing rats. Land PW, et al. **Brain Res** 1985 Sep;354(1):135–40

Growth cones isolated from developing rat forebrain: uptake and release of GABA and noradrenaline. Lockerbie RO, et al. **Brain Res** 1985 Aug;353(2):265–75

Effects of norepinephrine on rat neocortical neurons in dissociated cell culture. Rosenberg PA, et al. **Brain Res** 1985 Oct 7;344(2):369–72

Amphetamine's effects on terminal excitability of noradrenergic locus coeruleus neurons are impulse-dependent at low but not high doses. Ryan LJ, et al. **Brain Res** 1985 Aug 19;341(1):155–63

In vivo modulation of norepinephrine-induced cerebral oxygenation states by hypoxia and hyperoxia. Sylvia AL, et al. **Brain Res** 1985 Jul 15;338(2):281–8

Norepinephrine stimulates serotonin secretion from rat pineal glands, in vitro. Walker RF, et al. **Brain Res** 1985 Sep 16;343(1):188–9

Neonatal monosodium glutamate administration alters noradrenergic measures in the brainstem of the mouse. Dawson R Jr, et al. **Brain Res Bull** 1985 Aug;15(2):117–21

Monoamine transmitter release induced by tetrahydro-beta-carboline perfused in hippocampus of the unrestrained rat. Huttunen P, et al. **Brain Res Bull** 1985 Aug;15(2):215–20

Action of serotonin and norepinephrine on spinal motoneurones following blockade of synaptic transmission. Neuman RS. **Can J Physiol Pharmacol** 1985 Jun;63(6):735–8

Neuronally released norepinephrine does not preferentially activate postjunctional alpha 1-adrenoceptors in human blood vessels in vitro. Stevens MJ, et al. **Circ Res** 1985 Sep;57(3):399–405

Increased sensitivity of rabbit ear artery to noradrenaline following perivascular nerve stimulation may be a response to neuropeptide Y released as cotransmitter. Glover WE. **Clin Exp Pharmacol Physiol** 1985 May–Jun;12(3):227–30

Increased plasma noradrenaline during low dose adrenaline infusion in resting man and during sympathetic stimulation. Musgrave IF, et al. **Clin Exp Pharmacol Physiol** 1985 May–Jun;12(3):285–9

Beta-adrenoceptor responsiveness and plasma catecholamines as determinants of cardiovascular reactivity to mental stress. Eisenhofer G, et al. **Clin Sci** 1985 Oct;69(4):483–92

Effect of gonadectomy on brain catecholamines during the postnatal period. Leret ML, et al. **Comp Biochem Physiol [C]** 1985;81(2):405–9

Adrenergic stimulation of adrenocortical secretion in immature fowl. Rees A, et al. **Comp Biochem Physiol [C]** 1985;81(2):387–9

Effect of norepinephrine on ketogenesis, fatty acid oxidation, and esterification in isolated rat hepatocytes. Oberhaensli RD, et al. **Diabetes** 1985 Aug;34(8):774–9

Effect of microelectrophoretically applied acetylcholine, noradrenaline, dopamine and serotonin on the discharge of paraventricular oxytocinergic neurones in the rat. Honda K, et al. **Endocrinol Jpn** 1985 Feb;32(1):127–33

Elevated catecholamines in porcine follicular fluid before ovulation. Bahr JM, et al. **Endocrinology** 1985 Aug;117(2):620–3

Examination of the effects of epinephrine, norepinephrine, and dopamine on aldosterone production in bovine glomerulosa cells in vitro. Sequeira SJ, et al. **Endocrinology** 1985 Nov;117(5):1947–52

Rapid bidirectional effects of insulin on hypothalamic noradrenergic and serotoninergic neuronal activity in the rat: role in glucose homeostasis. Smythe GA, et al. **Endocrinology** 1985 Oct;117(4):1590–7

Plasma testosterone and catecholamine responses to physical exercise of different intensities in men. Ježová D, et al. **Eur J Appl Physiol** 1985;54(1):62–6

Postsynaptic alpha 2-noradrenergic receptors mediate feeding induced by paraventricular nucleus injection of norepinephrine and clonidine. Goldman CK, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):11–9

Trimipramine, a tricyclic antidepressant exerting atypical actions on the central noradrenergic system. Hauser K, et al. **Eur J Pharmacol** 1985 Apr 23;111(1):23–30

Chronic clonidine induces functional down-regulation of presynaptic alpha 2-adrenoceptors regulating [3H]noradrenaline and [3H]5-hydroxytryptamine release in the rat brain. Maura G, et al. **Eur J Pharmacol** 1985 May 28;112(1):105–10

Action of norepinephrine in the dentate gyrus. I. Stimulation of locus coeruleus. Dahl D, et al. **Exp Brain Res** 1985;59(3):491–6

Substantial reduction of noradrenaline in kitten visual cortex by intraventricular injections of 6-hydroxydopamine does not always prevent ocular dominance shifts after monocular deprivation. Daw NW, et al. **Exp Brain Res** 1985;59(1):30–5

Sex-specific effects of estradiol on hypothalamic noradrenaline turnover in gonadectomized rats. Hiemke C, et al. **Exp Brain Res** 1985;59(1):68–72

Action of norepinephrine in the dentate gyrus. II. Iontophoretic studies. Winson J, et al. **Exp Brain Res** 1985;59(3):497–506

Diet and weight loss: their effect on norepinephrine renin and aldosterone levels. Grossman E, et al. **Int J Obes** 1985;9(2):107–14

Vascular responses to intravenous catecholamines in hands and forearms with normal and with increased skin blood flow. Allen JA, et al. **Ir J Med Sci** 1985 May;154(5):178–86

The hemodynamic and plasma catecholamine responses to routine restorative dental care. Cioffi GA, et al. **J Am Dent Assoc** 1985 Jul;111(1):67–70

Reserpic acid as an inhibitor of norepinephrine transport into chromaffin vesicle ghosts. Chaplin L, et al. **J Biol Chem** 1985 Sep 15;260(20):10981–5

Association of the changes in cytosolic Ca2+ and iodide efflux induced by thyrotropin and by the stimulation of alpha 1-adrenergic receptors in cultured rat thyroid cells. Corda D, et al. **J Biol Chem** 1985 Aug 5;260(16):9230–6

Catecholamine and vasopressin stimulation of gluconeogenesis from dihydroxyacetone in the presence of atractyloside. Warnette-Hammond

ME, et al. **J Biol Chem** 1985 Oct 15;260(23):12647–52

In vitro studies on responses to noradrenaline, serotonin, and potassium of intramyocardial and mesenteric resistance vessels from Wistar rats. Nyborg NC, et al. **J Cardiovasc Pharmacol** 1985 May-Jun; 7(3):417–23

Norepinephrine and epidermal growth factor: dynamics of their interaction in the stimulation of hepatocyte DNA synthesis. Cruise JL, et al. **J Cell Physiol** 1985 Oct;125(1):45–50

Determination of adult sheep plasma catecholamines using [3H]norepinephrine as the internal standard. Boylan JM, et al. **J Chromatogr** 1985 Feb 27;338(1):192–4

Haemodynamic and catecholamine responses to hypothermia in the fetal sheep in utero. Gunn TR, et al. **J Dev Physiol** 1985 Aug;7(4):241–9

Antioestrogen inhibition of oestradiol-induced alterations in hypothalamic noradrenaline turnover. Hiemke C, et al. **J Endocrinol** 1985 Jul; 106(1):37–42

Time-dependent effects of oestradiol and progesterone on hypothalamic catecholamine turnover in ovariectomized rats. Hiemke C, et al. **J Endocrinol** 1985 Sep;106(3):303–9

Differential coupling of GABA-A and GABA-B receptors to the noradrenergic system. Suzdak PD, et al. **J Neural Transm** 1985; 62(1-2):77–89

Cholinergic- and adrenergic-stimulated inositide hydrolysis in brain: interaction, regional distribution, and coupling mechanisms. Gonzales RA, et al. **J Neurochem** 1985 Oct;45(4):1076–84

Norepinephrine turnover in the hypothalamus of adult male rats: alteration of circadian patterns by semistarvation. Schweiger U, et al. **J Neurochem** 1985 Sep;45(3):706–9

Alteration in the postnatal ontogeny of cerebellar norepinephrine content following chronic prenatal carbon monoxide. Storm JE, et al. **J Neurochem** 1985 Sep;45(3):965–9

DSP-4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine) depletes noradrenaline in kitten visual cortex without altering the effects of monocular deprivation. Daw NW, et al. **J Neurosci** 1985 Jul; 5(7):1925–33

Depletion of norepinephrine, but not serotonin, reduces long-term potentiation in the dentate gyrus of rat hippocampal slices. Stanton PK, et al. **J Neurosci** 1985 Aug;5(8):2169–76

Ouabain-evoked norepinephrine release from intact rat sympathetic neurons: evidence for carrier-mediated release. Sweadner KJ. **J Neurosci** 1985 Sep;5(9):2397–406

Effect of uptake-one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. Tobes MC, et al. **J Nucl Med** 1985 Aug; 26(8):897–907

Energy intake, norepinephrine excretion, and oxygen consumption in low birthweight infants. Weinstein MR, et al. **J Pediatr Gastroenterol Nutr** 1985 Oct;4(5):774–7

Hypernoradrenergic innervation of the caudal artery of the spontaneously hypertensive rat: an influence upon neuroeffector mechanisms. Cassis LA, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):792–803

Effect of imipramine and adrenocorticotropin administration on the rat brain norepinephrine-coupled cyclic nucleotide generating system: alterations in alpha and beta adrenergic components. Duman RS, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):409–14

Neuropeptide Y potentiates noradrenaline-evoked vasoconstriction: mode of action. Wahlestedt C, et al. **J Pharmacol Exp Ther** 1985 Sep; 234(3):735–41

Non-uniform effects of neurohumoral agents on the internal diameter in parallel and series arranged small arteries in rabbit hindlimb. Sada K, et al. **Jpn J Physiol** 1985;35(2):321–34

Evidence for a role of PTH in the reduced pressor response to norepinephrine in chronic renal failure. Iseki K, et al. **Kidney Int** 1985 Jul;28(1):11–5

Free and conjugated catecholamines in digestive tissues of rats. Gaudin C, et al. **Life Sci** 1985 Oct 21;37(16):1469–74

Plasma dihydroxyphenylglycol (DHPG) in the in vivo assessment of human neuronal norepinephrine metabolism. Izzo JL Jr, et al. **Life Sci** 1985 Sep 16;37(11):1033–8

Differential effects of DSP-4 administration on regional brain norepinephrine turnover in rats. Logue MP, et al. **Life Sci** 1985 Aug 5;37(5):403–9

Dopamine-beta-hydroxylase inhibition acutely stimulates rats hypothalamic noradrenaline and dopamine neuronal activity as assessed from metabolic ratios and circulating glucose and ACTH responses. Smythe GA, et al. **Life Sci** 1985 Sep 2,37(9):841–7

The effect of long-term intraarterial norepinephrine infusion on transcapillary fluid and protein transport. Friedman JJ, et al. **Microvasc Res** 1985 Jul;30(1):45–55

In vivo fluorescence microscopy of blood flow in mouse pancreatic islets: adrenergic effects in lean and obese-hyperglycemic mice. Rooth P, et al. **Microvasc Res** 1985 Sep;30(2):176–84

Role of adenosine 3',5'-cyclic monophosphate in adrenoceptor-mediated control of 3H-noradrenaline secretion in guinea-pig ileum myenteric nerve terminals. Alberts P, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug;330(2):114–20

Very rapid turnover of dopamine in noradrenaline cell body regions. Andén NE, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 May; 329(3):258–63

Endogenous noradrenaline as modulator of hippocampal serotonin (5-HT)-release. Dual effects of yohimbine, rauwolscine and corynanthine as alpha-adrenoceptor antagonists and 5-HT-receptor agonists. Feuerstein TJ, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 May;329(3):216–21

Dopaminergic modulation of hippocampal noradrenaline release. Evidence for alpha 2-antagonistic effects of some dopamine receptor agonists and antagonists. Jackisch R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug;330(2):105–13

Cyclic AMP facilitates the electrically evoked release of radiolabelled noradrenaline, dopamine and 5-hydroxytryptamine from rat brain slices. Schoffelmeer AN, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jul;330(1):74–6

Interaction of norepinephrine with Purkinje cell responses to cerebellar afferent inputs in aged rats. Bickford PC, et al. **Neurobiol Aging** 1985 Summer;6(2):89–94

Effects of advancing age on hypothalamic neurotransmitter content and on basal and norepinephrine-stimulated LHRH release. Steger RW, et al. **Neurobiol Aging** 1985 Summer;6(2):113–6

Noradrenergic afferents facilitate the activity of tuberoinfundibular neurons of the hypothalamic paraventricular nucleus. Day TA, et al. **Neuroendocrinology** 1985 Jul;41(1):17–22

Adenosine: an endogenous modulator of hippocampal noradrenaline release. Jackisch R, et al. **Neuropharmacology** 1985 Jun;24(6):499–507

Interaction between the baroreflex and anterior hypothalamic stimulation. Demonstration of a noradrenergic involvement. Simon OR, et al. **Neuropharmacology** 1985 Jul;24(7):665–75

Serotonin and norepinephrine-dependent effects of fenfluramine on plasma renin activity in conscious male rats. Van de Kar LD, et al. **Neuropharmacology** 1985 Jun;24(6):487–94

Brain noradrenergic activity in wakefulness and paradoxical sleep: the effect of clonidine. Gaillard JM. **Neuropsychobiology** 1985; 13(1-2):23–5

Biochemical, physical and psychological findings in patients suffering from cardiac neurosis. Gasic S, et al. **Neuropsychobiology** 1985; 13(1-2):12–6

Neuroendocrine differences between violent and non-violent parasuicides. Prasad AJ. **Neuropsychobiology** 1985;13(4):157–9

Electrical stimulation of the ventral noradrenergic tract (VNAT) releases hypothalamic noradrenaline and stimulates prolactin secretion in ovariectomized female rats treated with oestrogen. Dean AD, et al. **Neurosci Lett** 1985 Jun 4;57(1):73–8

Inactivation by 6-hydroxydopamine of the cerebral factor(s) responsible for the inhibition of the autoxidation of norepinephrine in vitro. Kovachich GB. **Neurosci Lett** 1985 Jul 31;58(2):245–50

Laminar distributions of neurons sensitive to acetylcholine, noradrenaline and dopamine in the dorsolateral prefrontal cortex of the monkey. Sawaguchi T, et al. **Neurosci Res** 1985 Apr;2(4):255–73

Substance P given intrathecally at the spinal T9 level increases adrenal output of adrenaline and noradrenaline in the rat. Yashpal K, et al. **Neuroscience** 1985 Jun;15(2):529–36

Polychlorinated biphenyls induce regional changes in brain norepinephrine concentrations in adult rats. Seegal RF, et al. **Neurotoxicology** 1985 Fall;6(3):13–23

The role of central noradrenergic neurons in electroconvulsive shock-induced muricide inhibition in olfactory bulbectomized rats. Liou SY, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):65–70

Norepinephrine-facilitated eating: reduction in saccharin preference and conditioned flavor preferences with increase in quinine aversion. Matthews JW, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):1045–52

Suppressant effect of REM sleep deprivation on neophobia in normal rats and in rats with selective DSP-4 induced damage of locus coeruleus neurons. Mogilnicka E, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):93–7

Central serotonin neurones in avoidance learning: interactions with noradrenaline and dopamine neurones. Ogren SO. **Pharmacol Biochem Behav** 1985 Jul;23(1):107–23

Differential sensitivity to prazosin and yohimbine blockade of tyramine and noradrenaline. Lucchelli A, et al. **Pharmacol Res Commun** 1985 Aug;17(8):787–801

Noradrenergic modulation of 4-aminopyridine-induced acetylcholine release from rat cerebral cortex. Magnani M, et al. **Pharmacol Res Commun** 1985 Jul;17(7):653–8

Evidence of norepinephrine-mediated suppression of para-chlorophenylalanine-induced muricidal behavior. Pucilowski O, et al. **Pharmacol Res Commun** 1985 May;17(5):457–62

Human class I alcohol dehydrogenases catalyze the oxidation of glycols in the metabolism of norepinephrine. Mårdh G, et al. **Proc Natl Acad Sci USA** 1985 Aug;82(15):4979–82

The effect of etidocaine on spontaneous and evoked release of norepinephrine from rat brain synaptosomes. Freas W, et al. **Proc Soc Exp Biol Med** 1985 Nov;180(2):264–9

The efflux from and the metabolism of 3H-norepinephrine in sow Graafian

follicles. Variable involvement of some prostaglandins during two different stages of the sex cycle. Fernandez-Pardal J, et al. **Prostaglandins Leukotrienes Med** 1985 Jul;19(1):1–10

Adrenergic stimulation modifies prostaglandin synthesis by rat vas deferens. Peredo H, et al. **Prostaglandins Leukotrienes Med** 1985 Jul; 19(1):51–61

Altered norepinephrine metabolism following long-term weight recovery in patients with anorexia nervosa. Kaye WH, et al. **Psychiatry Res** 1985 Apr;14(4):333–42

Serotonergic modulation of cortical rat noradrenergic system in the mechanism of action of antidepressant drugs. Brunello N, et al. **Psychopharmacol Bull** 1985;21(3):379–84

Disturbances of norepinephrine metabolism and alpha-2 adrenergic receptor activity in anorexia nervosa: relationship to nutritional state. Kaye WH, et al. **Psychopharmacol Bull** 1985;21(3):419–23

CSF, plasma, and urine: what do concomitant measurements of norepinephrine and its metabolites mean? Linnoila M, et al. **Psychopharmacol Bull** 1985;21(3):389–95

The serotonin/norepinephrine-linked beta-adrenoceptor system and the mode of action of antidepressants. Sanders-Bush E, et al. **Psychopharmacol Bull** 1985;21(3):373–8

Ro 11-2465 (cyan-imipramine), citalopram and their N-desmethyl metabolites: effects on the uptake of 5-hydroxytryptamine and noradrenaline in vivo and related pharmacological activities. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):156–63

Plasma adrenaline and noradrenaline during mental stress and isometric exercise in man. The role of arterial sampling. Jörgensen LS, et al. **Scand J Clin Lab Invest** 1985 Sep;45(5):447–52

The effect of stimulus preexposure upon the context effect in taste-aversion learning in noradrenaline-depleted rats. Archer T. et al. **Scand J Psychol** 1985;26(2):158–69

Relationship between pelviureteral peristaltic frequency and urine flow change evoked by autonomic drug administration. Morita T, et al. **Tohoku J Exp Med** 1985 Jul;146(3):265–71

[Study of the metabolism of cerebral noradrenaline in depressed patients by the assay of plasma dihydroxyphenylethylene glycol] Loo H, et al. **Presse Med** 1985 Jun 22;14(25):1363–6 (Eng. Abstr.) **(Fre)**

[Psychoneurotic disorders in puberty and the activity of the adrenergic system] Szewczyk L. **Pediatr Pol** 1985 Apr;60(4):306–11 (Eng. Abstr.) **(Pol)**

[Effect of leu-enkephalin and the delta-sleep-inducing peptide, M (DSIP), on endogenous noradrenaline release by brain synaptosomes in the rat] Rozhanets VV, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):199–201 (Eng. Abstr.) **(Rus)**

[Effect of Na+, K+ and Ca++ ions on catecholamine release in the caudal mesenteric ganglion] Reprintseva VM. **Fiziol Zh SSSR** 1985 May; 71(5):561–8 (Eng. Abstr.) **(Rus)**

[Action of noradrenaline and dopamine on the pacemaker cells of the normal rat sinus node and in pharmacological sympathectomy] Sutiagin PV, et al. **Kardiologiia** 1985 May;25(5):88–93 (Eng. Abstr.) **(Rus)**

[Changes in the ultrastructure of synapses of neurons of the cerebral cortex of the rat in response to isolated and combined microapplications of mediators] Kotliar BI, et al. **Neirofiziologiia** 1985;17(4):476–81 (Eng. Abstr.) **(Rus)**

[Effect of carbon dioxide baths on the content of catecholamines in the brain and processes of their inactivation] Mirzoian SA, et al. **Vopr Kurortol Fizioter Lech Fiz Kult** 1985 May–Jun;(3):16–9 (Eng. Abstr.) **(Rus)**

[Functional differentiation of the theta-rhythm of the hippocampus in the cat] Melikov EM. **Zh Vyssh Nerv Deiat** 1985 May–Jun; 35(3):457–64 (Eng. Abstr.) **(Rus)**

[Effect of noradrenaline, microapplied to the dorsal hippocampus of the rat, on conditioned reflex memory] Melikov EM, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):780–2 **(Rus)**

[Formation and extinction of drinking conditioned reflexes after unilateral intercollicular sectioning of the brain in the rat] Shabanov PD, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):777–9 **(Rus)**

[Effect of corticosteroid therapy of various durations on urinary excretion of norepinephrine] Ješić S, et al. **Srp Arh Celok Lek** 1984 Nov–Dec; 112(11–12):1135–44 (Eng. Abstr.) **(Scc)**

NORTRIPTYLINE

Separate and combined anxiolytic and anti-depressant treatment of mixed anxiety/depression. A double-blind, placebo controlled comparison. Sussex Clinical Trials Group. **Acta Psychiatr Scand** 1985 Jul; 72(1):81–8

Relationship of free nortriptyline levels to therapeutic response. Perry PJ, et al. **Acta Psychiatr Scand** 1985 Aug;72(2):120–5

Serial ECG measurements at controlled plasma levels of nortriptyline in depressed children. Geller B, et al. **Am J Psychiatry** 1985 Sep; 142(9):1095–7

Nortriptyline in the treatment of a monosymptomatic delusion [letter] Pylko T, et al. **Am J Psychiatry** 1985 Oct;142(10):1223

Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients—relationship to the debrisoquine hydroxylation metabolic ratio. Nordin C, et al. **Br J Clin Pharmacol** 1985 Jun; 19(6):832–5

Cerebrospinal fluid levels of amitriptyline, nortriptyline, imipramine and desmethylimipramine. Relationship to plasma levels and treatment outcome. Hanin I, et al. **J Affective Disord** 1985 Jul;9(1):69–78

Nortriptyline pharmacokinetics and plasma levels: implications for clinical practice. Rubin EH, et al. **J Clin Psychiatry** 1985 Oct;46(10):418–24 (56 ref.)

Serial monitoring and achievement of steady state nortriptyline plasma levels in depressed children and adolescents: preliminary data. Geller B, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):213–6

[Serum levels of amitriptyline and nortriptyline in a case of poisoning (letter)] Fernández de Gatta M, et al. **Med Clin (Barc)** 1985 May 18; 84(19):798–9 **(Spa)**

OBSESSIVE-COMPULSIVE DISORDER

Antiobsessive effect of fluoxetine [letter] Fontaine R, et al. **Am J Psychiatry** 1985 Aug;142(8):989

Clomipramine treatment of childhood obsessive-compulsive disorder. A double-blind controlled study. Flament MF, et al. **Arch Gen Psychiatry** 1985 Oct;42(10):977–83

Fluoxetine treatment of obsessive-compulsive disorder. Turner SM, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):207–12

ORGANIC MENTAL DISORDERS

Involutional dementias: new perspectives. Borromei A, et al. **Ital J Neurol Sci** 1985 Jun;6(2):167–71

Double-blind, placebo-controlled, clinical, psychometric and neurophysiological investigations with oxiracetam in the organic brain syndrome of late life. Saletu B, et al. **Neuropsychobiology** 1985; 13(1–2):44–52

Effect of neuroleptic treatments on attention, information processing, and thought disorder. Spohn HE, et al. **Psychopharmacol Bull** 1985; 21(3):582–7

ORGANIC MENTAL DISORDERS, PSYCHOTIC

De Clérambault's syndrome—a nosological entity [letter] Munro A. **Br J Psychiatry** 1985 May;146:561

OXAZEPAM

The influence of diflunisal on the pharmacokinetics of oxazepam. van Hecken AM, et al. **Br J Clin Pharmacol** 1985 Sep;20(3):225–34

Inhibition of diazepam metabolism in microsomal- and perfused liver preparations of the rat by desmethyldiazepam, N-methyloxazepam and oxazepam. Savenije-Chapel EM, et al. **Eur J Drug Metab Pharmacokinet** 1985 Jan–Mar;10(1):15–20

PAIRED-ASSOCIATE LEARNING

Psychostimulant plasma concentration and learning performance. Kupietz SS, et al. **J Clin Psychopharmacol** 1985 Oct;5(5):293–5

PARASYMPATHOMIMETICS

Affinity and efficacy correlate with chemical structure more than potency does in a series of pentatomic cyclic muscarinic agonists. Angeli P, et al. **Br J Pharmacol** 1985 Aug;85(4):783–6

Enthalpy-entropy relationship in drug-cholinoceptor interaction: a new approach. Cohen S, et al. **Br J Pharmacol** 1985 Aug;85(4):889–96

Presynaptic actions of cholinergic agents upon the hair cell-afferent fiber synapse in the vestibular labyrinth of the frog. Bernard C, et al. **Brain Res** 1985 Jul 15;338(2):225–36

Effects of cholinergic drugs and 4-aminopyridine on cat ciliary muscle contractility. Zacharias J, et al. **Invest Ophthalmol Vis Sci** 1985 Sep; 26(9):1309–13

Potential types of response of the parasympathetic denervated human parotid gland to cholinergic ligands. Levin SL. **J Auton Nerv Syst** 1985 Jun;13(2):161–70

Muscarinic receptor agonist-antagonist interaction in the rat rectum: are there ways of activating the same receptors? Akah PA, et al. **J Pharm Pharmacol** 1985 Aug;37(8):589–92

Rapid induction of supersensitivity to muscarinic antagonists-induced motor excitation by continuous stimulation of cholinergic receptors. Fernando JC, et al. **Life Sci** 1985 Sep 2;37(9):883–92

Reduced muscarinic receptor plasticity in frontal cortex of aged rats after chronic administration of cholinergic drugs. Pedigo NW Jr, et al. **Life Sci** 1985 Oct 14;37(15):1443–9

Muscarinic depression of evoked surface-negative field potentials recorded from guinea-pig olfactory cortex in vitro. Williams SH, et al. **Neurosci Lett** 1985 May 23;56(3):301–6

Memory enhancement: supra-additive effect of subcutaneous cholinergic drug combinations in mice. Flood JF, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):61–7

[Effect of cholino- and adrenomimetic substances on B-lymphocyte proliferation in mice during a primary immune response to a protein antigen] Ado AD, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):46-8 (Eng. Abstr.) **(Rus)**

PARGYLINE

Epinephrine accumulation in rat brain after chronic administration of pargyline and LY 51641—comparison with other brain amines. Mefford IN, et al. **Brain Res** 1985 Jul 29;339(2):342-5

Trace amines inhibit the electrically evoked release of [3H]acetylcholine from slices of rat striatum in the presence of pargyline: similarities between beta-phenylethylamine and amphetamine. Baud P, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):220-9

Inhibition of tyrosine hydroxylation in rat striatal tissue slices by 1-methyl-4-phenylpyridinium ion. Hirata Y, et al. **Neurosci Lett** 1985 Jun 24;57(3):301-5

PEMOLINE

Pemoline pharmacokinetics and long term therapy in children with attention deficit disorder and hyperactivity. Collier CP, et al. **Clin Pharmacokinet** 1985 May-Jun;10(3):269-78

Treatment of chronic cocaine abuse and attention deficit disorder, residual type, with magnesium pemoline. Weiss RD et al. **Drug Alcohol Depend** 1985 May;15(1-2):69-72

PENTOBARBITAL

Effect of pentobarbital and hemorrhage on renal autoregulation. Kremser PC, et al. **Am J Physiol** 1985 Sep;249(3 Pt 2):F356-60

Fate of sodium pentobarbital in rendered products. O'Connor JJ, et al. **Am J Vet Res** 1985 Aug;46(8):1721-4

Local cerebral glucose utilization during nitrous oxide and pentobarbital anesthesia in rats. Sakabe T, et al. **Anesthesiology** 1985 Sep;63(3):262-6

Pharmacokinetics of high-dose pentobarbital in severe head trauma. Bayliff CD, et al. **Clin Pharmacol Ther** 1985 Oct;38(4):457-61

Blocking action of pentobarbital on receptors for excitatory amino acids in the guinea pig hippocampus. Sawada S. et al. **Exp Brain Res** 1985;59(2):226-31

Recovery from dispositional and pharmacodynamic tolerance after chronic pentobarbital treatment. Okamoto M, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):26-31

Studies on the effects of felodipine on the vascular resistance and reactivity in pentobarbital anesthetized dogs. Jandhyala BS. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun;329(4):398-403

Estradiol-induced LH release in juvenile female rats: nembutal blocks both the decline and the exposure of nonavailable pituitary LHRH receptor sites. Smith SS, et al. **Neuroendocrinology** 1985 Sep;41(3):246-51

Pentobarbital-induced drinking does not rely on a renal dipsogen. Asin KE, et al. **Physiol Behav** 1985 Jan;34(1):151-3

A conveyor belt task for assessing visuo-motor coordination in the marmoset (Callithrix jacchus): effects of diazepam, chlorpromazine, pentobarbital and d-amphetamine. D'Mello GD, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):125-31

[Resin hemoperfusion for acute pentobarbital intoxication in rats and rabbits] Lu ZN, et al. **Chung Kuo Yao Li Hsueh Pao** 1984 Dec;5(4):281-5 (Eng. Abstr.) **(Chi)**

PEPTIDES

Effect of GRP on beta-adrenergic-stimulated gastrin and somatostatin release in the isolated rat stomach. Short GM, et al. **Am J Physiol** 1985 Aug;249(2 Pt 1):G197-202

Introduction of the dansyl group into histidine and tyrosine residues in peptides and proteins. Buchta R, et al. **Biochem Biophys Res Commun** 1985 Jul 16;130(1):350-7

Synthesis and characterization of six sequential polypeptides containing tyrosine, glutamic acid, alanine, and glycine by circular dichroism and difference spectroscopy. Zeiger AR, et al. **Biopolymers** 1985 Jul;24(7):1215-32

Immunohistochemistry of synaptic input and functional characterizations of neurons near the spinal central canal. Honda CN, et al. **Brain Res** 1985 Sep 16;343(1):120-8

An antiserum to locust adipokinetic hormone reveals a novel peptidergic system in the rat central nervous system. Sasek CA, et al. **Brain Res** 1985 Sep 16;343(1):172-5

Three dimensional analysis of retinal neuropeptides and amine in the chick. Kiyama H, et al. **Brain Res Bull** 1985 Aug;15(2):155-65

Distribution and localization of regulatory peptides. Ballesta J, et al. **CRC Crit Rev Clin Lab Sci** 1985;22(3):185-218 (250 ref.)

Effect of vagal blockade on food- and hormone-stimulated release of pancreatic polypeptide and motilin in dogs. Greenberg GR, et al. **Dig Dis Sci** 1985 Oct;30(10):946-53

Effect of passive immunization with antisera to vasoactive intestinal polypeptide and peptide histidine isoleucine amide on 5-hydroxy-L-tryptophan-induced prolactin release in rats. Kaji H, et al. **Endocrinology** 1985 Nov;117(5):1914-9

Prolonged inhibition of growth hormone secretion by peripheral injection of bombesin is mediated by somatostatin in the rat. Murphy WA, et al. **Endocrinology** 1985 Sep;117(3):1179-83

Thrombin specificity. Requirement for apolar amino acids adjacent to the thrombin cleavage site of polypeptide substrate. Chang JY. **Eur J Biochem** 1985 Sep 2;151(2):217-24

Inhibition of substance P degradation in rat brain preparations by peptide hydroxamic acids. Laufer R, et al. **Eur J Biochem** 1985 Jul 1;150(1):135-40

The proenkephalin A fragment, peptide E: central processing and CNS activity in vivo. Davis TP, et al. **Eur J Pharmacol** 1985 May 8;111(2):177-83

Use of immunoblockade to study the involvement of peptidergic afferent nerves in the intestinal vasodilatory response to capsaicin in the dog. Rózsa Z, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):59-64

beta-Endorphin and ACTH related peptides in primary cultures of rat anterior pituitary cells: evidence for different intracellular pools. Ham J, et al. **FEBS Lett** 1985 Oct 14;190(2):253-8

Peptide N-alkylamides by solid phase synthesis. Kornreich W, et al. **Int J Pept Protein Res** 1985 Apr;25(4):414-20

Opioid peptides in human adrenal: partial characterization and presence of adrenal peptide E. Boarder MR, et al. **J Clin Endocrinol Metab** 1985 Oct;61(4):658-65

Peptide diversity from exon choice: RNA processing regulation in the neuroendocrine system. Amara SG. **Mol Cell Endocrinol** 1985 Oct;42(3):191-205 (111 ref.)

The subcellular distribution of peptides immunoreactive for the carboxyl-terminal extension of cholecystokinin in rat brain. Allard LR, et al. **Neuropeptides** 1985 Jun;6(3):239-45

Catabolism of gastrin releasing peptide and substance P by gastric membrane-bound peptidases. Bunnett NW, et al. **Peptides (Fayetteville)** 1985 Mar-Apr;6(2):277-83

Influence of vagotomy in domestic fowls on feeding activity, food passage, digestibility and satiety effects of two peptides. Savory CJ, et al. **Physiol Behav** 1984 Dec;33(6):937-44

(Glu62, Ala30, Tyr8)n serves as high-affinity substrate for tyrosylprotein sulfotransferase: a Golgi enzyme. Lee RW, et al. **Proc Natl Acad Sci USA** 1985 Sep;82(18):6143-7

Peptide-catecholamine interaction: feeding and satiety. Myers RD. **Psychopharmacol Bull** 1985;21(3):406-11

The metabolism of phenothiazine in the neonatal calf: identification of drug-polypeptide conjugates from urine. Waring RH, et al. **Xenobiotica** 1985 Jun;15(6):459-68

[Endogenous peptides in the organization of somato-vegetative responses to hypothalamic stimulation] Badikov VI, et al. **Fiziol Zh SSSR** 1985 Jul;71(7):840-7 (Eng. Abstr.) **(Rus)**

[Vasoactive peptides of the lungs] Goncharova VA. **Klin Med (Mosk)** 1985 May;63(5):59-63 (53 ref.) **(Rus)**

[Neuroendocrine action of thyroliberin, luliberin, beta-endorphin and methionine enkephalin] Babichev VN. **Usp Fiziol Nauk** 1985 Jul-Sep;16(3):52-72 (137 ref.) **(Rus)**

[Concentration of regulatory peptides in the cerebral cortex and their central activity] Ashmarin IP, et al. **Zh Vyssh Nerv Deiat** 1985 Mar-Apr;35(2):211-21 (68 ref.) **(Rus)**

PERPHENAZINE

Quantitative determination of perphenazine and its dealkylated metabolite using high-performance liquid chromatography. Larsen NE, et al. **J Chromatogr** 1985 May 31;341(1):244-50

PERSONALITY DISORDERS

Suicidal and parasuicidal behavior in borderline personality disorder. Gardner DL, et al. **Psychiatr Clin North Am** 1985 Jun;8(2):389-403 (36 ref.)

Psychodynamics and psychotherapeutic management of the self-destructive character-disordered patient. Silver D. **Psychiatr Clin North Am** 1985 Jun;8(2):357-75 (66 ref.)

Pills as transitional objects: a dynamic understanding of the use of medication in psychotherapy. Adelman SA. **Psychiatry** 1985 Aug;48(3):246-53

PHENCYCLIDINE

Hair analysis for detection of phencyclidine in newly admitted psychiatric patients. Sramek JJ, et al. **Am J Psychiatry** 1985 Aug;142(8):950-3

Binding of [3H]perhydrohistrionicotoxin and [3H]phencyclidine to the nicotinic receptor-ion channel complex of Torpedo electroplax. Inhibition by histrionicotoxins and derivatives. Aronstam RS, et al. **Biochem Pharmacol** 1985 Sep 1;34(17):3037-47

Quantitative localization of [3H]TCP binding in rat brain by light microscopy autoradiography. Sircar R, et al. **Brain Res** 1985 Sep 30;344(1):142-5

A specific alkylating ligand for phencyclidine (PCP) receptors antagonizes PCP behavioral effects. Contreras PC, et al. **Eur J Pharmacol** 1985

May 20;111(3):405-6

Phencyclidine and sigma opiate receptors in brain: biochemical and autoradiographical differentiation. Gundlach AL, et al. **Eur J Pharmacol** 1985 Jul 31;113(3):465-6

Phencyclidine (PCP) blocks glutamate-activated postsynaptic currents. Idriss M, et al. **FEBS Lett** 1985 Sep 9;189(1):150-6

Acute and chronic behavioral interactions between phencyclidine (PCP) and amphetamine: evidence for a dopaminergic role in some PCP-induced behaviors. Greenberg BD, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):99-105

Effects of phencyclidine on active avoidance and escape in rats. Martin P, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):237-40

Comparison between locomotor activity changes produced by phencyclidine and D-amphetamine in CD-1 male mice. Stavchansky S, et al. **Res Commun Chem Pathol Pharmacol** 1985 May; 48(2):189-202

PHENCYCLIDINE ABUSE

Hair analysis for detection of phencyclidine in newly admitted psychiatric patients. Sramek JJ, et al. **Am J Psychiatry** 1985 Aug;142(8):950-3

PHENELZINE

A double-blind trial of phenelzine in bulimia. Walsh BT, et al. **J Psychiatr Res** 1985;19(2-3):485-9

PHENETHYLAMINES

Effects of amiflamine and related compounds on the accumulation of biogenic monoamines in rat brain slices in vitro and ex vivo in relation to their behavioural effects. Rényi L, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):416-26

Increased total activity in the rat after L-tryptophan plus the monoamine oxidase-A inhibitor amiflamine but not after L-tryptophan plus clorgyline. Archer T, et al. **Br J Pharmacol** 1985 Jul;85(3):581-90

Inhibition of monoamine oxidase in 5-hydroxytryptaminergic neurones by substituted p-aminophenylalkylamines. Ask AL, et al. **Br J Pharmacol** 1985 Jul;85(3):683-90

Behavioral and neurochemical effects of deprenyl and beta-phenylethylamine in Wistar rats. Greenshaw AJ, et al. **Brain Res Bull** 1985 Aug;15(2):183-9

Spin state control of cytochrome P-450 reduction and catalytic activity in a reconstituted P-450 LM2 system as induced by a series of benzphetamine analogues. Schwarze W, et al. **Chem Biol Interact** 1985 Jul;54(2):127-41

Examination of the bronchoconstrictor response of guinea-pig isolated lung to beta-phenylethylamine. Hawthorn MH, et al. **Gen Pharmacol** 1985;16(4):371-8

Monoamine oxidase-A selective inhibition in human hypothalamus and liver in-vitro by amiflamine and its metabolites. Tipton KF, et al. **J Pharm Pharmacol** 1985 May;37(5):352-4

Characterization of alpha 2-adrenoceptor binding properties of imidazoline-like drugs, azoloazepine derivatives and beta-phenethylamine-like drugs in human platelet membranes. Vago T, et al. **J Pharm Pharmacol** 1985 Aug;37(8):593-6

Trace amines inhibit the electrically evoked release of [3H]acetylcholine from slices of rat striatum in the presence of pargyline: similarities between beta-phenylethylamine and amphetamine. Baud P, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):220-9

Comparison of brown adipose tissue thermogenesis induced by congeners and isomers of phenylpropanolamine. Wellman PJ, et al. **Life Sci** 1985 Sep 16;37(11):1023-8

Beta-phenylethylamines and the isoquinoline alkaloids. Bentley KW. **Nat Prod Rep** 1984 Aug;1(4):355-70 (473 ref.)

Tyramine pressor sensitivity changes during deprenyl treatment. Sunderland T, et al. **Psychopharmacology (Berlin)** 1985;86(4):432-7

PHENOBARBITAL

Pentobarbital inhibits the vasoconstrictor response to renal venous pressure elevation in the dog kidney. Abildgaard U. **Acta Physiol Scand** 1985 Aug;124(4):625-7

Transcriptional regulation of rat liver glutathione S-transferase genes by phenobarbital and 3-methylcholanthrene. Ding VD, et al. **Arch Biochem Biophys** 1985 Aug 1;240(2):553-9

Turnover of messenger RNA, apoprotein and haem of cytochrome P-450b + e induced by phenobarbitone in rat liver. Ravishankar H, et al. **Biochem J** 1985 Jul 1;229(1):73-9

Effects of phenobarbitone and beta-naphthoflavone on hepatic microsomal drug metabolising enzymes of the male beagle dog. McKillop D. **Biochem Pharmacol** 1985 Sep 1;34(17):3137-42

Effects of detergent on substrate binding and spin state of purified liver microsomal cytochrome P-450LM2 from phenobarbital-treated rabbits. Wagner SL, et al. **Biochemistry** 1985 Jul 2;24(14):3809-14

Heteroassociation of O- and N-isopropyl derivatives of barbital and phenobarbital with 9-ethyladenine. Gentric E, et al. **Chem Biol Interact** 1985 Jun;54(1):117-25

Ligand displacement immunoassay--demonstration of its use for the measurement of serum phenobarbital and phenytoin. Hinds JA, et al. **Clin Chim Acta** 1985 Jul 15;149(2-3):105-15

Regulation of hepatic monooxygenases by phenobarbital, 3-methylcholanthrene, and polychlorinated biphenyls in rapid and slow acetylator mice. Elves RG, et al. **Drug Metab Dispos** 1985 May-Jun; 13(3):354-8

Differential regulation of pulsatile luteinizing hormone (LH) and follicle-stimulating hormone secretion in ovariectomized rats disclosed by treatment with a LH-releasing hormone antagonist and phenobarbital. De Paolo LV. **Endocrinology** 1985 Nov; 117(5):1826-33

Nuclear ADP-ribosyl transferase activity correlates with induction of P-450 monooxygenases by phenobarbital in rat liver microsomes. Lechner MC, et al. **Eur J Biochem** 1985 Sep 16;151(3):621-4

Separate site(s) of action of optical isomers of 1-methyl-5-phenyl-5-propylbarbituric acid with opposite pharmacological activities at the GABA receptor complex. Ticku MK, et al. **Eur J Pharmacol** 1985 May 28;112(1):1-9

Long-term survival of functional hepatocytes from adult rat in the presence of phenobarbital in primary culture. Miyazaki M, et al. **Exp Cell Res** 1985 Jul;159(1):176-90

Inducibility of the hepatic microsomal monooxygenase system experimentally reduced to a minimum amount/activity. Effect of hypophysectomy, partial hepatectomy and phenobarbital/toluene treatment on the hepatic polysubstrate monooxygenase system in rats. Ungváry G, et al. **Exp Pathol** 1985;27(4):207-20

The modulation of growth of normal rat liver epithelial cells in calcium-poor medium by epidermal growth factor, phenobarbital, phorbol ester, and retinoic acid. Tsao MS, et al. **In Vitro Cell Dev Biol** 1985 May;21(5):249-53

Comparison of the impact of continuous and intermittent exposure to vinyl chloride, including phenobarbital effect. Jedrychowski RA, et al. **J Hyg Epidemiol Microbiol Immunol** 1985;29(2):111-20

Comparison of equilibrium dialysis, ultrafiltration, and gel permeation chromatography for the determination of free fractions of phenobarbital and phenytoin. Melten JW, et al. **J Pharm Sci** 1985 Jun;74(6):692-4

Natural (-)- and unnatural (+)-enantiomers of morphine: comparative metabolism and effect of morphine and phenobarbital treatment. Rane A, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):761-5

Absorption kinetics and bioavailability of phenobarbital after oral administration to dogs. Al-Tahan F, et al. **J Vet Pharmacol Ther** 1985 Jun;8(2):205-7

Increased anticonvulsant effect of phenobarbital with age in mice--a possible pharmacological index for brain aging. Kitani K, et al. **Life Sci** 1985 Oct 14;37(15):1451-60

Isolation and comparison of four cytochrome P-450 enzymes from phenobarbital-induced rat liver: three forms possessing identical NH2-terminal sequences. Backes WL, et al. **Pharmacology** 1985; 31(3):155-69

Pulmonary cytochromes P-450 from rabbits treated with phenobarbital. Ueng TH, et al. **Pharmacology** 1985;31(1):40-9

The comparative potency of phenobarbital and five 1,3-propanediol dicarbamates for hepatic cytochrome P450 induction in rats. Segelman FH, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jun; 48(3):467-70

Effects of 3-methylcholanthrene and phenobarbital on the capacity of embryos to bioactivate teratogens during organogenesis. Juchau MR, et al. **Toxicol Appl Pharmacol** 1985 Aug;80(1):137-46

Effect of promethazine and isosafrole on rat-hepatic microsomal mono-oxygenase activity: comparison with classic inducers phenobarbitone and beta-naphthoflavone. Taylor G, et al. **Xenobiotica** 1985 Mar;15(3):243-9

PHENOTHIAZINE TRANQUILIZERS

Ten-year follow-up of schizophrenic patients on pipothiazine palmitate. Imlah NW, et al. **Curr Med Res Opin** 1985;9(7):449-53

Agranulocytosis in the course of phenothiazine therapy: case reports. Yassa R. **J Clin Psychiatry** 1985 Aug;46(8):341-3

Radioimmunoassay of tricyclic antidepressant and some phenothiazine drugs in forensic toxicology. Robinson K, et al. **J Immunoassay** 1985; 6(1-2):11-22

Phenothiazine associated hyperthermia. A case report. Roberts DE. **J Tenn Med Assoc** 1985 Aug;78(8):489-90

[The affinity of aromatic fluoride derivatives of phenothiazine neuroleptics to spiroperidol binding sites of dopamine receptors by the radioligand technic in vitro] Oelssner W Jr, et al. **Pharmazie** 1985 May; 40(5):341-2 (Eng. Abstr.) **(Ger)**

[Parenteral form of pipothiazine in the treatment of endogenous psychoses] Matkowski K, et al. **Psychiatr Pol** 1984 Nov-Dec;18(6):567-70 (Eng. Abstr.) **(Pol)**

PHENOTHIAZINES

Unusual electrochemical behaviour of a new phenothiazine. Kauffmann

JM, et al. **Analyst** 1985 Apr;110(4):349–51

Inhibition of the hydro–osmotic response to vasopressin and hypertonicity by phenothiazines and W7, calmodulin antagonists. Yorio T, et al. **Gen Pharmacol** 1985;16(4):347–53

Sheep–erythrocyte–capping by human T–lymphocytes. Pharmacological inhibition by phenothiazine drugs. Brohée D, et al. **Int J Immunopharmacol** 1985;7(5):739–46

Rapid microchemical identification of four phenothiazine antiemetics with gold bromide and iodine–potassium iodide reagents: collaborative study. Rabkin M. **J Assoc Off Anal Chem** 1985 May–Jun;68(3):527–9

Release of superoxide and change in morphology by neutrophils in response to phorbol esters: antagonism by inhibitors of calcium–binding proteins. Robinson JM, et al. **J Cell Biol** 1985 Sep;101(3):1052–8

Thionin: spectrophotometry and thin–layer chromatography in relation to biological staining. Allison RT, et al. **Med Lab Sci** 1985 Jul; 42(3):213–20

Toxicity and interaction of topical organophosphate insecticide dichlorvoscrotoxyphos and phenothiazine anthelmintic in sheep previously exposed to both drugs. Mohammad FK, et al. **Vet Hum Toxicol** 1985 Jun;27(3):181–4

The metabolism of phenothiazine in the neonatal calf: identification of drug–polypeptide conjugates from urine. Waring RH, et al. **Xenobiotica** 1985 Jun;15(6):459–68

[Positive reaction of serum anti–DNA antibody induced by phenothiazines in schizophrenic patients] Yang JS. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Dec; 17(6):333–5 (Eng. Abstr.) **(Chi)**

[Oxidation of phenothiazine and its N–methyl derivative by the combination of iodobenzene and vanadium acetylacetonate] Pautet F, et al. **Pharmazie** 1985 Mar;40(3):202–3 **(Fre)**

[Effect of etatsizin on blood coagulability and the anticoagulant effect of heparin] Petrov AD. **Farmakol Toksikol** 1985 Jul–Aug; 48(4):112–4 (Eng. Abstr.) **(Rus)**

PHENOXYBENZAMINE

The effects of phenoxybenzamine on specific binding and function of central alpha–adrenoceptors in the rabbit. Hamilton CA, et al. **Brain Res** 1985 Sep 30;344(1):89–95

Effect of phenoxybenzamine and clonidine on the adrenergic receptor in the rat brain; histofluorescence and ultrastructure examinations. Wawrzyniak M, et al. **Folia Histochem Cytobiol** 1985;23(1–2):91–2

Influence of phenoxybenzamine on the stereotyped behaviour induced by fencamfamine in rats: evidence for a qualitative alteration. Bernardi MM, et al. **Gen Pharmacol** 1985;16(4):403–5

Effect of phenoxybenzamine on indomethacin induced systemic vasoconstriction in dogs. Anderson FL, et al. **Prostaglandins Leukotrienes Med** 1985 Jun;18(3):287–92

PHENYLALANINE

Effect of cocaine dependence on plasma phenylalanine and tyrosine levels and on urinary MHPG excretion. Tennant FS Jr. **Am J Psychiatry** 1985 Oct;142(10):1200–1

L–phenylalanine [letter] Simonson M. **J Clin Psychiatry** 1985 Aug; 46(8):355

Biopterin, neopterin and tyrosine responses to combined oral phenylalanine and tetrahydrobiopterin loading tests in two normal children and in a girl with partial biopterin deficiency. Lykkelund C, et al. **J Inherited Metab Dis** 1985;8 Suppl 2:95–6

PHENYLPROPANOLAMINE

Therapeutic doses of phenylpropanolamine increase supine systolic blood pressure. Pentel PR, et al. **Int J Obes** 1985;9(2):115–9

Comparison of brown adipose tissue thermogenesis induced by congeners and isomers of phenylpropanolamine. Wellman PJ, et al. **Life Sci** 1985 Sep 16;37(11):1023–8

PHENYTOIN

Resistance to metocurine–induced neuromuscular blockade in patients receiving phenytoin. Ornstein E, et al. **Anesthesiology** 1985 Sep; 63(3):294–8

Plasma protein binding of salicylic acid, phenytoin, chlorpromazine, propranolol and pethidine using equilibrium dialysis and ultracentrifugation. Verbeeck RK, et al. **Arzneimittelforschung** 1985; 35(6):903–6

The effects of sucralfate upon phenytoin absorption in man. Smart HL, et al. **Br J Clin Pharmacol** 1985 Sep;20(3):238–40

Suppression by phenytoin of convulsant–induced afterdischarges at presynaptic nerve terminals. David G, et al. **Brain Res** 1985 Jul 22; 339(1):57–65

Inhibitory effect of phenytoin on intracellular cyclic nucleotide and calcium changes during pentylenetetrazole–induced bursting activity in snail neurons. Sugaya E, et al. **Brain Res** 1985 Aug 26;341(2):313–9

Specific binding of [3H]phenytoin in the human brain. Spero L. **Can J Physiol Pharmacol** 1985 May;63(5):517–8

In situ molecular weight determination of rat brain [3H]phenytoin binding sites. Spero L. **Can J Physiol Pharmacol** 1985 May;63(5):515–6

Liver DNA synthesis after phenytoin injection in adult NMRI mice. Lombard MN, et al. **Cell Tissue Kinet** 1985 Sep;18(5):569–71

Ligand displacement immunoassay––demonstration of its use for the measurement of serum phenobarbital and phenytoin. Hinds JA, et al. **Clin Chim Acta** 1985 Jul 15;149(2–3):105–15

Phenytoin once–daily dosing in geriatric patients [letter] Clark BG. **Drug Intell Clin Pharm** 1985 Jul–Aug;19(7–8):584

In vitro adsorption of sodium phenytoin by anion exchange resin [letter] Laurent D, et al. **Drug Intell Clin Pharm** 1985 Jul–Aug; 19(7–8):584–5

Inhibition of microsomal phenytoin metabolism by nafimidone and related imidazoles. Potency and structural considerations. Kapetanovic IM, et al. **Drug Metab Dispos** 1985 Jul–Aug;13(4):430–7

Phenytoin enhances epoxide metabolism in human fetal liver cultures. Rane A, et al. **Drug Metab Dispos** 1985 May–Jun;13(3):382–5

Aplastic anaemia induced by intravenous phenytoin and lidocaine administration [letter] Tomita S, et al. **Eur J Pediatr** 1985 Jul; 144(2):207–8

Analysis of the toxicologically relevant metabolites of phenytoin in biological samples by high–performance liquid chromatography. Lum JT, et al. **J Chromatogr** 1985 Feb 27;338(1):242–8

H–2 histocompatibility region influences the inhibition of arachidonic acid cascade by dexamethasone and phenytoin in mouse embryonic palates. Gupta C, et al. **J Craniofac Genet Dev Biol** 1985;5(3):277–85

Diphenylhydantoin inhibits parathyroid hormone and prostaglandin E2–stimulated bone resorption in mouse calvaria without affecting cyclic AMP formation. Lerner U, et al. **J Oral Pathol** 1985 Sep; 14(8):644–53

A comparative study of the bioavailability of five different phenytoin preparations. Hirji MR, et al. **J Pharm Pharmacol** 1985 Aug; 37(8):570–2

Comparison of equilibrium dialysis, ultrafiltration, and gel permeation chromatography for the determination of free fractions of phenobarbital and phenytoin. Melten JW, et al. **J Pharm Sci** 1985 Jun;74(6):692–4

Effects of stimulation and diphenylhydantoin on the intracellular sodium activity in Purkinje fibres of sheep heart. Ellis D. **J Physiol (Lond)** 1985 May;362:331–48

Phenytoin–dexamethasone: a possible drug–drug interaction [letter] Wong DD, et al. **JAMA** 1985 Oct 18;254(15):2062–3

Phenytoin absorption in adults: effect of aging [letter] Ensom RJ, et al. **N Engl J Med** 1985 Sep 12;313(11):697

Modulation of specific [3H]phenytoin binding by benzodiazepines. Spero L. **Neurochem Res** 1985 Jun;10(6):755–65

Extent of urinary excretion of p–hydroxyphenytoin in healthy subjects given phenytoin. Dickinson RG, et al. **Ther Drug Monit** 1985; 7(3):283–9

Rapid protein determinations on ultrafiltrates prepared for free phenytoin quantification. Turley CP, et al. **Ther Drug Monit** 1985;7(3):313–4

[Dental plaque and gingival hyperplasia due to Dilantin] Maisonneuve C. **J Dent Que** 1985 Feb;22:55–7 (47 ref.) (Eng. Abstr.) **(Fre)**

[Effect of phenytoin on Purkinje cells in the cerebellum] Nikolarakis K, et al. **Zentralbl Allg Pathol** 1985;130(3):229–32 (Eng. Abstr.) **(Ger)**

[Immunopathological studies of phenytoin–induced gingival hyperplasia] Kassai Y, et al. **Nippon Shishubyo Gakkai Kaishi** 1985 Mar; 27(1):197–205 (Eng. Abstr.) **(Jpn)**

[Hydantoin gingival hyperplasia: diagnosis, prevention and treatment] Martos Molino F, et al. **Rev Actual Estomatol Esp** 1984 Sep; 44(340):23–30 **(Spa)**

[Experimental study of the effect of the administration of diphenyl hydantoin and estrogens in rats. III. Microbiological aspects of variations in the gingival flora in rats treated with estrogens] Bascones A, et al. **Rev Esp Estomatol** 1984 Sep–Oct;32(5):319–28 **(Spa)**

[Experimental study of the effect of the administration of diphenyl hydantoin and estrogens. II. Histopathological aspects of gingival changes in rats treated with diphenylhydantoin] Hernandez Vallejo G, et al. **Rev Esp Estomatol** 1984 Jul–Aug;32(4):223–32 **(Spa)**

[Morphological aspects of gingival hyperplasia caused by hydantoin] Sampedro Nuno A, et al. **Rev Esp Estomatol** 1985 Jan–Feb; 33(1):39–44 **(Spa)**

PHOBIC DISORDERS

Imipramine in the treatment of agoraphobia: dose–response relationships. Mavissakalian M, et al. **Am J Psychiatry** 1985 Sep;142(9):1032–6

Platelet monoamine oxidase activity in patients with panic disorder. Gorman J, et al. **Biol Psychiatry** 1985 Aug;20(8):852–7

Treatment of social phobia with atenolol. Gorman JM, et al. **J Clin Psychopharmacol** 1985 Oct;5(5):298–301

Efficacy and tolerability of sustained–release clomipramine (Anafranil SR) in the treatment of phobias: a comparison with the conventional formulation of clomipramine (Anafranil). Allsopp LF, et al. **J Int Med Res** 1985;13(4):203–8

Effect of beta–receptor blockade on anxiety with reference to the three–systems model of phobic behavior. Fagerström KO, et al.

Neuropsychobiology 1985;13(4):187–93

Agoraphobia. Is fear the basis of symptoms? Laybourne PC Jr, et al. **Postgrad Med** 1985 Oct;78(5):109–12, 114, 117–8

Psychopharmacological treatment of social phobia. Liebowitz MR, et al. **Psychopharmacol Bull** 1985;21(3):610–4

PHYSOSTIGMINE

The first reversal of curare. A translation of Pal's original paper, 'Physostigmine, an antidote to curare', 1900. Nickalls RW, et al. **Anaesthesia** 1985 Jun;40(6):572–5

Sensitive liquid chromatographic method for physostigmine in biological fluids using dual-electrode electrochemical detection. Whelpton R, et al. **J Chromatogr** 1985 Jun 14;341(2):361–71

Interactions of edrophonium, physostigmine and methanesulfonyl fluoride with the snake end-plate acetylcholine receptor-channel complex. Fiekers JF. **J Pharmacol Exp Ther** 1985 Sep;234(3):539–49

A comparison of physostigmine and soman using taste aversion and nociception. Romano JA, et al. **Neurobehav Toxicol Teratol** 1985 May–Jun;7(3):243–9

[Differences in the cholinergic effects of eserine and pilocarpine on the uvea and retina of the bovine eye] Kováčik L, et al. **Bratisl Lek Listy** 1985 Jul;84(1):45–9 (Eng. Abstr.) **(Slo)**

PILOCARPINE

Controlled release of pilocarpine hydrochloride from ethylene-vinyl alcohol copolymer matrices. Hou WM, et al. **Chem Pharm Bull (Tokyo)** 1985 Mar;33(3):1242–8

Effects of the substance P antagonist [D-Arg1,D-Pro2,D-Trp7,9,Leu11]SP on miosis caused by echothiophate iodide or pilocarpine hydrochloride. Mandahl A. **Eur J Pharmacol** 1985 Aug 15;114(2):121–7

Pilocarpine used to stimulate normal saliva production. **J Am Dent Assoc** 1985 Aug;111(2):310

Use of pilocarpine intraocularly [letter] Girard LJ. **J Am Intraocul Implant Soc** 1985 Jul;11(4):390

Pilocarpic acid esters as novel sequentially labile pilocarpine prodrugs for improved ocular delivery. Bundgaard H, et al. **J Med Chem** 1985 Aug;28(8):979–81

pH of mucus in rabbit trachea: cholinergic stimulation and block. Gatto LA. **Lung** 1985;163(2):109–15

Central muscarinic receptors and male rat sexual behavior: facilitation by oxotremorine but not arecoline or pilocarpine in methscopolamine pretreated animals. Ahlenius S, et al. **Psychopharmacology (Berlin)** 1985; 87(2):127–9

Glycoprotein secretion from mouse gallbladder principal cells after chronic variation in parasympathetic activity. A morphometric study after vagotomy and cholinergic superstimulation. Axelsson H, et al. **Scand J Gastroenterol** 1985 Aug;20(6):727–33

[The application of computer to volumetric analysis of drugs: the assay of weakly acidic water-soluble drugs] Luo GA, et al. **Yao Hsueh Hsueh Pao** 1985 Feb;20(2):146–50 (Eng. Abstr.) **(Chi)**

[Biopharmaceutics of ophthalmic drugs] Etter JC, et al. **Klin Monatsbl Augenheilkd** 1985 Jun;186(6):417–20 (Eng. Abstr.)**(Fre)**

[Determination of ethylmorphine chloride, pilocarpine chloride and tetracaine chloride in drops and ointments for the eye] Banović V, et al. **Vojnosanit Pregl** 1985 May–Jun;42(3):202–5 (Eng. Abstr.) **(Ser)**

[Differences in the cholinergic effects of eserine and pilocarpine on the uvea and retina of the bovine eye] Kováčik L, et al. **Bratisl Lek Listy** 1985 Jul;84(1):45–9 (Eng. Abstr.) **(Slo)**

PITUITARY HORMONE RELEASING HORMONES

Desensitization of testicular ornithine decarboxylase to gonadotropin releasing hormone and gonadotropic hormones. Madhubala R, et al. **Biochem Int** 1985 Aug;11(2):225–32

Pulsatile administration of gonadotropin-releasing hormone to anestrous sows: endocrine changes associated with GnRH-induced and spontaneous estrus. Armstrong JD, et al. **Biol Reprod** 1985 Sep; 33(2):375–80

A suppression of gonadotropin secretion by cortisol in castrated male rhesus monkeys (Macaca mulatta) mediated by the interruption of hypothalamic gonadotropin-releasing hormone release. Dubey AK, et al. **Biol Reprod** 1985 Sep;33(2):423–31

The effects of cycloheximide on in vitro response of Rana pipiens pituitaries to continuously superfused gonadotropin-releasing hormone. Porter DA. **Biol Reprod** 1985 Sep;33(2):393–400

Gonadotropin-releasing hormone within the organum vasculosum lamina terminalis in the ovariectomized, estrogen/progesterone-treated rat: a quantitative immunocytochemical study using image analysis. Rothfeld JM, et al. **Brain Res** 1985 Jul 15;338(2):309–15

LH secretion in response to gonadotropin releasing hormone (GnRH) by superfused pituitaries from two species of turtles. Licht P, et al. **Gen Comp Endocrinol** 1985 Sep;59(3):442–8

Effects of dihydrotestosterone benzoate administration on gonadotropin secretion in ovariectomized pony mares. Garza F Jr, et al. **J Anim Sci** 1985 Jul;61(1):240–4

Changes of luteinizing hormone and progesterone for dairy cows after gonadotropin-releasing hormone at first postpartum breeding. Lee CN, et al. **J Dairy Sci** 1985 Jun;68(6):1463–70

Role of GnRH in the maturation of pituitary gonadotroph function. Clayton RN. **J Reprod Fertil** 1985 Sep;75(1):307–15 (62 ref.)

Plasma LH and FSH responses and ovarian activity in prepubertal heifers treated with repeated injections of low doses of GnRH for 72 h. McLeod BJ, et al. **J Reprod Fertil** 1985 Jul;74(2):589–96

Role of GnRH in the regulation of pituitary GnRH receptors in female mice. Naik SI, et al. **J Reprod Fertil** 1985 Jul;74(2):605–14

Evidence for a pituitary site of gonadal steroid stimulation of GnRH receptors in female mice. Naik SI, et al. **J Reprod Fertil** 1985 Jul; 74(2):615–24

Ovarian hyperstimulation with exogenous pulsatile gonadotropin releasing hormone therapy. Corenblum B, et al. **J Ultrasound Med** 1985 Aug; 4(8):405–10

Electrophysiological recordings from gonadotrophs. Evidence for Ca2+ channels mediated by gonadotrophin-releasing hormone. Mason WT, et al. **Neuroendocrinology** 1985 Sep;41(3):258–68

A new family member for gonadotropin-releasing hormone. Sherwood NM, et al. **Neuropeptides** 1985 Jun;6(3):205–14

[Pulsed administration of gonadoliberine (GnRH) in the treatment of anovulation] Jaffiol C, et al. **Bull Acad Natl Med (Paris)** 1985 Jan; 169(1):95–8 (Eng. Abstr.) **(Fre)**

[Cellular biochemistry of hypophysiotropic peptides. II. Liberation, action and inactivation] Charli JL, et al. **Bol Estud Med Biol** 1983 Jul–Oct; 32(7–8 Suppl 1):243–52 **(Spa)**

[Biochemistry of hypophysiotropic peptides. I. Biosynthesis and its regulation] Joseph-Bravo P, et al. **Bol Estud Med Biol** 1983 Jul–Oct; 32(7–8 Suppl 1):233–41 (Eng. Abstr.) **(Spa)**

PITUITARY HORMONES

Salmonid melanin-concentrating hormone inhibits corticotrophin release. Baker BI, et al. **J Endocrinol** 1985 Aug;106(2):R5–8

[Intermediate lobe of the amphibian pituitary gland: an endocrine gland with multiple secretions and under multi-hormonal control] Tonon MC, et al. **Ann Endocrinol (Paris)** 1985;46(2):69–87 (126 ref.) (Eng. Abstr.) **(Fre)**

PITUITARY HORMONES, ANTERIOR

Differential secretion of O-glycosylated gonadotropin alpha-subunit and luteinizing hormone (LH) in the presence of LH-releasing hormone. Corless CL, et al. **Endocrinology** 1985 Oct;117(4):1699–706

Effect of acute ether stress on monoamine metabolism in median eminence and discrete hypothalamic nuclei of the rat brain and on anterior pituitary hormone secretion. Johnston CA, et al. **Neuroendocrinology** 1985 Jul;41(1):83–8

[Measurement of basal plasma levels of 3 anterior pituitary hormones during acute or chronic treatment with tricyclic antidepressants] Goyot C, et al. **Encephale** 1985 Mar–Apr;11(2):45–51 (Eng. Abstr.) **(Fre)**

PITUITARY HORMONES, POSTERIOR

Conformational flexibility of neurophysin as investigated by local motions of fluorophores. Relationships with neurohypophyseal hormone binding. Rholam M, et al. **Biochemistry** 1985 Apr 9;24(8):1928–33

PREDNISONE

[Effect of corticosteroid therapy of various durations on urinary excretion of norepinephrine] Jelić S, et al. **Srp Arh Celok Lek** 1984 Nov–Dec; 112(11–12):1135–44 (Eng. Abstr.) **(Scc)**

[Urinary excretion of epinephrine in patients on short-term and long-term corticosteroid therapy] Jelić S, et al. **Srp Arh Celok Lek** 1985 Jan; 113(1):29–40 (Eng. Abstr.) **(Scc)**

PROCHLORPERAZINE

A comparison of the antiemetic efficacy of prochlorperazine and metoclopramide for the treatment of cisplatin-induced emesis: a prospective, randomized, double-blind study. Carr BI, et al. **J Clin Oncol** 1985 Aug;3(8):1127–32

PROGESTERONE

Progesterone decreases the responsiveness of ovine pituitary cultures to luteinizing hormone-releasing hormone. Batra SK, et al. **Endocrinology** 1985 Oct;117(4):1436–40

Effects of ovarian hormones on the concentrations of immunoreactive neuropeptide Y in discrete brain regions of the female rat: correlation with serum luteinizing hormone (LH) and median eminence LH-releasing hormone. Crowley WR, et al. **Endocrinology** 1985 Sep; 117(3):1151–5

Effect of local GABA administration on rat ovarian blood flow, and on progesterone and estradiol secretion. Erdő S, et al. **Eur J Pharmacol** 1985 May 20;111(3):397–400

Evidence that progesterone binding uteroglobin is similar to myosin alkali light chain. Baker ME. **FEBS Lett** 1985 Sep 23;189(2):188–94

Progesterone has no effect on serum thyroxine-binding globulin concentration in men. Chen JJ, et al. **J Clin Endocrinol Metab** 1985 Nov;61(5):983–5

Changes of luteinizing hormone and progesterone for dairy cows after gonadotropin-releasing hormone at first postpartum breeding. Lee CN, et al. **J Dairy Sci** 1985 Jun;68(6):1463–70

Antioestrogen inhibition of oestradiol-induced alterations in hypothalamic noradrenaline turnover. Hiemke C, et al. **J Endocrinol** 1985 Jul; 106(1):37–42

Time-dependent effects of oestradiol and progesterone on hypothalamic catecholamine turnover in ovariectomized rats. Hiemke C, et al. **J Endocrinol** 1985 Sep;106(3):303–9

Catechol oestradiol control of FSH-stimulated granulosa cell steroidogenesis. Hudson KE, et al. **J Endocrinol** 1985 Jul; 106(1):R1–4

Hormonal modulation of the responsiveness of midbrain central gray neurons to LH-RH. Chan A, et al. **Neuroendocrinology** 1985 Aug; 41(2):163–8

Progesterone and the control of functional luteolysis, of secretion of prolactin and of pituitary LHRH responsiveness. A study with pseudopregnant rats kept in alternating and constant lighting conditions. Schuiling GA, et al. **Neuroendocrinology** 1985 Jul;41(1):52–9

Progesterone action on the LHRH and the nigrostriatal dopamine neuronal systems: in vitro and in vivo studies. Ramirez VD, et al. **Recent Prog Horm Res** 1985;41:421–72 (110 ref.)

Current concepts in premenstrual syndrome. Ullman LE. **RI Med J** 1985 Jun;68(6):269–72

[Effect of ACTH on the corticosteroid and progesterone levels in female hamadryas baboons in relation to the menstrual cycle phase] Todua TN, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):135–7 (Eng. Abstr.) **(Rus)**

[Inhibitory effect of progesterone on the stimulation of tryptophan pyrrolase and tyrosine aminotransferase by endogenous corticosteroids in the liver of female rats] Németh S, et al. **Bratisl Lek Listy** 1985 Jul;84(1):3–10 (Eng. Abstr.) **(Slo)**

PROLACTIN

Side effects of drugs stimulating prolactin secretion on the behavior of male rats. Drago F, et al. **Arch Int Pharmacodyn Ther** 1985 Aug; 276(2):271–8

A new in vitro assay system for prolactin-releasing activity and its application for demonstration of porcine hypothalamic prolactin-releasing factor (PRF). Nomura M, et al. **Asia Oceania J Obstet Gynaecol** 1985 Jun;11(2):271–8

Bromoergocryptine decreases serum prolactin and delays sexual maturation in male golden hamsters. Stroud CM, et al. **Biol Reprod** 1985 Jun;32(5):1191–9

Influence of bromocriptine on plasma prolactin, human placental lactogen, beta-HCG and steroid hormones in early human pregnancy. Tolino A, et al. **Biol Res Pregnancy Perinatol** 1985;6(2):70–2

Secretory granules of prolactin cells of neonatally thyroidectomized female rats. Shiino M, et al. **Cell Tissue Res** 1985;242(1):179–83

The interaction of trh and dopaminergic mechanisms in the regulation of stimulated prolactin release in man. Ho KY, et al. **Clin Endocrinol (Oxf)** 1985 Jul;23(1):7–16

Plasma concentrations of arginine vasotocin, prolactin, aldosterone and corticosterone in relation to oviposition and dietary NaCl in the domestic fowl. Rice GE, et al. **Comp Biochem Physiol [A]** 1985; 81(4):769–77

Growth hormone, thyrotropin and prolactin responses to simultaneous administration of human growth hormone-releasing factor and thyrotropin releasing hormone in the bovine. Hodate K, et al. **Endocrinol Jpn** 1985 Jun;32(3):375–83

Stimulation of the adenosine 3',5'-monophosphate and the Ca2+ messenger systems together reverse dopaminergic inhibition of prolactin release. Delbeke D, et al. **Endocrinology** 1985 Aug;117(2):439–46

Hyperprolactinemia inhibits gonadotropin-releasing hormone (GnRH) stimulation of the number of pituitary GnRH receptors. Garcia A, et al. **Endocrinology** 1985 Sep;117(3):954–9

Effect of passive immunization with antisera to vasoactive intestinal polypeptide and peptide histidine isoleucine amide on 5-hydroxy-L-tryptophan-induced prolactin release in rats. Kaji H, et al. **Endocrinology** 1985 Nov;117(5):1914–9

Thyrotropin-releasing hormone and epidermal growth factor stimulate prolactin synthesis by a pathway(s) that differs from that used by phorbol esters: dissociation of actions by calcium dependency and additivity. Ramsdell JS, et al. **Endocrinology** 1985 Nov; 117(5):2050–60

Pantethine, a cysteamine precursor, depletes immunoreactive somatostatin and prolactin in the rat. Reichlin S, et al. **Endocrinology** 1985 Aug; 117(2):492–5

The effects of growth hormone, prolactin, corticotropin, and thyrotropin on the production and secretion of somatostatin by hypothalamic cells in vitro. Robbins RJ, et al. **Endocrinology** 1985 Aug;117(2):538–43

Histidyl-proline-diketopiperazine (cyclo-his-pro) inhibits the suckling- and domperidone-induced transformation of prolactin in the lactating rat. Shyr SW, et al. **Endocrinology** 1985 Nov;117(5):2170–5

Interaction of SCH 23390, a D-1-selective antagonist, with the anterior pituitary D-2 receptors and prolactin secretion in the rat. Apud JA, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):187–93

Phorbol esters affect pituitary growth hormone (GH) and prolactin release: the interaction with GH releasing factor, somatostatin and bromocriptine. Summers ST, et al. **Eur J Pharmacol** 1985 May 20; 111(3):371–6

The influence of thyrotropin releasing hormone on in vivo prolactin release and in vitro prolactin, luteinizing hormone, and growth hormone release from dispersed pituitary cells of the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Gen Comp Endocrinol** 1985 Jul; 59(1):64–72

Hypothalamic and serum factors influence on prolactin and luteinizing hormone release by the pituitary gland of the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Gen Comp Endocrinol** 1985 Jul; 59(1):73–81

Somatostatin-like immunoreactivity in the pituitary and brain of three teleost fish species: somatostatin as a potential regulator of prolactin cell function. Grau EG, et al. **Gen Comp Endocrinol** 1985 Sep; 59(3):350–7

Thyroid function in adult rough-skinned newts (Taricha granulosa): effects of hypophysectomy and hormone replacement. Specker JL, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):326–31

Evidence for serotoninergic control of exercise-induced prolactin secretion. De Meirleir K, et al. **Horm Metab Res** 1985 Jul; 17(7):380–1

Gonadal steroids deficiency and prolactin response to a met-enkephalin analog in man. Foresta C, et al. **Horm Metab Res** 1985 Jun; 17(6):319–20

In vivo and in vitro effects of cholecystokinin octapeptide on the release of prolactin in rats. Matsumura M, et al. **Horm Metab Res** 1985 Jun; 17(6):293–7

Effect of acute intravenous growth hormone-releasing factor on plasma prolactin in short children and patients with growth hormone deficiency. Chatelain PG, et al. **Horm Res** 1985;22(1–2):46–51

Pregnancy despite continued elevation of prolactin levels while on bromergocryptine. Corson SL, et al. **Int J Gynaecol Obstet** 1985 Apr; 23(2):105–7

Molecular mechanisms of phorbol ester, thyrotropin-releasing hormone, and growth factor stimulation of prolactin gene transcription. Murdoch GH, et al. **J Biol Chem** 1985 Sep 25;260(21):11852–8

Prolactin permits the expression of a circadian variation in lipogenic responsiveness to insulin in hepatocytes of the golden hamster (Mesocricetus auratus). Cincotta AH, et al. **J Endocrinol** 1985 Aug; 106(2):173–6

Prolactin permits the expression of a circadian variation in insulin receptor profile in hepatocytes of the golden hamster (Mesocricetus auratus). Cincotta AH, et al. **J Endocrinol** 1985 Aug;106(2):177–81

Prolactin in cerebrospinal fluid increases the synthesis and release of hypothalamic gamma-aminobutyric acid. Locatelli V, et al. **J Endocrinol** 1985 Sep;106(3):323–8

Effect of immunoneutralization of thyrotrophin-releasing hormone on the release of thyrotrophin and prolactin during suckling or in response to electrical stimulation of the hypothalamus in the anaesthetized rat. Sheward WJ, et al. **J Endocrinol** 1985 Jul;106(1):113–9

Prolactin influences sexual behavior during aging. Ferrara N, et al. **J Endocrinol Invest** 1985;8 Suppl 2:23–32

Histamine H1 receptor participation in the control of prolactin secretion in postpartum. Messinis IE, et al. **J Endocrinol Invest** 1985 Apr; 8(2):143–6

Effect of 1,25-dihydroxyvitamin D3 and nifedipine on prolactin release in normal man. Verbeelen D, et al. **J Endocrinol Invest** 1985 Apr; 8(2):103–6

Effects of the 1,5-benzodiazepine clobazam on pituitary hormones in the male rat. Valli M, et al. **Methods Find Exp Clin Pharmacol** 1985 Apr; 7(4):179–81

Neurotensin stimulates polyphosphoinositide breakdown and prolactin release in anterior pituitary cells in culture. Canonico PL, et al. **Mol Cell Endocrinol** 1985 Oct;42(3):215–20

Has the prolactin inhibiting peptide at last been found? [news] Fink G. **Nature** 1985 Aug 8–14;316(6028):487–8

A prolactin-inhibiting factor within the precursor for human gonadotropin-releasing hormone. Nikolics K, et al. **Nature** 1985 Aug 8–14;316(6028):511–7

Immunocytochemical localization in rat brain of a prolactin release-inhibiting sequence of gonadotropin-releasing hormone prohormone. Phillips HS, et al. **Nature** 1985 Aug 8–14; 316(6028):542–5

Hormonal modulation of the responsiveness of midbrain central gray neurons to LH-RH. Chan A, et al. **Neuroendocrinology** 1985 Aug; 41(2):163–8

Effect of histamine on basal and TRH/LH-RH-stimulated PRL and LH secretion during different phases of the menstrual cycle in normal women. Knigge U, et al. **Neuroendocrinology** 1985 Oct;41(4):337–41

Effects of endogenous opioid peptides and opiates on luteinizing hormone and prolactin secretion in ovariectomized rats. Leadem CA, et al. **Neuroendocrinology** 1985 Oct;41(4):342–52

Progesterone and the control of functional luteolysis, of secretion of prolactin and of pituitary LHRH responsiveness. A study with pseudopregnant rats kept in alternating and constant lighting conditions. Schuiling GA, et al. **Neuroendocrinology** 1985 Jul;41(1):52–9

Pharmacological studies on the serotoninergic and nonserotonin-mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pretreatment with fluoxetine, indalpine, PCPA, and L–tryptophan. Van de Kar LD, et al. **Neuroendocrinology** 1985 Oct; 41(4):283–8

Electrical stimulation of the ventral noradrenergic tract (VNAT) releases hypothalamic noradrenaline and stimulates prolactin secretion in ovariectomized female rats treated with oestrogen. Dean AD, et al. **Neurosci Lett** 1985 Jun 4;57(1):73–8

A nonmitogenic pituitary function of fibroblast growth factor: regulation of thyrotropin and prolactin secretion. Baird A, et al. **Proc Natl Acad Sci USA** 1985 Aug;82(16):5545–9

Effect of various catecholamine antagonists on prolactin secretion in conscious male rabbits. Kaji H, et al. **Proc Soc Exp Biol Med** 1985 Oct;180(1):144–8

Thyrotropin–releasing hormone action: mechanism of calcium–mediated stimulation of prolactin secretion. Gershengorn MC. **Recent Prog Horm Res** 1985;41:607–53 (61 ref.)

Role of brain epinephrine neurons in the regulation of serum prolactin and luteinizing hormone release in female rats. Liang NY, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jun;48(3):459–62

Effects of pimozide and domperidone administration on prolactin levels in neonatally estrogenized female rats. Aguilar E, et al. **Rev Esp Fisiol** 1985 Jun;41(2):183–6

[Lack of effect of aging on dopaminergic inhibition of aldosterone and prolactin increase] Preis P, et al. **Z Gerontol** 1985 Jul–Aug; 18(4):241–3 (Eng. Abstr.) **(Ger)**

[Low blood values of prolactin in women with psychogenic amenorrhea and anorexia nervosa] Natoli A, et al. **Clin Ter** 1985 Jun 30; 113(6):499–501 (Eng. Abstr.) **(Ita)**

[Effect of dopaminergic agents on the endocrine profile in labor and early puerperium] Kubota T, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Jun;37(6):945–54 (Eng. Abstr.) **(Jpn)**

PROMAZINE

Hemodynamic and acid–base effects of promazine on unanesthetized pregnant sheep and fetus. Ayromlooi J. **Dev Pharmacol Ther** 1985; 8(5):302–10

PROMETHAZINE

Effects of H1–receptor blocking drugs on the frog sartorius neuromuscular junction. Katayama S, et al. **Br J Pharmacol** 1985 Aug;85(4):747–53

Determination of promethazine in human plasma by automated high–performance liquid chromatography with electrochemical detection and by gas chromatography–mass spectrometry. Leelavathi DE, et al. **J Chromatogr** 1985 Apr 12;339(1):105–15

Degradation products of the promethazine radical cation. De Mol NJ, et al. **Pharm Weekbl [Sci]** 1985 Jun 21;7(3):121–4

Effect of promethazine and isosafrole on rat–hepatic microsomal mono–oxygenase activity: comparison with classic inducers phenobarbitone and beta–naphthoflavone. Taylor G, et al. **Xenobiotica** 1985 Mar;15(3):243–9

[Determination of aminophylline and promethazine in suppositories] Senf HJ. **Pharmazie** 1985 May;40(5):331–2 (Eng. Abstr.) **(Ger)**

[Effect of antidepressive drugs and histamine H1 receptor blockaders on histamine level in rat brain] Zawilska J, et al. **Folia Med Cracov** 1984; 25(3–4):297–306 (Eng. Abstr.) **(Pol)**

PROPANEDIOLS

Exhaustive laccase–catalysed oxidation of a lignin model compound (vanillyl glycol) produces methanol and polymeric quinoid products. Lundquist K, et al. **Biochem J** 1985 Jul 1;229(1):277–9

Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. Yu DK, et al. **J Pharm Sci** 1985 Aug;74(8):876–9

The possible effect of high concentrations of propylene glycol on mitosis in human lymphocytes in vitro. Georgian L, et al. **Morphol Embryol (Bucur)** 1985 Jul–Sep;31(3):159–61

Propylene glycol plasma level [letter] Hall AH, et al. **Pediatrics** 1985 Oct;76(4):654

[Synthesis and analysis of glycol bis–phosphates, regulators of reversible hemoglobin oxygenation] Chuvilin AN, et al. **Bioorg Khim** 1985 Jun; 11(6):845–8 (Eng. Abstr.) **(Rus)**

PROPRANOLOL

Propranolol inhibits the maturational effect of adrenocorticotropin in the fetal sheep lung. Vilos GA, et al. **Am J Obstet Gynecol** 1985 Oct 15; 153(4):472–7

Effects of aspirin and propranolol on feline platelet aggregation. Greene CE. **Am J Vet Res** 1985 Sep;46(9):1820–3

Propranolol–induced hypertension in treatment of cocaine intoxication. Ramoska E, et al. **Ann Emerg Med** 1985 Nov;14(11):1112–3

Plasma protein binding of salicylic acid, phenytoin, chlorpromazine, propranolol and pethidine using equilibrium dialysis and ultracentrifugation. Verbeeck RK, et al. **Arzneimittelforschung** 1985; 35(6):903–6

Effect of plasma on human erythrocyte beta–adrenergic receptors. Sager G, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3767–71

Effect of propranolol on lecithin:cholesterol acyl transferase activity in vitro. Schauer UJ, et al. **Biomed Biochim Acta** 1985;44(4):603–9

The haemodynamic and myocardial contractile effects of celiprolol, atenolol and propranolol in mecamylamine–verapamil pretreated, anaesthetised dogs. Smith RD, et al. **Br J Clin Pract [Symp Suppl]** 1985 Jun;42:35–43

Increase in PaO2 following intravenous administration of propranolol in acutely hypoxemic patients. Vincent JL, et al. **Chest** 1985 Oct; 88(4):558–62

Sodium restriction amplifies and propranolol loading inhibits circadian rhythm of plasma renin–angiotensin and aldosterone. Cugini P, et al. **Chronobiologia** 1985 Apr–Jun;12(2):155–65

Propranolol's effect on phagocytizing ability of polymorphonuclears and monocytes [letter] Djaldetti M, et al. **Drug Intell Clin Pharm** 1985 Jul–Aug;19(7–8):583

Stereoselective sulfate conjugation of 4–hydroxypropranolol in vitro by different species. Christ DD, et al. **Drug Metab Dispos** 1985 May–Jun; 13(3):380–1

Stereochemistry of the in vivo disposition and metabolism of propranolol in dog and man using deuterium–labeled pseudoracemates. Walle T. **Drug Metab Dispos** 1985 May–Jun;13(3):279–82

Serum myoglobin concentrations are decreased by beta–adrenergic stimulation. Ljunghall S, et al. **Eur J Appl Physiol** 1985;54(1):54–7

A carrier–protein receptor is not a prerequisite for avid hepatic elimination of highly bound compounds: a study of propranolol elimination by the isolated perfused rat liver. Jones DB, et al. **Hepatology** 1985 Jul–Aug; 5(4):590–3

Plasma growth hormone responses to microinfusion of noradrenergic agents into or electrical stimulation of the hypothalamus and amygdala in baboons. McWilliam JR, et al. **Horm Metab Res** 1985 Sep; 17(9):443–7

The influence of reserpine and propranolol upon the IOP response to vanadate in the rabbit. Delamere NA, et al. **Invest Ophthalmol Vis Sci** 1985 Oct;26(10):1442–5

Effect of age on the hepatic clearance of propranolol in rats. Iwamoto K, et al. **J Pharm Pharmacol** 1985 Jul;37(7):466–70

Effect of vitamin K3 on the first–pass elimination of propranolol in the rat. Ishida R, et al. **J Pharm Sci** 1985 May;74(5):578–81

Reduced hepatic clearance of propranolol induced by chronic carbon tetrachloride treatment in rats. Iwamoto K, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):470–5

Effects of dimethylpropranolol (UM–272) on the electrophysiological properties of guinea–pig ventricular muscles. Kodama I, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):507–14

Site and mechanism of the centrally mediated hypotensive action of propranolol. Tackett RL, et al. **J Pharmacol Exp Ther** 1985 Oct; 235(1):66–70

A method for the assay of alpha 1–acid glycoprotein in dog serum and its application to the plasma binding of propranolol and oxprenolol in animals receiving rifampicin. Delcroix C, et al. **J Pharmacol Methods** 1984 Sep;12(2):97–105

Glucagon for propranolol overdose [letter] Smith RC, et al. **JAMA** 1985 Nov 1;254(17):2412

Effects of chronic beta–adrenergic blockade on hemodynamic and metabolic responses to endurance training. Lawlor MR, et al. **Med Sci Sports Exerc** 1985 Jun;17(3):393–400

Effect of beta–receptor blockade on anxiety with reference to the three–systems model of phobic behavior. Fagerström KO, et al. **Neuropsychobiology** 1985;13(4):187–93

Blockade of peripheral beta–adrenergic receptors fails to suppress the cerebral spread of an engram in mice. Church AC, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):27–31

Effect of propranolol on thyroid homeostasis of healthy volunteers. Wilkins MR, et al. **Postgrad Med J** 1985 May;61(715):391–4

Effects of d,l–propranolol on open field behavior of rats. Poli A, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):153–5

Opposing acute and chronic behavioural effects of a beta–blocker, propranolol, in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1985;86(4):480–6

Comparison between the effects of propranolol and chlordiazepoxide on timing behaviour in the rat. Salmon P, et al.

Psychopharmacology (Berlin) 1985;87(2):219–24

Assessment of blood collection systems for the high performance liquid chromatography measurement of propranolol. Wong SH, et al. **Ther Drug Monit** 1985;7(3):358–63

[Cardiodynamics of the conscious dog undergoing treadmill exercise, blood pressure reduction or isoproterenol and its modification by beta-blockade] Lehmann HD. **DTW** 1985 Apr 9;92(4):135–9 (Eng. Abstr.) **(Ger)**

[The effect of propranolol on the pentetrazole-induced spindle activity in the EEG of the rat] Lasek R. **Pharmazie** 1985 May;40(5):364 **(Ger)**

[The anticonvulsant effect of propranolol in maximal electroshock in sub chronic applications] Lasek R. **Pharmazie** 1985 Jun;40(6):430 **(Ger)**

[A modified gas chromatographic method for the determination of propranolol in blood plasma] Stenzel WR, et al. **Pharmazie** 1985 May; 40(5):360–1 **(Ger)**

[Effect of propranolol on the vascular resistance of the human placenta perfused in vitro] Samberger M, et al. **Ginekol Pol** 1984 Dec; 55(12):895–900 (Eng. Abstr.) **(Pol)**

[Possibilities of using neurotropic agents for preventing the development of aphthous stomatitis] Airapetian GO, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):42–3 (Eng. Abstr.) **(Rus)**

[Prevention of the stress-induced decrease in natural killer activity by using a beta-adrenergic blocker and vitamin E] Meerson FZ, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):646–7 (Eng. Abstr.) **(Rus)**

[Thermoregulatory effect of beta-adrenoreceptor block in the cold-adapted rat at rest and during exertion] Divert VE, et al. **Fiziol Zh SSSR** 1985 Jun;71(6):777–81 (Eng. Abstr.) **(Rus)**

PROSTAGLANDINS

Prostaglandins enhance trigeminal substance P-ergic responses in the rabbit iris sphincter muscles. Ueda N, et al. **Brain Res** 1985 Jul 1; 337(2):347–51

Behavioral and neurochemical aspects of prostaglandins in brain function. Chiu EK, et al. **Gen Pharmacol** 1985;16(3):163–75 (115 ref.)

Evidence that the beta-adrenergic system and prostaglandins stimulate renin release through different mechanisms. Hsueh WA, et al. **J Clin Endocrinol Metab** 1985 Sep;61(3):399–403

Prostaglandin output from the early pregnant rat uterus superfused in vitro, and the effect of A23187 and trifluoperazine. Poyser NL. **J Reprod Fertil** 1985 May;74(1):271–7

Adrenergic stimulation modifies prostaglandin synthesis by rat vas deferens. Peredo H, et al. **Prostaglandins Leukotrienes Med** 1985 Jul; 19(1):51–61

[Role of the kallikrein-kinin system and prostaglandins in the action of dopamine on blood flow and sodium transport in the rat kidney] Kuz'min OB, et al. **Fiziol Zh SSSR** 1985 May;71(5):619–24 (Eng. Abstr.) **(Rus)**

PSILOCYBINE

Mushroom use by college students. Thompson JP, et al. **J Drug Educ** 1985;15(2):111–24

PSYCHIATRIC STATUS RATING SCALES

Profiles of antidepressant activity with the Montgomery-Asberg Depression Rating Scale. Montgomery SA, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:38–42

The clinical interview for depression. Development, reliability and validity. Paykel ES. **J Affective Disord** 1985 Jul;9(1):85–96

PSYCHIATRY

Cultural phenomenology and residency training revisited: a personal account. Zimmer B. **Int J Soc Psychiatry** 1985 Autumn;31(3):188–93

PSYCHOMOTOR PERFORMANCE

Task-dependent development of cross-tolerance to psychomotor effects of lorazepam in man. Aranko K. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):373–81

Psychomotor effects of alprazolam and diazepam during acute and subacute treatment, and during the follow-up phase. Aranko K, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 May;56(5):364–72

Central effects during the continuous osmotic infusion of a benzodiazepine (triazolam). Breimer DD, et al. **Br J Clin Pharmacol** 1985 Jun; 19(6):807–15

A conveyor belt task for assessing visuo-motor coordination in the marmoset (Callithrix jacchus): effects of diazepam, chlorpromazine, pentobarbital and d-amphetamine. D'Mello GD, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):125–31

[Pharmacology in automobile driving and medical practice. II. Euhypnotic effect of Elenium and psychomotor efficiency in humans] Galuszko P, et al. **Psychiatr Pol** 1984 Nov–Dec;18(6):555–60 (Eng. Abstr.) **(Pol)**

PSYCHOPHARMACOLOGY

Comparison of fixed-ratio and progressive-ratio schedules of maintenance of stimulant drug-reinforced responding. Winger G, et al. **Drug Alcohol Depend** 1985 May;15(1–2):123–30

A conveyor belt task for assessing visuo-motor coordination in the marmoset (Callithrix jacchus): effects of diazepam, chlorpromazine, pentobarbital and d-amphetamine. D'Mello GD, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):125–31

Drug discrimination training with a single choice trial per session. Tomie A, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):217–22

[A simply designed apparatus and its use for measuring vertical and horizontal motor activities in methamphetamine-treated mice] Itoh T, et al. **Yakubutsu Seishin Kodo** 1985 May;5(1):19–23 (Eng. Abstr.) **(Jpn)**

PSYCHOPHYSIOLOGIC DISORDERS

Clonidine treatment in vegetative dysfunction—experimental rationales. Svensson TH. **Acta Obstet Gynecol Scand [Suppl]** 1985;132:23–8

Experimental comparison of low doses of 1.5 mg fluspirilene and bromazepam in out-patients with psychovegetative disturbances. Hassel P. **Pharmacopsychiatry** 1985 Sep;18(5):297–302

[Low blood values of prolactin in women with psychogenic amenorrhea and anorexia nervosa] Natoli A, et al. **Clin Ter** 1985 Jun 30; 113(6):499–501 (Eng. Abstr.) **(Ita)**

PSYCHOSES, SUBSTANCE-INDUCED

Lorazepam dependence and chronic psychosis [letter] Fraser AA, et al. **Br J Psychiatry** 1985 Aug;147:211

PSYCHOSEXUAL DISORDERS

Erotomania in Schneider-positive schizophrenia. A case report. Hayes M, et al. **Br J Psychiatry** 1985 Jun;146:661–3

PSYCHOTHERAPY

Maintenance treatment of recurrent unipolar depression: pharmacology and psychotherapy. Frank E, et al. **Adv Biochem Psychopharmacol** 1985; 40:139–51

Patterns of attrition for psychosocial and pharmacologic treatments of depression. Last CG, et al. **J Clin Psychiatry** 1985 Sep;46(9):361–6

Carbamazepine and psychotherapy in the treatment of schizoaffective psychosis. Cegalis JA, et al. **Yale J Biol Med** 1985 Jul–Aug; 58(4):327–36

[Witchcraft: parallel practice] Glachant A. **Soins Psychiatr** 1985 May; (55):10–2 **(Fre)**

PSYCHOTHERAPY, GROUP

[Value of group psychotherapy in the after care of schizophrenic patients. A 5 year follow-up study] Hartwich P, et al. **Nervenarzt** 1985 Jul; 56(7):365–72 **(Ger)**

PSYCHOTIC DISORDERS

Chronic treatments in neuropsychiatry. **Adv Biochem Psychopharmacol** 1985;40:1–219

Response to lithium prophylaxis in schizoaffective psychoses. Kemali D, et al. **Adv Biochem Psychopharmacol** 1985;40:153–8

An open clinical trial of carbamazepine in treatment-resistant bipolar and schizo-affective psychotics. Elphick M. **Br J Psychiatry** 1985 Aug; 147:198–200

Early clinical experiences with sulpiride [letter] Soni SD, et al. **Br J Psychiatry** 1985 Jun;146:673

Assessment and treatment of the late-onset psychoses. Leuchter AF. **Hosp Community Psychiatry** 1985 Aug;36(8):815–6, 818

Slow-release lithium in treatment of schizoaffective syndromes. Romeo R, et al. **Int J Clin Pharmacol Res** 1985;5(3):205–11

Lithium dosage in the elderly. A study with matched age groups. Greil W, et al. **J Affective Disord** 1985 Jul;9(1):1–4

Pharmacology of neuroleptics in use in the United States. Richelson E. **J Clin Psychiatry** 1985 Aug;46(8 Pt 2):8–14

The late-onset psychoses. Clinical and diagnostic features. Leuchter AF, et al. **J Nerv Ment Dis** 1985 Aug;173(8):488–94

Early relapse after sudden withdrawal or dose reduction of clozapine [letter] Perényi A, et al. **Psychopharmacology (Berlin)** 1985; 86(1–2):244

Comparative efficacy of red cell and plasma haloperidol as predictors of clinical response in schizophrenia. Smith RC, et al. **Psychopharmacology (Berlin)** 1985;85(4):449–55

Carbamazepine and psychotherapy in the treatment of schizoaffective psychosis. Cegalis JA, et al. **Yale J Biol Med** 1985 Jul–Aug; 58(4):327–36

[Witchcraft: parallel practice] Glachant A. **Soins Psychiatr** 1985 May; (55):10–2 **(Fre)**

[Report of a patient thought to have a reactive psychosis] Borišev L. **Med Pregl** 1985;38(5-6):265-7 (Eng. Abstr.) **(Scr)**

[Evaluation of the efficacy of haloperidol decanoate in the treatment of chronic psychotic hospital patients] Marchant N, et al. **Acta Psiquiatr Psicol Am Lat** 1985 Mar;31(1):37-41 (Eng. Abstr.) **(Spa)**

QUINIDINE

Digoxin interactions. The influence of quinidine and verapamil on the pharmacokinetics and receptor binding of digitalis glycosides. Pedersen KE. **Acta Med Scand [Suppl]** 1985;697:1-40

Correlation of a quinidine-induced platelet-specific antibody with development of thrombocytopenia. Garty M, et al. **Am J Med** 1985 Aug;79(2):253-5

Inhibition of Ca2+-activated K+ channels in pig pancreatic acinar cells by Ba2+, Ca2+, quinine and quinidine. Iwatsuki N, et al. **Biochim Biophys Acta** 1985 Oct 10;819(2):249-57

Liquid chromatographic determination of quinine, hydroquinine, saccharin, and sodium benzoate in quinine beverages. Valenti LP. **J Assoc Off Anal Chem** 1985 Jul-Aug;68(4):782-4

Interrelationships among quinidine, amiloride, and lithium as inhibitors of the renal Na+-H+ exchanger. Mahnensmith RL, et al. **J Biol Chem** 1985 Oct 15;260(23):12586-92

The influence of chemical agents on the level of ionized [Ca2+] in squid axons. Requena J, et al. **J Gen Physiol** 1985 Jun;85(6):789-804

Digoxin quinidine interaction: a pharmacokinetic study in the isolated perfused rat liver. Ben-Itzhak J, et al. **Life Sci** 1985 Aug 5; 37(5):411-5

Specific immunoassays for quinine and quinidine: comparison of radioimmunoassay and enzyme-linked immunosorbent assay procedures. Morgan MR, et al. **Planta Med** 1985 Jun;(3):237-41

Kinetics of microsomal metabolism of quinidine in rats. Rakhit A, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jul;49(1):109-24

REACTION TIME

Temazepam and the perceptual-motor performance of professional footballers. Golby J, et al. **Br J Sports Med** 1985 Jun;19(2):115-8

Effects of diazepam and triazolam on auditory and visual thresholds and reaction times in the baboon. Lukas SE, et al. **Psychopharmacology (Berlin)** 1985;87(2):167-72

RECEPTORS, ADRENERGIC

Postsynaptic alpha 2-noradrenergic receptors mediate feeding induced by paraventricular nucleus injection of norepinephrine and clonidine. Goldman CK, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):11-9

Autoregulation of endogenous epinephrine release via presynaptic adrenoceptors in the rat hypothalamic slice. Goshima Y, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):248-53

Role of adenosine 3',5'-cyclic monophosphate in adrenoceptor-mediated control of 3H-noradrenaline secretion in guinea-pig ileum myenteric nerve terminals. Alberts P, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug;330(2):114-20

Neurochemical studies on GABAergic and aminergic systems in the rat brain following acute and chronic piracetam administration. Masotto C, et al. **Pharmacol Res Commun** 1985 Aug;17(8):749-72

Adrenergic stimulation modifies prostaglandin synthesis by rat vas deferens. Peredo H, et al. **Prostaglandins Leukotrienes Med** 1985 Jul; 19(1):51-61

[Catecholaminergic receptors of the blood cells of schizophrenics] Ackenheil M, et al. **Encephale** 1985 May-Jun;11(3):95-100 (Eng. Abstr.) **(Fre)**

[Monoaminergic structures of the hypothalamus in chronic stress] Konstantinova MS, et al. **Probl Endokrinol (Mosk)** 1985 Jul-Aug; 31(4):49-51 (Eng. Abstr.) **(Rus)**

RECEPTORS, ADRENERGIC, ALPHA

Adrenoreceptor interactions of the enantiomers and metabolites of mianserin: are they responsible for the antidepressant effect? Pinder RM. **Acta Psychiatr Scand [Suppl]** 1985;320:1-9 (29 ref.)

Arylazide photoaffinity probe for alpha 2-adrenoceptors. Regan JW, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3667-72

The effects of phenoxybenzamine on specific binding and function of central alpha-adrenoceptors in the rabbit. Hamilton CA, et al. **Brain Res** 1985 Sep 30;344(1):89-95

Regulation of central alpha-adrenoceptors by serotoninergic denervation. Rappaport A, et al. **Brain Res** 1985 Sep 30;344(1):158-61

Renal nerve stimulation causes alpha 1-adrenoceptor-mediated sodium retention but not alpha 2-adrenoceptor antagonism of vasopressin. Smyth DD, et al. **Circ Res** 1985 Aug;57(2):304-11

Neuronally released norepinephrine does not preferentially activate postjunctional alpha 1-adrenoceptors in human blood vessels in vitro. Stevens MJ, et al. **Circ Res** 1985 Sep;57(3):399-405

Electrophysiological and receptor studies in rat brain: effects of clorgyline. Campbell IC, et al. **Eur J Pharmacol** 1985 May 20;111(3):355-64

Postsynaptic alpha 2-noradrenergic receptors mediate feeding induced by paraventricular nucleus injection of norepinephrine and clonidine. Goldman CK, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):11-9

The importance of the alpha-adrenoceptor agonist activity of dobutamine to inotropic selectivity in the anaesthetized cat. Kenakin TP, et al. **Eur J Pharmacol** 1985 May 20;111(3):347-54

Chronic clonidine induces functional down-regulation of presynaptic alpha 2-adrenoceptors regulating [3H]noradrenaline and [3H]5-hydroxytryptamine release in the rat brain. Maura G, et al. **Eur J Pharmacol** 1985 May 28;112(1):105-10

Chronic haloperidol causes increase in salivary response and alpha 1-adrenoceptors in submandibular gland of the rat. Pazo JH, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):121-4

Relationship between alpha 2-adrenoceptor occupancy and response for B-HT 933 in canine saphenous vein. Ruffolo RR Jr, et al. **Eur J Pharmacol** 1985 May 8;111(2):267-71

Permissive role of spinal alpha 1-adrenoceptors in sudomotor efferents. Rybarczyk MC, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):339-48

Effects of iminodibenzyl antipsychotic drugs on cerebral dopamine and alpha-adrenergic receptors. Setoguchi M, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):313-22

Effect of phenoxybenzamine and clonidine on the adrenergic receptor in the rat brain; histofluorescence and ultrastructure examinations. Wawrzyniak M, et al. **Folia Histochem Cytobiol** 1985;23(1-2):91-2

Association of the changes in cytosolic Ca2+ and iodide efflux induced by thyrotropin and by the stimulation of alpha 1-adrenergic receptors in cultured rat thyroid cells. Corda D, et al. **J Biol Chem** 1985 Aug 5;260(16):9230-6

Characterization of alpha 2-adrenoceptor binding properties of imidazoline-like drugs, azoloazepine derivatives and beta-phenethylamine-like drugs in human platelet membranes. Vago T, et al. **J Pharm Pharmacol** 1985 Aug;37(8):593-6

Nimodipine and inhibition of alpha adrenergic activation of the isolated canine saphenous vein. Cooke JP, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):598-602

Effect of imipramine and adrenocorticotropin administration on the rat brain norepinephrine-coupled cyclic nucleotide generating system: alterations in alpha and beta adrenergic components. Duman RS, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):409-14

Synergistic interaction between alpha- and beta-adrenergic receptors in rat brain slices: possible site for antidepressant drug action. Pilc A, et al. **Life Sci** 1985 Sep 30;37(13):1183-94

The relationships between receptor binding capacity for norepinephrine, angiotensin II, and vasopressin and release of inositol trisphosphate, Ca2+ mobilization, and phosphorylase activation in rat liver. Lynch CJ, et al. **Mol Pharmacol** 1985 Aug;28(2):93-9

Dopaminergic modulation of hippocampal noradrenaline release. Evidence for alpha 2-antagonistic effects of some dopamine receptor agonists and antagonists. Jackisch R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug;330(2):105-13

Disturbances of norepinephrine metabolism and alpha-2 adrenergic receptor activity in anorexia nervosa: relationship to nutritional state. Kaye WH, et al. **Psychopharmacol Bull** 1985;21(3):419-23

RECEPTORS, ADRENERGIC, BETA

Beta receptors in peripheral mononuclear cells increase acutely during exercise. Burman KD, et al. **Acta Endocrinol (Copenh)** 1985 Aug; 109(4):563-8

Influence of beta-receptor stimulation on catecholamine and phospholipid concentrations in lungs of fetal rabbits. Urban J, et al. **Acta Paediatr Hung** 1985;26(2):127-32

Participation of the beta-adrenergic receptor in the enteroruminal reflex and enteroenteric reflex. Wegrzyn T, et al. **Acta Physiol Pol** 1984 May-Jun;35(3):193-8

Effect of GRP on beta-adrenergic-stimulated gastrin and somatostatin release in the isolated rat stomach. Short GM, et al. **Am J Physiol** 1985 Aug;249(2 Pt 1):G197-202

Effect of plasma on human erythrocyte beta-adrenergic receptors. Sager G, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3767-71

Desensitization of beta-receptors on primary astrocyte cultures by norepinephrine but not by tricyclic antidepressants. Frangakis MV, et al. **Brain Res** 1985 Jul 22;339(1):49-56

Primary cultures from defined brain areas; effects of seeding time on the development of beta-adrenergic- and dopamine-stimulated cAMP-activity during cultivation. Hansson E. **Brain Res** 1985 Aug; 353(2):187-92

Beta-adrenergic binding and secretory responses of the anterior pituitary. Perkins SN, et al. **Endocrinology** 1985 Nov;117(5):1818-25

Trimipramine, a tricyclic antidepressant exerting atypical actions on the central noradrenergic system. Hauser K, et al. **Eur J Pharmacol** 1985 Apr 23;111(1):23-30

Evidence that the beta-adrenergic system and prostaglandins stimulate renin release through different mechanisms. Hsueh WA, et al. **J Clin Endocrinol Metab** 1985 Sep;61(3):399-403

The affinity and efficacy of naturally occurring catecholamines at beta-adrenoceptor subtypes. McPherson GA, et al. **J Pharm Pharmacol** 1985 Jul;37(7):499-501

Effect of imipramine and adrenocorticotropin administration on the rat brain norepinephrine-coupled cyclic nucleotide generating system: alterations in alpha and beta adrenergic components. Duman RS, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):409-14

Rapid down regulation of beta adrenergic receptors by combining antidepressant drugs with forced swim: a model of antidepressant-induced neural adaptation. Duncan GE, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):402-8

Synergistic interaction between alpha- and beta-adrenergic receptors in rat brain slices: possible site for antidepressant drug action. Pilc A, et al. **Life Sci** 1985 Sep 30;37(13):1183-94

Behavioral evidence for beta-adrenoceptor subsensitivity after subacute antidepressant/alpha 2-adrenoceptor antagonist treatment. Goldstein JM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun; 329(4):355-8

Blockade of peripheral beta-adrenergic receptors fails to suppress the cerebral spread of an engram in mice. Church AC, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):27-31

Studies of beta-adrenergic receptors in leukocytes of patients with affective illness and effects of antidepressant drugs. Pandey GN, et al. **Psychopharmacol Bull** 1985;21(3):603-5

The serotonin/norepinephrine-linked beta-adrenoceptor system and the mode of action of antidepressants. Sanders-Bush E, et al. **Psychopharmacol Bull** 1985;21(3):373-8

A strong influence of serotonin axons on beta-adrenergic receptors in rat brain. Stockmeier CA, et al. **Science** 1985 Oct 18; 230(4723):323-5

[Thermoregulatory effect of beta-adrenoreceptor block in the cold-adapted rat at rest and during exertion] Divert VE, et al. **Fiziol Zh SSSR** 1985 Jun;71(6):777-81 (Eng. Abstr.) **(Rus)**

RECEPTORS, CHOLINERGIC

Open channel noise. I. Noise in acetylcholine receptor currents suggests conformational fluctuations. Sigworth FJ. **Biophys J** 1985 May; 47(5):709-20

Histamine is an antagonist of the acetylcholine receptor at the frog endplate. Ariyoshi M, et al. **Br J Pharmacol** 1985 May;85(1):65-73

Enthalpy-entropy relationship in drug-cholinoceptor interaction: a new approach. Cohen S, et al. **Br J Pharmacol** 1985 Aug;85(4):889-96

Interactions of edrophonium, physostigmine and methanesulfonyl fluoride with the snake end-plate acetylcholine receptor-channel complex. Fiekers JF. **J Pharmacol Exp Ther** 1985 Sep;234(3):539-49

Acetylcholine- and 5-hydroxytryptamine-stimulated contraction and calcium uptake in bovine coronary arteries: evidence for two populations of receptor-operated calcium channels. Ratz PH, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):641-7

Rapid induction of supersensitivity to muscarinic antagonists-induced motor excitation by continuous stimulation of cholinergic receptors. Fernando JC, et al. **Life Sci** 1985 Sep 2;37(9):883-92

Reduced muscarinic receptor plasticity in frontal cortex of aged rats after chronic administration of cholinergic drugs. Pedigo NW Jr, et al. **Life Sci** 1985 Oct 14;37(15):1443-9

RECEPTORS, DOPAMINE

Blockade of renal effects of dopamine in the dog by the DA1 antagonist SCH 23390. Frederickson ED, et al. **Am J Physiol** 1985 Aug; 249(2 Pt 2):F236-40

Evidence for cholecystokinin-dopamine receptor interactions in the central nervous system of the adult and old rat. Studies on their functional meaning. Agnati LF, et al. **Ann NY Acad Sci** 1985; 448:315-33

Cholecystokinin neuron systems and their interactions with the presynaptic features of the dopamine neuron systems. A morphometric and neurochemical analysis involving studies on the action of cholecystokinin-8 and cholecystokinin-58. Fuxe K, et al. **Ann NY Acad Sci** 1985;448:231-54

Electrophysiological studies of the role of cholecystokinin in the substantia nigra and its interactions with dopamine. Skirboll LR, et al. **Ann NY Acad Sci** 1985;448:275-82

Distinct properties of cholecystokinin-8 and mixed dopamine-cholecystokinin-8 neurons innervating the nucleus accumbens. Studler JM, et al. **Ann NY Acad Sci** 1985;448:306-14

Photoaffinity labeling of D-2 dopamine binding subunits from rat striatum, anterior pituitary and olfactory bulb with a new probe, [3H]azidosulpride. Redouane K, et al. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):1086-92

Effects of heavy metal cations, sulfhydryl reagents and other chemical agents on striatal D2 dopamine receptors. Scheuhammer AM, et al. **Biochem Pharmacol** 1985 Oct 1;34(19):3405-13

Partial purification of dopamine D2 receptors using lectin affinity columns. Abbott WM, et al. **Biosci Rep** 1985 Apr;5(4):303-8

Selective effects of thiol reagents on the binding sites for imipramine and neurotransmitter amines in the rat brain. Biassoni R, et al. **Br J Pharmacol** 1985 Jun;85(2):447-56

Vasomotor responses of cerebral arterioles in situ to putative dopamine receptor agonists. Edvinsson L, et al. **Br J Pharmacol** 1985 Jun; 85(2):403-10

Dopamine D-2 receptors in rat caudate-putamen: the lateral to medial gradient does not correspond to dopaminergic innervation. Joyce JN, et al. **Brain Res** 1985 Jul 15;338(2):209-18

In vivo voltammetric and behavioural evidence for somatodendritic autoreceptor control of mesolimbic dopamine neurones. Maidment NT, et al. **Brain Res** 1985 Jul 15;338(2):317-25

SCH 23390, a selective D1 dopamine receptor blocker, enhances the firing rate of nigral dopaminergic neurons but fails to activate striatal tyrosine hydroxylase. Onali P, et al. **Brain Res** 1985 Aug 5;340(1):1-7

The functional state of the dopamine receptor in the anterior pituitary is in the high affinity form. George SR, et al. **Endocrinology** 1985 Aug; 117(2):690-7

Interaction of SCH 23390, a D-1-selective antagonist, with the anterior pituitary D-2 receptors and prolactin secretion in the rat. Apud JA, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):187-93

SCH-23390 antagonism of a D-2 dopamine agonist depends upon catecholaminergic neurons. Breese GR, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):109-14

DSP-4 lesioning prevents the enhancement of dopamine and 5-hydroxytryptamine mediated behavioural changes by repeated electroconvulsive shock. Heal DJ, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):117-21

Presynaptic dopamine and serotonin receptors modulating tyrosine hydroxylase activity in synaptosomes of the nucleus accumbens of rats. Hetey L, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):1-10

Effect of transition or heavy metals on [3H]haloperidol binding in rat striatal membranes in vitro. Komulainen H, et al. **Eur J Pharmacol** 1985 Aug 15;114(2):113-9

SCH 23390, a selective dopamine D1 antagonist, activates dopamine neurons but fails to prevent their inhibition by apomorphine. Mereu G, et al. **Eur J Pharmacol** 1985 May 20;111(3):393-6

Striatal dopamine receptor sensitivity after subchronic fencamfamine in the rat. Scavone C, et al. **Eur J Pharmacol** 1985 May 28; 112(1):11-6

Lack of evidence supporting a role for dopamine in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity. Schmidt CJ, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):149-50

Effects of iminodibenzyl antipsychotic drugs on cerebral dopamine and alpha-adrenergic receptors. Setoguchi M, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):313-22

Progabide reverses the nigral substance P reduction induced by chronic impairment of dopaminergic transmission. Zivkovic B, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):253-5

Behavioral and eegraphic changes induced by dopaminergic antidepressants in rabbits. Bo P, et al. **Farmaco [Sci]** 1985 Aug; 40(8):608-16

Effects of phospholipids on the specific binding of [3H]spiroperidol to the cholate extract of rat brain synaptic membranes. Moroi K, et al. **Int J Biochem** 1985;17(5):637-44

Novel dopamine receptor agonists and antagonists with preferential action on autoreceptors. Johansson AM, et al. **J Med Chem** 1985 Aug; 28(8):1049-53

Dopamine-receptor agonists: mechanisms underlying autoreceptor selectivity. I. Review of the evidence. Clark D, et al. **J Neural Transm** 1985;62(1-2):1-52 (168 ref.)

Dopamine receptor agonists: mechanisms underlying autoreceptor selectivity. II. Theoretical considerations. Clark D, et al. **J Neural Transm** 1985;62(3-4):171-207 (69 ref.)

[3H]205-501, a non-catechol dopaminergic agonist, labels selectively and with high affinity dopamine D2 receptors. Closse A, et al. **J Neural Transm** 1985;62(3-4):231-48

Development of dopamine autoreceptors in the postnatal rat brain. Hedner T, et al. **J Neural Transm** 1985;62(1-2):53-63

Hypothesis: bromocriptine lacks intrinsic dopamine receptor stimulating properties. Jackson DM, et al. **J Neural Transm** 1985;62(3-4):219-30 (31 ref.)

Mesolimbic dopamine function is not altered during continuous chronic treatment of rats with typical or atypical neuroleptic drugs. Rupniak NM, et al. **J Neural Transm** 1985;62(3-4):249-66

Effect of iron chelators on dopamine D2 receptors. Ben-Shachar D, et al. **J Neurochem** 1985 Oct;45(4):999-1005

D2 dopamine receptors in calf globus pallidus: agonist high- and low-affinity sites not regulated by guanine nucleotide. De Keyser J, et al. **J Neurochem** 1985 Sep;45(3):977-9

Binding of [3H]SCH23390 in rat brain: regional distribution and effects of assay conditions and GTP suggest interactions at a D1-like dopamine receptor. Schulz DW, et al. **J Neurochem** 1985 Nov;45(5):1601-11

Properties of rat striatal D-2 dopamine receptors solubilized with the zwitterionic detergent CHAPS. Kilpatrick GJ, et al. **J Pharm Pharmacol** 1985 May;37(5):320-8

Cis- and trans-4-n-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(*f*)quinolines.

Cannon JG, et al. **J Pharm Sci** 1985 Jun;74(6):672–5

Dopamine agonist–induced locomotor activity in rats treated with 6–hydroxydopamine at differing ages: functional supersensitivity of D–1 dopamine receptors in neonatally lesioned rats. Breese GR, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):447–55

Pharmacological analysis of the actions of SKF 82526 on cardiovascular dopamine receptors. Lokhandwala MF, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):337–44

Simple method for evaluation of stimulatory effect of drugs on presynaptic dopamine receptors in mice. Watanabe H. **J Pharmacol Methods** 1985 Aug;14(1):41–7

Hyperactivity induced by stimulation of separate dopamine D–1 and D–2 receptors in rats with bilateral 6–OHDA lesions. Arnt J. **Life Sci** 1985 Aug 26;37(8):717–23

Effects of isomers of apomorphines on dopamine receptors in striatal and limbic tissue of rat brain. Kula NS, et al. **Life Sci** 1985 Sep 16; 37(11):1051–7

Dopamine D–2 receptor–mediated excitation of caudate nucleus neurons from the substantia nigra. Ohno Y, et al. **Life Sci** 1985 Oct 21; 37(16):1515–21

Characterization of dopamine receptors mediating inhibition of adenylate cyclase activity in rat striatum. Onali P, et al. **Mol Pharmacol** 1985 Aug;28(2):138–45

Antistereotypic effects of dopamine D–1 and D–2 antagonists after intrastriatal injection in rats. Pharmacological and regional specificity. Arnt J. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug; 330(2):97–104

Dopaminergic modulation of hippocampal noradrenaline release. Evidence for alpha 2–antagonistic effects of some dopamine receptor agonists and antagonists. Jackisch R, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug;330(2):105–13

Dopamine D2 receptors selectively labeled by a benzamide neuroleptic: [3H]–YM–09151–2. Niznik HB, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun;329(4):333–43

S(+)Apomorphines. Selective inhibition of excitatory effects of dopamine injected into the limbic system of the rat. Campbell A, et al. **Neuropharmacology** 1985 May;24(5):391–9

Effects on the caudate spindle in rats of dopamine microinjected into the caudate nucleus. Okuyama S, et al. **Neurosci Lett** 1985 Aug 16; 59(1):27–32

Mesolimbic and striatal dopamine receptor supersensitivity: prophylactic and reversal effects of L–prolyl–L–leucyl–glycinamide (PLG). Chiu P, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):179–83

Reduced head–twitch response to quipazine of rats previously treated with methiothepin: possible involvement of dopaminergic system. Dall'Olio R, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):43–8

Lidocaine kindling is accompanied by an increase in apomorphine stereotypy and mesolimbic dopamine D2 receptor density. Csernansky JG, et al. **Psychopharmacol Bull** 1985;21(3):707–11

The window of vulnerability in the ontogeny of the dopamine receptor. Miller JC, et al. **Psychopharmacol Bull** 1985;21(3):683–5

Dopamine receptor binding of C–11–3–N–methylspiperone in the caudate in schizophrenia and bipolar disorder: a preliminary report. Wong DF, et al. **Psychopharmacol Bull** 1985;21(3):595–8

Cocaine: excitatory effects on sensorimotor reactivity measured with acoustic startle. Davis M. **Psychopharmacology (Berlin)** 1985; 86(1–2):31–6

Effects of discontinuous drug administration on the development of dopamine receptor supersensitivity during chronic trifluoperazine or cis–flupenthixol administration to rats. Murugaiah K, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):228–32

The comparative long–term effects of ciladopa (AY–27,110), a chemically novel dopaminergic agonist, in 6–OHDA–lesioned and intact rats. Voith K. **Psychopharmacology (Berlin)** 1985;85(4):405–9

Progesterone action on the LHRH and the nigrostriatal dopamine neuronal systems: in vitro and in vivo studies. Ramirez VD, et al. **Recent Prog Horm Res** 1985;41:421–72 (110 ref.)

[Effect of l–stepholidine on rotational behavior in rats] Shi WX, et al. **Chung Kuo Yao Li Hsueh Pao** 1984 Dec;5(4):222–5 (Eng. Abstr.) **(Chi)**

[The affinity of aromatic fluoride derivatives of phenothiazine neuroleptics to spiroperidol binding sites of dopamine receptors by the radioligand technic in vitro] Oelssner W Jr, et al. **Pharmazie** 1985 May; 40(5):341–2 (Eng. Abstr.) **(Ger)**

[Effect of dopaminergic agents on the endocrine profile in labor and early puerperium] Kubota T, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Jun;37(6):945–54 (Eng. Abstr.) **(Jpn)**

[Regulation of dopamine release through the system of presynaptic receptors] Nowak JZ. **Folia Med Cracov** 1984;25(3–4):287–96 (22 ref.) (Eng. Abstr.) **(Pol)**

[Dopaminergic receptor activity and the evolution of schizophrenia] Fodoreanu L. **Rev Med Interna [Neurol Psihiatr]** 1985 Apr–Jun; 30(2):131–4 (15 ref.) **(Rum)**

[Effect of carbidine on the dopamine and serotonin receptors of the central nervous system] Zharkovskil AM, et al. **Biull Eksp Biol Med** 1985 Jun; 99(6):700–2 (Eng. Abstr.) **(Rus)**

[Effect of arachidonic acid on stereotyped behavior in the rabbit induced by a dopamine receptor agonist] Kurchikov AL, et al. **Zh Vyssh Nerv Deiat** 1985 Jul–Aug;35(4):783–5 **(Rus)**

RECEPTORS, DRUG

Digoxin interactions. The influence of quinidine and verapamil on the pharmacokinetics and receptor binding of digitalis glycosides. Pedersen KE. **Acta Med Scand [Suppl]** 1985;697:1–40

In situ molecular weight determination of rat brain [3H]phenytoin binding sites. Spero L. **Can J Physiol Pharmacol** 1985 May;63(5):515–6

A common single binding site for many psychotropic drugs on human alpha 1–acid glycoprotein. Therapeutically relevant observation? Müller WE. **Pharmacopsychiatry** 1985 Jul;18(4):257–8

RECEPTORS, ENDOGENOUS SUBSTANCES

Somatostatin agonists and antagonists—peptide control of growth hormone secretion. Coy DH, et al. **Adv Exp Med Biol** 1985; 188:325–37

Mechanisms of somatostatin action in pituitary cells. Schonbrunn A, et al. **Adv Exp Med Biol** 1985;188:305–24

Somatostatin receptors. Srikant CB, et al. **Adv Exp Med Biol** 1985; 188:291–304

Cholecystokinin and cultured spinal neurons. Immunohistochemistry, receptor binding, and neurophysiology. Rogawski MA, et al. **Ann NY Acad Sci** 1985;448:403–12

Receptors and phosphoinositide–generated second messengers. Hokin LE. **Annu Rev Biochem** 1985;54:205–35 (351 ref.)

Protein–tyrosine kinases. Hunter T, et al. **Annu Rev Biochem** 1985; 54:897–930 (239 ref.)

Thyroid–dependent maturation of neonatal brain but not lung epidermal growth factor receptors. Sadiq HF, et al. **Dev Pharmacol Ther** 1985; 8(5):292–301

Hyperprolactinemia inhibits gonadotropin–releasing hormone (GnRH) stimulation of the number of pituitary GnRH receptors. Garcia A, et al. **Endocrinology** 1985 Sep;117(3):954–9

Photoaffinity labeling of pituitary and gonadal receptors for gonadotropin–releasing hormone. Iwashita M, et al. **Endocrinology** 1985 Aug;117(2):738–46

Modulation of somatostatin binding to rat pituitary membranes by exogenously administered growth hormone. Katakami H, et al. **Endocrinology** 1985 Aug;117(2):557–60

Structural requirements for the activation of rat anterior pituitary adenylate cyclase by growth hormone–releasing factor (GRF): discovery of (N–Ac–Tyr1, D–Arg2)–GRF(1–29)–NH2 as a GRF antagonist on membranes. Robberecht P, et al. **Endocrinology** 1985 Nov; 117(5):1759–64

Chronic carbamazepine treatment increases brain adenosine receptors. Marangos PJ, et al. **Epilepsia** 1985 Sep–Oct;26(5):493–8

A carrier–protein receptor is not a prerequisite for avid hepatic elimination of highly bound compounds: a study of propranolol elimination by the isolated perfused rat liver. Jones DB, et al. **Hepatology** 1985 Jul–Aug; 5(4):590–3

Inhibition of fibrinogen receptor expression and serotonin release by leupeptin and antipain. Baldassare JJ, et al. **J Biol Chem** 1985 Sep 5; 260(19):10531–5

Pituitary receptors for LH–releasing hormone (LHRH) and responsiveness to LHRH in adult female rats after neonatal monosodium L–glutamate treatment. Inkster SE, et al. **J Endocrinol** 1985 Oct; 107(1):9–13

Pituitary gonadotrophin–releasing hormone receptor up–regulation in vitro: dependence on calcium and microtubule function. Young LS, et al. **J Endocrinol** 1985 Oct;107(1):49–56

Thyrotropin–releasing hormone receptor binding sites: autoradiographic distribution in the rat and guinea pig brain. Pazos A, et al. **J Neurochem** 1985 Nov;45(5):1448–63

Role of GnRH in the regulation of pituitary GnRH receptors in female mice. Naik SI, et al. **J Reprod Fertil** 1985 Jul;74(2):605–14

Evidence for a pituitary site of gonadal steroid stimulation of GnRH receptors in female mice. Naik SI, et al. **J Reprod Fertil** 1985 Jul; 74(2):615–24

The mechanisms of LHRH agonist action in gonadal tissues. Cooke BA, et al. **Mol Cell Endocrinol** 1985 Jul;41(2–3):115–22 (68 ref.)

The relationships between receptor binding capacity for norepinephrine, angiotensin II, and vasopressin and release of inositol trisphosphate, Ca2+ mobilization, and phosphorylase activation in rat liver. Lynch CJ, et al. **Mol Pharmacol** 1985 Aug;28(2):93–9

Ovarian LHRH receptors increase following lesions of the major LHRH structures in the rat brain: involvement of a direct neural pathway. Marchetti B, et al. **Neuroendocrinology** 1985 Oct;41(4):321–31

Estradiol–induced LH release in juvenile female rats: nembutal blocks both the decline and the exposure of nonavailable pituitary LHRH receptor sites. Smith SS, et al. **Neuroendocrinology** 1985 Sep; 41(3):246–51

Effects of transition metals on TRH–receptor interaction. Ogawa N, et al. **Neurosci Res** 1984 Oct;1(5):363–8

Peripheral models for the study of neurotransmitter receptors in man. Stahl SM. **Psychopharmacol Bull** 1985;21(3):663–71

[Age aspects of receptor–effector reactions and the regulation of adenylate cyclase activity] Burchinskii SG, et al. **Ukr Biokhim Zh** 1985 Jul–Aug; 57(4):86–98 (101 ref.) (Eng. Abstr.) **(Rus)**

RECEPTORS, ENDORPHIN

Quantitative localization of [3H]TCP binding in rat brain by light microscopy autoradiography. Sircar R, et al. **Brain Res** 1985 Sep 30; 344(1):142–5

Evidence that beta–endorphin binds to specific receptors in rat peripheral tissues and stimulates the adenylate cyclase–adenosine 3',5'–monophosphate system. Dave JR, et al. **Endocrinology** 1985 Oct; 117(4):1389–96

Phencyclidine and sigma opiate receptors in brain: biochemical and autoradiographical differentiation. Gundlach AL, et al. **Eur J Pharmacol** 1985 Jul 31;113(3):465–6

Increased affinity and selectivity of enkephalin tripeptide (Tyr–D–Ala–Gly) dimers. Lutz RA, et al. **Eur J Pharmacol** 1985 May 8;111(2):257–61

Beta–endorphin does not protect alkylation of opiate receptor by N–ethylmaleimide. Westphal M, et al. **Int J Pept Protein Res** 1985 Apr; 25(4):403–7

Isolation of a specific mu–opiate receptor peptide, morphiceptin, from an enzymatic digest of milk proteins. Chang KJ, et al. **J Biol Chem** 1985 Aug 15;260(17):9706–12

Covalent labeling of opioid receptors with radioiodinated human beta–endorphin. Identification of binding site subunit. Howard AD, et al. **J Biol Chem** 1985 Sep 5;260(19):10833–9

Interaction of opiates with opioid binding sites in the bovine adrenal medulla: I. Interaction with delta and mu sites. Castanas E, et al. **J Neurochem** 1985 Sep;45(3):677–87

Kappa–binding and degradation of [3H]dynorphin A (1–8) and [3H]dynorphin A (1–9) in suspensions of guinea pig brain membranes. Gillan MG, et al. **J Neurochem** 1985 Oct;45(4):1034–42

Diuresis and suppression of vasopressin by kappa opioids: comparison with mu and delta opioids and clonidine. Leander JD, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):463–9

Lack of functional evidence for the involvement of sigma opiate receptors in the actions of the 3–PPP enantiomers on central dopaminergic systems: discrepancies between in vitro and in vivo observations. Hjorth S, et al. **Life Sci** 1985 Aug 19;37(7):673–84

Effects of ketamine on the dynorphin levels and the ethylketocyclazocine (EKC) receptor binding in discrete regions of rat brains. Pongdhana K, et al. **Neurochem Res** 1985 Jul;10(7):945–52

Interaction of dynorphin with kappa opioid receptors in bovine adrenal medulla. Dumont M, et al. **Neuropeptides** 1985 Jul;6(4):321–9

Sulfonic acid enkephalin: binding specificity to rat brain opiate receptors. Martin JL, et al. **Neuropeptides** 1985 Jul;6(4):293–302

Ontogeny and regional distribution of proenkephalin– and prodynorphin–derived peptides and opioid receptors in rat hippocampus. Zamir N, et al. **Neuroscience** 1985 Aug;15(4):1025–34

Central effects of mu, delta, and kappa receptor agonists in hemorrhagic shock. Feuerstein G, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 1:11–3

Changes in brain opiate receptors in rats with isolation syndrome. Petkov VV, et al. **Pharmacol Res Commun** 1985 Jun;17(6):575–84

The Wellcome Foundation lecture, 1982. Opioid Peptides and their Receptors. Kosterlitz HW. **Proc R Soc Lond [Biol]** 1985 Jul 22; 225(1238):27–40 (48 ref.)

[Differential method of analyzing ligand complex formation with binding centers. The detection of the superhigh–affinity binding centers of opiate ligands] Zaitsev SV, et al. **Dokl Akad Nauk SSSR** 1985; 281(3):727–31 **(Rus)**

RECEPTORS, GABA-BENZODIAZEPINE

Micromolar benzodiazepine binding sites of central type characteristics are present in the cerebral cortex of the rat. Lowenstein PR, et al. **Acta Physiol Pharmacol Latinoam** 1984;34(4):441–3

Late evolutionary appearance of 'peripheral–type' binding sites for benzodiazepines. Bolger GT, et al. **Brain Res** 1985 Jul 15; 338(2):366–70

Involvement of benzodiazepine recognition sites in the foot shock–induced decrease of low affinity GABA receptors in the rat cerebral cortex. Concas A, et al. **Brain Res** 1985 Aug 19;341(1):50–6

Correlation of [3H]diazepam binding density with anxiolytic locus in the amygdaloid complex of the rat. Thomas SR, et al. **Brain Res** 1985 Sep 2;342(1):85–90

GABA activates different types of chloride–conducting receptor–ionophore complexes in a dose–dependent manner. Yasui S, et al. **Brain Res** 1985 Sep 30;344(1):176–80

Evidence that a benzodiazepine receptor mechanism regulates the secretion of pituitary beta–endorphin in rats. Maiewski SF, et al. **Endocrinology** 1985 Aug;117(2):474–80

Effects of GABA receptor agonists on [3H]dopamine release from median eminence and pituitary neurointermediate lobe. Anderson R, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):109–12

Effects of PK 8165, a partial benzodiazepine receptor agonist, on cholecystokinin–induced activation of hippocampal pyramidal neurons: a microiontophoretic study in the rat. Bradwejn J, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):415–8

Benzodiazepine receptor binding with a new ligand, Ro 22–8515. Goeders NE, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):147–8

Actions and interactions of benzodiazepine agonists, antagonists and inverse agonists on suprahyoid muscle twitching. James V, et al. **Eur J Pharmacol** 1985 Jul 17;113(2):233–8

Increase in nigral type II benzodiazepine recognition sites following striatonigral denervation. Porceddu ML, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):265–7

Separate site(s) of action of optical isomers of 1–methyl–5–phenyl–5–propylbarbituric acid with opposite pharmacological activities at the GABA receptor complex. Ticku MK, et al. **Eur J Pharmacol** 1985 May 28;112(1):1–9

Neuronal mechanisms involved in drug–induced jumping behavior in mice. Ushijima I, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):225–9

Progabide reverses the nigral substance P reduction induced by chronic impairment of dopaminergic transmission. Zivkovic B, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):253–5

Synthesis and binding studies of 1–arylpyrazolo[4,5–c]– and 2–arylpyrazolo[4,3–c]quinolin–4–ones. I. Cecchi L, et al. **Farmaco [Sci]** 1985 Jul;40(7):509–16

Differential coupling of GABA–A and GABA–B receptors to the noradrenergic system. Suzdak PD, et al. **J Neural Transm** 1985; 62(1–2):77–89

Existence of sites for anions and divalent cations in the solubilized gamma–aminobutyric acid/benzodiazepine receptor complex. Gavish M, et al. **J Neurochem** 1985 Sep;45(3):760–5

Photoaffinity labelling of benzodiazepine receptors: lack of effect on ligand binding to the nucleoside transport system. Hammond JR. **J Neurochem** 1985 Oct;45(4):1327–30

Modulation of neurotransmitter action: control of the gamma–aminobutyric acid response through the benzodiazepine receptor. Chan CY, et al. **J Neurosci** 1985 Sep;5(9):2365–73

Upregulation of gamma–aminobutyric acid (GABA) B binding sites in rat frontal cortex: a common action of repeated administration of different classes of antidepressants and electroshock. Lloyd KG, et al. **J Pharmacol Exp Ther** 1985 Oct;235(1):191–9

The sensitivity of GABA–receptor is increased by biogenic amines. Koketsu K, et al. **Kurume Med J** 1984;31(4):331–4

Molecular structure of Ro15–1788 and a model for the binding of benzodiazepine receptor ligands. Structural identification of common features in antagonists. Codding PW, et al. **Mol Pharmacol** 1985 Aug; 28(2):178–84

Theoretical structure–activity studies of beta–carboline analogs. Requirements for benzodiazepine receptor affinity and antagonist activity. Loew GH, et al. **Mol Pharmacol** 1985 Jul;28(1):17–31

Effect of picrotoxinin on benzodiazepine receptor binding. Chweh AY, et al. **Neurochem Res** 1985 Jul;10(7):871–7

Modulation of specific [3H]phenytoin binding by benzodiazepines. Spero L. **Neurochem Res** 1985 Jun;10(6):755–65

Further characterization of [3H] flunitrazepam binding sites on cultured mouse astroglia. Tardy M, et al. **Neurochem Res** 1985 Jun; 10(6):809–17

Tolerance to the anticonvulsant action of benzodiazepines. Relationship to decreased receptor density. Rosenberg HC, et al. **Neuropharmacology** 1985 Jul;24(7):639–44

Selective blockade of benzodiazepine receptors by Ro 15–1788 prevents foot shock–induced decrease of low affinity gamma–aminobutyric acid receptors. Corda MG, et al. **Neurosci Lett** 1985 May 23;56(3):265–9

Antagonistic effect of delta–aminovaleric acid on bicuculline–insensitive gamma–aminobutyric acid B (GABA B) sites in the rat's brain. Nakahiro M, et al. **Neurosci Lett** 1985 Jun 24;57(3):263–6

The development of type I and type II benzodiazepine receptors in the mouse cortex and cerebellum. Garrett KM, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):985–92

Benzodiazepine–receptor mediated inhibition of isolation–induced aggression in mice. Skolnick P, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):17–20

Neurochemical studies on GABAergic and aminergic systems in the rat brain following acute and chronic piracetam administration. Masotto C, et al. **Pharmacol Res Commun** 1985 Aug;17(8):749–72

Demonstration of benzodiazepine–like molecules in the mammalian brain with a monoclonal antibody to benzodiazepines. Sangameswaran L, et al. **Proc Natl Acad Sci USA** 1985 Aug;82(16):5560–4

The effects of compounds related to gamma–aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: choice behaviour in the T–maze. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;86(3):328–33

[3 new GABA–ergics: research on their possible site of action] Vamvakidès A. **Agressologie** 1985 Jun;26(7):591–4 (Eng. Abstr.) **(Fre)**

[Effects of calcium hopantenate on GABA receptors in the aged rat brain cortex] Ogawa N, et al. **Nippon Ronen Igakkai Zasshi** 1985 May; 22(3):264–5 **(Jpn)**

[Effect of fenibut on the GABA B receptors of the spinal motor neurons] Abramets II, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):698–700 (Eng. Abstr.) **(Rus)**

RECEPTORS, SEROTONIN

Lactate-induced panic attacks: possible involvement of serotonin reuptake stimulation. Lingjaerde O. **Acta Psychiatr Scand** 1985 Aug; 72(2):206–8

Serotonin-induced contraction of canine saphenous vein: mediation by 5-HT1 receptors. Tuncer M, et al. **Arch Int Pharmacodyn Ther** 1985 Apr;274(2):305–12

Selective interaction of novel anxiolytics with 5-hydroxytryptamine1A receptors. Peroutka SJ. **Biol Psychiatry** 1985 Sep;20(9):971–9

Two types of receptors for 5-hydroxytryptamine on the cholinergic nerves of the guinea-pig myenteric plexus. Kilbinger H, et al. **Br J Pharmacol** 1985 Jun;85(2):529–39

Stimulation of spinal serotonergic receptors facilitates seminal emission and suppresses penile erectile reflexes. Mas M, et al. **Brain Res** 1985 Sep 2;342(1):128–34

2-Nitroimipramine: a photoaffinity probe for the serotonin uptake/tricyclic binding site complex. Wennogle LP, et al. **EMBO J** 1985 Apr;4(4):971–7

Short-term lithium administration enhances serotonergic neurotransmission: electrophysiological evidence in the rat CNS. Blier P, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):69–77

DSP-4 lesioning prevents the enhancement of dopamine and 5-hydroxytryptamine mediated behavioural changes by repeated electroconvulsive shock. Heal DJ, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):117–21

Presynaptic dopamine and serotonin receptors modulating tyrosine hydroxylase activity in synaptosomes of the nucleus accumbens of rats. Hetey L, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):1–10

Neuronal mechanisms involved in drug-induced jumping behavior in mice. Ushijima I, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):225–9

Elevated density of [3H]imipramine binding in aged human brain. Severson JA, et al. **J Neurochem** 1985 Nov;45(5):1382–9

Specific antagonism of enteric neural serotonin receptors by dipeptides of 5-hydroxytryptophan: evidence that serotonin is a mediator of slow synaptic excitation in the myenteric plexus. Takaki M, et al. **J Neurosci** 1985 Jul;5(7):1769–80

The putative 5-HT1 receptor agonist, RU 24969, inhibits the efflux of 5-hydroxytryptamine from rat frontal cortex slices by stimulation of the 5-HT autoreceptor. Middlemiss DN. **J Pharm Pharmacol** 1985 Jun; 37(6):434–7

Acetylcholine- and 5-hydroxytryptamine-stimulated contraction and calcium uptake in bovine coronary arteries: evidence for two populations of receptor-operated calcium channels. Ratz PH, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):641–7

Target size analysis of serotonin 5-HT1 and 5-HT2 receptors in bovine brain membranes. Nishino N, et al. **Life Sci** 1985 Sep 23; 37(12):1167–74

Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Goodwin GM, et al. **Nature** 1985 Oct 10–16;317(6037):531–3

Analysis of the heart rate effects of 5-hydroxytryptamine in the cat; mediation of tachycardia by 5-HT1-like receptors. Saxena PR, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug;330(2):121–9

Reduced head-twitch response to quipazine of rats previously treated with methiothepin: possible involvement of dopaminergic system. Dall'Olio R, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):43–8

Serotonin involvement in lisuride-induced mounting and in sleep. Da Prada M, et al. **Pharmacopsychiatry** 1985 Mar;18(2):202–8

Receptor-mediated regulation of 5-hydroxytryptamine metabolism: current knowledge and open questions. Kehr W. **Pharmacopsychiatry** 1985 Mar;18(2):193–7

Human aggression and the role of central serotonin. Mühlbauer HD. **Pharmacopsychiatry** 1985 Mar;18(2):218–21

The importance of brain serotonergic receptor mechanisms for the action of antidepressant drugs. Ogren SO, et al. **Pharmacopsychiatry** 1985 Mar; 18(2):209–13

The 5-HT syndrome and the drug discrimination paradigm in rats: application in behavioral studies on the central 5-HT system. Ortmann R. **Pharmacopsychiatry** 1985 Mar;18(2):198–201

Circadian variation in behavioural responses to central 5-HT receptor stimulation in the mouse. Moser PC, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):223–7

[Characteristics of serotonin binding by the cells of immunocompetent tissues and synaptosomes] Eliseeva LS, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):210–3 (Eng. Abstr.) **(Rus)**

[Correlation between the number of serotonin type 2 receptors in the frontal cortex of the mouse brain and the expressivity of serotonin-dependent head twitches] Popova NK, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):322–4 (Eng. Abstr.) **(Rus)**

[Effect of carbidine on the dopamine and serotonin receptors of the central nervous system] Zharkovskiĭ AM, et al. **Biull Eksp Biol Med** 1985 Jun; 99(6):700–2 (Eng. Abstr.) **(Rus)**

REFLEX

Effects of nasal capsaicin pretreatment and cryosurgery on sneezing reflexes, neurogenic plasma extravasation, sensory and sympathetic neurons. Lundblad L, et al. **Acta Otolaryngol (Stockh)** 1985 Jul–Aug; 100(1–2):117–27

Participation of the beta-adrenergic receptor in the enteroruminal reflex and enteroenteric reflex. Wegrzyn T, et al. **Acta Physiol Pol** 1984 May–Jun;35(3):193–8

Apparent reduction in baroreflex sensitivity to adenosine in conscious dogs. Hintze TH, et al. **Am J Physiol** 1985 Sep;249(3 Pt 2):H554–9

Role of the pituitary in reflex natriuresis following acute unilateral nephrectomy. Lin SY, et al. **Am J Physiol** 1985 Aug; 249(2 Pt 2):F282–90

Infusion of branched-chain amino acids and ammonium salts in rats with portacaval shunts. Rigotti P, et al. **Arch Surg** 1985 Nov; 120(11):1290–5

Lower body negative pressure in the tranquilized rat. Bedford TG, et al. **Aviat Space Environ Med** 1985 Aug;56(8):786–90

The effect of enalapril on baroreceptor mediated reflex function in normotensive subjects. Giudicelli JF, et al. **Br J Clin Pharmacol** 1985 Sep;20(3):211–8

Stimulation of spinal serotonergic receptors facilitates seminal emission and suppresses penile erectile reflexes. Mas M, et al. **Brain Res** 1985 Sep 2;342(1):128–34

Inhibition of the baroreceptor heart rate reflex by angiotensin II in normal man. Mace PJ, et al. **Cardiovasc Res** 1985 Sep;19(9):525–7

Effects of a new benzodiazepine derivative, ethyl loflazepate (CM6912), on the arousal level of normal humans assessed by the averaged photopalpebral reflex. Tanaka M, et al. **Clin Neuropharmacol** 1985; 8(3):271–9

Reflex responses to reductions in functioning renal mass. Humphreys MH, et al. **Fed Proc** 1985 Oct;44(13):2840–5 (40 ref.)

The effects of buspirone, BMY-13805 and 1-(2-pyrimidinyl)-piperazine on cat spinal reflexes. Matheson GK, et al. **Methods Find Exp Clin Pharmacol** 1985 May;7(5):231–8

Yawning elicited by systemic and intrastriatal injection of piribedil and apomorphine in the rat. Dourish CT, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):175–81

REINFORCEMENT (PSYCHOLOGY)

The conditioned place preference is affected by two independent reinforcement processes. White NM, et al. **Pharmacol Biochem Behav** 1985 Jul;23(1):37–42

The abolition of the partial reinforcement extinction effect (PREE) by amphetamine. Weiner I, et al. **Psychopharmacology (Berlin)** 1985; 86(3):318–23

REINFORCEMENT SCHEDULE

Comparison of fixed-ratio and progressive-ratio schedules of maintenance of stimulant drug-reinforced responding. Winger G, et al. **Drug Alcohol Depend** 1985 May;15(1–2):123–30

Effects of triethyltin and its interaction with d-amphetamine and chlorpromazine on responding under a multiple schedule of food presentation in rats. Rastogi SK, et al. **Neurobehav Toxicol Teratol** 1985 May–Jun;7(3):239–42

Behavioral screen for antidepressants: the effects of drugs and electroconvulsive shock on performance under a differential-reinforcement-of-low-rate schedule. Seiden LS, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):55–60

RESERPINE

The effect of reserpine on the pars intermedia of the rat pituitary. An electron-microscopic, fluorescence-histochemical and immunohistochemical study. Bäck N, et al. **Cell Tissue Res** 1985; 241(1):1–8

Repetitive measurement of monoamine metabolite levels in cerebrospinal fluid of conscious rats: effects of reserpine and haloperidol. Scheinin H, et al. **Eur J Pharmacol** 1985 Jul 31;113(3):345–51

Demonstration of reduced levels of zinc in rat brain after treatment with d-amphetamine, but not after treatment with reserpine. Szerdahelyi P, et al. **Histochemistry** 1985;83(2):181–7

The influence of reserpine and propranolol upon the IOP response to vanadate in the rabbit. Delamere NA, et al. **Invest Ophthalmol Vis Sci** 1985 Oct;26(10):1442–5

Tricyclic antidepressive treatment reinforced by reserpine. Moscovich D, et al. **Isr J Psychiatry Relat Sci** 1984;21(4):283–9

Determination of reserpine in commercial tablets by liquid chromatography with fluorescence detection. Cieri UR. **J Assoc Off Anal Chem** 1985 May–Jun;68(3):542–4

Reserpic acid as an inhibitor of norepinephrine transport into chromaffin vesicle ghosts. Chaplin L, et al. **J Biol Chem** 1985 Sep 15; 260(20):10981-5

Elevation of RNA coding for tyrosine hydroxylase in rat adrenal gland by reserpine treatment and exposure to cold. Tank AW, et al. **J Neurochem** 1985 Oct;45(4):1030-3

Estradiol increases growth hormone secretion in rats exposed to swimming stress or reserpine treatment. Eriksson E, et al. **Life Sci** 1985 Sep 30; 37(13):1241-8

GABAergic effects of reserpine following chronic treatment. Suzdak PD, et al. **Psychopharmacology (Berlin)** 1985;87(2):157-60

[A TRH analog (DN-1417). Antagonistic effects on reserpine-induced decreases in local cerebral glucose utilization and cerebral monoamine levels] Nagai Y, et al. **Nippon Yakurigaku Zasshi** 1985 May; 85(5):315-26 (Eng. Abstr.) **(Jpn)**

[Effect of reserpine on inhibition of preganglionic neurons induced by stimulation of the vagus nerve] Itina LV. **Fiziol Zh SSSR** 1985 Jun; 71(6):790-2 **(Rus)**

RUBIDIUM

Transepithelial cation movements in gerbil utricles. Marcus NY, et al. **Am J Otolaryngol** 1985 Jul-Aug;6(4):268-74

Determination of lithium, rubidium and strontium in foodstuffs. Evans WH, et al. **Analyst** 1985 Jun;110(6):619-23

Lack of effect of synthetic atrial natriuretic factor on rubidium uptake by human erythrocytes. Hernando N, et al. **Biochem Biophys Res Commun** 1985 Aug 15;130(3):1066-71

Cholinergic stimulation of ion fluxes in pancreatic islets. Mathias PC, et al. **Biochem Pharmacol** 1985 Oct 1;34(19):3451-7

Delta endotoxin inhibits Rb+ uptake, lowers cytoplasmic pH and inhibits a K+-ATPase in Manduca sexta CHE cells. English LH, et al. **J Membr Biol** 1985;85(3):199-204

SCHIZOPHRENIA

An open multicentre study of the treatment of florid schizophrenia with remoxipride. McCreadie RG, et al. **Acta Psychiatr Scand** 1985 Aug; 72(2):139-43

Negative syndrome in schizophrenia: strategies for long-term management. Andreasen NC. **Adv Biochem Psychopharmacol** 1985; 40:1-7

Reduced cholecystokinin levels in the limbic lobe in schizophrenia. A marker for pathology underlying the defect state? Ferrier IN, et al. **Ann NY Acad Sci** 1985;448:495-506

The effects of cholecystokinin-like peptides in schizophrenics and normal human subjects. Hommer DW, et al. **Ann NY Acad Sci** 1985; 448:542-52

Antipsychotic effects of ceruletide in chronic schizophrenia. An appraisal of the long-term, intermittent medication of ceruletide in chronic schizophrenia. Moroji T, et al. **Ann NY Acad Sci** 1985;448:518-34

Clinical and neuroendocrine studies with cholecystokinin peptides. Nair NP, et al. **Ann NY Acad Sci** 1985;448:535-41

Rehabilitation of the chronic schizophrenic: areas of intervention. Jacobs HE, et al. **Annu Rev Rehabil** 1985;4:83-113 (99 ref.)

Family management in the prevention of morbidity of schizophrenia. Clinical outcome of a two-year longitudinal study. Falloon IR, et al. **Arch Gen Psychiatry** 1985 Sep;42(9):887-96

Apomorphine's antipsychotic activity [letter] Schaffer MH, et al. **Arch Gen Psychiatry** 1985 Sep;42(9):927-8

A treatment trial with an analog of thyrotropin-releasing hormone (DN-1417) in schizophrenia. Mizuki Y, et al. **Biol Psychiatry** 1985 Sep; 20(9):1030-5

Pilot study on the effects of fenfluramine on negative symptoms in twelve schizophrenic inpatients. Stahl SM, et al. **Biol Psychiatry** 1985 Oct; 20(10):1098-102

Stable abnormalities in the lateralisation of early cortical somatosensory evoked potentials in schizophrenic patients. Cooper JE, et al. **Br J Psychiatry** 1985 Jun;146:585-93

Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial. III. Relapse postponement or relapse prevention? The implications for long-term outcome. Curson DA, et al. **Br J Psychiatry** 1985 May;146:474-80

Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial I. Course of illness, stability of diagnosis, and the role of a special maintenance clinic. Curson DA, et al. **Br J Psychiatry** 1985 May;146:464-9

Lorazepam dependence and chronic psychosis [letter] Fraser AA, et al. **Br J Psychiatry** 1985 Aug;147:211

Erotomania in Schneider-positive schizophrenia. A case report. Hayes M, et al. **Br J Psychiatry** 1985 Jun;146:661-3

A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. Leff J, et al. **Br J Psychiatry** 1985 Jun; 146:594-600

Changes in the diagnoses of the functional psychoses associated with the introduction of lithium. Parker G, et al. **Br J Psychiatry** 1985 Apr; 146:377-82

Neuroleptic serum levels measured by radioreceptor assay in patients receiving intramuscular depot neuroleptics. Some preliminary findings. Turbott J, et al. **Br J Psychiatry** 1985 Apr;146:439-42

Prediction of response to neuroleptic drug therapy in schizophrenia. Awad AG. **Can J Psychiatry** 1985 Jun;30(4):241-2

Early subjective response and prediction of outcome to neuroleptic drug therapy in schizophrenia. Hogan TP, et al. **Can J Psychiatry** 1985 Jun; 30(4):246-8

Schizophrenia: an amotivational syndrome in men. Lewine R. **Can J Psychiatry** 1985 Aug;30(5):316-8 (17 ref.)

Clinical and demographic correlates of neuroleptic response. Seeman MV. **Can J Psychiatry** 1985 Jun;30(4):243-5

Prediction of treatment response in schizophrenia: clinical use of neuroleptic blood levels. Tang SW. **Can J Psychiatry** 1985 Jun; 30(4):249-50

Liquid-chromatographic assay of diazepam and its major metabolites in serum, and application to pharmacokinetic study of high doses of diazepam in schizophrenics. Tada K, et al. **Clin Chem** 1985 Oct; 31(10):1712-5

Ten-year follow-up of schizophrenic patients on pipothiazine palmitate. Imlah NW, et al. **Curr Med Res Opin** 1985;9(7):449-53

Multidimensional study of the outcome of schizophrenic patients 1 year after clinic discharge. Predictors and influence of neuroleptic treatment. Gaebel W, et al. **Eur Arch Psychiatry Neurol Sci** 1985;235(1):45-52

The schizophrenic clients reinforcement and punishment for medication adherence. Davidhizar R. **Issues Ment Health Nurs** 1984; 6(1-2):173-87

Comparison of injectable molindone and haloperidol followed by oral dosage forms in acutely ill schizophrenics. Escobar JI, et al. **J Clin Psychiatry** 1985 Aug;46(8 Pt 2):15-9

The strategy and value of neuroleptic drug monitoring. Curry SH. **J Clin Psychopharmacol** 1985 Oct;5(5):263-71 (56 ref.)

On the clinical relevance and methods of quantification of plasma concentrations of neuroleptics. Ko GN, et al. **J Clin Psychopharmacol** 1985 Oct;5(5):253-62 (49 ref.)

Low HVA and normal 5HIAA CSF levels in drug-free schizophrenic patients compared to healthy volunteers: correlations to symptomatology and family history. Lindström LH. **Psychiatry Res** 1985 Apr;14(4):265-73

Social skills training for patients with schizophrenia: a controlled clinical trial. Wallace CJ, et al. **Psychiatry Res** 1985 Jul;15(3):239-47

CSF monoamine metabolites in chronic schizophrenic patients who attempt suicide. Roy A, et al. **Psychol Med** 1985 May;15(2):335-40

Evidence for a daily rhythm of plasma HVA in normal controls but not in schizophrenic patients. Doran AR, et al. **Psychopharmacol Bull** 1985; 21(3):694-7

High-dose versus low-dose strategies in the treatment of schizophrenia. Kane JM, et al. **Psychopharmacol Bull** 1985;21(3):533-7

Dopamine receptor binding of C-11-3-N-methylspiperone in the caudate in schizophrenia and bipolar disorder: a preliminary report. Wong DF, et al. **Psychopharmacol Bull** 1985;21(3):595-8

An open study of remoxipride, a benzamide derivative, in schizophrenia. Lindström L, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):241-3

Early relapse after sudden withdrawal or dose reduction of clozapine [letter] Perényi A, et al. **Psychopharmacology (Berlin)** 1985; 86(1-2):244

Comparative efficacy of red cell and plasma haloperidol as predictors of clinical response in schizophrenia. Smith RC, et al. **Psychopharmacology (Berlin)** 1985;85(4):449-55

Treatment of negative symptoms. Carpenter WT Jr, et al. **Schizophr Bull** 1985;11(3):440-52

The two-syndrome concept: origins and current status. Crow TJ. **Schizophr Bull** 1985;11(3):471-86

Negative and deficit symptoms in schizophrenia do respond to neuroleptics. Goldberg SC. **Schizophr Bull** 1985;11(3):453-6

Informed consent in psychiatric research: preliminary findings from an ongoing investigation. Benson PR, et al. **Soc Sci Med** 1985; 20(12):1331-41

Comparative determination of flupentixol in plasma by gas chromatography and radioimmunoassay in schizophrenic patients. Balant-Gorgia AE, et al. **Ther Drug Monit** 1985;7(2):229-35

A group approach to psychopharmacology with schizophrenics. Skolnick MR. **Yale J Biol Med** 1985 Jul-Aug;58(4):317-26

[Changes in the CSF levels of monoamine metabolites in 102 chronic schizophrenic patients following probenecid before and after neuroleptic medication] Chen YF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Oct; 17(5):273-7 (Eng. Abstr.) **(Chi)**

[An analysis of 106 cases of schizophrenia treated with clozapine] Yang JS. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Aug; 17(4):242-4 (Eng. Abstr.) **(Chi)**

[Positive reaction of serum anti-DNA antibody induced by phenothiazines in schizophrenic patients] Yang JS. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Dec; 17(6):333-5 (Eng. Abstr.) **(Chi)**

[Administration of maintenance therapy in endogenous psychoses in out-patient practice] Mrňa B, et al. **Cesk Psychiatr** 1985 Aug; 81(4):273-5 (Eng. Abstr.) **(Cze)**

[Clinical effectiveness of isofloxythepin—an open study] Zapletálek M, et al. **Cesk Psychiatr** 1985 Aug;81(4):242-6 (Eng. Abstr.) **(Cze)**

[Catecholaminergic receptors of the blood cells of schizophrenics] Ackenheil M, et al. **Encephale** 1985 May-Jun;11(3):95-100 (Eng. Abstr.) **(Fre)**

[Value of group psychotherapy in the after care of schizophrenic patients. A 5 year follow-up study] Hartwich P, et al. **Nervenarzt** 1985 Jul; 56(7):365-72 **(Ger)**

[Therapy of schizophrenic diseases] Berthold H. **Psychiatr Neurol Med Psychol Beih** 1966;4-5:172-86 **(Ger)**

[Intensive neuroleptic treatment in schizophrenias] Pocher G, et al. **Psychiatr Neurol Med Psychol Beih** 1977;22-23:171-4 (Eng. Abstr.) **(Ger)**

[Schizophrenically disordered time perception and its modification by neuroleptics] Heim M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Jul;37(7):410-5 (Eng. Abstr.) **(Ger)**

[Patient cooperation in schizophrenics under drug therapy] Bartkó G. **Orv Hetil** 1985 Sep 15;126(37):2277-80, 2283 (Eng. Abstr.) **(Hun)**

[Parenteral form of pipothiazine in the treatment of endogenous psychoses] Matkowski K, et al. **Psychiatr Pol** 1984 Nov-Dec;18(6):567-70 (Eng. Abstr.) **(Pol)**

[Dopaminergic receptor activity and the evolution of schizophrenia] Fodoreanu L. **Rev Med Interna [Neurol Psihiatr]** 1985 Apr-Jun; 30(2):131-4 (15 ref.) **(Rum)**

[Immunoglobulins of classes G, A and M in the serum of schizophrenics] Burbaeva GSh, et al. **Zh Nevropatol Psikhiatr** 1985;85(6):901-5 (Eng. Abstr.) **(Rus)**

SCHIZOPHRENIA, PARANOID

Vasopressin—oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls. Beckmann H, et al. **Psychoneuroendocrinology** 1985; 10(2):187-91

SELF STIMULATION

Psychopharmacological profile of cholecystokinin using the self-stimulation and the drug discrimination paradigms. De Witte P, et al. **Ann NY Acad Sci** 1985;448:470-87

A response-specific conditioned aversion to rewarding hypothalamic stimulation in rats. Greenshaw AJ, et al. **Brain Res** 1985 Jul 22; 339(1):130-5

Behavioral and neurochemical effects of deprenyl and beta-phenylethylamine in Wistar rats. Greenshaw AJ, et al. **Brain Res Bull** 1985 Aug;15(2):183-9

Unilateral lesion of the intrinsic cells in the medial forebrain bundle depresses self-stimulation but not stimulus-bound locomotor activity. Velley L. **Neurosci Lett** 1985 Jun 12;57(2):199-204

Selective neonatal depletion of dopamine has no effect on medial prefrontal cortex self-stimulation in the rat. Umemoto M, et al. **Neurosci Res** 1984 Oct;1(5):295-307

Electrical self-stimulation deficits in the anterior and posterior parts of the medial forebrain bundle after ibotenic acid lesion of the middle lateral hypothalamus. Lestang I, et al. **Neuroscience** 1985 Jun; 15(2):379-88

[Endogenous peptides in the organization of somato-vegetative responses to hypothalamic stimulation] Badikov VI, et al. **Fiziol Zh SSSR** 1985 Jul;71(7):840-7 (Eng. Abstr.) **(Rus)**

SENSORY DEPRIVATION

Unilateral odor deprivation: effects on the development of olfactory bulb catecholamines and behavior. Brunjes PC, et al. **Brain Res** 1985 Sep; 354(1):1-6

The effects of monocular deprivation on the size of GAD+ neurons in the cat's dorsal lateral geniculate nucleus. Robson JA, et al. **J Comp Neurol** 1985 Sep 1;239(1):62-74

SEROTONIN

Sexual differences in the effect of serotonin on LH secretion in rats. Moguilevsky JA, et al. **Acta Endocrinol (Copenh)** 1985 Jul; 109(3):320-5

A series of new antileprosy compounds derived from serotonin. Mester de Parajd L, et al. **Acta Leprol (Geneve)** 1985 Jan-Mar;(96):21-8

The participation of serotoninergic system in the regulation of emotional-defensive behavior evoked by intrahypothalamic carbachol injections in the cat. Gołebiewski H, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(1-2):25-36

Quantity of DNA in the organs of 19-day-old foetuses after AET, MEA, or 5-HT treatment of mice on the first day of gestation. Mazur L. **Acta Physiol Hung** 1985;66(1):65-8

Effects of histamine and cimetidine on the levels of serotonin and 5-hydroxyindoleacetic acid in various parts of the digestive tract and in the blood and brain of rats. Kleinrok Z, et al. **Acta Physiol Pol** 1984 Mar-Apr;35(2):125-30

Lactate-induced panic attacks: possible involvement of serotonin reuptake stimulation. Lingjaerde O. **Acta Psychiatr Scand** 1985 Aug; 72(2):206-8

From clomipramine to mianserin: therapeutic relevance of interactions with serotonin uptake and storage, as studied in the blood platelet model. Lingjaerde O. **Acta Psychiatr Scand [Suppl]** 1985;320:10-9 (18 ref.)

Distribution of 5-hydroxytryptamine (5HT) in tissue of a mutant mouse deficient in mast cell (W/Wv). Demonstration of the contribution of mast cells to the 5HT content in various organs. Inoue F, et al. **Agents Actions** 1985 Jul;16(5):295-301

Serotonin content of foods: effect on urinary excretion of 5-hydroxyindoleacetic acid. Feldman JM, et al. **Am J Clin Nutr** 1985 Oct;42(4):639-43

Effect of gastrin, histamine, serotonin, and adrenergic amines on gastroesophageal sphincter pressure in the dog. Strombeck DR, et al. **Am J Vet Res** 1985 Aug;46(8):1684-90

Application of the dual-cell coulometric detector: a method for assaying monoamines and their metabolites. Achilli G, et al. **Anal Biochem** 1985 Jul;148(1):1-9

Substance P and 5-hydroxytryptamine immunoreactive presynaptic boutons on presumed alpha-motoneurons in the chicken ventral horn. Atsumi S, et al. **Arch Histol Jpn** 1985 Apr;48(2):159-72

Serotonin-induced contraction of canine saphenous vein: mediation by 5-HT1 receptors. Tuncer M, et al. **Arch Int Pharmacodyn Ther** 1985 Apr;274(2):305-12

ATP depletion in human platelets caused by permeabilization with saponin does not prevent serotonin secretion induced by collagen. Ruggiero M, et al. **Biochem Biophys Res Commun** 1985 Sep 16;131(2):620-7

Muramyl peptides and serotonin interact at specific binding sites on macrophages and enhance superoxide release. Silverman DH, et al. **Biochem Biophys Res Commun** 1985 Sep 30;131(3):1160-7

Effect of superior cervical ganglionectomy on melatonin stimulation by specific MAO-A inhibition. McIntyre IM, et al. **Biochem Pharmacol** 1985 Sep 15;34(18):3393-4

High concentrations of arachidonic acid induce platelet aggregation and serotonin release independent of prostaglandin endoperoxides and thromboxane A2. Hashimoto Y, et al. **Biochim Biophys Acta** 1985 Sep 6;841(3):283-91

Biological stress responses in high and low trait anxious students. Davis DD, et al. **Biol Psychiatry** 1985 Aug;20(8):843-51

Daily patterns of serotonin uptake in platelets from psychiatric patients and control volunteers. Humphries LL, et al. **Biol Psychiatry** 1985 Oct; 20(10):1073-81

Inhibition of monoamine oxidase in 5-hydroxytryptaminergic neurones by substituted p-aminophenylalkylamines. Ask AL, et al. **Br J Pharmacol** 1985 Jul;85(3):683-90

Response and sensitivity of guinea-pig airway muscle preparations to 5-hydroxytryptamine during ontogenesis. Bayol A, et al. **Br J Pharmacol** 1985 Jul;85(3):569-74

Effects of intracerebral injections of quinolinic acid on serotonergic neurons in the rat brain. Aldinio C, et al. **Brain Res** 1985 Aug 19; 341(1):57-65

The involvement of serotonin neurones in the inhibition of renal nerve activity during desynchronized sleep. Coote JH, et al. **Brain Res** 1985 Aug 12;340(2):277-84

The possible modulation of the development of rat dorsal root ganglion cells by the presence of 5-HT-containing neurones of the brainstem in dissociated cell culture. Forda S, et al. **Brain Res** 1985 Sep; 354(1):55-65

Intrahypothalamic 5,7-dihydroxytryptamine: temporal analysis of effects on 5-hydroxytryptamine content in brain nuclei and on facilitated lordosis behavior. Frankfurt M, et al. **Brain Res** 1985 Aug 5; 340(1):127-33

Serotonergic innervation of cat cerebral arteries. Marco EJ, et al. **Brain Res** 1985 Jul 8;338(1):137-9

Regulation of central alpha-adrenoceptors by serotoninergic denervation. Rappaport A, et al. **Brain Res** 1985 Sep 30;344(1):158-61

Sodium-independent binding of [3H]cocaine in mouse striatum is serotonin related. Reith ME, et al. **Brain Res** 1985 Sep 2;342(1):145-8

Neurochemical studies on the existence, origin and characteristics of the serotonergic innervation of small pial vessels. Scatton B, et al. **Brain Res** 1985 Oct 21;345(2):219-29

Reversal of the sexually dimorphic distribution of serotonin-immunoreactive fibers in the medial preoptic nucleus by treatment with perinatal androgen. Simerly RB, et al. **Brain Res** 1985 Aug 5;340(1):91-8

Norepinephrine stimulates serotonin secretion from rat pineal glands, in vitro. Walker RF, et al. **Brain Res** 1985 Sep 16;343(1):188-9

Monoamine transmitter release induced by tetrahydro-beta-carboline perfused in hippocampus of the unrestrained rat. Huttunen P, et al. **Brain Res Bull** 1985 Aug;15(2):215-20

Serotonergic modulation of the feeding behavior of the medicinal leech. Lent CM. **Brain Res Bull** 1985 Jun;14(6):643-55

ACh and 5-HT stimulated thermogenesis at different core temperatures in the He-Cold hypothermic hamster. Simpson CW, et al. **Brain Res Bull** 1985 Aug;15(2):123-7

Isolation of glomeruli from areas of bovine cerebellum and comparison of [3H]serotonin uptake. Terrian DM, et al. **Brain Res Bull** 1985 May; 14(5):469-75

Calcium regulates the activity of serotonin-containing dorsal raphe neurons in vitro. Trulson ME, et al. **Brain Res Bull** 1985 Aug; 15(2):107-10

On the interaction between 5-hydroxytryptamine and N-acetylneuraminic acid under aqueous conditions. Berry LR, et al. **Can J Biochem Cell Biol** 1985 Jul;63(7):757-63

Action of serotonin and norepinephrine on spinal motoneurones following blockade of synaptic transmission. Neuman RS. **Can J Physiol Pharmacol** 1985 Jun;63(6):735-8

Localization of serotonin in the hypothalamus and the mesencephalon of the guinea-pig. An immunohistochemical study using monoclonal antibodies. Warembourg M, et al. **Cell Tissue Res** 1985; 240(3):711-21

Morphological and pharmacological analysis of putative serotonergic bipolar and amacrine cells in the retina of a turtle, Pseudemys scripta elegans. Weiler R, et al. **Cell Tissue Res** 1985;241(2):373-82

Rapid procedure for finger-stick whole-blood analysis for serotonin by electrochemical-array-cell liquid chromatography [letter] Matson WR, et al. **Clin Chem** 1985 Aug;31(8):1407

Precise determination of 5-hydroxytryptamine in platelets and platelet-poor plasma [letter] Molyneux SG, et al. **Clin Chem** 1985 Sep; 31(9):1573-4

Amine-containing neurons in the brain of Lymnaea stagnalis: distribution and effects of precursors. Audesirk G. **Comp Biochem Physiol [A]** 1985; 81(2):359-65

2-Nitroimipramine: a photoaffinity probe for the serotonin uptake/tricyclic binding site complex. Wennogle LP, et al. **EMBO J** 1985 Apr;4(4):971-7

Effect of microelectrophoretically applied acetylcholine, noradrenaline, dopamine and serotonin on the discharge of paraventricular oxytocinergic neurones in the rat. Honda K, et al. **Endocrinol Jpn** 1985 Feb;32(1):127-33

Thyrotropin-releasing hormone release from rat pancreas is stimulated by serotonin but inhibited by carbachol. Lamberton P, et al. **Endocrinology** 1985 Nov;117(5):1834-8

Rapid bidirectional effects of insulin on hypothalamic noradrenergic and serotoninergic neuronal activity in the rat: role in glucose homeostasis. Smythe GA, et al. **Endocrinology** 1985 Oct;117(4):1590-7

Characterization of [3H]5-hydroxytryptamine uptake within rat cerebrovascular tree. Amenta F, et al. **Eur J Pharmacol** 1985 Jun 7; 112(2):181-6

Pharmacological analysis of 5-hydroxytryptamine actions on guinea-pig ileal mucosa. Cooke HJ, et al. **Eur J Pharmacol** 1985 May 20; 111(3):329-37

Effect of substances influencing brain serotonergic transmission on plasma vasopressin levels in the rat. Iovino M, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):99-103

Chronic clonidine induces functional down-regulation of presynaptic alpha 2-adrenoceptors regulating [3H]noradrenaline and [3H]5-hydroxytryptamine release in the rat brain. Maura G, et al. **Eur J Pharmacol** 1985 May 28;112(1):105-10

Quinolinic acid stimulates luteinizing hormone secretion through a serotonin-dependent mechanism. Johnson MD, et al. **Exp Brain Res** 1985;59(1):62-7

Schistosoma mansoni: effects of in vitro serotonin (5-HT) on aerobic and anaerobic carbohydrate metabolism. Rahman MS, et al. **Exp Parasitol** 1985 Aug;60(1):10-7

Serotonergic and cholinergic interaction in the regulation of pituitary-adrenal function in rats. Kile JP, et al. **Experientia** 1985 Sep 15;41(9):1123-7

Serotonergic conversion of MPTP and dopaminergic accumulation of MPP+. Shen RS, et al. **FEBS Lett** 1985 Sep 23;189(2):225-30

Relation between inhibition of calmodulin and mediator release from rat mast cells. Ohishi K, et al. **Gen Pharmacol** 1985;16(4):335-9

Ultrastructural immunocytochemical co-localization of serotonin and PNMT in adrenal medullary vesicles. Brownfield MS, et al. **Histochemistry** 1985;83(1):41-6

Studies on in vitro effect of serotonin on calcitonin secretion by rat thyroid C cells. Zabel M. **Histochemistry** 1985;83(1):71-5

Evidence for serotoninergic control of exercise-induced prolactin secretion. De Meirleir K, et al. **Horm Metab Res** 1985 Jul; 17(7):380-1

The neurochemistry of mania. The effect of lithium on catecholamines, indoleamines and calcium mobilization. Wood K. **J Affective Disord** 1985 May-Jun;8(3):215-23

Inhibition of fibrinogen receptor expression and serotonin release by leupeptin and antipain. Baldassare JJ, et al. **J Biol Chem** 1985 Sep 5; 260(19):10531-5

Serotonergic mechanisms in the cardiovascular system. **J Cardiovasc Pharmacol** 1985;7 Suppl 7:S1-182

Platelet hypersensitivity to serotonin after prolonged ketanserin intake? Arnout J, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 7:S20-2

Serotonin release and phosphoinositide breakdown in thrombin-induced activation of human platelets. Marche P, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 7:S18-9

Serotonin-induced vasoconstriction in the perfused canine femoral artery can be blocked in vivo by ketanserin. Meschig R, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 7:S56-9

In vitro studies on responses to noradrenaline, serotonin, and potassium of intramyocardial and mesenteric resistance vessels from Wistar rats. Nyborg NC, et al. **J Cardiovasc Pharmacol** 1985 May-Jun; 7(3):417-23

Serotonin depression of local cerebral glucose utilisation after monoamine oxidase inhibition. Grome JJ, et al. **J Cereb Blood Flow Metab** 1985 Sep;5(3):473-5

Determination of serotonin in plasma by liquid chromatography with electrochemical detection. Picard M, et al. **J Chromatogr** 1985 Jun 14; 341(2):445-51

Depression and serotonin metabolism: rationale for neurotransmitter precursor treatment. Byerley WF, et al. **J Clin Psychopharmacol** 1985 Aug;5(4):191-206 (188 ref.)

Localization of some neuropeptide- and serotonin-like immunoreactivities in the vegetative network of guinea pig spinal cord. Davidoff MS, et al. **J Hirnforsch** 1985;26(2):153-65

The effects of different pretreatment conditions and fixation regimes on serotonin immunoreactivity: a quantitative light microscopic study. Clements JR, et al. **J Histochem Cytochem** 1985 Aug;33(8):778-84

Characterization of an immunofluorescence technique for the demonstration of coexisting neurotransmitters within nerve fibers and terminals. Wessendorf MW, et al. **J Histochem Cytochem** 1985 Oct; 33(10):984-94

Spontaneously prolonged dioestrus and serotonin in various regions of the rat brain. Chomicka LK, et al. **J Neural Transm** 1985;63(1):31-8

Monitoring of circadian fluctuations of N-acetylserotonin in the rat pineal body by differential pulse voltammetry. Ikeda M, et al. **J Neural Transm** 1985;62(3-4):321-9

On the nature of the contractile motor responses of the rat stomach elicited by serotonin or substance P in vitro. Lidberg P, et al. **J Neural Transm** 1985;63(1):73-89

Measurement of 5-HIAA levels in ventricular CSF (by LCEC) and in striatum (by in vivo voltammetry) during pharmacological modifications of serotonin metabolism in the rat. Mignot E, et al. **J Neural Transm** 1985;62(1-2):117-24

Serotonin and cyclic adenosine 3':5'-monophosphate modulate the potassium current in tail sensory neurons in the pleural ganglion of Aplysia. Pollock JD, et al. **J Neurosci** 1985 Jul;5(7):1862-71

Depletion of norepinephrine, but not serotonin, reduces long-term potentiation in the dentate gyrus of rat hippocampal slices. Stanton PK, et al. **J Neurosci** 1985 Aug;5(8):2169-76

Serotonin and distribution of radiocarbon from D-[14C-U]-glucose in Schistosoma mansoni. Rahman MS, et al. **J Parasitol** 1985 Aug; 71(4):403-8

The putative 5-HT1 receptor agonist, RU 24969, inhibits the efflux of 5-hydroxytryptamine from rat frontal cortex slices by stimulation of the 5-HT autoreceptor. Middlemiss DN. **J Pharm Pharmacol** 1985 Jun; 37(6):434-7

Serotonergic prejunctional inhibition of canine coronary adrenergic nerves. Cohen RA. **J Pharmacol Exp Ther** 1985 Oct;235(1):76-80

Acetylcholine- and 5-hydroxytryptamine-stimulated contraction and calcium uptake in bovine coronary arteries: evidence for two populations of receptor-operated calcium channels. Ratz PH, et al. **J Pharmacol Exp Ther** 1985 Sep;234(3):641-7

Serotoninergic immunofluorescent nerve fibres appear in human temple skin after lithium treatment [letter] Dhital K, et al. **Lancet** 1985 Oct 5;2(8458):779

In vitro evidence for a blood-borne renin-releasing factor. Urban JH, et al. **Life Sci** 1985 Oct 7;37(14):1335-42

Photoinactivation of serotonin uptake by an arylazido derivative of 5-hydroxytryptamine. Ransom RW, et al. **Mol Pharmacol** 1985 Aug; 28(2):185-90

Endogenous noradrenaline as modulator of hippocampal serotonin (5-HT)-release. Dual effects of yohimbine, rauwolscine and corynanthine as alpha-adrenoceptor antagonists and 5-HT-receptor agonists. Feuerstein TJ, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 May;329(3):216-21

Efflux of 3H-5-hydroxytryptamine from rat hypothalamic slices by continuous electrical stimulation: frequency-dependent responses to serotonergic antagonists and 5-hydroxytryptamine. Richards MH. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun;329(4):359-66

Analysis of the heart rate effects of 5-hydroxytryptamine in the cat; mediation of tachycardia by 5-HT1-like receptors. Saxena PR, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug;330(2):121-9

Cyclic AMP facilitates the electrically evoked release of radiolabelled noradrenaline, dopamine and 5-hydroxytryptamine from rat brain slices. Schoffelmeer AN, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jul;330(1):74-6

Cardiovascular and sympathetic responses to intracarotid and intravenous injections of serotonin in rats. Takahashi H. **Naunyn Schmiedebergs Arch Pharmacol** 1985 May;329(3):222-6

Serotonin coexists with epinephrine in rat adrenal medullary cells. Holzwarth MA, et al. **Neuroendocrinology** 1985 Sep;41(3):230-6

Hypothalamic monoaminergic activity and pituitary function in male rats with estrogen-induced pituitary hyperplasia. Terry LC, et al. **Neuroendocrinology** 1985 Oct;41(4):269-75

Pharmacological studies on the serotoninergic and nonserotonin-mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pretreatment with fluoxetine, indalpine, PCPA, and L-tryptophan. Van de Kar LD, et al. **Neuroendocrinology** 1985 Oct; 41(4):283-8

Potentiation of motoneurone excitability by combined administration of 5-HT agonist and TRH analogue. Clarke KA, et al. **Neuropeptides** 1985 Jun;6(3):269-82

Increase in levels and ex vivo release of thyrotrophin-releasing hormone (TRH) in specific regions of the CNS of the rat by chronic treatment with antidepressants. Lighton C, et al. **Neuropharmacology** 1985 May; 24(5):401-6

Serotonin and norepinephrine-dependent effects of fenfluramine on plasma renin activity in conscious male rats. Van de Kar LD, et al. **Neuropharmacology** 1985 Jun;24(6):487-94

Intracerebroventricular administration of cholecystokinin inhibits the activity of the dopaminergic and serotoninergic systems of the brain. Vasar EE, et al. **Neurosci Behav Physiol** 1985 May-Jun;15(3).232-6

Dopaminergic toxicity after the stereotaxic administration of the 1-methyl-4-phenylpyridinium ion (MPP+) to rats. Heikkila RE, et al. **Neurosci Lett** 1985 Aug 16;59(1):135-40

A spinal projection of serotonergic neurons of the locus coeruleus in the cat. Lai YY, et al. **Neurosci Lett** 1985 Jul 31;58(2):159-64

Forebrain serotonergic involvement in avoidance learning. Ogren SO, et al. **Neurosci Lett** 1985 Aug 5;58(3):305-9

In vitro demonstration of dopamine uptake by neostriatal serotonergic neurons of the rat. Schmidt CJ, et al. **Neurosci Lett** 1985 Aug 16; 59(1):9-14

Ontogenesis of the central serotonin neuron system of the rat--an immunohistochemical study. Goto M, et al. **Neurosci Res** 1984 Feb; 1(1):3-18

Possible role of serotonin in the secretory activity of the subcommissural organ of the cat. Sakumoto T, et al. **Neurosci Res** 1984 Jun; 1(3):191-7

A facilitatory role for serotonin in the sexual behavior of the female rat. Mendelson SD, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):1025-33

Central serotonin neurones in avoidance learning: interactions with noradrenaline and dopamine neurones. Ogren SO. **Pharmacol Biochem Behav** 1985 Jul;23(1):107-23

Serotonin uptake and imipramine binding in rat platelets after chronic dexamethasone and amitriptyline treatment. Chan MY, et al. **Pharmacol Res Commun** 1985 Jul;17(7):619-32

Cholecystokinin-induced hypothermia: possible involvement of serotoninergic mechanisms in the rat hypothalamus. Liu HJ, et al. **Pharmacology** 1985;31(2):108-14

Transport systems and enzymes involved in the metamorphosis of tryptophan into serotonin. Baumann P. **Pharmacopsychiatry** 1985 Mar; 18(2):188-92

Anatomical features and physiological properties of central serotonin neurons. Baumgarten HG, et al. **Pharmacopsychiatry** 1985 Mar; 18(2):180-7

Serotonin involvement in lisuride-induced mounting and in sleep. Da Prada M, et al. **Pharmacopsychiatry** 1985 Mar;18(2):202-8

Receptor-mediated regulation of 5-hydroxytryptamine metabolism: current knowledge and open questions. Kehr W. **Pharmacopsychiatry** 1985 Mar;18(2):193-7

Significance of serotonin in central nervous functions. Maître L. **Pharmacopsychiatry** 1985 Mar;18(2):179

Human aggression and the role of central serotonin. Mühlbauer HD. **Pharmacopsychiatry** 1985 Mar;18(2):218-21

The importance of brain serotonergic receptor mechanisms for the action of antidepressant drugs. Ogren SO, et al. **Pharmacopsychiatry** 1985 Mar; 18(2):209-13

The 5-HT syndrome and the drug discrimination paradigm in rats: application in behavioral studies on the central 5-HT system. Ortmann R. **Pharmacopsychiatry** 1985 Mar;18(2):198-201

Serotonergic modulation of cortical rat noradrenergic system in the mechanism of action of antidepressant drugs. Brunello N, et al. **Psychopharmacol Bull** 1985;21(3):379-84

Persistent effects of amphetamine, p-chloroamphetamine, and related compounds on central dopamine and serotonin neurons in rodents. Fuller RW. **Psychopharmacol Bull** 1985;21(3):528-32

Serotonin-behavior interactions in vervet monkeys. McGuire MT, et al. **Psychopharmacol Bull** 1985;21(3):458-63

The serotonin/norepinephrine-linked beta-adrenoceptor system and the mode of action of antidepressants. Sanders-Bush E, et al. **Psychopharmacol Bull** 1985;21(3):373-8

Circadian variation in behavioural responses to central 5-HT receptor stimulation in the mouse. Moser PC, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):223-7

Ro 11-2465 (cyan-imipramine), citalopram and their N-desmethyl metabolites: effects on the uptake of 5-hydroxytryptamine and noradrenaline in vivo and related pharmacological activities. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1985;86(1-2):156-63

Changes in human platelet 5 HT level after 1 week of chlorimipramine treatment. Poirier MF, et al. **Psychopharmacology (Berlin)** 1985; 86(1-2):194-6

Antidepressants and serotonergic neurotransmission: an integrative review. Willner P. **Psychopharmacology (Berlin)** 1985;85(4):387-404 (244 ref.)

The menstrual cycle and platelet 5-HT uptake. Tam WY, et al. **Psychosom Med** 1985 Jul-Aug;47(4):352-62

Synaptic arrangements formed by serotonin-immunoreactive axons in the substantia gelatinosa of the rat spinal cord. Maxwell DJ, et al. **Q J Exp Physiol** 1985 Jul;70(3):377-88

Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. Ricaurte G, et al. **Science** 1985 Sep 6;229(4717):986-8

A strong influence of serotonin axons on beta-adrenergic receptors in rat brain. Stockmeier CA, et al. **Science** 1985 Oct 18; 230(4723):323-5

Effects of different anticoagulants on human platelet size distribution and serotonin (5-HT) induced shape change and uptake kinetics. Malmgren R, et al. **Thromb Res** 1985 Jun 15;38(6):649-61

Serotonin-binding protein: function in synaptic vesicles. Tamir H. **Trans NY Acad Sci** 1983;41:237-42

[The spinal enkephalinergic and serotoninergic systems in the control of transmission of nociceptive messages] Cesselin F, et al. **J Pharmacol** 1985;16 Suppl 1:119-37 (70 ref.) (Eng. Abstr.) **(Fre)**

[Serotonergic effect on cerebrospinal fluid production] Nakamura S, et al. **No To Shinkei** 1985 Mar;37(3):237-42 (Eng. Abstr.) **(Jpn)**

[Seasonal rhythms of the indolamine content in the epiphysis of rats] Bondarenko LA. **Biull Eksp Biol Med** 1985 Aug;100(8):137-9 (Eng. Abstr.) **(Rus)**

[Characteristics of serotonin binding by the cells of immunocompetent tissues and synaptosomes] Eliseeva LS, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):210-3 (Eng. Abstr.) **(Rus)**

[Changes in the number of Ec cells in the small intestine and the serotonin level in the blood plasma of fasting rats] Solomatina TM, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):162-4 (Eng. Abstr.) **(Rus)**

[Combined action of lithium salts and serotonin on the caudate nucleus] Zamoshchina TA, et al. **Biull Eksp Biol Med** 1985 Aug; 100(8):191-3 (Eng. Abstr.) **(Rus)**

[Cyclic nucleotide levels in the regenerating liver of rats following irradiation and protection by serotonin] Aslamova LI, et al. **Radiobiologiia** 1985 May-Jun;25(3):324-7 (Eng. Abstr.) **(Rus)**

[Regulation of the plastic properties of an electro-excitable neuronal membrane by serotonin] D'iakonova TL. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):753-9 (Eng. Abstr.) **(Rus)**

[Effect of serotonin and acetylcholine on the electrical activity of isolated cortex in the rabbit] Ignat'ev DA, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):733-41 (Eng. Abstr.) **(Rus)**

[Effect of serotonin on cholinergic septo-hippocampal reactions in the rabbit] Kozhedub RG. **Zh Vyssh Nerv Deiat** 1985 May-Jun; 35(3):537-43 (Eng. Abstr.) **(Rus)**

[Functional differentiation of the theta-rhythm of the hippocampus in the cat] Melikov EM. **Zh Vyssh Nerv Deiat** 1985 May-Jun; 35(3):457-64 (Eng. Abstr.) **(Rus)**

[Changes in the serotonin system of the brains of rats genetically predisposed to catalepsy] Popova NK, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):742-6 (Eng. Abstr.) **(Rus)**

SEX BEHAVIOR, ANIMAL

Side effects of drugs stimulating prolactin secretion on the behavior of male rats. Drago F, et al. **Arch Int Pharmacodyn Ther** 1985 Aug; 276(2):271-8

Intrahypothalamic 5,7-dihydroxytryptamine: temporal analysis of effects on 5-hydroxytryptamine content in brain nuclei and on facilitated lordosis behavior. Frankfurt M, et al. **Brain Res** 1985 Aug 5; 340(1):127-33

GABAergic drugs and sexual behaviour in the male rat. Agmo A, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):371-8

A monoamine oxidase inhibitor reverses the 'separation syndrome' in a new hamster separation model of depression. Crawley JN. **Eur J Pharmacol** 1985 May 28;112(1):129-33

Prolactin influences sexual behavior during aging. Ferrara N, et al. **J Endocrinol Invest** 1985;8 Suppl 2:23-32

LHRH and mating behavior: sexual receptivity versus sexual preference. Dudley CA, et al. **Pharmacol Biochem Behav** 1985 Jun;22(6):967-72

A facilitatory role for serotonin in the sexual behavior of the female rat. Mendelson SD, et al. **Pharmacol Biochem Behav** 1985 Jun; 22(6):1025-33

Sexual excitement and stretching and yawning induced by B-HT 920. Ferrari F. **Pharmacol Res Commun** 1985 Jun;17(6):557-64

Serotonin involvement in lisuride-induced mounting and in sleep. Da

Prada M, et al. **Pharmacopsychiatry** 1985 Mar;18(2):202-8

Central muscarinic receptors and male rat sexual behavior: facilitation by oxotremorine but not arecoline or pilocarpine in methscopolamine pretreated animals. Ahlenius S, et al. **Psychopharmacology (Berlin)** 1985; 87(2):127-9

SLEEP

Changes in sleep EEG architecture during the treatment of depressed patients with mianserin. Mendlewicz J, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:26-9

Stress, catecholamines, and sleep. Harrison GA. **Aviat Space Environ Med** 1985 Jul;56(7):651-3

Central effects during the continuous osmotic infusion of a benzodiazepine (triazolam). Breimer DD, et al. **Br J Clin Pharmacol** 1985 Jun; 19(6):807-15

A microiontophoretic study of the actions of the putative sleep factor, piperidine, in the rat brainstem. Horton RC, et al. **Br J Pharmacol** 1985 May;85(1):37-44

The involvement of serotonin neurones in the inhibition of renal nerve activity during desynchronized sleep. Coote JH, et al. **Brain Res** 1985 Aug 12;340(2):277-84

Sleep and wake after benzodiazepine hypnotics: a 20-hour EEG comparison of lormetazepam and flunitrazepam. Timsit-Berthier M, et al. **Curr Med Res Opin** 1985;9(8):552-9

Route- and dose-dependent pharmacokinetics of hexobarbitone in the rat: a re-evaluation of the use of sleeping times in metabolic studies. Van der Graaff M, et al. **J Pharm Pharmacol** 1985 Aug;37(8):550-4

Simultaneous determination of blood levels of corticosterone and growth hormone in the male rat: relation to sleep-wakefulness cycle. Mitsugi N, et al. **Neuroendocrinology** 1985 Aug;41(2):125-30

Effects of alprazolam and diazepam on the daytime sleepiness of non-anxious subjects. Seidel WF, et al. **Psychopharmacology (Berlin)** 1985;87(2):194-7

[Action of clovoxamine on the sleep of depressed patients. 'Polygraphic recordings'] Minot R, et al. **Encephale** 1985 Mar-Apr;11(2):65-70 (Eng. Abstr.) **(Fre)**

SLEEP DEPRIVATION

Plasma renin activity and serum aldosterone during prolonged physical strain. The significance of sleep and energy deprivation. Opstad PK, et al. **Eur J Appl Physiol** 1985;54(1):1-6

Periodic sleep deprivation in drug-refractory depression. Dessauer M, et al. **Neuropsychobiology** 1985;13(3):111-6

Suppressant effect of REM sleep deprivation on neophobia in normal rats and in rats with selective DSP-4 induced damage of locus coeruleus neurons. Mogilnicka E, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):93-7

REM sleep deprivation effect on apomorphine-induced gnawing is reversed by dexamethasone. Nez L, et al. **Sleep** 1985;8(3):283-7

[Effect of 24-hour sleep deprivation on the metabolism of biogenic amines] Bol'shkova TD, et al. **Fiziol Cheloveka** 1985 Jul-Aug;11(4):652-6 **(Rus)**

SLEEP, REM

Superfusion of clomipramine within the ventromedial hypothalamus selectively suppresses paradoxical sleep in freely moving rats. Danguir J, et al. **Brain Res Bull** 1985 Jul;15(1):1-4

Brain noradrenergic activity in wakefulness and paradoxical sleep: the effect of clonidine. Gaillard JM. **Neuropsychobiology** 1985; 13(1-2):23-5

Suppressant effect of REM sleep deprivation on neophobia in normal rats and in rats with selective DSP-4 induced damage of locus coeruleus neurons. Mogilnicka E, et al. **Pharmacol Biochem Behav** 1985 Jul; 23(1):93-7

REM sleep deprivation effect on apomorphine-induced gnawing is reversed by dexamethasone. Nez L, et al. **Sleep** 1985;8(3):283-7

SLEEP STAGES

Reversal of slow-wave sleep by benzodiazepine antagonist Ro 15-1788 [letter] Ziegler G, et al. **Lancet** 1985 Aug 31;2(8453):510

Serotonin involvement in lisuride-induced mounting and in sleep. Da Prada M, et al. **Pharmacopsychiatry** 1985 Mar;18(2):202-8

Effects of alprazolam and diazepam on the daytime sleepiness of non-anxious subjects. Seidel WF, et al. **Psychopharmacology (Berlin)** 1985;87(2):194-7

SOCIAL ADJUSTMENT

Planned change: an innovative nursing rehabilitation model. Bevvino CA, et al. **Perspect Psychiatr Care** 1984 Oct-Dec;22(4):149-58

Social skills training for patients with schizophrenia: a controlled clinical trial. Wallace CJ, et al. **Psychiatry Res** 1985 Jul;15(3):239-47

SODIUM

Transepithelial cation movements in gerbil utricles. Marcus NY, et al. **Am J Otolaryngol** 1985 Jul-Aug;6(4):268-74

Intracellular mediators of Na+-K+ pump activity in guinea pig pancreatic acinar cells. Hootman SR, et al. **Am J Physiol** 1985 Oct; 249(4 Pt 1):G470-8

Sodium dependence of luminal alkalinization by rabbit ileal mucosa. Smith PL, et al. **Am J Physiol** 1985 Sep;249(3 Pt 1):G358-68

Adrenergic-agonist-induced Ca2+ fluxes in rat parotid cells are not Na+-dependent. Helman J, et al. **Biochem J** 1985 Sep 1; 230(2):313-20

Effects of ATP and cyclic AMP on the (Na+ + K+ + 2Cl-)-cotransport system in turkey erythrocytes. Ueberschär S, et al. **Biochim Biophys Acta** 1985 Aug 27;818(2):260-6

In vitro dopamine biosynthesis in the median eminence of rat hypothalamic slices: possible involvement of a Na+-Ca2+ exchange mechanism. Arita J, et al. **Brain Res** 1985 Jul 15;338(2):384-6

Influence of the extracellular ionic environment on ganglionic fast excitatory postsynaptic currents. Connor EA, et al. **Brain Res** 1985 Jul 29;339(2):227-35

Sodium-independent binding of [3H]cocaine in mouse striatum is serotonin related. Reith ME, et al. **Brain Res** 1985 Sep 2;342(1):145-8

Effects of thermal adaptation at 40 degrees C on membrane viscosity and the sodium-potassium pump in Chinese hamster ovary cells. Bates DA, et al. **Cancer Res** 1985 Oct;45(10):4895-9

Effect of hypophysectomy on plasma electrolytes and adrenal mineralocorticoid secretion in the terrestrial chelonian Testudo hermanni. Vallarino M, et al. **Comp Biochem Physiol [A]** 1985; 81(2):283-6

The characterization of a sodium-dependent high affinity choline uptake system unassociated with acetylcholine biosynthesis. Ivy MT, et al. **Comp Biochem Physiol [C]** 1985;81(2):351-7

Sodium and proton transport in Mycoplasma gallisepticum. Linker C, et al. **J Bacteriol** 1985 Sep;163(3):1250-7

Reconstitution and purification of the sodium- and chloride-coupled gamma-aminobutyric acid transporter from rat brain. Radian R, et al. **J Biol Chem** 1985 Sep 25;260(21):11859-65

Reconstitution of a bacterial Na+/H+ antiporter. Seto-Young D, et al. **J Biol Chem** 1985 Sep 25;260(21):11393-5

Effects of ketanserin on the intracellular concentration and transmembrane fluxes of sodium and potassium in erythrocytes of normal male subjects. Lijnen P, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 7:S38-40

Characterization of a BALB/c 3T3 preadipose cell mutant with altered Na+K+Cl- cotransport activity. Sussman I, et al. **J Cell Physiol** 1985 Jul;124(1):153-9

Isotachophoresis as a candidate reference method in analytical chemistry. Determination of sodium in serum. Lemmens AA, et al. **J Chromatogr** 1985 Feb 22;320(1):193-7

Control of sodium and potassium transport in the cortical collecting duct of the rat. Effects of bradykinin, vasopressin, and deoxycorticosterone. Tomita K, et al. **J Clin Invest** 1985 Jul;76(1):132-6

Removal of sodium channel inactivation in squid axon by the oxidant chloramine-T. Wang GK, et al. **J Gen Physiol** 1985 Aug; 86(2):289-302

Effect of metabolic depletion on the furosemide-sensitive Na and K fluxes in human red cells. Dagher G, et al. **J Membr Biol** 1985; 86(2):145-55

Effects of stimulation and diphenylhydantoin on the intracellular sodium activity in Purkinje fibres of sheep heart. Ellis D. **J Physiol (Lond)** 1985 May;362:331-48

The dependence of the salt appetite of the rat on the hormonal consequences of sodium deficiency. Epstein AN. **J Physiol (Paris)** 1984; 79(6):496-8

Acute effects of hemodialysis on erythrocyte sodium fluxes in uremic patients. Quarello F, et al. **Nephron** 1985;41(1):22-5

Sodium-dependent, calmodulin-dependent transmitter release from synaptosomes. Sandoval ME, et al. **Neurosci Lett** 1985 May 23; 56(3):271-7

[Changes in cerebral calcium, sodium and potassium after single or repeated administration of lithium in the rat] Scotto di Tella AM, et al. **Encephale** 1985 Mar-Apr;11(2):53-6 (Eng. Abstr.) **(Fre)**

[Role of the kallikrein-kinin system and prostaglandins in the action of dopamine on blood flow and sodium transport in the rat kidney] Kuz'min OB, et al. **Fiziol Zh SSSR** 1985 May;71(5):619-24 (Eng. Abstr.) **(Rus)**

[Effect of Na+, K+ and Ca++ ions on catecholamine release in the caudal mesenteric ganglion] Reprintseva VM. **Fiziol Zh SSSR** 1985 May; 71(5):561-8 (Eng. Abstr.) **(Rus)**

SOMATOSTATIN

Plasma growth hormone (GH) and somatomedin C response to continuous growth hormone-releasing factor (GRF) infusion in patients with GH deficiency. Hizuka N, et al. **Acta Endocrinol (Copenh)** 1985 Sep; 110(1):17-23

BIBLIOGRAPHY

Thyrotrophin-releasing hormone (TRH) and hormone secretion from the follicular and C-cells of perfused dog thyroid lobes. Iversen E, et al. **Acta Endocrinol (Copenh)** 1985 Aug;109(4):499-504

Dual inhibitory actions of somatostatin on isolated gastric glands. Nylander O, et al. **Acta Physiol Scand** 1985 Sep;125(1):111-9

Somatostatin. Proceedings of a satellite symposium of the Seventh International Congress of Endocrinology. June 29-30, 1984, Montreal, Quebec. **Adv Exp Med Biol** 1985;188:1-524

Somatostatin-28 [1-12]-like peptides. Benoit R, et al. **Adv Exp Med Biol** 1985;188:89-107

Central nervous system actions of somatostatin-related peptides. Brown MR, et al. **Adv Exp Med Biol** 1985;188:217-28

Proteolytic events in the post-translational processing of somatostatin precursors from rat brain cortex and anglerfish pancreatic islets. Cohen P, et al. **Adv Exp Med Biol** 1985;188:109-21

Somatostatin agonists and antagonists--peptide control of growth hormone secretion. Coy DH, et al. **Adv Exp Med Biol** 1985; 188:325-37

Somatostatins of the channel catfish. Dixon JE, et al. **Adv Exp Med Biol** 1985;188:19-29

Immunocytochemical studies of somatostatin neurons in brain. Elde R, et al. **Adv Exp Med Biol** 1985;188:167-81

Biosynthesis of rat preprosomatostatin. Goodman RH, et al. **Adv Exp Med Biol** 1985;188:31-47

Distribution and morphology of somatostatin cells. Larsson LI. **Adv Exp Med Biol** 1985;188:383-402

Post-translational processing of anglerfish islet somatostatin precursors. Noe BD, et al. **Adv Exp Med Biol** 1985;188:123-40

Somatostatin-14 like immunoreactive forms in the rat: characterization, distribution and biosynthesis. Patel YC, et al. **Adv Exp Med Biol** 1985; 188:71-87

Somatostatin secretion from the hypothalamus. Peterfreund RA, et al. **Adv Exp Med Biol** 1985;188:183-200

Regulation and actions of gastrointestinal somatostatin. Pittenger GL, et al. **Adv Exp Med Biol** 1985;188:447-62

Mechanisms of somatostatin action in pituitary cells. Schonbrunn A, et al. **Adv Exp Med Biol** 1985;188:305-24

Expression of anglerfish preprosomatostatin genes in mammalian cells: studies on the synthesis and post-translational processing of somatostatin precursors. Shields D, et al. **Adv Exp Med Biol** 1985;188:3-18

The effects of somatostatin and selected analogs on lipid absorption in animals. Slater EE, et al. **Adv Exp Med Biol** 1985;188:355-68

Anglerfish pancreatic islets produce two forms of somatostatin-28. Spiess J, et al. **Adv Exp Med Biol** 1985;188:141-54

Somatostatin receptors. Srikant CB, et al. **Adv Exp Med Biol** 1985; 188:291-304

Physiological role of somatostatin in regulation of pulsatile growth hormone secretion. Tannenbaum GS. **Adv Exp Med Biol** 1985; 188:229-59 (119 ref.)

Approaches to the study of somatostatin biosynthesis. Zingg HH, et al. **Adv Exp Med Biol** 1985;188:49-58

Effect of GRP on beta-adrenergic-stimulated gastrin and somatostatin release in the isolated rat stomach. Short GM, et al. **Am J Physiol** 1985 Aug;249(2 Pt 1):G197-202

Mode of action of somatostatin to inhibit secretion by shark rectal gland. Silva P, et al. **Am J Physiol** 1985 Sep;249(3 Pt 2):R329-34

Somatostatin and peripheral blood flow in man. Savi L, et al. **Angiology** 1985 Aug;36(8):511-5

Partial retro-inverso analogues of somatostatin: pairwise modifications at residues 7 and 8 and at residues 8 and 9. Pallai PV, et al. **Biochemistry** 1985 Apr 9;24(8):1933-41

Localization by immunoelectron microscopy of somatostatin-containing cells in the gastric mucosa of a teleost fish, Perca fluviatilis. Noaillac-Depeyre J. **Biol Cell** 1985;53(3):263-7

Somatostatin binding sites in cytosolic fractions of parietal and non-parietal cells from rabbit fundic mucosa. Arilla E, et al. **Biosci Rep** 1985 Apr;5(4):321-8

Growth hormone secretion and pancreatic function following somatostatin infusion in ducks (Anas platyrhynchos). Strosser MT, et al. **Br Poult Sci** 1985 Jul;26(3):425-32

Ultrastructural morphometric analysis of somatostatin-like immunoreactive neurones in the rat central nervous system after labelling with colloidal gold. Foster GA, et al. **Brain Res** 1985 Sep 2;342(1):117-27

The development of somatostatin immunoreactivity in the interpeduncular nucleus of the cat. Morley BJ, et al. **Brain Res** 1985 Jun; 352(2):241-8

Interrelationships between somatostatin-like cells and other endocrine cells in the pancreas of some cartilaginous fish. Tagliafierro G, et al. **Cell Mol Biol** 1985;31(3):201-7

The half-life of endogenous insulin and C-peptide in man assessed by somatostatin suppression. Matthews DR, et al. **Clin Endocrinol (Oxf)** 1985 Jul;23(1):71-9

Somatostatin binding sites in cytosolic fraction of rabbit intestinal mucosa: distribution throughout the intestinal tract. López-Ruiz MP, et al. **Comp Biochem Physiol [B]** 1985;81(4):1041-4

Effect of glucagon antibodies on plasma glucose, insulin and somatostatin in the fasting and fed rat. Tan K, et al. **Diabetologia** 1985 Jul; 28(7):435-40

The effect of pancreatic acinar atrophy upon the concentration of vasoactive intestinal polypeptide, substance P, somatostatin and glucagon in the pancreas and gastrointestinal tract of the rat. Ballmann M, et al. **Digestion** 1985;32(1):70-5

Effect of simultaneous infusion of a somatostatin analogue, insulin and glucose on serum triglycerides and blood glucose levels in man. Fukushima H, et al. **Endocrinol Jpn** 1985 Apr;32(2):241-8

Stimulation of somatostatin release in vitro by synthetic human growth hormone-releasing factor by a nondopaminergic mechanism. Aguila MC, et al. **Endocrinology** 1985 Aug;117(2):762-5

Internalization and cellular processing of somatostatin in primary culture of rat anterior pituitary cells. Draznin B, et al. **Endocrinology** 1985 Sep; 117(3):960-6

Effects of rat growth hormone (rGH)-releasing factor and somatostatin on the release and synthesis of rGH in dispersed pituitary cells. Fukata J, et al. **Endocrinology** 1985 Aug;117(2):457-67

Modulation of somatostatin binding to rat pituitary membranes by exogenously administered growth hormone. Katakami H, et al. **Endocrinology** 1985 Aug;117(2):557-60

Hypothalamic somatostatin mediates the suppression of growth hormone secretion by centrally administered thyrotropin-releasing hormone in conscious rats. Katakami H, et al. **Endocrinology** 1985 Sep; 117(3):1139-44

Somatostatin-like material is present in flowering plants. LeRoith D, et al. **Endocrinology** 1985 Nov:117(5):2093-7

Prolonged inhibition of growth hormone secretion by peripheral injection of bombesin is mediated by somatostatin in the rat. Murphy WA, et al. **Endocrinology** 1985 Sep;117(3):1179-83

Effects of intracellular glucopenia on pulsatile growth hormone secretion: mediation in part by somatostatin. Painson JC, et al. **Endocrinology** 1985 Sep;117(3):1132-8

Pantethine, a cysteamine precursor, depletes immunoreactive somatostatin and prolactin in the rat. Reichlin S, et al. **Endocrinology** 1985 Aug; 117(2):492-5

The effects of growth hormone, prolactin, corticotropin, and thyrotropin on the production and secretion of somatostatin by hypothalamic cells in vitro. Robbins RJ, et al. **Endocrinology** 1985 Aug;117(2):538-43

Somatostatin metabolism by the isolated rat lung. Ruggere MD, et al. **Endocrinology** 1985 Nov;117(5):1870-3

Cellular distribution of insulin, glucagon, pancreatic polypeptide hormone and somatostatin in the fetal and adult pancreas of the guinea pig: a comparative immunohistochemical study. Reddy SN, et al. **Eur J Cell Biol** 1985 Sep;38(2):301-5

Blood pressure following microinjection of somatostatin related peptides into the rat nucleus tractus solitarii. Koda LY, et al. **Eur J Pharmacol** 1985 Jul 31;113(3):425-30

Phorbol esters affect pituitary growth hormone (GH) and prolactin release: the interaction with GH releasing factor, somatostatin and bromocriptine. Summers ST, et al. **Eur J Pharmacol** 1985 May 20; 111(3):371-6

Somatostatin-like immunoreactivity in the pituitary and brain of three teleost fish species: somatostatin as a potential regulator of prolactin cell function. Grau EG, et al. **Gen Comp Endocrinol** 1985 Sep; 59(3):350-7

Autonomic regulation of postprandial plasma somatostatin, gastrin, and insulin. Lucey MR, et al. **Gut** 1985 Jul;26(7):683-8

DNA synthesis in lactotrophs of primary rat anterior pituitary cell cultures. Effects of thyroliberin, bromocriptine and somatostatin. Komolov IS, et al. **Histochemistry** 1985;82(5):497-500

Islet isolation from atrophied pancreas after short-term duct ligature--evidence for normal in vitro release of insulin and somatostatin. Bodziony J, et al. **Horm Metab Res** 1985 Jun; 17(6):314-6

Hexapeptide analogue of somatostatin, Sandoz 201-456. Conformational study in dimethylsulfoxide by 1D and 2D n.m.r. methods. Wynants C, et al. **Int J Pept Protein Res** 1985 Jun;25(6):622-7

SMS 201-995, a very potent analogue of somatostatin. Assignment of the 1H 500 MHz n.m.r. spectra and conformational analysis in aqueous solution. Wynants C, et al. **Int J Pept Protein Res** 1985 Jun; 25(6):608-14

SMS 201-995, an octapeptide somatostatin analogue. Assignment of the 1H 500 MHZ n.m.r. spectra and conformational analysis of SMS 201-995 in dimethylsulfoxide. Wynants C, et al. **Int J Pept Protein Res** 1985 Jun;25(6):615-21

Effects of dopamine and morphine on immunoreactive somatostatin and LH-releasing hormone secretion from hypothalamic fragments in vitro. Lengyel AM, et al. **J Endocrinol** 1985 Sep;106(3):317-22

Effect of somatostatin and thyrotrophin-releasing hormone on the levels of growth hormone in the circulation of the chronically catheterized pig fetus in utero. Spencer GS, et al. **J Endocrinol** 1985 Jul; 106(1):121-4

Somatostatin precursor in the rat striatum: changes after local injection of kainic acid. Sperk G, et al. **J Neurochem** 1985 Nov;45(5):1441-7

Effect of somatostatin on the zona glomerulosa of rats treated with angiotensin II or captopril: stereology and plasma hormone concentrations. Mazzocchi G, et al. **J Steroid Biochem** 1985 Sep; 23(3):353-6

Is somatostatin a directly acting cholestatic hormone? Schirmer BD, et al. **J Surg Res** 1985 Sep;39(3):237-45

Vagal modulation of arginine- and glucagon-induced pancreatic somatostatin secretion. Seino Y, et al. **Life Sci** 1985 Aug 19; 37(7):651-6

Amino acids release somatostatin-like immunoreactivity from isolated rat glomeruli. Fujibayashi S, et al. **Mol Cell Endocrinol** 1985 Jul; 41(2-3):263-7

Different patterns of molecular forms of somatostatin are released by the rat median eminence and hypothalamus. Pierotti AR, et al. **Neurosci Lett** 1985 Jun 24;57(3):215-20

Actions of somatostatin on lipid metabolism in mouse cerebral cortex slices. Catalán RE, et al. **Neurosci Res** 1985 Feb;2(3):201-4

Primary explants as a model of the hypothalamus in situ. Baldino F Jr, et al. **Peptides (Fayetteville)** 1985 Mar-Apr;6(2):249-56

The localization and origin of somatostatin-containing fibers in an auditory brainstem nucleus. Morley BJ. **Peptides (Fayetteville)** 1985; 6 Suppl 1:165-72

Somatostatin mediates the effect of growth hormone surges on splanchnic biogenic amines. Hussain MN, et al. **Proc Soc Exp Biol Med** 1985 Sep; 179(4):517-21

The kidney growth in animals treated with somatostatin. Polić L, et al. **Przegl Lek** 1985;42(4):436-8

Somatostatin and intestinal calcium transport in the rat. Rümenapf G, et al. **Regul Pept** 1985 Aug;11(4):299-308

Pharmacological effects of gastric inhibitory polypeptide, cholecystokinin, and somatostatin on the serum levels of cationic trypsin-like immunoreactivity in man. Florholmen J, et al. **Scand J Gastroenterol** 1985 Sep;20(7):829-34

Release of gastrointestinal regulatory peptides after a soap enema. Jenssen TG, et al. **Scand J Gastroenterol** 1985 Aug;20(6):762-6

Antramine (antral histamine) antagonizes somatostatin inhibition on endogenous gastrin-induced gastric secretion. A new hypothesis for the role of histamine in gastric secretion regulation. Vatier J, et al. **Scand J Gastroenterol** 1985 Aug;20(6).671-6

Patterns of growth hormone-releasing factor and somatostatin secretion into the hypophysial-portal circulation of the rat. Plotsky PM, et al. **Science** 1985 Oct 25;230(4724):461-3

Plasma secretin, pancreozymin, and somatostatin-like hormone in chronic renal failure patients. Grekas DM, et al. **Uremia Invest** 1984-85; 8(2):117-20

[Hormone-producing (paracrine) cells in the human labyrinth] Arnold W, et al. **Laryngol Rhinol Otol (Stuttg)** 1985 Jul;64(7):359-63 (Eng. Abstr.) (Ger)

SOMATOTROPIN RELEASING HORMONE

Effects of in vivo gonadal hormone environment on in vitro hGRF-40-stimulated GH release. Evans WS, et al. **Am J Physiol** 1985 Sep;249(3 Pt 1):E276-80

Growth hormone responses to growth hormone releasing factor in neonates. Shimano S, et al. **Biol Neonate** 1985;47(6):367-70

Immunoreactive neuronal pathways of growth hormone-releasing hormone (GRH) in the brain and pituitary of the teleost Gadus morhua. Pan JX, et al. **Cell Tissue Res** 1985;241(3):487-93

Effects on growth hormone secretion following intravenous and subcutaneous injections of growth hormone-releasing factor (hGRF-44 NH2): comparison of immunoreactive plasma GRF levels. Sassolas G, et al. **Clin Endocrinol (Oxf)** 1985 May;22(5):645-53

Growth hormone, thyrotropin and prolactin responses to simultaneous administration of human growth hormone-releasing factor and thyrotropin releasing hormone in the bovine. Hodate K, et al. **Endocrinol Jpn** 1985 Jun;32(3):375-83

Plasma GH and somatomedin C responses to single and repeated administrations of human growth hormone releasing factor (hGRF). Takano K, et al. **Endocrinol Jpn** 1985 Feb;32(1):73-80

Plasma growth hormone and somatomedin-C responses to continuous growth hormone-releasing factor infusion in normal adult men. Takano K, et al. **Endocrinol Jpn** 1985 Apr;32(2):287-93

Stimulation of somatostatin release in vitro by synthetic human growth hormone-releasing factor by a nondopaminergic mechanism. Aguila MC, et al. **Endocrinology** 1985 Aug;117(2):762-5

Immunoreactive and biologically active growth hormone-releasing factor in the rat placenta. Baird A, et al. **Endocrinology** 1985 Oct; 117(4):1598-601

Presence of growth hormone-releasing factor-like immunoreactivity in rat duodenum. Bruhn TO, et al. **Endocrinology** 1985 Oct; 117(4):1710-2

Effects of rat growth hormone (rGH)-releasing factor and somatostatin on the release and synthesis of rGH in dispersed pituitary cells. Fukata J, et al. **Endocrinology** 1985 Aug;117(2):457-67

Involvement of growth hormone-releasing factor in growth hormone secretion induced by gamma-aminobutyric acid in conscious rats. Murakami Y, et al. **Endocrinology** 1985 Aug;117(2):787-9

Structural requirements for the activation of rat anterior pituitary adenylate cyclase by growth hormone-releasing factor (GRF): discovery of (N-Ac-Tyr1, D-Arg2)-GRF(1-29)-NH2 as a GRF antagonist on membranes. Robberecht P, et al. **Endocrinology** 1985 Nov; 117(5):1759-64

Phorbol esters affect pituitary growth hormone (GH) and prolactin release: the interaction with GH releasing factor, somatostatin and bromocriptine. Summers ST, et al. **Eur J Pharmacol** 1985 May 20; 111(3):371-6

Variability of GH response to GRF shows no relationship with peripheral somatostatin and somatomedin C levels. Plewe G, et al. **Horm Metab Res** 1985 Sep;17(9):481

Effect of acute intravenous growth hormone-releasing factor on plasma prolactin in short children and patients with growth hormone deficiency. Chatelain PG, et al. **Horm Res** 1985;22(1-2):46-51

Effects of intravenous, subcutaneous, and intranasal administration of growth hormone (GH)-releasing hormone-40 on serum GH concentrations in normal men. Evans WS, et al. **J Clin Endocrinol Metab** 1985 Nov;61(5):846-50

Effects of pulsatile administration of growth hormone (GH)-releasing hormone on short term linear growth in children with GH deficiency. Gelato MC, et al. **J Clin Endocrinol Metab** 1985 Sep;61(3):444-50

The distribution of growth-hormone-releasing factor (GRF) immunoreactivity in the central nervous system of the rat: an immunohistochemical study using antisera directed against rat hypothalamic GRF. Sawchenko PE, et al. **J Comp Neurol** 1985 Jul 1;237(1):100-15

Growth hormone response to growth hormone-releasing factor in selected and control Holstein heifer calves. Massri YG, et al. **J Dairy Sci** 1985 Jul;68(7):1819-21

Effects of a fragment of human growth hormone-releasing factor in normal and 'Little' mice. Clark RG, et al. **J Endocrinol** 1985 Jul; 106(1):1-5

Growth hormone responses to multiple injections of a fragment of human growth hormone-releasing factor in conscious male and female rats. Clark RG, et al. **J Endocrinol** 1985 Sep;106(3):281-9

Coexistence of growth hormone releasing factor-like and tyrosine hydroxylase-like immunoreactivities in neurons of the rat arcuate nucleus. Okamura H, et al. **Neuroendocrinology** 1985 Aug; 41(2):177-9

Pituitary secretion of growth hormone in response to opioid peptides and opiates is mediated through growth hormone-releasing factor. Wehrenberg WB, et al. **Neuroendocrinology** 1985 Jul;41(1):13-6

Immunohistochemical demonstration of a new neurone system in rat brain using antibodies against human growth hormone-releasing factor (1-37). Fellmann D, et al. **Neurosci Lett** 1985 Jul 4;58(1):91-6

Patterns of growth hormone-releasing factor and somatostatin secretion into the hypophysial-portal circulation of the rat. Plotsky PM, et al. **Science** 1985 Oct 25;230(4724):461-3

SPATIAL BEHAVIOR

Facilitation of spontaneous and learned spatial behaviours following 6-hydroxydopamine lesions of the lateral septum: a cholinergic hypothesis. Galey D, et al. **Brain Res** 1985 Aug 5;340(1):171-4

STARTLE REACTION

Cocaine: excitatory effects on sensorimotor reactivity measured with acoustic startle. Davis M. **Psychopharmacology (Berlin)** 1985; 86(1-2):31-6

Effects of 8-OH-DPAT, lisuride and some ergot-related compounds on the acoustic startle response in the rat. Svensson L. **Psychopharmacology (Berlin)** 1985;85(4):469-75

STEREOTYPED BEHAVIOR

Effects of single and repeated application of clonazepam and diazepam combined with cyproheptadine on apomorphine stereotypy in rats. Georgiev VP, et al. **Agressologie** 1985 Jan;26(1):57-60

Clonidine sensitizes mice for apomorphine-induced stereotypic gnawing: antagonism by neuroleptics and cholecystokinin-like peptides. Zetler G. **Eur J Pharmacol** 1985 May 20;111(3):309-18

Influence of phenoxybenzamine on the stereotyped behaviour induced by fencamfamine in rats: evidence for a qualitative alteration. Bernardi MM, et al. **Gen Pharmacol** 1985;16(4):403-5

Effect of ergometrine on methamphetamine and apomorphine stereotypy in the guinea-pig. Balsara JJ, et al. **J Pharm Pharmacol** 1985 Jul; 37(7):514-7

Sensitization to stress: the enduring effects of prior stress on amphetamine-induced rotational behavior. Robinson TE, et al. **Life Sci** 1985 Sep 16;37(11):1039-42

Antistereotypic effects of dopamine D-1 and D-2 antagonists after intrastriatal injection in rats. Pharmacological and regional specificity. Arnt J. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Aug; 330(2):97-104

Central nervous system effect of 2,5-hexane diol. Agrawal AK, et al. **Neurotoxicology** 1985 Fall;6(3):53-9

Lidocaine kindling is accompanied by an increase in apomorphine stereotypy and mesolimbic dopamine D2 receptor density. Csernansky JG, et al. **Psychopharmacol Bull** 1985;21(3):707-11

The comparative long-term effects of ciladopa (AY-27,110), a chemically novel dopaminergic agonist, in 6-OHDA-lesioned and intact rats. Voith K. **Psychopharmacology (Berlin)** 1985;85(4):405-9

[Effect of 2 new GABA-ergic agents on apomorphine stereotypy in the rat] Vamvakidès A. **Agressologie** 1985 Jan;26(1):63-5 (Eng. Abstr.) **(Fre)**

[Effect of arachidonic acid on stereotyped behavior in the rabbit induced by a dopamine receptor agonist] Kurchikov AL, et al. **Zh Vyssh Nerv Deiat** 1985 Jul-Aug;35(4):783-5 **(Rus)**

STRESS, PSYCHOLOGICAL

Biological stress responses in high and low trait anxious students. Davis DD, et al. **Biol Psychiatry** 1985 Aug;20(8):843-51

Beta-adrenoceptor responsiveness and plasma catecholamines as determinants of cardiovascular reactivity to mental stress. Eisenhofer G, et al. **Clin Sci** 1985 Oct;69(4):483-92

Stress-induced elevation of plasma alpha-MSH and endorphin in brown trout, Salmo trutta L. Sumpter JP, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):257-65

Behaviorally equivalent stressors differentially modify the monoamine altering property of d-amphetamine. Klauenberg BJ, et al. **Pharmacol Biochem Behav** 1985 Sep;23(3):417-23

Plasma adrenaline and noradrenaline during mental stress and isometric exercise in man. The role of arterial sampling. Jörgensen LS, et al. **Scand J Clin Lab Invest** 1985 Sep;45(5):447-52

[Stress and the excretion of catecholamines in patients after kidney transplantation] Honzák R, et al. **Cas Lek Cesk** 1985 Jul 19; 124(29):912-3 (Eng. Abstr.) **(Cze)**

[Modification of psychic, autonomic and metabolic reactions during examinations by a single dose of beta-receptor blockers] Pietruschka WD, et al. **Z Gesamte Inn Med** 1985 May 15;40(10):289-92 (Eng. Abstr.) **(Ger)**

[Dopamine beta-hydroxylase activity in the plasma of women as an indicator of perioperative stress] Zrubek H, et al. **Ginekol Pol** 1984 Nov;55(11):859-62 (Eng. Abstr.) **(Pol)**

[Role of the adrenergic system in the pathomechanism of functional disorders in puberty] Szewczyk L. **Pediatr Pol** 1985 Apr;60(4):300-5 (Eng. Abstr.) **(Pol)**

[Immunological aspects of surgical stress] Gadalov VP. **Anesteziol Reanimatol** 1985 May-Jun;(3):69-72 (103 ref.) **(Rus)**

[Changes in the adrenal medulla of the rat during immobilization stress] Shvalev VN, et al. **Arkh Anat Gistol Embriol** 1985 Aug; 89(8):97-102 (Eng. Abstr.) **(Rus)**

[Effect of stress-inducing factors on the behavior of monkeys. I. The behavior of monkeys under acute emotional stress] Butovskaia ML, et al. **Biol Nauki** 1985;(6):67-74 (Eng. Abstr.) **(Rus)**

[State of the peripheral catecholaminergic systems during pharmacologic correction of immobilization stress using sodium oxybutyrate] Khaisman EB, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):317-9 (Eng. Abstr.) **(Rus)**

[ACTH, corticosterone and beta-endorphin in the blood plasma of rats under prolonged immobilization stress] Kiiatkin EA, et al. **Biull Eksp Biol Med** 1985 Aug;100(8):157-60 (Eng. Abstr.) **(Rus)**

[Prevention of the stress-induced decrease in natural killer activity by using a beta-adrenergic blocker and vitamin E] Meerson FZ, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):646-7 (Eng. Abstr.) **(Rus)**

[Effect of chronic psychogenic stress on the characteristics of synaptic membrane receptors in the rat brain] Nikuradze VO, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):275-7 (Eng. Abstr.) **(Rus)**

[Emotional stress-induced changes in catecholamines in the nuclei of the brains of rats differing in 'open-field' behavior] Belova TI, et al. **Fiziol Zh SSSR** 1985 Jul;71(7):813-22 (Eng. Abstr.) **(Rus)**

[Catecholamines in nuclei of the brains of the August strain rat during immobilization stress] Ivanova TM, et al. **Fiziol Zh SSSR** 1985 Jul; 71(7):823-8 (Eng. Abstr.) **(Rus)**

[Monoaminergic structures of the hypothalamus in chronic stress] Konstantinova MS, et al. **Probl Endokrinol (Mosk)** 1985 Jul-Aug; 31(4):49-51 (Eng. Abstr.) **(Rus)**

[Concentration of biogenic amines in different brain structures of the rat adapted to chronic emotional stress] Anokhina IP, et al. **Zh Vyssh Nerv Deiat** 1985 Mar-Apr;35(2):348-53 (Eng. Abstr.) **(Rus)**

SUBSTANCE P

Blockade of substance P receptors inhibits non-nicotinic, non-adrenergic colonic contractions induced by stimulation of the lumbar sympathetic nerves to the feline large intestine. Fändriks L, et al. **Acta Physiol Scand** 1985 Aug;124(4):565-71

Pharmacological analysis of the mechanism of action for colonic contraction induced by neurotensin, substance P and methionine-enkephalin. Hellström PM. **Acta Physiol Scand** 1985 Sep; 125(1):13-24

Cholecystokinin inhibits binding of substance P to pancreatic acinar cells. Sjödin L. **Acta Physiol Scand** 1985 Jul;124(3):471-4

Some effects of substance P on central respiratory control in rabbit pups. Yamamoto Y, et al. **Acta Physiol Scand** 1985 Jul;124(3):449-55

High-affinity substance P binding sites in rat sympathetic ganglia. Niwa M, et al. **Am J Physiol** 1985 Sep;249(3 Pt 2):H694-7

Substance P and 5-hydroxytryptamine immunoreactive presynaptic boutons on presumed alpha-motoneurons in the chicken ventral horn. Atsumi S, et al. **Arch Histol Jpn** 1985 Apr;48(2):159-72

Substance P-like immunoreactive nerves in the human eye. Stone RA, et al. **Arch Ophthalmol** 1985 Aug;103(8):1207-11

Dopamine-mediated increases in nigral substance P-like immunoreactivity. Ritter JK, et al. **Biochem Pharmacol** 1985 Sep 1; 34(17):3161-6

Analysis of the mechanism of histamine release induced by substance P. Shibata H, et al. **Biochim Biophys Acta** 1985 Jul 30;846(1):1-7

CSF substance P immunoreactivity in affective disorders. Berrettini WH, et al. **Biol Psychiatry** 1985 Sep;20(9):965-70

Evidence for the existence of substance P in the prepubertal rat ovary. II. Immunocytochemical localization. Dees WL, et al. **Biol Reprod** 1985 Sep;33(2):471-6

Evidence for the existence of substance P in the prepubertal rat ovary. I. Biochemical and physiologic studies. Ojeda SR, et al. **Biol Reprod** 1985 Sep;33(2):286-95

The regional distribution of kassinin-like immunoreactivity in central and peripheral tissues of the cat. Hunter JC, et al. **Brain Res** 1985 Aug 26;341(2):228-32

Increase in substance P in the dorsal horn during a chemogenic nociceptive stimulus. Kantner RM, et al. **Brain Res** 1985 Jul 8; 338(1):196-9

LH-RH analogue acts as substance P antagonist by inhibiting spinal cord vasomotor responses. Takano Y, et al. **Brain Res** 1985 Jul 1; 337(2):357-61

Prostaglandins enhance trigeminal substance P-ergic responses in the rabbit iris sphincter muscles. Ueda N, et al. **Brain Res** 1985 Jul 1; 337(2):347-51

Localization of substance P-like, leucine-enkephalin-like, methionine-enkephalin-like, and FMRFamide-like immunoreactivity in the eyestalk of the fiddler crab, Uca pugilator. Fingerman M, et al. **Cell Tissue Res** 1985;241(3):473-7

Substance P-immunoreactive neurons in the brainstem of the cat related to cardiovascular centers. Triepel J, et al. **Cell Tissue Res** 1985; 241(1):31-41

The effect of pancreatic acinar atrophy upon the concentration of vasoactive intestinal polypeptide, substance P, somatostatin and glucagon in the pancreas and gastrointestinal tract of the rat. Ballmann M, et al. **Digestion** 1985;32(1):70-5

Effects of substance P and substance P-(6-11) on hormone release from isolated perfused pancreas: their opposite actions on rat and canine islets. Chiba Y, et al. **Endocrinology** 1985 Nov;117(5):1996-2000

Age-, sex-, and gonadal steroid-related changes in immunoreactive substance P in the rat anterior pituitary gland. DePalatis LR, et al. **Endocrinology** 1985 Oct;117(4):1368-73

Inhibition of substance P degradation in rat brain preparations by peptide hydroxamic acids. Laufer R, et al. **Eur J Biochem** 1985 Jul 1; 150(1):135-40

Both substance P agonists and antagonists inhibit ion conductance through nicotinic acetylcholine receptors on PC12 cells. Eardley D, et al. **Eur J Pharmacol** 1985 Aug 7;114(1):101-4

Tachykinin responses in the rat cingulate cortex: a comparison of the effects of iontophoretically applied substance P and neurokinin A. Jones RS, et al. **Eur J Pharmacol** 1985 Sep 10;115(1):113-6

Effects of the substance P antagonist [D-Arg1,D-Pro2,D-Trp7,9,Leu11]SP on miosis caused by echothiophate iodide or pilocarpine hydrochloride. Mandahl A. **Eur J Pharmacol** 1985 Aug 15;114(2):121-7

Progabide reverses the nigral substance P reduction induced by chronic impairment of dopaminergic transmission. Zivkovic B, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):253-5

Immunoreactive substance P and LH-RH content in median eminence and pituitary gland during proestrus, oestrus, lactation and after anterior hypothalamic deafferentation. Jakubowska-Naziemblo B, et al. **Exp Clin Endocrinol** 1985 Apr;85(2):155-66

Effects of analogues of substance P fragments on the MAO activity in rat brain. Turska E, et al. **Gen Pharmacol** 1985;16(3):293-5

Neurokinin A-like immunoreactivity in rat primary sensory neurons; coexistence with substance P. Dalsgaard CJ, et al. **Histochemistry** 1985; 83(1):37-9

Substance P-like immunoreactivity in adrenal chromaffin cells and intra-adrenal nerve fibers of rats. Kuramoto H, et al. **Histochemistry** 1985;82(6):507-12

Anti-substance P anti-idiotypic antibodies. Characterization and biological activities. Couraud JY, et al. **J Biol Chem** 1985 Aug 5; 260(16):9461-9

Characterization of an immunofluorescence technique for the demonstration of coexisting neurotransmitters within nerve fibers and terminals. Wessendorf MW, et al. **J Histochem Cytochem** 1985 Oct; 33(10):984–94

Conformationally restricted C–terminal peptides of substance P. Synthesis, mass spectral analysis and pharmacological properties. Theodoropoulos D, et al. **J Med Chem** 1985 Oct;28(10):1536–9

On the nature of the contractile motor responses of the rat stomach elicited by serotonin or substance P in vitro. Lidberg P, et al. **J Neural Transm** 1985;63(1):73–89

Presence and ontogeny of enkephalin and substance P in the chick ciliary ganglion. White JD, et al. **J Neurochem** 1985 Oct;45(4):1319–22

Properties of choroid and ciliary neurons in the avian ciliary ganglion and evidence for substance P as a neurotransmitter. Dryer SE, et al. **J Neurosci** 1985 Oct;5(10):2654–61

Enzyme–linked immunosorbent assay of substance P and its metabolite SP 1–7. A comparison with RIA. Folkesson R, et al. **J Neurosci Methods** 1985 Aug;14(3):169–76

Altered respiratory response to substance P in capsaicin–treated rats. Towle AC, et al. **J Neurosci Res** 1985;14(2):239–53

Evidence against VIP or substance P being the transmitter in non–cholinergic excitatory nerves supplying the guinea–pig bladder. Meldrum LA, et al. **J Pharm Pharmacol** 1985 Jun;37(6):432–4

Substance P provoked gamma–aminobutyric acid release from the myenteric plexus of the guinea–pig small intestine. Tanaka C, et al. **J Physiol (Lond)** 1985 May;362:319–29

Possible influence of tachykinins on body fluid homeostasis in the rat. Cantalamessa F, et al. **J Physiol (Paris)** 1984;79(6):524–30

Catabolism of substance P in the stomach wall of the rat. Bunnett NW, et al. **Life Sci** 1985 Aug 19;37(7):599–606

Substance P antagonists and mucociliary activity in rabbit. Lindberg S, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun;329(4):376–81

Multiple tachykinin receptors in guinea pig brain. High densities of substance K (neurokinin A) binding sites in the substantia nigra. Quirion R, et al. **Neuropeptides** 1985 Jun;6(3):191–204

Neuronal sensitivity to substance P is increased after repeated treatment with tranylcypromine, carbamazepine or oxaprotaline, but decreased after repeated electroconvulsive shock. Jones RS, et al. **Neuropharmacology** 1985 Jul;24(7):627–33

Co–localization of calcitonin gene–related peptide–like immunoreactivity with substance P in cutaneous, vascular and visceral sensory neurons of guinea pigs. Gibbins IL, et al. **Neurosci Lett** 1985 Jun 12; 57(2):125–30

Substance K and substance P in the ventral tegmental area. Kalivas PW, et al. **Neurosci Lett** 1985 Jun 24;57(3):241–6

Immunocytochemical localization of substance P in the rat spinal cord with special reference to fibers within the ventral column of the rostral lumbar segments. Uda K, et al. **Neurosci Lett** 1985 Jun 12; 57(2):185–90

Regional distribution of substance P, neurokinin alpha and neurokinin beta in rat central nervous system. Kanazawa I, et al. **Neurosci Res** 1984 Dec;2(1–2):111–20

Distribution of calcitonin gene–related peptide in the rat peripheral nervous system with reference to its coexistence with substance P. Lee Y, et al. **Neuroscience** 1985 Aug;15(4):1227–37

Substance P–containing sensory nerves in the rat iris. Normal distribution, ontogeny and innervation of intraocular iris grafts. Seiger A, et al. **Neuroscience** 1985 Jun;15(2):519–28

Substance P given intrathecally at the spinal T9 level increases adrenal output of adrenaline and noradrenaline in the rat. Yashpal K, et al. **Neuroscience** 1985 Jun;15(2):529–36

Catabolism of gastrin releasing peptide and substance P by gastric membrane–bound peptidases. Bunnett NW, et al. **Peptides (Fayetteville)** 1985 Mar–Apr;6(2):277–83

Capsaicin reduces substance P immunoreactivity in the lateral nucleus of the solitary tract and nodose ganglion. Helke CJ, et al. **Peptides (Fayetteville)** 1985;6 Suppl 1:121–6

Precursor forms of substance P (SP) in nervous tissue: detection with antisera to SP, SP–Gly, and SP–Gly–Lys. Kream RM, et al. **Proc Natl Acad Sci USA** 1985 Jul;82(14):4832–6

Guanine nucleotides regulate [3H]substance P binding in rat small intestine. Smith KE, et al. **Regul Pept** 1985 Aug;11(4):275–85

Verapamil inhibition of the intestinal effects of substance P. Zinner MJ, et al. **Surgery** 1985 Aug;98(2):230–5

Effects of dopamine and substance P infusion on gastric acid secretion in Pavlov and Heidenhain pouched dogs. Ogoshi K, et al. **Tokai J Exp Clin Med** 1984 Aug;9(3):183–90

[Capillary isotachophoresis––a new method in drug analysis. 2. Analytical capillary isotachophoresis of the synthetic peptide substance P] Jannasch R. **Pharmazie** 1985 Jun;40(6):398–403 (Eng. Abstr.) **(Ger)**

[Substance P in the central mechanisms of the escape reaction] Zilov VG, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):6–8 (Eng. Abstr.) **(Rus)**

SUCKING BEHAVIOR

Histidyl–proline–diketopiperazine (cyclo–his–pro) inhibits the suckling– and domperidone–induced transformation of prolactin in the lactating rat. Shyr SW, et al. **Endocrinology** 1985 Nov;117(5):2170–5

SYMPATHOMIMETICS

Effect of gastrin, histamine, serotonin, and adrenergic amines on gastroesophageal sphincter pressure in the dog. Strombeck DR, et al. **Am J Vet Res** 1985 Aug;46(8):1684–90

Beta 1–adrenoceptor selectivity and intrinsic sympathomimetic activity [letter] De Bono GG. **Br J Clin Pharmacol** 1985 Jul;20(1):92

Intrinsic sympathomimetic activity of cardioselective beta–adrenoceptor blockers and effects on renal function. Mackay IG, et al. **Br J Clin Pharmacol** 1985 Sep;20(3):197–203

Effects of adrenergic agonists and cyclic AMP on the short–circuit current across the isolated rabbit iris–ciliary body. Chu TC, et al. **Curr Eye Res** 1985 Apr;4(4):523–9

[The problem of the characterization of butoxamine as a specific antagonist of the metabolic effects of sympathomimetics] Ankermann H. **Biomed Biochim Acta** 1985;44(4):645–8 **(Ger)**

[Effect of cholino– and adrenomimetic substances on B–lymphocyte proliferation in mice during a primary immune response to a protein antigen] Ado AD, et al. **Biull Eksp Biol Med** 1985 Jul;100(7):46–8 (Eng. Abstr.) **(Rus)**

[Interaction of beta–adrenergic agents with the plasma membranes of the myocardium] Chekman IS, et al. **Biull Eksp Biol Med** 1985 Aug; 100(8):208–10 (Eng. Abstr.) **(Rus)**

SYNAPTIC RECEPTORS

Blockade of substance P receptors inhibits non–nicotinic, non–adrenergic colonic contractions induced by stimulation of the lumbar sympathetic nerves to the feline large intestine. Fändriks L, et al. **Acta Physiol Scand** 1985 Aug;124(4):565–71

High–affinity substance P binding sites in rat sympathetic ganglia. Niwa M, et al. **Am J Physiol** 1985 Sep;249(3 Pt 2):H694–7

Displacement of DL–[3H]–2–amino–4–phosphonobutanoic acid ([3H]APB) binding with methyl–substituted APB analogues and glutamate agonists. Robinson MB, et al. **Biochemistry** 1985 May 7; 24(10):2401–5

Selective effects of thiol reagents on the binding sites for imipramine and neurotransmitter amines in the rat brain. Biassoni R, et al. **Br J Pharmacol** 1985 Jun;85(2):447–56

A specific alkylating ligand for phencyclidine (PCP) receptors antagonizes PCP behavioral effects. Contreras PC, et al. **Eur J Pharmacol** 1985 May 20;111(3):405–6

Phencyclidine and sigma opiate receptors in brain: biochemical and autoradiographical differentiation. Gundlach AL, et al. **Eur J Pharmacol** 1985 Jul 31;113(3):465–6

Blocking action of pentobarbital on receptors for excitatory amino acids in the guinea pig hippocampus. Sawada S, et al. **Exp Brain Res** 1985; 59(2):226–31

Pharmacology of neuroleptics in use in the United States. Richelson E. **J Clin Psychiatry** 1985 Aug;46(8 Pt 2):8–14

Elevated density of [3H]imipramine binding in aged human brain. Severson JA, et al. **J Neurochem** 1985 Nov;45(5):1382–9

Multiple tachykinin receptors in guinea pig brain. High densities of substance K (neurokinin A) binding sites in the substantia nigra. Quirion R, et al. **Neuropeptides** 1985 Jun;6(3):191–204

Amitriptylinoxide: receptor–binding profile compared with other antidepressant drugs. Borbe HO, et al. **Pharmacopsychiatry** 1985 Sep; 18(5):314–9

Diazepam administration to mice prevents some of the changes in monoamine–mediated behaviour produced by repeated electroconvulsive shock treatment. Green AR, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):190–3

Guanine nucleotides regulate [3H]substance P binding in rat small intestine. Smith KE, et al. **Regul Pept** 1985 Aug;11(4):275–85

[Effect of chronic psychogenic stress on the characteristics of synaptic membrane receptors in the rat brain] Nikuradze VO, et al. **Biull Eksp Biol Med** 1985 Sep;100(9):275–7 (Eng. Abstr.) **(Rus)**

[Autoradiographic study of the ontogeny of the imipramine receptors in the cerebral cortex of rats] Pirogova MV, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):752–4 (Eng. Abstr.) **(Rus)**

[Mechanism of the modulating effect of met–enkephalin on glutamatergic synaptic transmission] Kuznetsov VI, et al. **Dokl Akad Nauk SSSR** 1985; 282(2):456–9 **(Rus)**

TESTOSTERONE

Selective and/or overlapping effect of pituitary hormones (thyrotropin, gonadotropin) on serum thyroxin and testosterone level in newly hatched cockerels. Dobozy O, et al. **Acta Physiol Hung** 1985; 66(2):177–81

Reversal of the sexually dimorphic distribution of serotonin–immunoreactive fibers in the medial preoptic nucleus by treatment with perinatal androgen. Simerly RB, et al. **Brain Res** 1985 Aug 5;340(1):91–8

Plasma testosterone and catecholamine responses to physical exercise of different intensities in men. Ježová D, et al. **Eur J Appl Physiol** 1985; 54(1):62–6

Testosterone and melatonin effects on adrenal cortex of orchiectomized and pinealectomized rats. Malendowicz LK, et al. **Exp Clin Endocrinol** 1985 Jun;85(3):283–8

Seasonal cycles in testicular activity, gonadotropin, and thyroxine in the painted turtle, Chrysemys picta, under natural conditions. Licht P, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):130–9

Effect of intraventricular injection of 5,6–dihydroxytryptamine on spermatogenesis and plasma testosterone levels in the rat. Das TK, et al. **J Endocrinol** 1985 Sep;106(3):395–400

Testosterone secretion is severely impaired after hepatectomy in rat, dog and man. Sultan C, et al. **J Steroid Biochem** 1985 Jun;22(6):851–3

Effects of delta 9–tetrahydrocannabinol on testosterone production in vitro: influence of Ca++, Mg++ or glucose. Dalterio S, et al. **Life Sci** 1985 Oct 14;37(15):1425–33

Intratesticular regulation of testosterone secretion: comparison of the effects and interactions of hCG, an LHRH agonist and testicular interstitial fluid on Leydig cell testosterone secretion in vitro. Sharpe RM. **Mol Cell Endocrinol** 1985 Jul;41(2–3):247–55

Further studies on the effects of testosterone on hypothalamic LH–RH and serum LH levels: castration–induced delayed response. Kalra PS. **Neuroendocrinology** 1985 Sep;41(3):219–23

THIORIDAZINE

Thioridazine: a selective inhibitor of peroxisomal beta–oxidation in vivo. Van den Branden C, et al. **FEBS Lett** 1985 Aug 5;187(2):331–3

Phenolic metabolites of thioridazine in man. Papadopoulos AS, et al. **Xenobiotica** 1985 Apr;15(4):309–16

[A case of agranulocytosis during treatment with thioridazine] Tuma I, et al. **Cesk Psychiatr** 1985 Apr;81(2):106–9 (Eng. Abstr.) **(Cze)**

THIRST

The effect of captopril on sodium appetite in adrenalectomized and deoxycorticosterone–treated rats. Elfont RM, et al. **J Physiol (Lond)** 1985 Aug;365:1–12

Side–effects of lithium at lower therapeutic levels: the significance of thirst. King JR, et al. **Psychol Med** 1985 May;15(2):355–61

THYROID HORMONES

Relationship between thyroid hormone and body fat in young Japanese. Nakashima T, et al. **Ann Physiol Anthropol** 1984 Apr;3(2):129–31

Thyroid–dependent maturation of neonatal brain but not lung epidermal growth factor receptors. Sadiq HF, et al. **Dev Pharmacol Ther** 1985; 8(5):292–301

Thyroid hormones in rats during long–term cold exposure and hypometabolic effect of reverse triiodothyronine on adrenaline induced thermogenesis. Vybiral S, et al. **Endocrinol Exp (Bratisl)** 1985 Sep; 19(3):179–85

Effects of thyroid hormone deficiency on glial constituents in developing cerebellum of the rat. Granholm AC. **Exp Brain Res** 1985; 59(3):451–6

5'–Flanking DNA of the rat growth hormone gene mediates regulated expression by thyroid hormone. Casanova J, et al. **J Biol Chem** 1985 Sep 25;260(21):11744–8

Role of thyroid function on CNS regeneration. Tator CH. **J Neurosurg Sci** 1984 Jul–Dec;28(3–4):133–5

[Modulation of thyroid hormone synthesis by thyroglobulin] Lissitzky S. **Bull Acad Natl Med (Paris)** 1985 Feb;169(2):261–6 (Eng. Abstr.) **(Fre)**

[Structure and function of thyroid follicular cells––biochemical and histochemical studies on the enzymes related to thyroid hormone synthesis] Matsubara F. **Rinsho Byori** 1985 Apr;33(4):406–20 **(Jpn)**

[Hormonal regulation of anabolic processes and of protein utilization efficiency in the early postnatal period] Adigamov LF, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):687–9 (Eng. Abstr.) **(Rus)**

THYROTROPIN

Effects of eledoisin on thyrotrophin secretion in rats. Mitsuma T, et al. **Acta Endocrinol (Copenh)** 1985 Sep;110(1):90–4

Selective and/or overlapping effect of pituitary hormones (thyrotropin, gonadotropin) on serum thyroxin and testosterone level in newly hatched cockerels. Dobozy O, et al. **Acta Physiol Hung** 1985; 66(2):177–81

Effect of thyrotropin (TSH) treatment on the vitamins A and E and lipid–peroxide status of domestic fowl. Mézes M. **Acta Vet Hung** 1984; 32(3–4):175–80

A novel method of transport for thyroxine (T4), cortisol, thyroid stimulating hormone (TSH), parathormone (PTH), and insulin. Ch'ng SL, et al. **Clin Chim Acta** 1985 Jul 15;149(2–3):253–6

Growth hormone, thyrotropin and prolactin responses to simultaneous administration of human growth hormone–releasing factor and thyrotropin releasing hormone in the bovine. Hodate K, et al. **Endocrinol Jpn** 1985 Jun;32(3):375–83

The effects of growth hormone, prolactin, corticotropin, and thyrotropin on the production and secretion of somatostatin by hypothalamic cells in vitro. Robbins RJ, et al. **Endocrinology** 1985 Aug;117(2):538–43

Effects of TRH and a rat TSH preparation on discrete hypothalamic and forebrain catecholamine nerve terminal networks in the hypophysectomized male rat. Andersson K, et al. **Eur J Pharmacol** 1985 May 20;111(3):295–307

Physalaemin inhibits thyrotropin secretion in rats. Mitsuma T, et al. **Exp Clin Endocrinol** 1985 Jun;85(3):319–25

Thyroid function in adult rough–skinned newts (Taricha granulosa): effects of hypophysectomy and hormone replacement. Specker JL, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):326–31

Effects of various drugs on thyrotropin secretion in rats. Mitsuma T, et al. **Horm Metab Res** 1985 Jul;17(7):337–41

Association of the changes in cytosolic Ca2+ and iodide efflux induced by thyrotropin and by the stimulation of alpha 1–adrenergic receptors in cultured rat thyroid cells. Corda D, et al. **J Biol Chem** 1985 Aug 5;260(16):9230–6

Thyroid indices in panic disorder. Fishman SM, et al. **J Clin Psychiatry** 1985 Oct;46(10):432–3

Effect of immunoneutralization of thyrotrophin–releasing hormone on the release of thyrotrophin and prolactin during suckling or in response to electrical stimulation of the hypothalamus in the anaesthetized rat. Sheward WJ, et al. **J Endocrinol** 1985 Jul;106(1):113–9

Comparison of the ability of thyroxine and triiodothyronine to suppress TRH–induced TSH secretion by perfused rat anterior pituitary fragments. Ikeda H, et al. **Neuroendocrinology** 1985 Jul;41(1):79–82

A nonmitogenic pituitary function of fibroblast growth factor: regulation of thyrotropin and prolactin secretion. Baird A, et al. **Proc Natl Acad Sci USA** 1985 Aug;82(16):5545–9

[Effect of dopaminergic pharmacological agents on thyrotropic hormone secretion by the hypophysis when stimulated with thyrotropin–releasing hormone] Boiadzhieva N, et al. **Eksp Med Morfol** 1985;24(1):29–32 (Eng. Abstr.) **(Bul)**

[Serum thyroxine and thyrotropin in the elderly] Mattila KS, et al. **Duodecim** 1985;101(14):1375–9 (Eng. Abstr.) **(Fin)**

THYROXINE

Post–natal thyroid function in low birth weight infants; a longitudinal assessment of free thyroxine and thyroid hormone binding globulin. Hirano T, et al. **Acta Endocrinol (Copenh)** 1985 Sep;110(1):56–60

Thyrotrophin–releasing hormone (TRH) and hormone secretion from the follicular and C–cells of perfused dog thyroid lobes. Iversen E, et al. **Acta Endocrinol (Copenh)** 1985 Aug;109(4):499–504

Acquisition of urine, kidney and submandibular gland epidermal growth factor responsiveness to thyroxine administration in neonatal mice. Lakshmanan J, et al. **Acta Endocrinol (Copenh)** 1985 Aug; 109(4):511–6

Selective and/or overlapping effect of pituitary hormones (thyrotropin, gonadotropin) on serum thyroxin and testosterone level in newly hatched cockerels. Dobozy O, et al. **Acta Physiol Hung** 1985; 66(2):177–81

Management of a child with acute thyroxine ingestion. Roesch C, et al. **Ann Emerg Med** 1985 Nov;14(11):1114–5

Thyroxine bioequivalency [letter] **Ann Intern Med** 1985 Oct; 103(4):646–7

A novel method of transport for thyroxine (T4), cortisol, thyroid stimulating hormone (TSH), parathormone (PTH), and insulin. Ch'ng SL, et al. **Clin Chim Acta** 1985 Jul 15;149(2–3):253–6

Minimal metabolism, summit metabolism and plasma thyroxine in rodents from different environments. Hulbert AJ, et al. **Comp Biochem Physiol** [A] 1985;81(3):687–93

Protein utilization in growth: effect of lysine deficiency on serum growth hormone, somatomedins, insulin, total thyroxine (T4) and triiodothyronine, free T4 index, and total corticosterone. Cree TC, et al. **Endocrinology** 1985 Aug;117(2):667–73

Evidence for induction by thyroid hormone of cytosolic proteins which control mitochondrial protein synthesis. Ichikawa K, et al. **Endocrinology** 1985 Nov;117(5):1749–58

Seasonal cycles in testicular activity, gonadotropin, and thyroxine in the painted turtle, Chrysemys picta, under natural conditions. Licht P, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):130–9

Immunofluorescent detection and localization of thyroxine in blood of Rana catesbeiana from early larval through metamorphic stages. Piotrowski DC, et al. **Gen Comp Endocrinol** 1985 Jul;59(1):82–90

Thyroid function in adult rough–skinned newts (Taricha granulosa): effects of hypophysectomy and hormone replacement. Specker JL, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):326–31

Thyroid indices in panic disorder. Fishman SM, et al. **J Clin Psychiatry** 1985 Oct;46(10):432–3

An enzyme–linked immunosorbent assay for thyroxine in dried blood spotted on filter paper. Maeda M, et al. **J Immunol Methods** 1985 Sep 3;82(1):83–9

Thyroxine analogue assay kits in clinical medicine [letter] **Lancet** 1985 Oct 5;2(8458):781–2

Binding protein variation and free thyroxine assay, and effect of venous stasis [letter] France NC, et al. **Lancet** 1985 Oct 5;2(8458):782–3

Free thyroxine assays: analogue methods [letter] Wilkins TA. **Lancet** 1985 Oct 19;2(8460):884

Cerebral myelinogenesis in the Snell dwarf mouse: stimulatory effects of GH and T4 restricted to the first 20 days of postnatal life. Sugisaki T, et al. **Neurochem Res** 1985 Jun;10(6):767–78

Neonatal levels of plasma thyroxine in male and female calves fed a colostrum or immunoglobulin diet or fasted for the first 28 hours of life. Grongnet JF, et al. **Reprod Nutr Dev** 1985;25(3):537–43

[Serum thyroxine and thyrotropin in the elderly] Mattila KS, et al. **Duodecim** 1985;101(14):1375–9 (Eng. Abstr.) **(Fin)**

[Action of thyroxine on the cytochrome content in the brain and liver mitochondria during the postnatal development of rats] Khamidov DKh, et al. **Biull Eksp Biol Med** 1985 Jun;99(6):696–7 (Eng. Abstr.) **(Rus)**

[Correlation between the thyroxine, 17–beta–estradiol and luteinizing hormones in the systemic circulation and the rectal and vaginal temperature in heifers and cows after administration of cloprostenol] Elečko J, et al. **Vet Med (Praha)** 1985 May;30(5):257–66 (Eng. Abstr.) **(Slo)**

TIME PERCEPTION

[Schizophrenically disordered time perception and its modification by neuroleptics] Heim M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Jul;37(7):410–5 (Eng. Abstr.) **(Ger)**

TRANQUILIZING AGENTS

[Treatment of vegetovascular dystonia with beta–blockaders and tranquilizers] Zubarev IuG, et al. **Sov Med** 1985;(3):82–5 **(Rus)**

[Development of passivity in the rat: effect of tranquilizers and antidepressants] Khonicheva NM, et al. **Zh Vyssh Nerv Deiat** 1985 Mar–Apr;35(2):339–47 (Eng. Abstr.) **(Rus)**

[Hypo–salivation and tranquilizers] Montana Ramonet JM. **Rev Esp Estomatol** 1984 Nov–Dec;32(6):407–20 **(Spa)**

TRANQUILIZING AGENTS, MAJOR

An open multicentre study of the treatment of florid schizophrenia with remoxipride. McCreadie RG, et al. **Acta Psychiatr Scand** 1985 Aug; 72(2):139–43

A treatment trial with an analog of thyrotropin–releasing hormone (DN–1417) in schizophrenia. Mizuki Y, et al. **Biol Psychiatry** 1985 Sep; 20(9):1030–5

Neuroleptics, lithium and renal function. Waller DG, et al. **Br J Psychiatry** 1985 May;146:510–4

Prediction of response to neuroleptic drug therapy in schizophrenia. Awad AG. **Can J Psychiatry** 1985 Jun;30(4):241–2

Early subjective response and prediction of outcome to neuroleptic drug therapy in schizophrenia. Hogan TP, et al. **Can J Psychiatry** 1985 Jun; 30(4):246–8

Clinical and demographic correlates of neuroleptic response. Seeman MV. **Can J Psychiatry** 1985 Jun;30(4):243–5

Prediction of treatment response in schizophrenia: clinical use of neuroleptic blood levels. Tang SW. **Can J Psychiatry** 1985 Jun; 30(4):249–50

Long–acting neuroleptics: technique for intramuscular injection. Bélanger–Annable MC. **Can Nurse** 1985 Sep;81(8):41–3

In vitro thiomethylation. Studies with flumezapine. Sullivan HR, et al. **Drug Metab Dispos** 1985 May–Jun;13(3):276–8

Multidimensional study of the outcome of schizophrenic patients 1 year after clinic discharge. Predictors and influence of neuroleptic treatment. Gaebel W, et al. **Eur Arch Psychiatry Neurol Sci** 1985;235(1):45–52

Interaction of SCH 23390, a D–1–selective antagonist, with the anterior pituitary D–2 receptors and prolactin secretion in the rat. Apud JA, et al. **Eur J Pharmacol** 1985 Jun 7;112(2):187–93

SCH–23390 antagonism of a D–2 dopamine agonist depends upon catecholaminergic neurons. Breese GR, et al **Eur J Pharmacol** 1985 Jul 11;113(1):109–14

Antagonism of the amphetamine cue by both classical and atypical antipsychotic drugs. Nielsen EB, et al. **Eur J Pharmacol** 1985 May 8; 111(2):167–76

Antipsychotic drugs depress acetylcholine release in the Torpedo electric organ, a purely cholinergic system. Schaller–Clostre F, et al. **Eur J Pharmacol** 1985 May 28;112(1):27–37

Effects of iminodibenzyl antipsychotic drugs on cerebral dopamine and alpha–adrenergic receptors. Setoguchi M, et al. **Eur J Pharmacol** 1985 Jun 19;112(3):313–22

Clonidine sensitizes mice for apomorphine–induced stereotypic gnawing: antagonism by neuroleptics and cholecystokinin–like peptides. Zetler G. **Eur J Pharmacol** 1985 May 20;111(3):309–18

Differential effects of some predominantly antiadrenergic and antidopaminergic neuroleptics on the preovulatory surge of FSH, LH and prolactin in rat. Kun I, et al. **Exp Clin Endocrinol** 1985 Jun; 85(3):269–75

Relationship between gas chromatographic behaviour and topological, physicochemical, and quantum chemically calculated charge parameters for neuroleptica. Buydens L, et al. **J Chromatogr Sci** 1985 Jul; 23(7):304–7

Antipsychotic or neuroleptic? [letter] Dove MJ. **J Clin Psychiatry** 1985 Oct;46(10):454–5

Pharmacology of neuroleptics in use in the United States. Richelson E. **J Clin Psychiatry** 1985 Aug;46(8 Pt 2):8–14

Neuroleptic drug monitoring and radioreceptor assays [editorial] Cooper TB. **J Clin Psychopharmacol** 1985 Oct;5(5):A15–6

The strategy and value of neuroleptic drug monitoring. Curry SH. **J Clin Psychopharmacol** 1985 Oct;5(5):263–71 (56 ref.)

On the clinical relevance and methods of quantification of plasma concentrations of neuroleptics. Ko GN, et al. **J Clin Psychopharmacol** 1985 Oct;5(5):253–62 (49 ref.)

Mesolimbic dopamine function is not altered during continuous chronic treatment of rats with typical or atypical neuroleptic drugs. Rupniak NM, et al. **J Neural Transm** 1985;62(3–4):249–66

Binding of [3H]SCH23390 in rat brain: regional distribution and effects of assay conditions and GTP suggest interactions at a D1–like dopamine receptor. Schulz DW, et al. **J Neurochem** 1985 Nov;45(5):1601–11

Dopamine D2 receptors selectively labeled by a benzamide neuroleptic: [3H]–YM–09151–2. Niznik HB, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Jun;329(4):333–43

Electrophysiological interactions between haloperidol and reduced haloperidol, and dopamine, norepinephrine and phencyclidine in rat brain. Kirch DG, et al. **Neuropharmacology** 1985 May;24(5):375–9

The effect of milenperone on the aggressive behavior of psychogeriatric patients. A double–blind placebo–controlled study. De Cuyper H, et al. **Neuropsychobiology** 1985;13(1–2):1–6

A rapid and simple behavioural screening method for simultaneous assessment of limbic and striatal blocking effects of neuroleptic drugs. Ljungberg T, et al. **Pharmacol Biochem Behav** 1985 Sep; 23(3):479–85

Discriminative stimulus properties and schedule effects of fencamfamine in rats. Risner ME, et al. **Pharmacol Biochem Behav** 1985 Sep; 23(3):449–56

Distribution and excretion of 3H–dapiprazole in the rat. Valeri P, et al. **Pharmacol Res Commun** 1985 May;17(5):417–24

High–dose versus low–dose strategies in the treatment of schizophrenia. Kane JM, et al. **Psychopharmacol Bull** 1985;21(3):533–7

Effect of neuroleptic treatments on attention, information processing, and thought disorder. Spohn HE, et al. **Psychopharmacol Bull** 1985; 21(3):582–7

An open study of remoxipride, a benzamide derivative, in schizophrenia. Lindström L, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):241–3

Negative and deficit symptoms in schizophrenia do respond to neuroleptics. Goldberg SC. **Schizophr Bull** 1985;11(3):453–6

Informed consent in psychiatric research: preliminary findings from an ongoing investigation. Benson PR, et al. **Soc Sci Med** 1985; 20(12):1331–41

[Changes in the CSF levels of monoamine metabolites in 102 chronic schizophrenic patients following probenecid before and after neuroleptic medication] Chen YF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1984 Oct; 17(5):273–7 (Eng. Abstr.) **(Chi)**

[Administration of maintenance therapy in endogenous psychoses in out–patient practice] Mrňa B, et al. **Cesk Psychiatr** 1985 Aug; 81(4):273–5 (Eng. Abstr.) **(Cze)**

[Clinical effectiveness of isofloxythepin––an open study] Zapletálek M, et al. **Cesk Psychiatr** 1985 Aug;81(4):242–6 (Eng. Abstr.) **(Cze)**

[Technics for intramuscular injections of delayed–action neuroleptics] Bélanger–Annable MC. **Infirm Can** 1985 Sep;27(8):26–9 **(Fre)**

[A study on application of the function of maintaining concentration (TAF) for chronic schizophrenia] Okamoto Y, et al. **Hokkaido Igaku Zasshi** 1985 May;60(3):445–9 (Eng. Abstr.) **(Jpn)**

[Neuroleptics in pregnancy (letter)] Karniol IG, et al. **Rev Paul Med** 1985 Jan–Feb;103(1):46 **(Por)**

[Effect of neurotropic drugs on calmodulin and troponin C–dependent processes] Baldenkov GN, et al. **Biokhimiia** 1985 Jul;50(7):1141–50 (Eng. Abstr.) **(Rus)**

[Effect of carbidine on the dopamine and serotonin receptors of the central nervous system] Zharkovskii AM, et al. **Biull Eksp Biol Med** 1985 Jun; 99(6):700–2 (Eng. Abstr.) **(Rus)**

[Malignant hyperthermia caused by neuroleptics] Escolano Villén F, et al. **Rev Esp Anestesiol Reanim** 1985 Jul–Aug;32(4):189–91 (Eng. Abstr.) **(Spa)**

TRANQUILIZING AGENTS, MINOR

Depression and anxiety: mianserin and nomifensine compared in a double–blind multicentre trial. Granier F, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:67–74

Chronic anxiolytic treatment: benefit and risk. Marks J. **Adv Biochem Psychopharmacol** 1985;40:173–83

Selective interaction of novel anxiolytics with 5–hydroxytryptamine1A receptors. Peroutka SJ. **Biol Psychiatry** 1985 Sep;20(9):971–9

The psychological effects of buspirone. Bond A. **Br J Clin Pract [Symp Suppl]** 1985 May;38:83–90

The pharmacological treatment of anxiety. Jenner FA, et al. **Br J Clin Pract [Symp Suppl]** 1985 May;38:48–52

Clinical profile of buspirone. Knapp JE. **Br J Clin Pract [Symp Suppl]** 1985 May;38:95–9

The risk of pharmacological dependence with buspirone. Tyrer P, et al. **Br J Clin Pract [Symp Suppl]** 1985 May;38:91–4

Buspirone: a new type of anxiolytic. Dommisse CS, et al. **Drug Intell Clin Pharm** 1985 Sep;19(9):624–8 (28 ref.)

The non-sedating anxiolytic CGS 9896 produces discriminative stimuli that may be related to an anxioselective effect. Bennett DA. **Life Sci** 1985 Aug 26;37(8):703–9

Metoprolol, a new selective beta-blocker in anxiety neurosis. Chaturvedi SK. **Psychopharmacology (Berlin)** 1985;85(4):488

Studies on the suanzaorentang in the treatment of anxiety. Chen HC, et al. **Psychopharmacology (Berlin)** 1985;85(4):486–7

Midazolam cue in rats: generalization tests with anxiolytic and other drugs. Garcha HS, et al. **Psychopharmacology (Berlin)** 1985;87(2):233–7

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: choice behaviour in the T-maze. Quintero S, et al. **Psychopharmacology (Berlin)** 1985;86(3):328–33

TRANYLCYPROMINE

Neuronal sensitivity to substance P is increased after repeated treatment with tranylcypromine, carbamazepine or oxaprotaline, but decreased after repeated electroconvulsive shock. Jones RS, et al. **Neuropharmacology** 1985 Jul;24(7):627–33

TRIAZOLAM

Comment: Triazolam-cimetidine reaction [letter] Greenblatt DJ. **Drug Intell Clin Pharm** 1985 Sep;19(9):679

Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. Pourbaix S, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Aug;23(8):447–51

Effects of diazepam and triazolam on auditory and visual thresholds and reaction times in the baboon. Lukas SE, et al. **Psychopharmacology (Berlin)** 1985;87(2):167–72

[Further data on the detection of triazolam (Halcion) and its main metabolites] Schütz H. **Beitr Gerichtl Med** 1985;43:465–7 (Eng. Abstr.) **(Ger)**

TRIFLUOPERAZINE

Inhibitors of calcium-dependent enzymes prevent the onset of afterdischarge in the peptidergic bag cell neurons of Aplysia. DeRiemer SA, et al. **Brain Res** 1985 Aug 5;340(1):175–80

Effect of trifluoperazine on DNA synthesis during liver regeneration. Soriano M, et al. **Cell Tissue Kinet** 1985 Sep;18(5):475–81

Modulation of the digestive lysosomal system in Paramecium caudatum. II. Physiological effects of cytochalasin B, colchicine and trifluoperazine. Fok AK, et al. **Eur J Cell Biol** 1985 May;37:27–34

Crystallization of calcium-calmodulin-trifluoperazine complex and an attempt at crystallizing calcium-free calmodulin. Kawasaki H, et al. **J Biochem (Tokyo)** 1985 Jun;97(6):1815–8

Effects of trifluoperazine on calcium binding by calmodulin. A microcalorimetric study. Tanokura M, et al. **J Biol Chem** 1985 Jul 25; 260(15):8680–2

Inhibition of epidermal growth factor-induced phosphorylation by trifluoperazine. Ross AH, et al. **J Cell Physiol** 1985 Sep; 124(3):499–506

Prostaglandin output from the early pregnant rat uterus superfused in vitro, and the effect of A23187 and trifluoperazine. Poyser NL. **J Reprod Fertil** 1985 May;74(1):271–7

Effects of discontinuous drug administration on the development of dopamine receptor supersensitivity during chronic trifluoperazine or cis-flupenthixol administration to rats. Murugaiah K, et al. **Psychopharmacology (Berlin)** 1985;86(1–2):228–32

Studies on the effect of platelet inhibitors on platelet adhesion to collagen and collagen-induced human platelet activation. Krishnamurthi S, et al. **Thromb Haemost** 1985 Jun 24;53(3):337–42

Effects of trifluoperazine on platelet activation. Ardlie NG, et al. **Thromb Res** 1985 Jun 15;38(6):695–706

TRIMEPRAZINE

Radioimmunoassay for trimeprazine in human plasma. McKay G, et al. **J Pharmacol Methods** 1984 Oct;12(3):203–11

TRYPTAMINES

Effects of benzene and pyridine on the concentration of mouse striatal tryptamine and 5-hydroxytryptamine. Juorio AV, et al. **Biochem Pharmacol** 1985 Oct 15;34(20):3774–6

Analysis of the cardiovascular responses to central injection of tryptamine in rats. Krstić MK, et al. **Neuropharmacology** 1985 Jun;24(6):517–25

TRYPTOPHAN

The effects of dietary neurotransmitter precursors on human behavior. Lieberman HR, et al. **Am J Clin Nutr** 1985 Aug;42(2):366–70

Use of L-tryptophan in treating bulimia [letter] Krahn D, et al. **Am J Psychiatry** 1985 Sep;142(9):1130

Disturbances of tryptophan metabolism in mice acutely deprived of tryptophan. Jones ML, et al. **Ann Nutr Metab** 1985;29(4):209–15

A comparison of the cyclic nucleotide-dependent protein kinases using chemical cleavage at tryptophan and cysteine. Monken CE, et al. **Arch Biochem Biophys** 1985 Aug 1;240(2):888–903

Tryptophan imaging of membrane proteins. Kleinfeld AM. **Biochemistry** 1985 Apr 9;24(8):1874–82

Increased total activity in the rat after L-tryptophan plus the monoamine oxidase-A inhibitor amiflamine but not after L-tryptophan plus clorgyline. Archer T, et al. **Br J Pharmacol** 1985 Jul;85(3):581–90

The effect of tryptophan on biogenic amines in the hepatic portal circulation of the dog. Hussain MN, et al. **Can J Physiol Pharmacol** 1985 Jul;63(7):863–6

Fluorescence studies on tryptophan and sulfhydryl group changes of bovine lens crystallins in a photodynamic system. Andley UP, et al. **Curr Eye Res** 1985 Aug;4(8):831–42

Maturation of Escherichia coli tryptophan operon mRNA: evidence for 3' exonucleolytic processing after rho-dependent termination. Mott JE, et al. **EMBO J** 1985 Jul;4(7):1887–91

Tyrosine-to-tryptophan energy transfer and the structure of calf gamma-II crystallin. Borkman RF, et al. **Exp Eye Res** 1985 Jun; 40(6):819–26

A temperature dependent transition in the Pribnow box of the trp promoter. Lefevre JF, et al. **FEBS Lett** 1985 Oct 7;190(1):37–40

Successful nicotinamide treatment in an autosomal dominant behavioral and psychiatric disorder. Blom W, et al. **J Inherited Metab Dis** 1985; 8 Suppl 2:107–8

Effect of L-tryptophan on electroconvulsive therapy seizure time. Price WA, et al. **J Nerv Ment Dis** 1985 Oct;173(10):636–8

Could supplementary dietary tryptophan prevent sudden infant death syndrome? Maurizi CP. **Med Hypotheses** 1985 Jun;17(2):149–54

Pharmacological studies on the serotoninergic and nonserotonin-mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pretreatment with fluoxetine, indalpine, PCPA, and L-tryptophan. Van de Kar LD, et al. **Neuroendocrinology** 1985 Oct; 41(4):283–8

Transport systems and enzymes involved in the metamorphosis of tryptophan into serotonin. Baumann P. **Pharmacopsychiatry** 1985 Mar; 18(2):188–92

The effect of pH on the aerobic and anaerobic photolysis of tryptophan and some tryptophan-containing dipeptides. Hibbard LB, et al. **Photochem Photobiol** 1985 Aug;42(2):99–106

Tryptophanyl fluorescence quenching of urocanase from Pseudomonas putida by acrylamide, cesium, iodide, and imidazolepropionate. O'Donnell PS, et al. **Photochem Photobiol** 1985 Aug;42(2):107–12

On gut membrane transport of tryptophan in the germfree mouse. Phillips AW. **Prog Clin Biol Res** 1985;181:81–5

[Chemical modification of tryptophan residues of leucyl tRNA synthetase by N-bromosuccinimide and 2-hydroxy-5-nitrobenzyl bromide] Korneliuk AI, et al. **Bioorg Khim** 1985 May;11(5):605–12 (Eng. Abstr.) **(Rus)**

[Tryptophan operon of methylotrophic facultative Pseudomonas sp. M bacteria. I. Isolation and characterization of auxotrophic Trp-mutants] Olekhnovich IN, et al. **Genetika** 1985 Jul;21(7):1099–104 (Eng. Abstr.) **(Rus)**

TRYPTOPHAN HYDROXYLASE

Regulatory properties of phenylalanine, tyrosine and tryptophan hydroxylases. Kaufman S. **Biochem Soc Trans** 1985 Apr;13(2):433–6

TYROSINE

The effects of dietary neurotransmitter precursors on human behavior. Lieberman HR, et al. **Am J Clin Nutr** 1985 Aug;42(2):366–70

Utilization of N-acetyl-L-tyrosine and glycyl-L-tyrosine during long-term parenteral nutrition in the growing rat. Neuhäuser M, et al. **Am J Clin Nutr** 1985 Oct;42(4):585–96

Effect of cocaine dependence on plasma phenylalanine and tyrosine levels and on urinary MHPG excretion. Tennant FS Jr. **Am J Psychiatry** 1985 Oct;142(10):1200–1

A simple and rapid method of quantitative analysis of phosphoamino acids by high-performance liquid chromatography. Morrice N, et al. **Anal Biochem** 1985 Jul;148(1):207–12

Protein-tyrosine kinases. Hunter T, et al. **Annu Rev Biochem** 1985; 54:897–930 (239 ref.)

Chorismate mutase-prephenate dehydrogenase from Escherichia coli: cooperative effects and inhibition by L-tyrosine. Christopherson RI.

Arch Biochem Biophys 1985 Aug 1;240(2):646–54

Chemical modification of liquefying alpha–amylase: role of tyrosine residues at its active center. Kochhar S, et al. **Arch Biochem Biophys** 1985 Aug 1;240(2):757–67

Purification of the catalytically active phosphorylated form of insulin receptor kinase by affinity chromatography with O–phosphotyrosyl–binding antibodies. Pang DT, et al. **Arch Biochem Biophys** 1985 Oct;242(1):176–86

A semisynthetic bovine pancreatic ribonuclease containing a unique nitrotyrosine residue. Sasaki DM, et al. **Arch Biochem Biophys** 1985 Aug 15;241(1):132–40

Introduction of the dansyl group into histidine and tyrosine residues in peptides and proteins. Buchta R, et al. **Biochem Biophys Res Commun** 1985 Jul 16;130(1):350–7

m–Fluorotyrosine substitution in beta–galactosidase; evidence for the existence of a catalytically active tyrosine. Ring M, et al. **Biochem Biophys Res Commun** 1985 Sep 16;131(2):675–80

Protein–bound glycogen is linked to tyrosine residues. Aon MA, et al. **Biochem J** 1985 Jul 1;229(1):269–72

1H n.m.r. studies of insulin. Assignment of resonances and properties of tyrosine residues. Bradbury JH, et al. **Biochem J** 1985 Aug 1; 229(3):731–7

Effect of metal ions on the kinetics of tyrosine oxidation catalysed by tyrosinase. Palumbo A, et al. **Biochem J** 1985 Jun 15;228(3):647–51

Observation of tyrosine–O–phosphate in Drosophila melanogaster larvae by 31P–NMR spectroscopy. Moore RR, et al. **Biochim Biophys Acta** 1985 Sep 30;846(3):394–7

The intrinsic tyrosine fluorescence of histone H1. Steady state and fluorescence decay studies reveal heterogeneous emission. Libertini LJ, et al. **Biophys J** 1985 Jun;47(6):765–72

Synthesis and characterization of six sequential polypeptides containing tyrosine, glutamic acid, alanine, and glycine by circular dichroism and difference spectroscopy. Zeiger AR, et al. **Biopolymers** 1985 Jul; 24(7):1215–32

Interaction of tyrosine residues with the chromophore in bacteriorhodopsin. Takeda K, et al. **Biosci Rep** 1985 Jul;5(7):615–23

Modification of the effects of repetitive restraint stress on brain biogenic amines by L–tyrosine. Quirce CM, et al. **Chung Kuo Yao Li Hsueh Pao** 1984 Dec;5(4):226–8

Vinculin and 36 kDa protein are not tyrosine–phosphorylated in Rous sarcoma virus infected cells which have been treated with interferon. Strube W, et al. **Eur J Cell Biol** 1985 Sep;38(2):226–33

Tyrosine–to–tryptophan energy transfer and the structure of calf gamma–II crystallin. Borkman RF, et al. **Exp Eye Res** 1985 Jun; 40(6):819–26

Structure and function of human C5a anaphylatoxin. Selective modification of tyrosine 23 alters biological activity but not antigenicity. Johnson RJ, et al. **J Biol Chem** 1985 Aug 25;260(18):10339–45

Affinity labeling of a tyrosine residue in the ATP binding site of the recA protein from Escherichia coli with 5'–p–fluorosulfonylbenzoyladenosine. Knight KL, et al. **J Biol Chem** 1985 Aug 25;260(18):10177–84

Tyrosine 264 in the recA protein from Escherichia coli is the site of modification by the photoaffinity label 8–azidoadenosine 5'–triphosphate. Knight KL, et al. **J Biol Chem** 1985 Aug 25; 260(18):10185–91

Biopterin, neopterin and tyrosine responses to combined oral phenylalanine and tetrahydrobiopterin loading tests in two normal children and in a girl with partial biopterin deficiency. Lykkelund C, et al. **J Inherited Metab Dis** 1985;8 Suppl 2:95–6

Deuterium isotope effect in the transamination of p–tyrosine by rat liver tyrosine transaminase. Yu PH, et al. **Life Sci** 1985 Oct 7; 37(14):1287–91

Comparison of the ability of thyroxine and triiodothyronine to suppress TRH–induced TSH secretion by perfused rat anterior pituitary fragments. Ikeda H, et al. **Neuroendocrinology** 1985 Jul;41(1):79–82

Dietary D–tyrosine as an antimetabolite in mice. **Nutr Rev** 1985 May; 43(5):156–8 (14 ref.)

(Glu62, Ala30, Tyr8)n serves as high–affinity substrate for tyrosylprotein sulfotransferase: a Golgi enzyme. Lee RW, et al. **Proc Natl Acad Sci USA** 1985 Sep;82(18):6143–7

Phosphotyrosine–containing proteins are concentrated in focal adhesions and intercellular junctions in normal cells. Maher PA, et al. **Proc Natl Acad Sci USA** 1985 Oct;82(19):6576–80

[Synthesis of tyrosine and 3,4–dihydroxyphenylalanine by Citrobacter freundii bacteria from lactic acid] Kupletskaia MB. **Prikl Biokhim Mikrobiol** 1985 May–Jun;21(3):342–8 (Eng. Abstr.) **(Rus)**

TYROSINE AMINOTRANSFERASE

A new glucocorticoid receptor species: relation to induction of tryptophan dioxygenase by glucocorticoids. Hirota T, et al. **Endocrinology** 1985 Nov;117(5):1788–95

Effect of selective parasympathetic denervation on the daily rhythm of tyrosine transaminase in the rat liver. Magni F, et al. **J Auton Nerv Syst** 1985 Jul;13(3):245–54

Complete complementary DNA of rat tyrosine aminotransferase messenger RNA. Deduction of the primary structure of the enzyme. Grange T, et al. **J Mol Biol** 1985 Jul 20;184(2):347–50

Isolation, characterization and chromosomal mapping of the mouse tyrosine aminotransferase gene. Müller G, et al. **J Mol Biol** 1985 Aug 5;184(3):367–73

Deuterium isotope effect in the transamination of p–tyrosine by rat liver tyrosine transaminase. Yu PH, et al. **Life Sci** 1985 Oct 7; 37(14):1287–91

[Inhibitory effect of progesterone on the stimulation of tryptophan pyrrolase and tyrosine aminotransferase by endogenous corticosteroids in the liver of female rats] Németh S, et al. **Bratisl Lek Listy** 1985 Jul;84(1):3–10 (Eng. Abstr.) **(Slo)**

TYROSINE HYDROXYLASE

Activation of tyrosine hydroxylase in the central nervous system by anaerobiosis. Pastuszko A, et al. **Biochem Pharmacol** 1985 Aug 15; 34(16):2975–82

Regulatory properties of phenylalanine, tyrosine and tryptophan hydroxylases. Kaufman S. **Biochem Soc Trans** 1985 Apr;13(2):433–6

Homology between phenylalanine and tyrosine hydroxylases reveals common structural and functional domains. Ledley FD, et al. **Biochemistry** 1985 Jul 2;24(14):3389–94

Trans–synaptic increase in RNA coding for tyrosine hydroxylase in a rat sympathetic ganglion. Black IB, et al. **Brain Res** 1985 Jul 22; 339(1):151–3

Evidence for specific immunolysis of nerve terminals using antisera against choline acetyltransferase, glutamate decarboxylase and tyrosine hydroxylase. Docherty M, et al. **Brain Res** 1985 Jul 22; 339(1):105–13

Changes in tyrosine hydroxylase, glutamic acid decarboxylase and choline acetyltransferase after local microinoculation of scrapie agent into the nigrostriatal system of the golden hamster. Durand–Gorde JM, et al. **Brain Res** 1985 Aug 26;341(2):243–51

Long–term regulation of tyrosine hydroxylase activity in the superior cervical ganglion in organ culture: effects of nerve stimulation and dexamethasone. Ip NY, et al. **Brain Res** 1985 Jul 8;338(1):61–70

Coexistence of immunoreactivities for glutamate decarboxylase and tyrosine hydroxylase in some neurons in the periglomerular region of the rat main olfactory bulb: possible coexistence of gamma–aminobutyric acid (GABA) and dopamine. Kosaka T, et al. **Brain Res** 1985 Sep 16; 343(1):166–71

Tyrosine hydroxylase immunohistochemistry fails to demonstrate dopaminergic interplexiform cells in the turtle retina. Nguyen–Legros J, et al. **Brain Res** 1985 Jul 29;339(2):323–8

SCH 23390, a selective D1 dopamine receptor blocker, enhances the firing rate of nigral dopaminergic neurons but fails to activate striatal tyrosine hydroxylase. Onali P, et al. **Brain Res** 1985 Aug 5;340(1):1–7

Identification of dopamine–containing cell bodies in the dorsal and median raphe nuclei of the rat brain using tyrosine hydroxylase immunochemistry. Trulson ME, et al. **Brain Res Bull** 1985 Aug; 15(2):229–34

Direct effects of adrenocorticotropic hormone on bovine adrenomedullary cells: adenosine 3',5'–monophosphate–dependent phosphorylation of tyrosine hydroxylase. Michener ML, et al. **Endocrinology** 1985 Aug; 117(2):730–7

Presynaptic dopamine and serotonin receptors modulating tyrosine hydroxylase activity in synaptosomes of the nucleus accumbens of rats. Hetey L, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):1–10

Genes for neurotransmitter synthesis, storage, and uptake. Joh TH, et al. **Fed Proc** 1985 Sep;44(12):2773–9

Nerve growth factor and other agents mediate phosphorylation and activation of tyrosine hydroxylase. A convergence of multiple kinase activities. McTigue M, et al. **J Biol Chem** 1985 Jul 25; 260(15):9047–56

The fine structural organization of tyrosine hydroxylase immunoreactive neurons in rat arcuate nucleus. Piotte M, et al. **J Comp Neurol** 1985 Sep 1;239(1):44–53

Study of dopamine turnover by monitoring the decline of dopamine metabolites in rat CSF after alpha–methyl–p–tyrosine. Mignot E, et al. **J Neurochem** 1985 Nov;45(5):1527–33

Elevation of RNA coding for tyrosine hydroxylase in rat adrenal gland by reserpine treatment and exposure to cold. Tank AW, et al. **J Neurochem** 1985 Oct;45(4):1030–3

Genetic effects and sexual dimorphism in tyrosine hydroxylase activity in two mouse strains and their reciprocal F1 hybrids. Vadász C, et al. **J Neurogenet** 1985 Jun;2(3):219–30

Regulation of the concentration of adenosine 3',5'–cyclic monophosphate and the activity of tyrosine hydroxylase in the rat superior cervical ganglion by three neuropeptides of the secretin family. Ip NY, et al. **J Neurosci** 1985 Jul;5(7):1947–54

Coexistence of growth hormone releasing factor–like and tyrosine hydroxylase–like immunoreactivities in neurons of the rat arcuate nucleus. Okamura H, et al. **Neuroendocrinology** 1985 Aug; 41(2):177–9

Simultaneous ultrastructural localization of cholecystokinin– and tyrosine hydroxylase-like immunoreactivity in nerve fibers of the rat nucleus accumbens. Loopuijt LD, et al. **Neurosci Lett** 1985 May 23; 56(3):329–34

Morphology and distribution of tyrosine hydroxylase-like immunoreactive neurons in the cat retina. Oyster CW, et al. **Proc Natl Acad Sci USA** 1985 Sep;82(18):6335–9

VANILMANDELIC ACID

The in vivo effects of prostaglandin F2 alpha and prostaglandin E2 on rat urinary excretion of vanillylmandelic acid. Yamada K, et al. **Res Commun Chem Pathol Pharmacol** 1985 Jul;49(1):137–40

Analysis of vanillylmandelic and homovanillic acids in urine using solid phase sample preparation and high pressure liquid chromatography with electrochemical detection. Bremmelgaard A. **Scand J Clin Lab Invest** 1985 Sep;45(5):387–91

VASOPRESSINS

Effect of norepinephrine and vasopressin on renal kallikrein excretion in rats. Martinez Seeber A, et al. **Arch Int Physiol Biochim** 1985 Jun; 93(2):83–8

Salt-dependent structural changes of neurohormones: lithium ions induce conformational rearrangements of ocytocin to a vasopressin-like structure. Rholam M, et al. **Biochemistry** 1985 Jun 18;24(13):3345–9

Coexistence of vasopressin, neurophysin and noradrenaline immunoreactivity in medium-sized cells of the locus coeruleus and subcoeruleus in the rat. Caffé AR, et al. **Brain Res** 1985 Jul 8; 338(1):160–4

Renal nerve stimulation causes alpha 1-adrenoceptor-mediated sodium retention but not alpha 2-adrenoceptor antagonism of vasopressin. Smyth DD, et al. **Circ Res** 1985 Aug;57(2):304–11

Augmentation of the response to CRF in man: relative contributions of endogenous angiotensin and vasopressin. Milsom SR, et al. **Clin Endocrinol (Oxf)** 1985 May;22(5):623–9

Effect of substances influencing brain serotonergic transmission on plasma vasopressin levels in the rat. Iovino M, et al. **Eur J Pharmacol** 1985 Jul 11;113(1):99–103

Inhibition of the hydro-osmotic response to vasopressin and hypertonicity by phenothiazines and W7, calmodulin antagonists. Yorio T, et al. **Gen Pharmacol** 1985;16(4):347–53

The role of extracellular Ca2+ in the response of the hepatocyte to Ca2+-dependent hormones. Joseph SK, et al. **J Biol Chem** 1985 Oct 15;260(23):12508–15

Catecholamine and vasopressin stimulation of gluconeogenesis from dihydroxyacetone in the presence of atractyloside. Warnette-Hammond ME, et al. **J Biol Chem** 1985 Oct 15;260(23):12647–52

Inhibition by prostaglandin E2 of the release of vasopressin and beta-endorphin from rat pituitary neurointermediate lobe or medial basal hypothalamus in vitro. Knepel W, et al. **J Endocrinol** 1985 Aug; 106(2):189–95

Diuresis and suppression of vasopressin by kappa opioids: comparison with mu and delta opioids and clonidine. Leander JD, et al. **J Pharmacol Exp Ther** 1985 Aug;234(2):463–9

Co-localization of corticotropin-releasing factor and vasopressin in median eminence neurosecretory vesicles. Whitnall MH, et al. **Nature** 1985 Sep 19–25;317(6034):248–50

VASOTOCIN

Plasma concentrations of arginine vasotocin, prolactin, aldosterone and corticosterone in relation to oviposition and dietary NaCl in the domestic fowl. Rice GE, et al. **Comp Biochem Physiol [A]** 1985; 81(4):769–77

Pineal ultrastructure and indole profiles spanning the summer rise in arginine vasotocin immunoactivity. McNulty JA, et al. **Endocrinology** 1985 Sep;117(3):1035–42

An immunohistochemical study of seasonal changes in luteinizing hormone-releasing hormone and vasotocin in the forebrain and the neurohypophysis of the toad, Bufo japonicus. Jokura Y, et al. **Gen Comp Endocrinol** 1985 Aug;59(2):238–45

VISUAL PERCEPTION

Role of intralaminar thalamus in gaze mechanisms: evidence from electrical stimulation and fiber-sparing lesions in cat. Merker B, et al. **Exp Brain Res** 1985;59(2):388–94

Early visual information processing in depressive patients treated with ORG 2766 (an ACTH 4-9 analogue). d'Elia G, et al. **Neuropsychobiology** 1985;13(1-2):63–8

WAKEFULNESS

Sleep and wake after benzodiazepine hypnotics: a 20-hour EEG comparison of lormetazepam and flunitrazepam. Timsit-Berthier M, et al. **Curr Med Res Opin** 1985;9(8):552–9

ZIMELIDINE

Synthesis and spectroscopic characterization of pyridyl N-oxidized zimeldine metabolites. Högberg T, et al. **Acta Pharm Suec** 1985; 22(3):123–30

Double-blind comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressed outpatients. Clinical aspects. Nyström C, et al. **Acta Psychiatr Scand** 1985 Jul;72(1):6–15

Profiles of antidepressant activity with the Montgomery-Asberg Depression Rating Scale. Montgomery SA, et al. **Acta Psychiatr Scand [Suppl]** 1985;320:38–42

The effects of zimeldine on voluntary ethanol consumption: studies on the mechanism of action. Gill K, et al. **Alcohol** 1985 Mar–Apr; 2(2):343–7

Influence of renal failure on the kinetics of zimeldine and norzimelidine. Ferry N, et al. **Eur J Clin Pharmacol** 1985;28(4):453–6

*U.S. GOVERNMENT PRINTING OFFICE: 1986-491-327:21002

The *Psychopharmacology Bulletin* is available on subscription from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Subscription price $19.00 per year for the United States. All other countries add $4.75 for postage. This price was in effect at time of printing. Prices are subject to change. Please make check or money order payable to the Superintendent of Documents. An annual subscription for four quarterly issues begins with the next issue following receipt of the order. Single copies and back issues may also be ordered from the Superintendent of Documents. The expiration date is printed on the top line of the address label. Change of address and complaints about non-receipt of issues should be sent to the Superintendent of Documents and should include the old address, preferably a mailing label, as well as the new address.

ORDER FORM Mail To: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

Enclosed is $________ ☐ check,
(U.S. Currency Only)
☐ money order, or charge to my
Deposit Account No.
☐☐☐☐☐☐☐–☐

Order No.______________

VISA®

master charge

Credit Card Orders Only

Total charges $________ Fill in the boxes below.

Credit Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiration Date Month/Year ☐☐☐☐

Please enter my subscription to: **PSYCHOPHARMACOLOGY BULLETIN [PSBU]**
@ $19.00 domestic, @ $23.75 foreign.

Name—First, Last

Street address

Company name or additional address line

City **State** **ZIP Code**

(or Country)

PLEASE PRINT OR TYPE

For Office Use Only.

	Quantity	Charges
Enclosed		
To be mailed		
Subscriptions		
Postage		
Foreign handling		
MMOB		
OPNR		
UPNS		
Discount		
Refund		

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
Alcohol, Drug Abuse, and
Mental Health Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

SPECIAL FOURTH CLASS MAIL
POSTAGE AND FEES PAID
PHS/ADAMHA
PERMIT NO. G-283

DHHS Publication No. (ADM) 86-173
Printed 1986

22/3

PSYCHOPHARMACOLOGY BULLETIN

NATIONAL INSTITUTE OF MENTAL HEALTH

LD [redacted] C
U.S. DOCUMENTS
NEWARK PUBLIC LIBRARY

Special Feature: ACNP Proceedings

1986

Vol. 22, No. 3

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

HE 20. 8109:

Editor-in-Chief:

Nina R. Schooler, Ph.D.
NIMH, Rockville, Md.

Special Features Editor:

Allen Raskin, Ph.D.
Lafayette Clinic, Wayne State University
Detroit, Mich.

Acting Managing Editor:

David Haddock
NIMH, Rockville, Md.

Associate Editors:

Jonathan O. Cole, M.D.
McLean Hospital, Belmont, Mass.

Seymour Fisher, Ph.D.
University of Texas Medical Center
Galveston, Texas

Arnold J. Friedhoff, M.D.
New York University School of Medicine

Gerald L. Klerman, M.D.
Cornell University Medical Center, New York

David J. Kupfer, M.D.
Western Psychiatric Institute & Clinic
University of Pittsburgh School of Medicine

Judith L. Rapoport, M.D.
NIMH, Bethesda, Md.

Donald S. Robinson, M.D.
Bristol-Myers Pharmaceuticals
Wallingford, Conn.

The *Psychopharmacology Bulletin* is prepared by the Division of Clinical Research of the National Institute of Mental Health. Its purpose is to facilitate the dissemination and exchange of information among the national and international scientific community. This emphasis is on rapid, informal reporting of work which has not appeared in the more formal literature. In accordance with new policy set forth by our Associate Editors, we are no longer accepting unsolicited papers for publication in the *Bulletin*.

All material published in the *Psychopharmacology Bulletin* is in the public domain unless otherwise noted. Publication in the *Bulletin* therefore does not preclude publication elsewhere.

Vol. 22, No. 3 1986

PSYCHOPHARMACOLOGY BULLETIN

Table of Contents

NEWARK PUBLIC LIBRARY
NOV 5 1986
U. S. GOVT.
DEPOSITORY 326

24th Annual Meeting of the ACNP–1985—Abridged Proceedings—

Strategies for Advance in Maintenance Therapies

553 Maintenance Phenelzine Treatment of Major Depression: An Interim Report—*Donald S. Robinson, Allen Kayser, Binni Bennett, Elizabeth Devereaux, Sidney C. Lerfald, Doris Albright, Desmonde Laux, and John Corcella*

558 Psychotherapeutic Approaches to Treatment of Recurrent Unipolar Depression: Work in Progress—*Ellen Frank and David J. Kupfer*

Peripheral Hormones: A Window on the Central MA?—

565 The Pitfalls of Serotonin Precursors as Challengers in Hormonal Probes of Central Serotonin Activity—*Herman M. van Praag, Carmen Lemus, and Rene Kahn*

571 The Desipramine Cortisol Test—A Selective Noradrenergic Challenge (Relationship to Other Cortisol Tests in Depressives and Normals)—*Gregory M. Asnis, Carmen Z. Lemus, and Uriel Halbreich*

Etiological Theories of Depression: Experimental Paradigms in Animals—

579 A Developmental Perspective on Recurrent Mood Disorders: A Review of Studies in Man—*Hagop S. Akiskal*

587 Developmental Theories of Depression in Nonhuman Primates—*Gary W. Kraemer*

Biochemical and Functional Studies of D-1 Dopamine Receptors—

593 Multiple Forms of the D_1 Dopamine Receptor: Its Linkage to Adenylate Cyclase and Psychopharmacological Effects—*Richard B. Mailman, David W. Schulz, Clinton D. Kilts, Mark H. Lewis, Hans Rollema, and Steven Wyrick*

599 Structural Analogs of SCH 23390 as Discriminators of Dopamine Receptor Subtypes: Behavioral Interactions Between D-1 and D-2 Agonists and Antagonists—*Kathy M. O'Boyle, Anthony G. Molloy, Marcellina Mashurano, and John L. Waddington*

605 Biochemical and Behavioral Studies of D_1 Dopamine Receptors Utilizing SCH23390—*Ellen J. Hess and Ian Creese*

Mixed Mania: Diagnosis and Treatment—

613 Sources of Lithium Resistance in Mixed Mania—*Jonathan M. Himmelhoch and Marc E. Garfinkel*

Expressed Emotion of Relatives, Maintenance Drug Treatment, and Relapse in Schizophrenia and Mania—

621 Expressed Emotion, Maintenance Pharmacotherapy, and Schizophrenic Relapse Among Mexican-Americans—*Janis H. Jenkins, Marvin Karno, Aurora de la Selva, Felipe Santana, Cynthia Telles, Steven Lopez, and Jim Mintz*

628 Expressed Emotion, Affective Style, Lithium Compliance, and Relapse in Recent Onset Mania—*David J. Miklowitz, Michael J. Goldstein, Keith H. Nuechterlein, Karen S. Snyder, and Jeri A. Doane*

633 Expressed Emotion, Fixed-Dose Fluphenazine Decanoate Maintenance, and Relapse in Recent-Onset Schizophrenia—*Keith H. Nuechterlein, Karen S. Snyder, Michael E. Dawson, Sandra*

Rappe, Michael Gitlin, and David Fogelson

The Benzodiazepine/GABA Receptor: From Molecular Structure to Function in Man—

641 Molecular Aspects of Benzodiazepine Receptor Function—*Paul Sweetnam, Peter Gallombardo, and John Tallman*

Neurochemical Correlates of Suicide—

647 Postmortem Serotonergic and Adrenergic Receptor Binding to Frontal Cortex: Correlations With Suicide—*J. John Mann, P. Anne McBride, and Michael Stanley*

650 Suicide and Adrenocortical Function—*James H. Kocsis, Sara Kennedy, Richard P. Brown, J. John Mann, and Barbara Mason*

656 Suicidal Potential in Depression: Focus on CSF Monoamine and Purine Metabolites—*Hans Ågren and Frank Niklasson*

661 Monoamines, Glucose Metabolism, Suicidal and Aggressive Behaviors—*Alec Roy, Matti Virkkunen, Sally Guthrie, Russell Poland, and Markku Linnoila*

666 Genetic Factors in Suicide—*Alec Roy*

669 (Auto)Aggression and CSF 5-HIAA in Depression and Schizophrenia—*Herman M. van Praag*

Acquired Immunodeficiency Syndrome (AIDS): Neuropsychologic and Psychoimmunologic Aspects—

675 Introduction—*T. Peter Bridge and Donald I. Macdonald*

678 Psychosocial Aspect of AIDS Risk—*David G. Ostrow, Jill Joseph, Andrew Monjan, Ronald Kessler, Carol Emmons, John Phair, Robin Fox, Lawrence Kingsley, Janice Dudley, Joan S. Chmiel, and Mark Van Raden*

684 Neuropsychiatric Aspects of AIDS—*Russell T. Joffe, David R. Rubinow, Kathleen Squillace, Clifford H. Lane, Connie C. Duncan, and Anthony S. Fauci*

689 Localization of the T4 Antigen/AIDS Virus Receptor in Monkey and Rat Brain: Prominence in Cortical Regions—*Joanna M. Hill, William L. Farrar, and Candace B. Pert*

695 Methionine Enkephalin: Enhancement of T-Cells in Patients With Kaposi's Sarcoma (AIDS)—*N.P. Plotnikoff, J. Wybran, N.F. Nimeh, and G.C. Miller*

Molecular Biology: Relevance to Neuropsychopharmacology and Psychiatry—

699 Introduction—*Samuel H. Barondes*

701 Identifying Neuropeptides by Gene Cloning—*Floyd E. Bloom*

708 Use of Gene Transfer Techniques to Study Neuropeptide Gene Regulation—*Edward Herbert, Audrey F. Seasholtz, and Michael Comb*

Neuropsychopharmacology of Alcohol and Drug Abuse—

717 Interactions of Alcohol and Drugs of Abuse—*Monique C. Braude*

Neuropharmacological Approaches to the Obsessive-Compulsive Syndrome—

723 Epidemiologic and Clinical Findings of Significance to the Design of Neuropharmacologic Studies of Obsessive-Compulsive Disorder—*Steven A. Rasmussen and Ming T. Tsuang*

730 A Possible Genetic Relationship Exists Between Tourette's Syndrome and Obsessive-Compulsive Disorder—*David L. Pauls, James F. Leckman, Kenneth E. Towbin, Gwendolyn Zahner, and Donald J. Cohen*

Problems and Promises of Post-Mortem Brain Tissue Analysis—

735 Role of the Serotonergic System in the Postmortem Analysis of Suicide—*Michael Stanley, J. John Mann, and Lee S. Cohen*

741 Aminergic Receptor Binding Correlates of Suicide: Methodological Issues—*J. John Mann, P. Anne McBride, and Michael Stanley*

Appetite and Satiety Regulation: Pharmacological Strategies—

745 Neuropeptides as Stimulators of Feeding—*John E. Morley, James E. Mitchell, and Allen S. Levine*

Psychotoxic Manifestations in Amphetamine Abuse—

751 Acute Exacerbation of Methamphetamine Psychosis and Lasting Dopaminergic Supersensitivity—A Clinical Survey—*Mitsumoto Sato*

757 Reverse Tolerance to the Ambulation-Increasing Effect of Methamphetamine in Mice as an Animal Model of Amphetamine-Psychosis—*Sakutaro Tadokoro and Hisashi Kuribara*

763 Psychotic Manifestations in Amphetamine Abuse—Experimental Study on the Mechanism of Psychotic Recurrence—*Kiyoshi Ando, Naoyuki Hironaka, and Tomoji Yanagita*

768 Visual Perception Process in Amphetamine Psychosis and Schizophrenia—*Takuya Kojima, Eisuke Matsushima, Hisayuki Iwama, Harunobu Ando, Hirobumi Moriya, Katsumi Ando, Ryo Takahashi, and Yasuo Shimazono*

Membrane Lipids: From Signal Transduction to Neuropsychiatric Disease—

775 Changes in Receptor Stimulated Phosphoinositide Hydrolysis in Brain During Ethanol Administration, Aging, and Other Pathological Conditions—*Fulton T. Crews, Rueben A. Gonzales, Reinhard Palovcik, M. Ian Phillips, Cynthia Theiss, and Mohan Raizada*

781 "Autocannibalism" of Membrane Choline-Phospholipids: Physiology and Pathology—*Jan K. Blusztajn, Pamela G. Holbrook, Michael Lakher, Mordechai Liscovitch, Jean-Claude Maire, Charlotte Mauron, U. Ingrid Richardson, Mariateresa Tacconi, and Richard J. Wurtman*

Panic Disorder: Clinical Characteristics, Epidemiology, and Treatment—

787 The Relationship Between Panic Disorder and Agoraphobia: An Epidemiologic Perspective—*Myrna M. Weissman, Philip J. Leaf, Dan G. Blazer, Jeffrey H. Boyd, and Louis Florio*

792 Recent Developments in the Understanding and Pharmacotherapy of Panic Attacks—*Michael R. Liebowitz, Abby J. Fyer, Jack Gorman, and Donald F. Klein*

797 Possible Respiratory Abnormalities in Panic Disorder—*Jack M. Gorman, Michael R. Liebowitz, Abby J. Fyer, Minna R. Fyer, and Donald F. Klein*

802 Behavioral Conception and Treatment of Panic—*David H. Barlow*

Etiology and Treatment: Basic and Clinical Neuroscience Investigations—

807 Nonbenzodiazepine Anxiolytics: Insights Into Possible Mechanisms of Action—*Cam P. VanderMaelen, Duncan P. Taylor, Greta Gehlbach, and Michael S. Eison*

Serotonin Receptor Subtypes: Biochemical, Physiological, Behavioral, and Clinical Implications—

813 Analysis of 5-HT$_1$ Binding Site Subtypes and Potential Functional Correlates—*Stephen J. Peroutka, Richard E. Heuring, Michael D. Mauk, and Jeffery D. Kocsis*

818 Labeling of the 5-HT$_{1A}$ Receptor Subtype—*Jean C. Shih, Kenneth B. Asarch, and Richard Ransom*

825 Substituted Phenylpiperazines as Serotonin Agonists: Structural Determinants of Potency and Interaction With Receptor Subtypes—*Ray W. Fuller*

829 Effector Systems Coupled to Serotonin Receptors in Brain: Serotonin Stimulated Phosphoinositide Hydrolysis—*Elaine Sanders-Bush and P. Jeffrey Conn*

837 Serotonin Receptor Subtype Agonists: Differential Effects on Sensorimotor Reactivity Measured With Acoustic Startle—*Michael Davis, James V. Cassella, William H. Wren, and John H. Kehne*

Influences of Pharmacologic and Psychosocial Factors on the Course of Schizophrenia—

845 Prediction of Relapse in Schizophrenia—*Jeffrey A. Lieberman, John M. Kane, Stavros Sarantakos, Dominick Gadaletta, Margaret Woerner, Jose Alvir, and Jorge Ramos-Lorenzi*

854 Interpersonal and Pharmacologic Treatment in Schizophrenia: A Comparative Study of New Approaches—*William T. Carpenter, Jr., Douglas W. Heinrichs, and Thomas E. Hanlon*

860 Medication, Family Psychoeducation, and Social Skills Training: First Year Relapse Results of a Controlled Study—*Gerard E. Hogarty and Carol M. Anderson*

Nicotine as a Psychoactive Drug: Anxiety and Pain Reduction, Arousal, and Appetite Regulation—

863 Introduction—*Ovide F. Pomerleau*

865 Nicotine as a Psychoactive Drug: Anxiety and Pain Reduction—*Ovide F. Pomerleau*

870 Nicotine: A Unique Psychoactive Drug—Arousal With Skeletal Muscle Relaxation—*Edward F. Domino*

875 Nicotine as a Psychoactive Drug: Appetite Regulation—*Neil E. Grunberg*

882 Nicotine as a Psychoactive Drug—Panel Summary—*Murray E. Jarvik*

Basic and Clinical Aspects of Prefrontal Cortex Physiology in Neuropsychiatry—

885 Electrophysiological Evidence Implicating Frontal Lobe Dysfunction in Schizophrenia—*John M. Morihisa*

Neuroleptic-Induced Psychological Supersensitivity Syndromes: Are These Syndromes Myth or Reality?—

891 Supersensitivity Psychosis and Tardive Dyskinesia: A Survey in Schizophrenic Outpatients—*Guy Chouinard, Lawrence Annable, and Andree Ross-Chouinard*

897 Associations Among Plasma Prolactin Levels, Tardive Dyskinesia, and Paranoia in Treated Schizophrenics: Relevance to Supersensitivity Psychosis—*John G. Csernansky, Sophia Vinogradov, Elisabeth Prosser, Jonathan Kaplan, Philip A. Berger, and Leo E. Hollister*

900 Basic and Clinical Studies of Neuroleptic-Induced Supersensitivity Psychosis and Dyskinesia—*Bruce I. Diamond and Richard L. Borison*

Recent Advances in HPA Physiology and Pathophysiology (II)—

907 Corticotropin-Releasing Hormone—A New Tool to Investigate Hypothalamic-Pituitary-Adrenocortical Physiology in Psychiatric Patients—*Florian Holsboer*

913 Multiendocrine Assessment in the Dexamethasone Suppression Test—*S. Craig Risch, David S. Janowsky, Lewis L. Judd, Christian Gillin, Mariam Mott, Jeffrey L. Rausch, and Leighton Y. Huey*

Recent Advances in Biomedical Research in Schizophrenia—

917 Introduction—*Robert O. Friedel*

918 The Genetics of Schizophrenia: A Current Perspective—*Kenneth S. Kendler*

923 The Dopamine Hypothesis: Variations on a Theme (II)—*Richard Jed Wyatt*

928 The Combined Use of Neuroleptics and ECT in Drug Resistant Schizophrenic Patients—*Robert O. Friedel*

Psychotropic Drug Receptors and Brain Function: Molecular Bases to Clinical Implications (CINP/ACNP)—

931 Lack of Serotonergic Modulation on ^{3}H-Imipramine Binding Sites in Basal Conditions and During Prolonged Treatment With Desmethylimipramine—*Nicoletta Brunello, Alessandra Cecilia Rovescalli, Marco Riva, and Giorgio Racagni*

Drug Washout Effects on Clinical Studies in Depression and Schizophrenia—

937 Effects of Drug Washout on CSF Monoamine and Psychoendocrine Variables—*Hans Ågren and William Z. Potter*

Brain Norepinephrine and Stress: A Vertical Synthesis—

943 Behavioral Depression Following Clonidine Withdrawal: A New Animal Model of Long-Lasting Depression?—*Laura J. Hoffman and Jay M. Weiss*

Mechanisms of Action of Indole and Phenylalkylamine Hallucinogens—

951 Introduction—*Richard H. Rech*

953 Structure-Activity Relationships and Mechanism of Action of Hallucinogenic Agents Based on Drug Discrimination and Radioligand Binding Studies—*Richard A. Glennon, Milt Titeler, and Richard Young*

959 The Use of Drug Discrimination Procedures to Characterize Hallucinogenic Drug Actions—*James B. Appel and Kathryn A. Cunningham*

968 Disruption of Operant Behavior by Hallucinogenic Drugs—*Richard H. Rech and David J. Mokler*

973 Comparison of Phencyclidine and Related Substances With Various Indole, Phenethylamine, and Other Psychotomimetics—*Edward F. Domino*

977 Clinical Aspects of Use of Phenylalkylamine and Indolealkylamine Hallucinogens—*Leo E. Hollister*

The "Pros" and "Cons" of Anticholinergic Prophylaxis—

981 Anticholinergic Prophylaxis in Young Adults Treated With Neuroleptic Drugs—*C. Raymond Lake, Daniel E. Casey, Joseph P. McEvoy, Samuel G. Siris, William F. Boyer, and George Simpson*

Poster Sessions—Editors' Choice

985 The Inventory of Depressive Symptomatology: Preliminary Findings—*A. John Rush, Donna E. Giles, Michael A. Schlesser, Carl L. Fulton, Jan Weissenburger, and Cheryl Burns*

991 Chronic Lithium and Desmethylimipramine Modulation of Locomotor Response to Growth Hormone Releasing Factor—*Cindy L. Ehlers, Alfred Lopez, and R. Ian Chaplin*

995 Postmarketing Surveillance of Long-Term Amitriptyline Side Effects—*Stephen G. Bryant, Seymour Fisher, and Ronica M. Kluge*

999 The Patient, the Family, and Compliance With Posthospital Treatment for Affective Disorders—*Gretchen L. Haas, Ira D. Glick, James H. Spencer, John F. Clarkin, Alfred B. Lewis, Marcie Good-Ellis, Joanne Peyser, Nancy DeMane, Elizabeth Harris, and Veronica Lestelle*

1006 The Antipsychotic Drug Haloperidol Decreases Basal Ganglia Substance P, Substance K, and Preprotachykinin mRNAs—*Michael J. Bannon, Jin-Moo Lee, Pierre Giraud, Alice Young, Hans-Urs Affolter, and Tom I. Bonner*

1011 Alpha-2 Adrenergic Agonist Binding in Schizophrenic Brains—*Grant N. Ko, James R. Unnerstall, Michael J. Kuhar, Richard J. Wyatt, and Joel E. Kleinman*

1017 Dose-Dependent Increases in Rat Spontaneous Chewing Rates During

Long-Term Administration of Haloperidol but Not Clozapine—*Per Johansson, Daniel E. Casey, and Lars M. Gunne*

1020 Identification and Testing of New Drugs for Modulating Alcohol Consumption—*Mary O. Lawrin, Claudio A. Naranjo, and Edward M. Sellers*

1026 Effects of Noon Meals, Varying in Nutrient Composition, on Plasma Amino Acids, Glucose, Insulin, and Behavior—*Bonnie Spring, June Chiodo, Margarette Harden, Michael Bourgeois, Lorenz Lutherer, Debra Harner, Sherry Crowell, and Geoffrey Swope*

1030 Mouse Strain Differences in Acquisition of Discrete Lever-Press and Shuttle Avoidance Responses, and Drug Effects Thereon—*Hisashi Kuribara and Sakutaro Tadokoro*

1036 Differential Erythropoietic Response to Oxiracetam in Alzheimer's Disease and Multi-Infarct Dementia: A Potential Biological Marker—*Roland J. Branconnier, Eric C. Dessain, Maureen E. McNiff, Nancy E. Harto, Karen F. Spera, Richard Katz, Frank Stallone, Joseph DeVeaugh-Geiss, and Jonathan O. Cole*

1040 Thioridazine Metabolism and Effects on Stereotyped Behavior in Mentally Retarded Patients—*Mark H. Lewis, Robert A. Steer, Judith Favell, James McGimsey, Luther Clontz, Carole Trivette, Wendy Jodry, Stephen R. Schroeder, Robert C. Kanoy, and Richard B. Mailman*

24th Annual Meeting of the ACNP-1985— Abridged Proceedings—

The 24th Annual Meeting of the American College of Neuropsychopharmacology (ACNP) was held in Maui, Hawaii, in December 1985.

This meeting annually brings together investigators actively involved in psychopharmacologic research. The papers presented at the sessions are indicative of the state of the art in psychopharmacology in this country and abroad.

For those who did not attend the conference, we publish summaries of the presentations. In some cases, not all of the papers in a session were received in time for inclusion. Publication of these summaries in the *Bulletin* does not prejudice later publication of the full papers elsewhere.

Because of the size of the ACNP meeting, we are no longer able to publish all Poster Session papers. Instead, an "Editors' Choice" section of the proceedings includes a limited number of Posters judged especially noteworthy by the Editors.

Strategies for Advance in Maintenance Therapies

Co-Chairs:

David J. Kupfer, M.D.
University of Pittsburgh
Western Psychiatric Institute and Clinic
Pittsburgh, PA 15261

Robert F. Prien, Ph.D.
National Institute of Mental Health
Rockville, MD 20857

Maintenance Phenelzine Treatment of Major Depression: An Interim Report[1]

Donald S. Robinson, M.D.,[2,3] Allen Kayser, M.D.,[3] Binni Bennett, M.S.W.,[3] Elizabeth Devereaux, A.C.S.W.,[3] Sidney C. Lerfald, M.D.,[3] Doris Albright, R.N.,[3] Desmonde Laux, Ph.D.,[3] and John Corcella, M.D.[3,4]

Introduction

The efficacy, safety, and optimal duration of long-term antidepressant drug treatment of depression are unresolved issues currently being investigated by several groups. There are no existing controlled studies of monoamine oxidase inhibitors (MAOI) in long-term maintenance therapy. In a 5-year study in progress at Marshall University, patients with a Research Diagnostic Criteria (RDC) diagnosis of major depressive disorder (Spitzer, Endicott, & Robins, 1978), and at least one prior lifetime episode of depression, are eligible for entry into a double-blind 2-year phenelzine maintenance treatment study. After initial clinical improvement and remission of depressive symptoms for a minimum of 16 weeks, patients are randomly assigned to placebo or one of two doses of phenelzine.

Method

After several months of regularly scheduled planning sessions, an interdisciplinary research group at Marshall University developed and submitted a study protocol to the National Institute of Mental Health in response to a request for applications to study long-term somatic treatment of affective disorders. The first patients entered into the study protocol in January 1983.

Specific aims of this study of maintenance treatment were to: (1) assess the efficacy and side effects of long-term phenelzine treatment, (2) establish an effective therapeutic maintenance dose range for phenelzine, (3) assess platelet MAO inhibition levels during long-term phenelzine treatment, and (4) study the pharmacokinetics of phenelzine during short- and long-term treatment. This interim report presents the preliminary findings related to the first specific aim of this study of maintenance phenelzine treatment for major depression.

---

[1] This research was supported in part by USPHS Grant MH 37617 from the National Institute of Mental Health.

[2] Clinical Director, CNS Research, Bristol-Myers Company, Pharmaceutical Research & Development Division, Wallingford, CT 06492.

[3] Department of Psychiatry, Marshall University School of Medicine, Huntington, WV 25701.

[4] Medical Director, Prestera Mental Health Center, Huntington, WV 25705.

The patient sample was drawn from the outpatient clinics at Marshall University Department of Psychiatry and Prestera Community Mental Health Center in Huntington, West Virginia. The patients were interviewed and screened by the research staff in the Mood Disorders Clinic at Marshall University School of Medicine. After written informed consent was obtained, patients who met entry criteria were assigned to one of four physician-therapist pairs who followed the patients throughout the course of treatment.

Criteria for entry into the study were: (1) major depressive disorder by Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978), (2) Hamilton depression (Ham-D) score ≥ 18, (3) Global Assessment Scale (GAS) score ≤ 60, (4) Raskin Depression Scale score ≥ 7, and (5) at least one prior lifetime episode of either RDC major or minor depression.

Exclusion criteria included: (1) a remission period of less than 20 weeks between the index episode and the most recent prior episode, (2) presence of a major nonaffective psychiatric disorder, (3) history of mania or hypomania, (4) history of alcohol or substance abuse during the year prior to entry, and (5) pregnancy, epilepsy, or any medical illness which contraindicated the use of phenelzine.

The rationale for requiring a prior lifetime episode of depression as an entry criterion was based on data from a previous 6-week antidepressant drug trial comparing amitriptyline and phenelzine for the treatment of depressed outpatients (Ravaris et al., 1980; Robinson et al., 1985). A retrospective study of the West Virginia outpatient sample indicated that these patients were at considerable risk for recurrence of depression within a 2-year period following remission of the acute episode. Sixty of 66 patients who participated in this double-blind comparison drug study responded to a post-study inquiry (85% follow-up rate). Forty of these 60 patients (67%) suffered a recurrence of depression in the ensuing 1–3 years after they completed a successful course (usually a minimum of 6 months) of antidepressant drug treatment for their index episode. Even though the recurrence rate for patients with no prior episodes was nearly as high as the rate for patients with a history of depression, the inclusion criterion of one or more prior episodes was established to achieve greater sample homogeneity and to address the ethical issue of committing patients to 2 years of drug treatment.

Patients were evaluated initially by a screening interview and re-evaluated after a drug-free interval of at least 1 week. Then, if patients qualified for entry into the study, baseline psychometric and laboratory evaluations were performed. Patients underwent physical examination, clinical laboratory tests, and an ECG. In addition, blood samples were collected for platelet MAO assay and plasma phenelzine concentration. Clinical evaluations included the Schedule for Affective Disorders (SADS) interview (Endicott & Spitzer, 1978), Hamilton Depression Scale, Raskin Severity of Depression Scale, and the Global Assessment Scale (Endicott et al., 1976). Patients were initially seen by both members of the physician-therapist treatment team, and the clinical assessments and ratings were jointly reviewed. Patients were then started on non-blind treatment with phenelzine (target dosage of 1 mg/kg/day). In the first study year, phenelzine treatment was initiated on an individualized dosage schedule during the first week, followed by a gradual increase to an optimal therapeutic dose based upon clinical response and/or tolerance of side effects. For the past two years, phenelzine treatment was initiated with the target dosage of approximately 1 mg/kg/day in divided doses. Most of the patients were seen weekly (during this acute treatment phase) until they achieved satisfactory therapeutic response (defined as Ham-D <10, Raskin ≤ 5, GAS ≥ 70). Patients were required to maintain this level of response, without interruption for a minimum period of 16 weeks (continuation treatment phase) before they were entered into one of three double-blind, randomly assigned drug treatment groups.

Upon satisfactory completion of the continuation treatment phase, patients were entered into the maintenance treatment phase, a 24-month double-blind comparison of three different maintenance dose regimens, phenelzine 60 mg/day, phenelzine 45 mg/day, or placebo, administered in two capsules twice a day. Patients who were randomized to the placebo treatment group had their phenelzine dose tapered weekly by 15 mg/day in prepackaged capsules during the first 3 weeks of the double-blind maintenance treatment phase. Patients were seen at least every 4 weeks during the 2-year maintenance phase, or more frequently if clinically indicated.

Psychotherapeutic interventions consisted mainly of patient and family education about depressive illness and importance of medication and dietary compliance. Recognizing that recurrent depression occurs within a social and interpersonal context which interacts with biological vulnerabilities and personality traits (Weissman et al., 1981), patient-initiated topics related to psychosocial stress and life crises occurring during the study were addressed using a supportive, "here and now," problem-solving psychotherapeutic approach. Possible side effects were elicited during all three phases of the study, and careful monitoring for early re-emergence of symptoms was assessed on a routine basis, especially during the maintenance treatment phase of the study. Re-emergence of symptoms was defined as Ham-D ≥ 18, Raskin ≥ 7, and GAS ≤ 60 in the presence of depressive symptoms meeting RDC criteria for major depressive episode of 2-weeks duration.

Results

From January 1983 to November 1985, 231 patients were evaluated for study eligibility in the Mood Disorders Clinic. Of these, 79 patients were eligible for admission and willing to participate in the study. Sixty-five of the 79 patients (82%) showed a favorable therapeutic response to phenelzine during the acute treatment phase. Fourteen patients were discontinued from the protocol during the acute treatment phase due to lack of therapeutic response (10 patients) and/or intolerable side effects (4 patients).

Sixty patients entered the continuation treatment phase. Seventeen of these patients were discontinued from the protocol during this phase, predominantly for intolerable side effects (12 patients) or for administrative reasons (5 patients).

Forty patients reached the maintenance treatment phase and were randomized into double-blind treatment. Twenty-seven of these patients were discontinued prematurely (less than 2-years participation in the maintenance treatment phase). Two patients have completed 2 years, and 11 patients are currently still participating in the maintenance treatment phase. Reasons for early discontinuation from the maintenance treatment phase included: re-emergence of symptoms (18 patients); moved away, but well, at the time of discontinuation (2 patients); unrelated medical problems (3 patients); and intolerable phenelzine side effects (4 patients). Table 1 shows the number of patients in each treatment group who were discontinued from the maintenance treatment phase for re-emergence or exacerbation of symptoms.

Most of the patients who experienced re-emergence of symptoms in ≤ 2 months were in the placebo group. Of the four patients with re-emergence of symptoms after >2 months, one was receiving placebo, none were receiving phenelzine 45 mg/day, and three were receiving phenelzine 60 mg/day. These data suggest a trend ($p = 0.12$) that a standard therapeutic dose of phenelzine is an effective maintenance treatment for preventing, or delaying, a return of depressive symptoms in patients who respond successfully to treatment with phenelzine for 5–6 months.

There were no significant differences in age or length of index episode between patient completers, patients with re-emergence of symptoms in ≤ 2 months (relapse), or patients with re-emergence of symptoms in >2 months (recurrence). The mean length of double-blind treatment was 5.8 weeks for patients with relapse, compared to 23.5 weeks for patients with a recurrence. The mean

TABLE 1. Relapse/Recurrence vs. Phenelzine Maintenance Dose.

Treatment Group	Relapse (≤ 2 mo.)	Recurrence (>2 mo.)
Placebo	8*	1
Phenelzine, 45 mg/day	3	0
Phenelzine, 60 mg/day	3	3

*$\chi^2 = 4.38$, $p = 0.12$

TABLE 2. Summary of Treatment-Emergent Effects Leading to Early Termination From Phenelzine Study.

Side Effect*	Acute Rx (*n* = 4 pts)	Cont. Rx (*n* = 12 pts)	Maint. Rx (*n* = 4 pts)
Weight Gain	0	7	3
Bipedal Edema	0	4	1
Hypomania	0	3	0
Orthostatic BP	1	2	0
Insomnia	1	2	0
Anorgasmia	1	1	1
Other (Decreased Concentration, Blurred Vision, Palpitation)	3	0	0

*More than 1 side effect per patient may apply.

length of the index episode from onset to relapse was 13 months.

The emergence of phenelzine side effects was a significant cause for early discontinuation from all three treatment phases. Table 2 lists the side effects reported by discontinued patients during each of the three phases. In nearly all cases the depressive symptoms had shown a favorable response to treatment, but the severity of the side effects caused sufficient discomfort to justify discontinuation of phenelzine.

Discussion

It has been estimated that an average of 65 percent of depressed patients have some degree of relapse within the first year following an index episode (Klerman, 1978). This preliminary report of interim findings from an ongoing study of the safety and efficacy of maintenance MAOI therapy suggests that patients who successfully respond to treatment with phenelzine may benefit from long-term maintenance treatment. Most patients with early re-emergence of symptoms after treatment with phenelzine for 5–6 months were in the placebo maintenance group.

There was no significant difference in the length of the index depressive episode between the patients with re-emergence of symptoms ≤ 2 months (relapse) and >2 months (recurrence). These findings are consistent with a typical cycle length of 1 year or longer for a major depressive episode in the majority of patients with recurrent major depression.

Interestingly, over 80 percent of patients with RDC major depression responded initially to treatment with phenelzine; but, 20 of the 79 patients (25%) who entered the study ultimately discontinued treatment because of troublesome side effects (4 patients during acute treatment, 12 during continuation treatment, and 4 during maintenance treatment). Three of the four patients discontinued from the 2-year maintenance phase experienced the onset of adverse side effects during the continuation phase of treatment. These three patients had excessive weight gain associated with carbohydrate craving and hyperphagia which resulted in weight gains of 30 to 45 lbs. Most of the patients who discontinued from treatment prematurely were reluctant to stop phenelzine therapy because of an otherwise excellent therapeutic response.

Acknowledgments

The authors wish to express appreciation for the valuable assistance of Marjory Kaib, Derek Nicoll, and Martha Allenbaugh, R.N.

References

Endicott, J., Spitzer, R.L., Fleiss, J.L., and Cohen, J. The global assessment scale. A procedure for measuring the overall severity of psychiatric disturbances. *Arch. Gen. Psychiatry*, 33:766–771, 1976.

Endicott, J., and Spitzer, R.L. A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Arch. Gen. Psychiatry*, 35:837–844, 1978.

Klerman, G.L. Long-term treatment of affective disorders. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.). *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978, pp. 1303–1311.

Ravaris, C.L., Robinson, D.S., Ives, J.O., et al. Phenelzine and amitriptyline in the treatment of depression. *Arch. Gen. Psychiatry*, 37:1075–1080, 1980.

Robinson, D.S., Kayser, A., Corcella, J., et al. Panic attacks in outpatients with depression: Response to antidepressant treatment. *Psychopharmacology Bull.*, 21:562–566, 1985.

Spitzer, R., Endicott, J., and Robins, E. Research diagnostic criteria. *Arch. Gen. Psychiatry*, 35:773–782, 1978.

Weissman, M.M., Klerman, G.L., Prusoff, B.A., et al. Depressed outpatients: Results one year after treatment with drugs and/or interpersonal psychotherapy. *Arch. Gen. Psychiatry*, 38:51–55, 1981.

Psychotherapeutic Approaches to Treatment of Recurrent Unipolar Depression: Work in Progress[1]

Ellen Frank, Ph.D.,[2] and
David J. Kupfer, M.D.[2]

Although much of the recent treatment research in depression has focused on comparisons of psychotherapy with pharmacotherapy (Kovacs et al., 1981; Elkin et al., 1985), few studies have explored the efficacy of combined treatment with this population. The work of Weissman and colleagues (Weissman et al., 1974; Weissman et al., 1978) is a notable exception. The present paper addresses acute and, in particular, continuation treatment results with a large group of recurrent unipolar depressives offered a combination of imipramine and Interpersonal Psychotherapy (IPT) (Klerman et al., 1984). The pace of treatment response, the low frequency of adverse effects, the low relapse rate, and the high level of patient adherence to the treatment protocol are explored as they relate to the combined treatment strategy.

Method

Patients between the ages of 21 and 65, suffering from a major depressive disorder were entered into the Maintenance Therapies in Recurrent Depression protocol if the index episode was at least their third episode of major depression and the immediately previous episode had occurred within the last 2½ years. Minimum Hamilton Rating Scale for Depression (HRS-D) (≥15) and Raskin Severity of Depression and Mania Scale (≥7) scores were also required. Following a 2-week, drug-free period, severity of depression was reevaluated and patients remaining symptomatic were given a complete initial assessment including biological (all-night sleep EEG and neuroendocrine studies) and psychosocial (e.g., social adjustment, social support) measures.

All patients then received the same acute treatment regimen: imipramine (150–300 mg per day) and IPT offered weekly for 12 weeks, biweekly for 8 weeks, and monthly thereafter. At the point when patients had maintained an HRS-D score of ≤7 and a Raskin score of ≤5 for 3 weeks, a second (continuation) biological and psychosocial evaluation was completed. Patients remained in continuation treatment for an additional 17 weeks, during which both Hamilton and Raskin scores and imipramine dose were required to remain stable. A third (premaintenance) evaluation was then conducted, after which patients were randomly assigned to one of the five maintenance treatment cells (psychotherapy alone, psychotherapy plus active medication, psychotherapy plus placebo, medication clinic plus active medication, or medication clinic plus placebo) for 3 years or until they experienced a recurrence of illness (*see* Figure 1).

Subjects

This report is based on the first 119 patients to enter the study. As can be seen in Table 1, the group of 119 patients consisted of 27 males and 92 females with a median age of 39.3 and a median age of onset of illness of 24.6. The mean duration of the index episode at the point of entry into the study was 23.4 weeks. Although a minimum baseline HRS-D rating of 15 was required for entry, most patients had considerably higher ratings; the mean rating on entry was 22.7. Three patients had had two previous episodes of major depressive disorder, while the remaining 116 had three or more previous episodes (median = 4.2). This determination was based on the Schedule for Affective Dis-

---

[1] This study was supported in part by National Institute of Mental Health Grants MH-29618 and MH-30915, as well as a grant from the John D. and Catherine T. MacArthur Research Network on the Psychobiology of Depression.

[2] Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

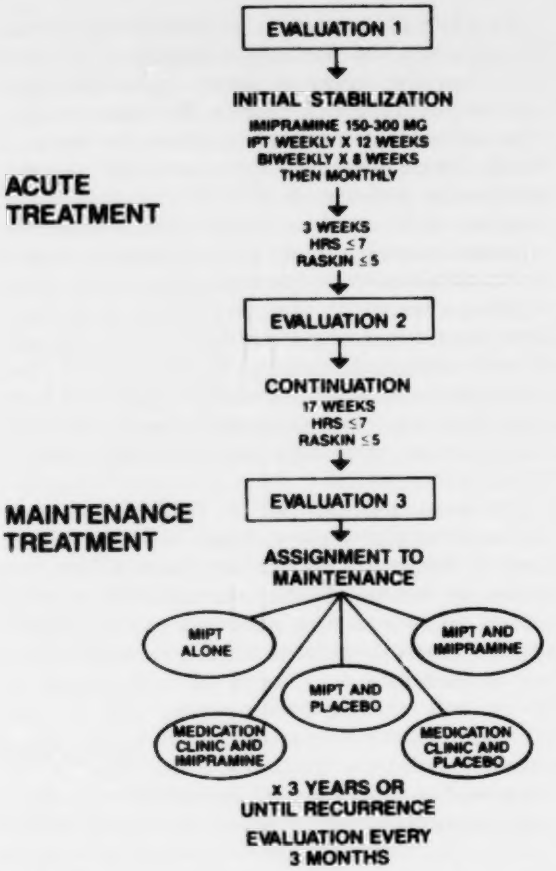

ACUTE TREATMENT
EVALUATION 1
INITIAL STABILIZATION
IMIPRAMINE 150-300 MG
IPT WEEKLY X 12 WEEKS
BIWEEKLY X 8 WEEKS
THEN MONTHLY
3 WEEKS
HRS ≤ 7
RASKIN ≤ 5
EVALUATION 2
CONTINUATION
17 WEEKS
HRS ≤ 7
RASKIN ≤ 5
MAINTENANCE TREATMENT
EVALUATION 3
ASSIGNMENT TO MAINTENANCE
MIPT ALONE
MIPT AND IMIPRAMINE
MIPT AND PLACEBO
MEDICATION CLINIC AND IMIPRAMINE
MEDICATION CLINIC AND PLACEBO
x 3 YEARS OR UNTIL RECURRENCE
EVALUATION EVERY 3 MONTHS

FIGURE 1. Maintenance Therapies in Recurrent Depression protocol.

TABLE 1. Clinical Characteristics of 119 Recurrent Depressives (27 Males; 92 Females).

	Mean ± S.D.	Median
Age (Years)	40.7 ± 10.8	39.3
Age of Onset (Years)	27.5 ± 10.1	24.6
Number of Previous Episodes	5.9 ± 5.5	4.2
Duration of Index Episode (Weeks)	23.4 ± 16.6	13.2
Baseline Hamilton Rating Scale	22.7 ± 4.8	
16-Week Hamilton Rating Scale	7.5 ± 6.2	

	No	Probable	Definite
Bipolar II	86.6%	6.7%	6.7%
Psychotic	97.5	0.8	1.7
Incapacitating	84.7	3.4	11.9
Endogenous	9.3	28.8	61.9
Agitated	82.2	7.6	10.1
Retarded	78.8	11.9	9.3

orders and Schizophrenia data obtained on admission to the study and on the Lifetime History of Affective Disorder obtained during the clinical remission period. Of these patients, over 90 percent remained in the study for the first 4 months; almost 62 percent of these developed a clinical response within 16 weeks (Frank et al., 1984). Fifty-seven of the 119 patients entered the maintenance phase.

Results

Response to Acute Treatment

Early in the study we observed three distinct patterns of response to the combined regimen of imipramine and IPT. About a third of the patients appeared to show a good remission of symptoms within 3 to 4 weeks and were fully remitted by 8 weeks. Another third had a much more variable course and required several months before they were regularly rated at levels consistent with a clinical remission. A final third appeared only partially responsive to the imipramine-IPT combination.

In order to assess the differences in rapidity of clinical response in this population, we developed a methodology to test the accuracy of the observations described above. At the end of 16 weeks of acute treatment patients were classified as Normal Responders, Slow Responders, or Nonresponders. Treatment response categories were determined in the following fashion. If the HRS–D at 8 weeks was less than or equal to 7, and the HRS–D at 16 weeks was less than or equal to 7, and the change score at 16 weeks was greater than or equal to 50 percent, then a patient was classified as a Normal Responder. However, if these criteria were met, but the HRS–D at 12 weeks was greater than or equal to 10 (signifying some level of clinical exacerbation), then an individual was classified as a Slow Responder. A patient could also be classified as a Slow Responder if the HRS–D was greater than 7 at 8 weeks and if the HRS-D at 16 weeks was between 8 and 10, but the total change score was greater than or equal to 60 percent. A third manner in which a patient could be classified as a Slow Responder was if none of the above criteria was met, but the HRS–D at 16 weeks was less than or equal to

7. If none of the aforementioned criteria for Normal or Slow response was met, the patient was considered a Partial or Nonresponder. Of the first 119 patients, 35 (29.4%) were classified as Normal Responders, 32 (26.9%) were classified as Slow Responders, and 28 (23.5%) were classified as Partial or Nonresponders. Twenty-three patients (19.3%) had to be terminated from the study prior to 16 weeks because of serious clinical worsening, intolerable side effects, or failure to comply with the study protocol. One patient, who developed an allergy to the pill coating and had to be restarted on a different formulation, could not be classified.

Absence of Adverse Effects

In our study we have purposely attempted to use a high dosage of imipramine during acute treatment and to maintain that dosage as individuals enter continuation treatment. The average dose of patients entering maintenance treatment was approximately 225 mg. This study, then, addresses the question of whether dosages higher than 150 mg of antidepressant are well tolerated, and whether they result in increased treatment efficacy.

An important issue in the assessment of the effectiveness of increased dosages in this study was the safety of these higher dosages in terms of their side effects. We assessed adverse effects of medication through the Somatic Symptoms Checklist, a scale developed specifically for use in this study. The scale consists of 20 somatic complaints frequently reported as side effects of imipramine treatment. Subjects were queried prior to the start of drug treatment and at each visit during treatment regarding the presence or absence of each symptom, rating the severity of the symptom as 0 (not present), 1 (present but tolerable), or 2 (present and causing significant distress), yielding a possible range of 0 to 40 for a total score.

The results presented in Table 2 indicate that overall the higher doses of imipramine used in this study do not adversely affect patients in terms of the side effects experienced. In examining these results, it would appear that side effects were a relatively minor consideration at week 16 and played a minor role during continuation and at the premaintenance evaluation. In fact, very few patients withdrew from the study because of adverse drug effects, and those that did also had accompanying medical problems. The

TABLE 2. Somatic Symptoms (numbers represent percentage of patients reporting severity of 1 or 2).

	Pre-Treatment	Week 16	Continuation	Premaintenance
*Dizziness	22	20	12	39
Clumsiness	17	11	7	7
Blurred Vision	17	20	14	16
*Headache	58	44	26	44
*Nervousness	70	42	35	36
*Nausea or Vomiting	17	9	9	33
*Sexual Difficulties	42	24	23	11
Diarrhea	6	2	7	16
Constipation	40	33	40	33
*Dry Mouth and Throat	53	78	91	39
*Decreased Appetite	31	11	5	21
*Increased Appetite	36	27	21	18
Difficulty Urinating	14	16	14	11
Palpitations	14	9	9	14
*Tiredness	58	33	35	35
Skin Rash	11	2	2	12
Tremor	25	13	12	11
*Increased Perspiration	45	56	51	19
*Weight Gain	36	20	23	23
Weight Loss	20	13	23	30
Total Score ≥ 6	64	47	35	45
Median Score	6.8	4.8	4.6	4.8

*Chi-square significant at at least $p < .05$.

percentage of patients reporting the presence of somatic symptoms did not deviate significantly across the three treatment periods. In fact, a number of somatic symptoms showed a decrease at premaintenance when compared to the earlier treatment phases. For example, the incidence of dry mouth, often an acute somatic symptom, decreased over time as did increased perspiration. In contrast, dizziness and nausea/vomiting increased over time.

Another way of examining these somatic symptoms is to explore what percentage of these patients reported a total score of 6 or more out of a possible 40. As Table 2 shows, the percentages of patients scoring 6 or more at pretreatment, week 16, continuation, and premaintenance were 64, 47, 35, and 45 percent, respectively. The median scores at those four time periods were 6.8, 4.8, 4.6, and 4.8, respectively. We conclude from these results that the frequency of adverse effects did not alter the course of the first 6 to 9 months of treatment in a major way.

Relapse Rate

The problems of defining and achieving recovery in recurrent disorders and avoiding relapses in such patients are now of major importance to clinicians, epidemiologists, and biological investigators. One of the first hurdles in developing this investigative expertise is defining what one means by "recovery" and "relapse." While there is considerable disagreement as to whether relapse represents an exacerbation of the symptomatology of an ongoing and incompletely treated episode after a recovery period or represents a new episode, there is agreement that the symptoms which constitute a relapse must follow a period of remission and must meet the criteria for either a major episode of depression or minor depression. Naturalistic studies have been available for 10 to 20 years on this topic (Angst, 1973; Zis & Goodwin, 1979). The recent reports coming from the NIMH Collaborative Study on the Psychobiology of Depression have added substantially to the database on relapse in major depression, especially in those individuals who have repeated episodes of depression (Keller et al., 1982a; Keller et al., 1982b; Keller et al., 1983). Data from these collaborative studies have demonstrated that individuals with three or more episodes of depression may, in fact, have a relapse rate as high as 40 percent within 12 to 15 weeks after recovery. While these data are revealing, there has been an increasing need for data on the rate of relapse in controlled treatment trials. Most studies indicate that during active drug treatment there is approximately a 22 percent relapse rate, and that under placebo or no pill conditions rates of relapse may reach 50 percent or greater (Prien & Kupfer, 1986). Our current investigation utilizing both pharmacologic and psychotherapeutic interventions offers a unique opportunity to examine the issue of relapse in recurrent depression in a controlled treatment trial.

Relapse in this investigation was defined as meeting the criteria for a major depressive episode after at least 8 weeks of recovery (Keller et al., 1982a). Of the 119 patients, 80 percent remained in the study for the first 4 months. Using our criterion of a Hamilton score of ≤ 7, 67 of these patients had developed a clinical response within 16 weeks. Seventy-seven of the 119 patients eventually completed the acute treatment phase and entered the continuation phase; 59 of the 77 patients completed the continuation phase and entered the maintenance phase of the study. Of the remaining 14 patients who reached continuation but who failed to complete the 20 weeks of continuation, 9 patients suffered a recurrence of symptoms—4 patients showed a recurrence of symptoms within 4 weeks of entering continuation (2 within 10 days, 1 within 2 weeks, 1 within 4 weeks), and 5 patients suffered a relapse after 8 weeks of recovery. Therefore, using the criterion of 8 weeks of recovery, there are only five patients who met our criterion for a relapse. If one utilizes a liberal definition of relapse, then 15.3 percent of this sample suffered a recurrence of symptoms. However, if one uses the criterion of a minimum of 8 weeks, then 8.5 percent of this sample suffered a relapse. Five patients did not complete the continuation phase and left the study in a state of clinical symptomatic remission—one patient who unexpectedly moved out of state, three patients who dropped out of the study (unilateral termination), and one patient who had sufficiently adverse side effects to withdraw from the study.

The paucity of relapses (five) necessitates a descriptive rather than a statistical approach. The mean length of time for the patient group going into relapse after entering continuation was 21.4 weeks and the median was 16.9 weeks (one patient stabilized at several different points during continuation, thus necessitating additional symptom-free periods in continuation).

The current literature on naturalistic follow-up suggests that the cumulative rate of relapse after recovery for those individuals with primary depression is approximately 15 percent at 6 months and 22 percent at 1 year (Zis & Goodwin, 1979; Keller et al., 1982a). While these patients met criteria for primary depression, they represent patients who, for the most part, had fewer than three episodes. A further refinement of the most recently published analyses indicates that 11 percent of patients with fewer than three episodes had a relapse within 12 to 15 weeks, but 43 percent of patients with three or more episodes suffered a relapse by the 12th week. Thus, recurrent unipolar patients not entered in a controlled treatment trial may very well experience a 40 percent relapse rate within 4 to 5 months following recovery. These data from the Collaborative Study on the Psychobiology of Depression are consistent with the recent review of continuation treatment recently compiled by Prien and Kupfer (1986) which demonstrates that the relapse rate for active drug versus placebo conditions is 22 percent versus 50 percent.

Our data suggest that the addition of psychotherapy as well as an educational workshop offered to our study participants and their families within the umbrella effort of a major research protocol may reduce the rate of relapse to a rate below 10 percent. While this finding needs to be replicated (the second half of the sample for this investigation will offer us the opportunity to do that), it should be recognized that the combination of psychotherapy and pharmacotherapy may offer the best approach to reducing relapse following recovery in the continuation phase of treatment.

Treatment Adherence in Premaintenance Phases

Many of the ingredients which relate to overall compliance or adherence have been addressed earlier in this report. As shown in Table 3, compared to previous studies, our "noncompliance" rate has remained very low over the duration of the study. Although evidence has accumulated that the drop-out rate for pharmacotherapy trials is higher than for psychotherapy, this rate cannot be attributed strictly to the inclusion of psychotherapy in the treatment approach. Rather, we would argue that the overall clinic approach as offered in our Depression Prevention Clinic and the psychoeducational workshop foster a climate of clinician/patient/family member alliance which leads to joint participation in the protocol. Indeed, patients who must be dropped from the protocol because of a failure to respond during the acute or continuation phases or who experience recurrences during maintenance have been unwilling to leave the clinic and most have been followed within the Western Psychiatric Institute and Clinic's Mood Disorders Module.

Summary

While a number of reasons account for the failure of all patients to reach the maintenance phase in this research design, three points are worthy of mention. The larger

TABLE 3. Tricyclic Noncompliance Rates.

Source	Percent
Johnson, 1978	68[a]
DiMascio et al., 1979	
TCA	47[b]
TCA + IPT	29[b]
Kovacs et al., 1981	32[a]
Blackwell, 1982	64-76[a]
Bellack et al., 1983	53[a]
Murphy et al., 1984	
TCA	33[a]
TCA + CBT	18[a]
Kupfer et al. (Unpublished data)	
TCA + IPT + F/SO Seminar	10

Note. TCA = tricyclic antidepressant; IPT = Interpersonal Psychotherapy; CBT = Cognitive Behavior Therapy.

[a] Reported "drop-out" as opposed to noncompliance rates.

[b] Noncompleters minus symptomatic failures.

than expected group of treatment nonresponders (i.e., not responsive *enough* to meet study remission criteria) is worthy of attention since this figure of 22 percent may represent a factor related to the clinical characteristics of the entire group at entrance. This is, to our knowledge, the first time any research group has attempted to study a population with a *minimum* of three episodes. If it is true, as Keller et al. (1986) have suggested, that with each additional episode a certain percentage of recurrent patients go on to have a chronic course, the entry criteria for the study may have selectively biased the study population, increasing the percentage of patients who failed to remit. Another factor which may have inflated the apparent rate of treatment failure is the exceptionally high rate (90%) of patient retention. Many of the 22 percent of treatment failures in this study would likely have been represented in the drop-out rates (25 to 50%) reported in other studies. The lower than expected rate of relapse during continuation, the low frequency of adverse effects, and the high rate of patient retention are also worthy of note. We view these as a direct result of the inclusion of psychotherapy as an integral part of the initial treatment phases and a result of the collaborative atmosphere developed in the Depression Prevention Clinic among clinicians, patients, and family members.

References

Angst, J. The course of monopolar depression and bipolar psychoses. *Psychiat. Neurol. Neurochir.*, 76:489–500, 1973.

Bellack, A.S., Hersen, M., and Himmelhoch, J.M. A comparison of social skills training, pharmacotherapy and psychotherapy for depression. *Behav. Res. Ther.*, 21:101–107, 1983.

Blackwell, B. Antidepressant drugs—Side effects and compliance. *J. Clin. Psychiatry*, 43:14–20, 1982.

DiMascio, A., Weissman, M.M., Prusoff, B.A., New, C., Zwilling, M., and Klerman, G.L. Differential symptom reduction by drugs and psychotherapy in acute depression. *Arch. Gen. Psychiatry*, 36:1450–1456, 1979.

Elkin, I., Parloff, M.B., Hadley, S.W., and Autry, J.H. NIMH Treatment of Depression Collaborative Research Program: Background and research plan. *Arch. Gen. Psychiatry*, 42:305–316, 1985.

Frank, E., Jarrett, D.B., Kupfer, D.J., and Grochocinski, V.J. Biological and clinical predictors of response in recurrent depression. *Psychiatry Res.*, 13:315–324, 1984.

Johnson, D.A.W. Treatment of depression in general practice. *Br. Med. J.*, 2:18–20, 1973.

Keller, M.B., Lavori, P.W., Lewis, C.E., et al. Predictors of relapse in major depressive disorder. *JAMA*, 250:3299–3304, 1983.

Keller, M.B., Lavori, P.W., Rice, J., et al. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: A prospective follow-up. *Am. J. Psychiatry*, 143:24–28, 1986.

Keller, M.B., Shapiro, R.W., Lavori, P.W., et al. Recovery in major depressive disorder—analysis with life table and contingency models. *Arch. Gen. Psychiatry*, 39:905–910, 1982a.

Keller, M.B., Shapiro, R.W., Lavori, P.W., et al. Relapse in major depressive disorder—analysis with the life table. *Arch. Gen. Psychiatry*, 39:911–915, 1982b.

Klerman, G.L., Weissman, M.M., Rounsaville, B.J., and Chevron, E.S. *Interpersonal Psychotherapy of Depression*. New York: Basic Books, 1984.

Kovacs, M., Rush, A.J., Beck, A.T., and Hollon, S.D. Depressed outpatients treated with cognitive therapy or pharmacotherapy: A one-year follow-up. *Arch. Gen. Psychiatry*, 38:33–39, 1981.

Murphy, G.E., Simons, A.D., Wetzel, R.D., and Lustman, P.J. Cognitive therapy and pharmacotherapy: Single and together in the treatment of depression. *Arch. Gen. Psychiatry*, 41:33–41, 1984.

Prien, R.F., and Kupfer, D.J. Continuation drug therapy for major depressive episodes: How long should it be maintained? *Am. J. Psychiatry*, 143:18–23, 1986.

Weissman, M.M., Klerman, G.L., Paykel, E.S., et al. Treatment effects on the social adjustment of depressed patients. *Arch. Gen. Psychiatry*, 30:771–778, 1974.

Weissman, M.M., Prusoff, B.A., and Klerman, G.L. Personality and the prediction of long-term outcome of depression. *Am. J. Psychiatry*, 135:797–800, 1978.

Zis, A.P., and Goodwin, F.K. Major affective disorder as a recurrent illness: A critical review. *Arch. Gen. Psychiatry*, 36:835–839, 1979.

Peripheral Hormones: A Window on the Central MA?

Co-Chairs:

Herman M. van Praag, M.D.
Gregory Asnis, M.D.
Stephen Zukin, M.D.

Department of Psychiatry
Albert Einstein College of Medicine, and
Montefiore Medical Center
Bronx, NY 10461

The Pitfalls of Serotonin Precursors as Challengers in Hormonal Probes of Central Serotonin Activity

Herman M. van Praag, M.D., Ph.D.,[1] Carmen Lemus, M.D.,[1] and Rene Kahn, M.D.[1]

Hormonal Probes of Central Serotonergic Activity

The response of a serotonin mediated function to a serotonin (5-hydroxytryptamine; 5-HT) agonist or antagonist has been used as a probe of the functional state of central 5-HT-ergic systems (Lemus & van Praag, 1986). Hormone release has been generally used as a 5-HT mediated function. The strategy is based on two assumptions; first, the challenger is 5-HT selective, and second, in the control of the marker-hormone 5-HT neurons play a significant role. In humans the two prerequisites are interdependent, in that the only way to ascertain the 5-HT-ergic involvement in a hormone's release is to measure its level in blood and cerebrospinal fluid (CSF) after administration of a 5-HT influencing drug. Hence the availability of 5-HT selective compounds is crucial. Challengers most frequently used have been the 5-HT precursors tryptophan and 5-hydroxytryptophan (5-HTP); the hormones most frequently measured are prolactin, cortisol, and growth hormone.

The issue here is the validity of hormonal 5-HT probes using 5-HT precursors as challengers.

Prolactin

Tryptophan

High doses of ℓ-tryptophan cause a release of prolactin. Charney et al. (1982) administered 7 g intravenously (i.v.) over a 20-minute period and observed a marked increase in serum prolactin, although the percent increase above baseline ranged widely (79 to 1100%). Likewise after i.v. administration of 5 to 10 g ℓ-tryptophan, MacIndoe and Turkington (1973) reported a substantial increase in plasma prolactin. Infusion of 4 g or less failed to produce consistent stimulation of prolactin secretion. After large oral doses (10 g) plasma prolactin rose but not significantly so (Woolf & Lee, 1977). Smaller oral doses of ℓ-tryptophan failed to induce prolactin release.

The central question is whether the prolactin-releasing effect of high i.v. doses of ℓ-tryptophan can be attributed to activation of 5-HT-ergic systems. There is reason for doubt. An oral dose of 5 g ℓ-tryptophan causes a significant increase in post-probenecid 5-hydroxyindoleacetic acid (5-HIAA) in CSF, indication of an augmented metabolism of 5-HT (van Praag, 1983). We demonstrated that the same dose of ℓ-tryptophan, administered i.v. over a 30-minute period, does not increase post-probenecid CSF 5-HIAA any further (Figure 1). The route of administration, however, does make a difference with regard to CSF concentration of homovanillic acid (HVA), the main dopamine (DA) metabolite, and 3-methoxy-4-hydroxyphenyl glycol (MHPG), the main CNS metabolite of noradrenaline (NA) (Figure 1). Oral administration of 5 g ℓ-tryptophan does not influence the HVA and MHPG concentration in CSF after probenecid administration. Both concentrations, however, diminish significantly if the i.v. route of administration is used, indicating a decrease in DA and NA metabolism. A likely explanation for this latter phenomenon is decreased influx of tyrosine in the CNS, due to competition with tryptophan for the same carrier mechanism (Wurtman, 1982; Wurtman et al., 1981). Rather than induced by an increased serotonergic "tone," the rise in plasma prolactin could have been caused by a decrease in DA synthesis and availability. It is true that MacIndoe and Turkington (1973) reported that methysergide inhibited the prolactin response to i.v. ℓ-tryptophan, but methysergide is not a selective 5-HT antagonist and has, e.g., antihistamine properties as well (Stone et al., 1961).

---

[1] Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY 10461.

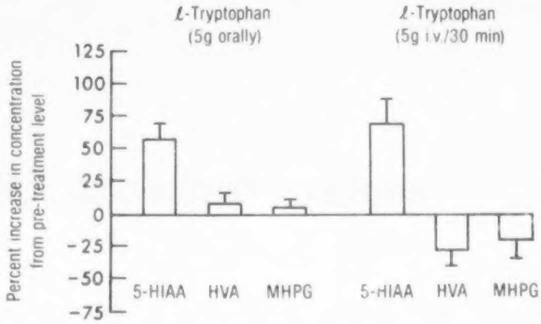


FIGURE 1. Percent increase in the concentration of 5-HIAA, HVA, and MHPG in lumbar CSF after administration to 5 test subjects of a single dose of 5 g ℓ-tryptophan either orally or i.v. 5-HIAA concentration rose significantly on both occasions and to the same extent. After oral administration, the changes in HVA and MHPG were insignificant; after i.v. administration both concentrations dropped significantly. Lumbar CSF was withdrawn after probenecid loading (5 g/5 hr), 8 hr after starting the load.

5-Hydroxytryptophan

Likewise, with 5-HTP it seems that only large doses influence prolactin release. Oral administration of 200 mg of the racemic mixture does not influence the plasma level of prolactin (Beck-Peccoz et al., 1976; Meltzer et al., 1983). The ℓ-isomer of 5-HTP, 200 mg orally, in combination with a peripheral decarboxylase inhibitor (PDI) had no effect either (Westenberg et al., 1982).

Administration of 50 mg i.v. of ℓ-5-HTP-ethyl-acetate after pretreatment with a PDI did result in a *decrease* of plasma prolactin (van Praag et al., 1976), while 200 mg of the same compound, also after pretreatment with the same PDI, induced a *rise* in prolactin release (Lancranjan et al., 1977). Are these effects to be explained in serotonergic terms?

We demonstrated that 200 mg ℓ-5-HTP orally in combination with a PDI gives rise not only to a substantial rise of post-probenecid CSF 5-HIAA, but to a significant rise of CSF HVA and MHPG as well (Figure 2), indicating that both 5-HT and catecholamine (CA) metabolism is increased (van Praag, 1983; van Praag & Lemus, 1986). We hypothesized the increase in CA metabolism to be a compensatory response to formation of 5-HT in CA-ergic neurons acting there as a false transmitter. The net effect of the two opposing effects: formation of false transmitter leading to decreased CA-ergic function, and increased CA synthesis resulting in increased CA-ergic function, is probably augmentation of CA-ergic activity (van Praag, 1984). The decrease in prolactin release we observed after i.v. 5-HTP could conceivably have been the result of increased DA activity. Perhaps the fourfold higher dose administered by Lancranjan et al. (1977) did set a 5-HT-ergic mechanism into action.

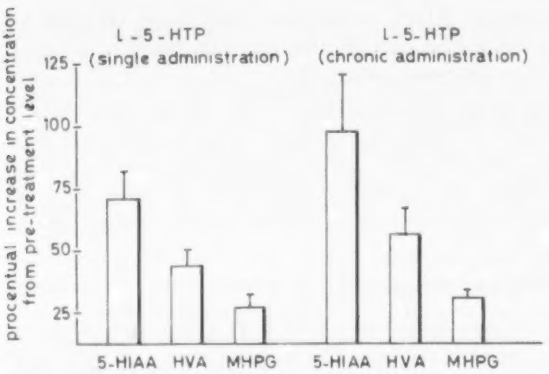


FIGURE 2. Percent increase in the concentration of 5-HIAA, HVA, and MHPG in lumbar CSF after administration to test subjects of a single dose of ℓ-5-HTP (200 mg orally) and after administration of the same dose for 1 week. In the acute experiment, the patients were pretreated with carbidopa (150 mg/day) for 3 days. In the chronic experiment, ℓ-5-HTP was combined with carbidopa in the same dose. In all cases, the increase in concentration in relation to the medication-free period was significant. Lumbar CSF was withdrawn after probenecid loading (5 g/5 hr), 8 hr after starting the load (van Praag, 1983).

Cortisol

Tryptophan

Modlinger et al. (1980) reported a significant increase of plasma ACTH and cortisol after an oral load of 10 g tryptophan in 11 normal volunteers. Activation of central 5-HT-ergic mechanisms is a conceivable mechanism, but there are others to be considered. First is increased adrenal steroid production due to a surplus of 5-HT formed in the periphery from tryptophan (Verdescu et al., 1961). This mechanism, however, is unlikely since ACTH production is also increased. A second possible mechanism for the increased release of ACTH and cortisol is decreased availability of NA, due to competition of tyrosine and tryptophan for transport into the CNS (Wurtman, 1982). The CRF/ACTH/cortisol axis is normally under β-adrenergic inhibitory control. Down-regulation of that mechanism would stimulate ACTH and cortisol release (Checkley, 1980; Nakai et al., 1973).

Several observations support the last mentioned hypothesis. ℓ-Tryptophan in relatively low doses, 2 to 5 g orally, does not significantly alter plasma cortisol (Hyyppa et al., 1979; Westenberg et al., 1982). However, it does increase post-probenecid 5-HIAA, without influencing CSF HVA and MHPG (van Praag, 1983; Westenberg et al., 1982). Higher doses, 5 g i.v. administered, while not further increasing CSF 5-HIAA, decreased CSF HVA and MHPG (Figure 1). These findings are hard to reconcile with 5-HT-ergic stimulation of cortisol release and suggest a CA-ergic mechanism.

The situation becomes confusing if one acknowledges the findings of Woolf and Lee (1977) who administered, like Modlinger et al. (1980), 10 g ℓ-tryptophan orally, but reported a *decrease* in plasma cortisol. Moreover, tryptophan blunted the ACTH and cortisol response to insulin hypoglycemia. They concluded that 5-HT is apparently a potent *inhibitor* of hypothalamic CRF in man. Peak plasma tryptophan levels were considerably lower in their experiment than in those of Modlinger et al. (1980) but well within the range we found to be effective in increasing CSF 5-HIAA.

5-Hydroxytryptophan (5-HTP)

The 5-HTP data are likewise controversial. Imura et al. (1973) administered 150 mg 5-HTP orally (isomer not mentioned) without PDI and observed a significant rise of plasma cortisol. Neither Westenberg et al. (1982) nor Meltzer et al. (1984) could replicate their findings, the former using much greater quantities of 5-HTP (200 mg of the ℓ-isomer with a PDI) than the latter (200 mg of the racemic mixture without PDI). In a group of patients suffering from major depression, however, Meltzer et al. (1984) found a rise in plasma cortisol, while we failed to find a response in this group either (Westenberg et al., 1982, 1984). The cortisol response to 5-HTP in depression was hypothesized to indicate hypersensitivity of postsynaptic 5-HT receptors.

A possible explanation for the discrepancy between the findings of Meltzer et al. and ourselves is the following. As discussed in the section on prolactin, the 5-HTP regimen we used increases both 5-HT and CA metabolism (van Praag, 1983) (Figure 2), and probably increases CA-ergic function (van Praag, 1984). Increased NA function would tend to decrease cortisol release and obscure a possible stimulating effect of surplus 5-HT in depressed patients. We found no evidence that cortisol release is induced by the PDI alone.

Against a serotonergic explanation of the increased cortisol response to 5-HTP observed in depression by Meltzer et al. (1984) speaks our observation that the dose of 5-HTP we administered definitely increases CSF 5-HIAA, while the low dose he used does not (van Praag, unpublished) (Figure 3). That is not to say that 5-HT metabolism in the CNS is not augmented by low doses of 5-HTP but that proof that that occurs is lacking.

Growth Hormone

Tryptophan

Most investigators but not all (MacIndoe & Turkington, 1973) have reported an increase in plasma growth hormone levels after administration of ℓ-tryptophan (Fraser et al., 1979; Muller et al., 1974; Westenberg et al., 1982; Woolf & Lee, 1977). The rise is modest and variable, and from the published data no clear dose/response relationship can be deducted. After a massive oral dose of 10g ℓ-tryptophan orally, the growth hormone level does not rise more than from 0.5 ± 0.2 ng/ml to 8.9 ± 3.4 ng/ml (Woolf & Lee, 1977). After a massive i.v. dose of 8.4 g, the rise was of comparable magnitude (Charney et al., 1982). A constant finding is that not all test persons respond to a tryptophan challenge.

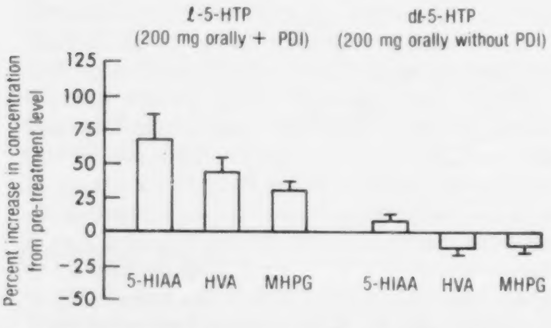


FIGURE 3. Percent increase in the concentration of 5-HIAA, HVA, and MHPG in lumbar CSF after administration to 5 test subjects of either a single dose of 200 mg ℓ-5-HTP after 3 days pretreatment with a peripheral decarboxylase inhibitor (PDI), or a single dose of 200 mg of the racemic mixture without PDI. Under the former regimen all three concentrations rose significantly. Under the latter circumstances they did not. Lumbar CSF was withdrawn after probenecid loading (5 g/5 hr), 8 hr after starting the load.

5-Hydroxytryptophan (5-HTP)

Large doses of 5-HTP do stimulate growth hormone release. Administration of 200 mg i.v. of ℓ-5-HTP in combination with a PDI induced a rise from <2 ng/ml to 32.0 ± 8.8 ng/ml (Lancranjan et al., 1977). The same dose orally prompted a tiny but significant increase from 1.7 ± 1.6 ng/ml to 2.6 ± 2.3 ng/ml (Westenberg et al., 1982). Smaller doses of 5-HTP with or without PDI have generally no effect (Ansseau et al., 1983; Handwerger et al., 1975; Muller et al., 1974). Only Imura et al. (1973) reported a rise of growth hormone of more than 5 ng/ml in six of eight subjects tested after no more than 150 mg 5-HTP (ℓ-isomer or racemic mixture is not stated) orally without PDI.

As explained above, 5-HTP in large doses stimulates CA turnover and the release of growth hormone could be attributed to that effect rather than to increased 5-HT availability. Supporting evidence is provided by a preliminary report of Imura et al. (1973)—reported by Checkley (1980)—that the growth hormone response to 5-HTP is blocked by the α-adrenoreceptor blocker phentolamine.

Discussion

No 5-HT precursor-mediated hormonal test can claim to be a valid probe of central 5-HT-ergic activity. The reason is that neither tryptophan nor 5-HTP are 5-HT selective and do influence CAs as well. The effect on CA becomes generally manifest after large amounts of the precursor, but most studies indicate that those are needed for a hormonal response to be observed. It is therefore impossible to decide whether the observed hormonal changes are 5-HT or CA mediated.

In attempts to develop a hormonal 5-HT probe, synthetic 5-HT agonists and antagonists have also been used. The results so far have been disappointing (van Praag et al., 1986) and for several reasons. Non-selectivity of the challenger is one of them. Using the same drug in different doses and routes of administration, not caring to establish proper dose-response relationships is another. Comparability of individual studies is therefore regrettably low.

A peripheral probe of central 5-HT activity, circumventing the need to measure CSF 5-HIAA, would be of great importance for biological studies of depression, suicide, and aggression disorders. A challenge test, however, should not be accepted as a 5-HT probe before: 1) dose-response relationship has been established; 2) studies in humans have rendered influences of the challenger on other monoaminergic systems unlikely; and 3) the hormonal effect of the challenger has been shown to be counteracted by a functional opponent of the challenger.

Summary

5-HT precursors have been used as challengers in hormonal probes of central 5-HT activity. Those tests, however, lack validity because both tryptophan and 5-HTP do influence CA as well, in particular if administered in large quantities; but these are generally needed to obtain a hormonal response. Hence it is impossible to conclude whether the response is 5-HT or CA mediated. Peripheral probes of central 5-HT activity are badly needed, but before being accepted as such, one should make sure that certain minimum requirements have been satisfied.

References

Ansseau, M., Doumont, A., Thiry, D., et al. Interest of 5-hydroxytryptophan (5-HTP) as a neuroendocrine marker in depressive illness. *Acta Psychiat. Belg.*, 83:50-56, 1983.

Beck-Peccoz, O., Ferrari, C., Rondena, M., et al. Failure of oral 5-hydroxytryptophan administration to affect prolactin secretion in man. *Hormone Res.*, 7:303-307, 1976.

Charney, D.S., Heninger, G.R., Reinhard, J.F., et al. The effect of IV ℓ-tryptophan on prolactin, growth hormone, and mood in healthy subjects. *Psychopharmacology*, 78:38-43, 1982.

Checkley, S.A. Neuroendocrine tests of monoamine function in man: A review of basic theory and its application to the study of depressive illness. *Psychol. Med.*, 10:35-53, 1980.

Fraser, W.M., Tucker, H.S., Grubb, S.R., et al. Effect of ℓ-tryptophan on growth hormone and prolactin release in normal volunteers and patients with secretory pituitary tumors. *Horm. Metab. Res.*, 11:149-155, 1979.

Handwerger, S., Plonk, J.W., Lebovitz, H.E., et al. Failure of 5-hydroxytryptophan to stimulate prolactin and growth hormone secretion in man. *Hormone Res.*, 6:214-216, 1975.

Hyyppa, M.T., Jolma, T., Lura, J., et al. ℓ-Tryptophan treatment and the episodic secretion of pituitary hormones and cortisol. *Psychoneuroendocrinology*, 4:29-35, 1979.

Imura, H., Nakai, Y., and Yoshimi, T. Effect of 5-hydroxytryptophan (5-HTP) on growth hormone and ACTH release in man. *J. Clin. Endocrinol. Metab.*, 36:204-206, 1973.

Lancranjan, I., Wirz-Justice, A., Puhringer, W., and Del Pozo, E. Effect of ℓ-5-hydroxytryptophan infusion on growth hormone and prolactin secretion in man. *J. Clin. Endocrinol. Metab.*, 45:588-593, 1977.

Lemus, C.Z., and van Praag, H.M. Monoamine precursors: Effects on neuroendocrine parameters. In: Nemeroff, C.B., and Loosen, P. (eds.), *Handbook of Clinical Psychoneuroendocrinology*. New York: Guilford Press. (in press)

MacIndoe, J.H., and Turkington, R.W. Stimulation of human prolactin secretion by intravenous infusion of ℓ-tryptophan. *J. Clin. Invest.*, 52:1972-1978, 1973.

Meltzer, H.Y., Tricou, B.J., Robertson, A., and Lowy, M. Hormone response to 5-hydroxytryptophan. *Psychiatry Res.*, 10:151-152, 1983.

Meltzer, H.Y., Umberkoman-Witta, B., Robertson, A., et al. Effect of 5-hydroxytryptophan on serum cortisol levels in major affective disorders. *Arch. Gen. Psychiatry*, 41:366-374, 1984.

Modlinger, R.S., Schonmuller, J.M., and Arora, S.P. Adrenocorticotropin release by tryptophan in man. *J. Clin. Endocrinol. Metab.*, 50:360-363, 1980.

Muller, E.E., Brambilla, F., Cavagnini, F., et al. Slight effect of ℓ-tryptophan on growth hormone release in normal human subjects. *J. Clin. Endocrinol. Metab.*, 39:1-5, 1974.

Nakai, Y., Imura, H., Sakhurai, H., et al. Effect of cyproheptidine on human growth hormone secretion. *J. Clin. Endocrinol. Metab.*, 38:446-449, 1974.

Stone, C.L., Wenger, H.C., Ludden, C.T., et al. Antiserotonin-antihistaminic properties of cyproheptidine. *J. Pharmacol. Exp. Ther.*, 131:73-84, 1961.

van Praag, H.M. Antidepressants today: Critical evaluation of some "established concepts." In: Racagni, G., Paoletti, R., and Kieholz, P. (eds.), *Clinical Neuropharmacology*. New York: Raven Press, 1984.

van Praag, H.M. In search of the mode of action of antidepressants: 5-HTP/tyrosine mixtures in depression. *Neuropharmacology*, 22:433-440, 1983.

van Praag, H.M., Korf, J., and Lequin, R.M. An unexpected effect of ℓ-5-hydroxytryptophan-ethyl-ester combined with a peripheral decarboxylase inhibitor on human serum prolactin. *Psychopharmacol Comm.*, 2:369-378, 1976.

van Praag, H.M., and Lemus, C. Monoamine precursors in the treatment of psychiatric disorders. In: Wurtman, R.J., and Wurtman, J.J. (eds.), *Nutrition and the Brain*, Vol. 7. New York: Raven Press, 1986.

van Praag, H.M., Lemus, C., and Kahn, R. Hormonal probes of central serotonergic activity. Do they really exist? (Submitted, 1986.)

Verdescu, A.S., Westermann, C.D., Crampton, R.S., et al. Direct adrenocortical stimulatory effect of serotonin. *Am. J. Physiol.*, 6:1065, 1961.

Westenberg, H.G.M., van Praag, H.M., de Jong, J.T.V.M., and Thyssen, J.H.H. Post-synaptic serotonergic activity in depressive patients: Evaluation of the neuroendocrine strategy. *Psychiatry Res.*, 7:361-371, 1982.

Woolf, P.D., and Lee, L. Effect of the serotonin precursor, tryptophan, on pituitary hormone secretion. *J. Clin. Endocrinol. Metab.*, 45:123-133, 1977.

Wurtman, R.J. Nutrients that modify brain functions. *Sci. Am.*, 246: 42-51, 1982.

Wurtman, R.J., Hefti, F., and Melamed, E. Precursor control of neurotransmitter synthesis. *Pharmacol. Rev.*, 32:315-335, 1981.

The Desipramine Cortisol Test—A Selective Noradrenergic Challenge (Relationship to Other Cortisol Tests in Depressives and Normals)

Gregory M. Asnis, M.D.,[1] Carmen Z. Lemus, M.D.,[1] and Uriel Halbreich, M.D.[1]

Introduction

The use of peripheral hormones to provide a "window into the brain" was proposed by Sachar (1975). This was based on the fact that hormone secretion was primarily regulated in the hypothalamus by certain neurotransmitters and peptides. Thus, hormone levels would convey specific neurotransmitter information. The catecholamines—dopamine and norepinephrine—act as neurotransmitters at the hypothalamic level and control the hypothalamic releasing and inhibiting factors that act on the anterior pituitary. By using pharmacologic agents which interfere with catecholamine synthesis or metabolism and concurrently measuring peripheral hormone levels, some conclusions can be made as to the effect of a particular catecholamine on a particular hormone.

We have been mainly interested in cortisol since increased cortisol secretion has been the most consistent neuroendocrine finding in depressive illness. But what neurotransmitter disturbances are associated with cortisol hypersecretion remains unclear.

The secretion of ACTH and cortisol is believed to be under the control of multiple neurotransmitters. The role of each neurotransmitter in relation to the release of these hormones is not well known. Dopamine seems to have no effect on ACTH secretion in humans (Westenberg et al., 1982) although it inhibits ACTH release in rats (Moore, 1978). Studies with serotonin agonists and antagonists implicate this neurotransmitter in the regulation of ACTH, although results have been inconsistent. Some studies have been unable to stimulate ACTH and cortisol release after administration of 5-hydroxytryptophan (5-HTP) (Westenberg et al., 1982; Wirz-Justice et al., 1976) or L-tryptophan (Westenberg et al., 1982), while others have reported increases in ACTH and cortisol (Meltzer et al., 1983; Modlinger et al., 1980). Results with administration of serotonin antagonists are more uniform and point to an excitatory influence. Cyproheptadine has been shown to inhibit the basal and nocturnal rise of cortisol (Chihara et al., 1976; Delitala et al., 1975) as well as the cortisol secretion secondary to insulin-hypoglycemia (Plonk et al., 1974).

As for the noradrenergic system, it is generally believed that α-adrenergic receptors have a stimulatory effect and β-adrenergic receptors have an inhibitory effect on ACTH secretion. α-Agonists such as methoxamine stimulate ACTH secretion while the α-blocker phentolamine inhibits the ACTH response to methoxamine and to insulin-hypoglycemia (Nakai et al., 1973). On the other hand, the β-blocker propranolol augments the ACTH response to hypoglycemia (Nakai et al., 1973). The effect of the noradrenergic system as a whole is believed by most to be inhibitory (Jones, 1978) although there are some proponents of a stimulatory action of norepinephrine on ACTH (Besser et al., 1969; Nakai et al., 1973).

As highlighted by this brief review of cortisol regulation, cortisol hypersecretion in depressive illness may be a final common pathway encompassing diverse groups of depressives with disturbances in multiple neurotransmitters. Thus, it seemed most important to utilize selective neurotransmitter probes to help evaluate cortisol secretion in man and possibly identify more homogeneous groups of depressives. In particular, a noradrenergic probe seemed warranted since NE is one of the neurotransmitters thought to be involved in the regulation of cortisol and is one of the main neurotransmitters im-

---

[1] Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467.

Supported in part by NIMH Grant MH-38807 to Dr. Asnis.

plicated in depressive illness (Bunney & Davis, 1965; Schildkraut, 1967).

In the past we have published extensively on the cortisol response to dextroamphetamine in normals and depressives. A blunted cortisol response to dextroamphetamine in depressives was a consistent finding (Halbreich, 1981; Sachar et al., 1980, 1981). Interpretation of this observation was complicated by the fact that dextroamphetamine, besides affecting norepinephrine, also releases dopamine, phenylethylamine, endorphin, and possibly serotonin (Halbreich et al., 1982; Moore, 1978). The latter has also been suggested to stimulate cortisol release, thus complicating any interpretation of mechanisms for the cortisol release to amphetamine (Checkley, 1980). Furthermore, since cortisol is a stress-sensitive hormone and amphetamine has significant behavioral effects in subjects, it is possible that cortisol differences between depressives and nondepressives were related to differences in their behavioral responses. This seems unlikely, though possible, since methylphenidate has been reported to induce similar behavioral changes as amphetamine without affecting cortisol (Brown et al., 1977). Ideally, the use of a noradrenergic agonist which is highly selective and does not cause significant mood or behavioral changes would be a most appropriate tool in assessing noradrenergic effects on cortisol secretion in man (depressives and nondepressives).

For this reason we were most interested in investigating the cortisol response to a relatively specific noradrenergic agonist, desipramine (DMI). Furthermore, we wanted to evaluate whether the cortisol response to DMI in depressives differed from normals as is the case with many other measures of cortisol secretion (e.g., DST and basal plasma cortisol). We hoped that the DMI-cortisol test would identify a group of depressives which in theory might be homogeneous (with a possible noradrenergic deficit) allowing for identification of particular clinical correlates which other tests of cortisol secretion have failed to do. Also, we wanted to compare the DMI cortisol response to other measures of cortisol secretion (mean 1 to 4 p.m. plasma cortisol test and the 1 mg DST) in depressives and normals. Thus, a pilot study was initiated. Preliminary findings of this project have been reported recently (Asnis et al., 1985).

Pilot Study

Thirteen endogenous depressives (8 females and 5 males), 23 to 64 years old (mean age 38.7 SE 2.8 years), and 20 normal controls (10 females and 10 males), 18 to 52 years old (mean age 33.0 SE 2.6 years), gave informed consent and participated in the study. Although subjects were not matched for age and sex, there were no significant differences in age (t = 1.50, 2-tailed t-test), nor frequency of sex ($\chi^2 = 0.423$). Patients were given a SADS interview and diagnosed by RDC criteria (Endicott & Spitzer, 1978; Spitzer et al., 1978) for major depressive disorder, endogenous subtype; normal controls were judged free of any psychiatric disorder after receiving a SADS interview. All patients had a Hamilton Depression score of ≥ 18 (mean Hamilton score 25.5 SE 2.1) and were free of psychotropics for a minimum of 10 days. In addition to the RDC diagnosis of major depressive disorder, endogenous subtype, which all 13 patients had, 4 patients had a psychotic depression, 3 had bipolar depression, and 3 had a secondary depression (2 secondary to alcoholism—abstinent from alcohol for at least 6 months—and 1 secondary to panic disorder).

DMI Procedure

All subjects fasted from midnight and awakened at 0700 h. A butterfly needle was inserted in the forearm vein at 0900 h and kept patent with sterile saline. After obtaining three baseline samples (4 cc each at 15 min intervals), 75 mg i.m. DMI was given in the gluteal muscle followed by sampling (4 cc) every 15 min for plasma cortisol for 120 min. All samples were centrifuged and then frozen at −20°C to await analysis.

Other Cortisol Assessments (the Mean 1–4 Plasma Cortisol Test and the 1 mg DST) Administered 5 Days After the DMI Procedure

The mean 1–4 p.m. plasma cortisol test is an integrated measure of plasma cortisol secretion since it has been shown to be highly correlated to the mean 24 h plasma cortisol in normals and depressives (Halbreich et al., 1981, 1982). All subjects had an angiocatheter inserted in a forearm vein prior to 1130 h (with sampling every 30 min for plasma cortisol). Subjects remained supine during the test and were all given breakfast at 0730 h and a light lunch at 1030 h; no snacks or naps were permitted. The average of the seven 30-minute samples from 1 p.m. to 4 p.m. was the mean 1 p.m.–4 p.m. plasma cortisol level.

The 1 mg DST is a test widely utilized in endocrinology and psychiatry. Dexamethasone, a synthetic corticosteroid many times more potent than cortisol, normally turns off endogenous cortisol secretion for 24 to 48 h by affecting feedback receptors. Investigators have found that approximately two-thirds of endogenous depressives failed to suppress cortisol. (For review *see* Arana et al., 1985.)

All the subjects were given 1 mg of dexamethasone to be taken orally at 11:00 p.m. (the same day of the 1–4 p.m. plasma cortisol test). The following day a postdexamethasone plasma cortisol level was obtained at 8 a.m., 4 and 11 p.m. A plasma postdexamethasone cortisol greater than 5 µg/dl at any time was used to define non-suppression to dexamethasone.

Cortisol Assay

All plasma samples were analyzed in duplicate by a modified competitive binding method, using Florisil to separate bound from free fractions (Murphy, 1967). Intra- and interassay coefficients of variation of duplicate samples were 2.8 and 9.0 percent, respectively. All samples from a given subject were assayed in the same run.

Results

The cortisol response to DMI over 120 min in both endogenous depressives and normal controls is seen in Figure 1. A repeated measures analysis of variance was performed on the group and time effects and their interaction. The group effect was not significantly larger than the between subject effect (F = 1.06, df 1/31, $p = 0.31$); there was a significant time and a group × time interaction (F = 13.65, df 10/307, $p = .001$ and $F = 2.68$, df 10/307, $p = .003$, respectively). The means of individual cells were compared at equivalent time points between groups as planned comparisons. It was found that these means were not significantly different at time points prior to 45 min or subsequent to 75 min. Significant differences did occur between 45 to 75 min ($p = .01$ at 45 min, $p = .02$ at 60 min, $p = .0001$ at 75 min). These data were also analyzed as percent increase above baseline cortisol; the data demonstrated similar differences between groups and with significant differences at the same time points (45 to 75 min).

The cortisol change scores (post–DMI cortisol minus baseline cortisol) of endogenous depressives and normal controls at the significant times (45 to 75 min) were evaluated for cutoff values which would best discriminate endogenous depressives from normal controls. A cutoff of 1.5 µg/dl increase above baseline at 45 min most significantly discriminated between normals and depressives. This criterion was the same as the one found best in discriminating endogenous depressives from normal controls utilizing the dextroamphetamine cortisol test (Sachar, 1981). The Δ45 min cortisol with a cutoff of 1.5 µg/dl identified 7 of 13 depressives and 1 of 20 normals (Fisher Exact Test=.003) (Figure 2).

It was decided on the basis of the repeated measures effect to convert the post-DMI cortisol levels to change scores from baseline (time 0) in order to examine the effect of

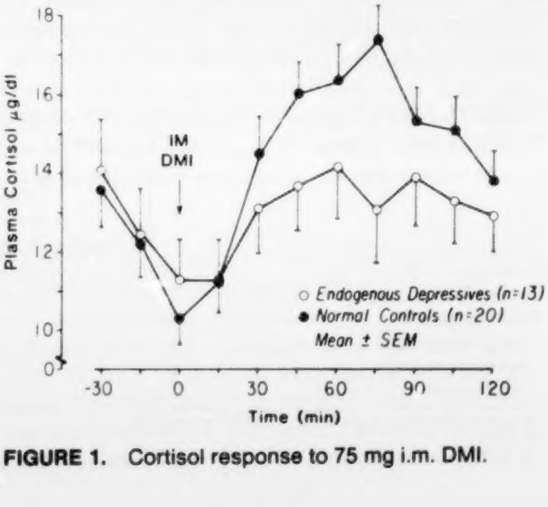


FIGURE 1. Cortisol response to 75 mg i.m. DMI.

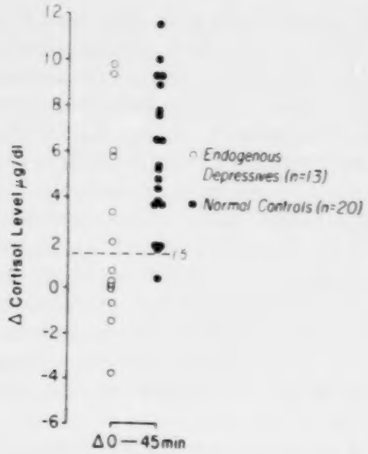


FIGURE 2. The Δ45-minute cortisol response to 75 mg i.m. DMI in 13 endogenous depressives and 20 normal controls as a discriminator between groups.

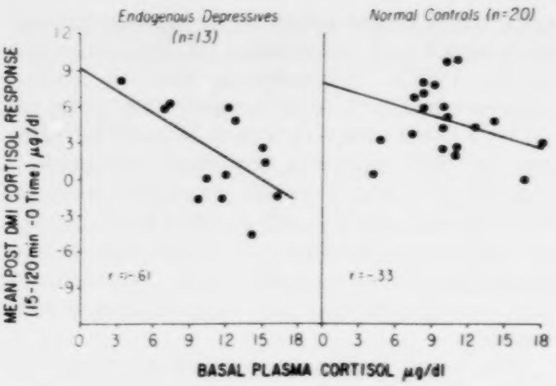


FIGURE 3. Mean post-DMI cortisol response vs. basal plasma cortisol in 13 endogenous depressives and 20 normal controls.

potential covariates: 1) basal cortisol just prior to i.m. DMI; 2) age; and 3) sex. Basal plasma cortisol just prior to i.m. DMI and sex were significant covariates in contrast to age, but only basal cortisol accounted for a sizable portion of the variance (30.9 percent). Nonetheless, the group difference (depressives versus normal controls) still remained highly significant after covarying out any of these factors (*see* Table 1).

Since basal cortisol was the most significant covariate examined, it was further evaluated and plotted against mean post-DMI cortisol in both endogenous depressives and normal controls (*see* Figure 3). As can be seen, baseline cortisol was negatively correlated to DMI-cortisol response in both depressives and controls. But of particular note is that, as a group, the slope of the response of the depressives was greater than that of the controls ($F = 4.98, p < .01$).

Although an actual placebo study was not conducted to definitively rule out that the DMI cortisol response might be a placebo response, or due to cortisol diurnal rhythmicity, stress of venipuncture, etc., a non-DMI procedure day with assessments of cortisol was available for comparison to several time points of the DMI day for many subjects. This non-DMI day procedure (from which the 1–4 p.m. plasma cortisol test was taken) was an assessment of basal cortisol involving an insertion of a cannula in a forearm vein 0900 to 1000 h with sampling of cortisol every 30 min for a minimum of 7 h (time for DMI was always at 0930 h, 30 min after the cannula insertion. Cortisol levels on the non-DMI day were used only after a 30 min adaptation to a post-cannula insertion). Cortisol

TABLE 1. Mean Post-DMI Cortisol Response (Baseline-Corrected) of Endogenous Depressives vs. Normal Controls and the Effect of Covariates.

	Mean ± SD Basal Cortisol (μg/dl)	Mean ± SD Post-DMI Cortisol (μg/dl)	Basal Plasma Cortisol[1]	Sex[1]	Age[1]
Controls $n = 20$	10.31 ± 3.04	4.68 ± 1.34	4.49	4.61	4.84
Depressives $n = 13$	11.31 ± 3.77	1.86 ± 1.55	2.14	1.91	1.80
F for covariates			4.58[2]	5.58[3]	0.37
F for group before/ after controlling for covariate	0.70	33.09[3]	26.72[3]	33.70[3]	39.91[3]

[1] Mean post-DMI response adjusted for the particular covariate.
[2] $p < 0.02$.
[3] $p < 0.001$.

values from the DMI day were compared to the non-DMI day using correlated *t* tests at each time point for both normals and depressives (Figures 4 and 5). Both normals and depressives had higher cortisol levels on the DMI day vs. non-DMI day at most time points after DMI administration. Thus, the cortisol response to DMI appears not to be due to placebo response, diurnal rhythmicity, stress of venipuncture, etc.; the definitive evaluation—a double blind i.m. DMI vs. i.m. placebo (saline) study—is in progress.

DST, Mean 1–4 p.m. Plasma Cortisol and Their Relationship to DMI-Cortisol Response

The 1 mg DST found 46 percent nonsuppressors in the depressives and 5 percent nonsuppressors in the normals (Fisher Exact Test = .008); the mean 1–4 p.m. plasma cortisol level was 9.48 (SE 0.97) μg/dl for the depressives vs. 7.24 (SE 0.52) μg/dl for the normals ($t = 2.22$, $p < .04$).

The DMI Δ45 cortisol, which best discriminated depressives from normals, was highly correlated to the basal cortisol assessment—the mean 1–4 p.m. plasma cortisol—and to the 1 mg DST in depressives (the DST was compared to continuous variables—DMI Δ45 min cortisol and mean 1–4 p.m. plasma cortisol—by point bi-serial correlations). (*See* Tables 2 and 3.) In contrast, there were no significant correlations of these variables within the normal controls.

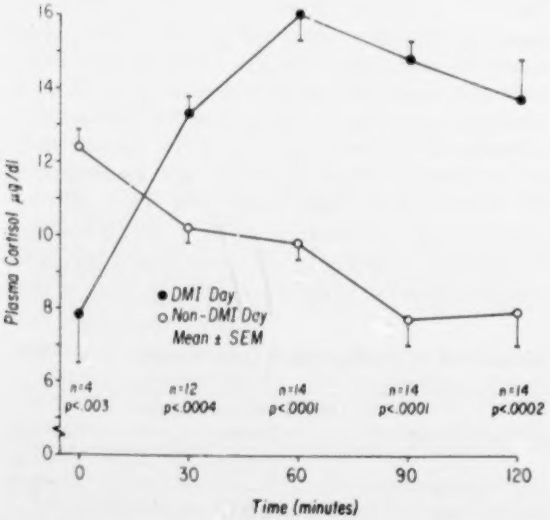


FIGURE 4. Plasma cortisol in a DMI day vs. a non-DMI day in normal controls.

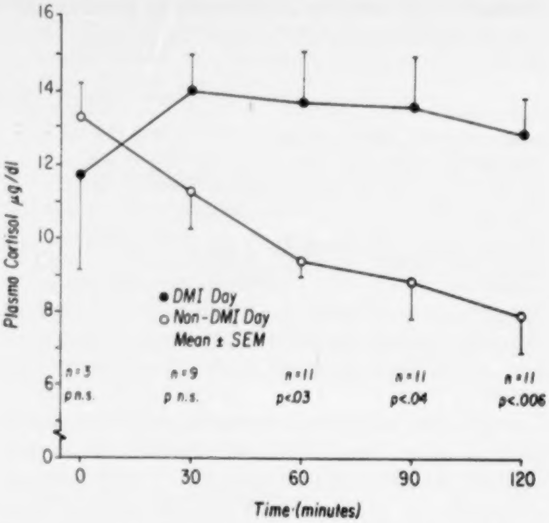


FIGURE 5. Plasma cortisol in a DMI day vs. a non-DMI day in endogenous depressives.

Although mean 1–4 p.m. plasma cortisol and DST significantly correlated to DMI Δ45 min cortisol, these parameters did not explain the group difference (DMI cortisol response) after covarying out DST ($F = 36.20$, $p < .001$) or covarying out mean 1–4 p.m. plasma cortisol ($F = 36.08$, $p < .001$).

Due to the small size of this sample, clinical correlates could not be reliably examined. However, it is useful to point out that, within endogenous depressives, the severity of depression (Hamilton score) was not correlated with mean cortisol post-DMI ($r = .17$, NS).

The DMI cortisol test was well tolerated. There was no significant effect on pulse or blood pressure. Mild dryness of mouth and nausea were occasionally noted in subjects, but side effects were not routinely assessed.

Discussion

The cortisol response to DMI (75 mg i.m.) was significantly decreased in endogenous depressives when compared to normal controls. A lack of a cortisol rise of 1.5 μg/dl above baseline at 45 min (Δ45 min) was the best discriminator between depressives and normals, identifying 7 of 13 depressives and 1

TABLE 2. Correlation Coefficients of Various Cortisol Measures in Normal Controls ($n = 20$).

	DMI Δ45 min	Mean 1-4 p.m. Plasma Cortisol	1 mg DST
DMI Δ45 min	—	*−0.05	*0.05
Mean 1-4 p.m. plasma cortisol	*−0.05	—	*0.35
1 mg DST	*0.05	*0.35	—

*p=NS.

of 20 normals (Fisher Exact Test = .003). This criterion for "inadequate cortisol response" was similar to the one found best in discriminating normals from depressives with i.v. dextroamphetamine by Sachar et al. (1981).

Age, sex, and basal cortisol (plasma cortisol just prior to i.m. DMI) were assessed as potential factors that might effect the cortisol response to DMI. Basal plasma cortisol and sex were significant covariates, but only basal cortisol contributed to a sizable portion of the variance, 30.9 percent. However, after controlling for each of these covariates, the group difference remained significant.

Among the various factors evaluated as to their potential effect on the cortisol response to DMI were other measures of cortisol secretion, namely the 1–4 p.m. plasma cortisol test and 1 mg DST. The DMI cortisol test was found to be negatively correlated to both the 1–4 p.m. plasma cortisol and to the DST in depressives. Interestingly, there were no significant correlations of these variables within the normal controls. It seems that with normal HPA axis functioning these multiple levels of cortisol secretion assessed (basal cortisol, cortisol suppression, and cortisol stimulation) are not correlated. Only when a clear disturbance in the HPA axis occurs (e.g., endogenous depression) do these cortisol parameters become correlated.

Due to the relatively small sample size and the lack of a patient control group or a placebo control in this pilot study, it is difficult to arrive at conclusions about the usefulness of the DMI-cortisol test as a laboratory aid to identify endogenous depressives. But more importantly, this test might serve to identify a biochemically homogeneous subgroup of depressed patients with similar clinical correlates and treatment responsivity. A study currently in progress will address this issue.

The mechanism of action of the cortisol response to DMI brings into question the role of NE in the regulation of cortisol secretion in man. Although animal studies suggest a predominantly inhibitory role of NE on cortisol secretion (Jones, 1978), the data presented in this paper on cortisol response to i.m. DMI—a relatively selective NE uptake inhibitor—suggest a stimulatory role of NE on cortisol secretion. This notion is supported by prior work with i.v. methylamphetamine and dextroamphetamine demonstrating a marked cortisol release in man (Besser et al., 1969; Sachar et al., 1981).

As stated, DMI is considered a relatively selective NE uptake inhibitor. On the other hand, to a lesser extent it is also a serotonin uptake inhibitor (Jarvaid et al., 1979; Randrup & Braestrup, 1977). Thus, it is possible that the blunted cortisol response to DMI in endogenous depression might be due to a serotonin deficit rather than a NE deficit and/or an α-adrenergic insensitivity. Laakman et al. (1985) have addressed this issue and reported that pretreatment of a small number of normal volunteers with methysergide (a serotonin blocker) had no effect on the cortisol

TABLE 3. Correlation Coefficients of Various Cortisol Measures in Endogenous Depressives ($n = 13$).

	DMI Δ45 min	Mean 1-4 p.m. Plasma Cortisol	1 mg DST
DMI Δ45 min	—	*−0.58	*−0.58
Mean 1-4 p.m. plasma cortisol	*−0.58	—	**0.72
1 mg DST	*−0.58	**0.72	—

* $p < .04$.
**$p < .005$.

response to DMI, whereas administration of prazosin, an α 1-adrenergic blocker, resulted in a blunted cortisol response. This finding further supports the notion of a NE deficit and/or α-adrenergic receptor insensitivity being responsible for the blunted cortisol response to DMI in depressives.

References

Arana, G.W., Baldessarini, R.J., and Ornsteen, M. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. *Arch. Gen. Psychiatry*, 42:1193–1204, 1985.

Asnis, G.M., Halbreich, U., Rabinovich, H., et al. The cortisol response to desipramine in endogenous depressives and normal controls: Preliminary findings. *Psychiatry Research*, 14:225–233, 1985.

Berger, M., Pirke, K.M., Doerr, P., et al. The limited utility of the dexamethasone suppression test for the diagnostic process in psychiatry. *Brit. J. Psychiatry*, 145:372–382, 1984.

Besser, G.M., Butler, P.W.P., Landon, J., and Rees, L. Influence of amphetamines on plasma corticosteroid and growth hormone levels in man. *Br. Med. J.*, 4:528–530, 1969.

Brown, W.A., Corrivear, D.P., and Ebert, M.H. Acute psychologic and neuroendocrine response to methylphenidate. *Arch. Gen. Psychiatry*, 34:1103–1108, 1977.

Bunney, W.E., and Davis, J.M. Norephinephrine in depressive reactions: A review. *Arch. Gen. Psychiatry*, 13:483–494, 1965.

Carroll, B.J., Feinberg, M., and Gredan, J.F. A specific laboratory test for diagnosis of melancholia: Standardization, validation and clinical utility. *Arch. Gen. Psychiatry*, 38:15–22, 1981.

Checkley, S.A. Neuroendocrine tests of monoamine function in man: A review of basic theory and its application to the study of depressive illness. *Psychol. Med.*, 10:35–53, 1980.

Chihara, K., Kato, Y., Maeda, K., et al. Suppression by cyproheptadine of human growth hormone and cortisol secretion during sleep. *J. Clin. Invest.*, 57:1393–1402, 1976.

Delitala, G., Masala, A., Alagna, S., and Devilla, D. Effect of cyproheptadine on the spontaneous diurnal variation of plasma ACTH-cortisol and ACTH-GH secretion induced by L-dopa. *Biomedical Express*, 23:406–409, 1975.

Endicott, J., and Spitzer, R.L. A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Arch. Gen. Psychiatry*, 35:837–844, 1978.

Halbreich, U., Sachar, E.J., Asnis, G.M., et al. Studies of cortisol diurnal rhythm and cortisol response to D-amphetamine in depressed patients. *Psychopharm. Bull.*, 17:114–116, 1981.

Halbreich, U., Zumoff, B., Kream, J., and Fukushuma, D.K. The mean 1-4PM plasma cortisol concentration as a diagnostic test for hypercortisolism. *J. Clin. Endocrinol. Metab.*, 54:1262–1264, 1982.

Halbreich, U., Goldstein, S., Low, S., and Endicott, J. Endorphins may be involved in the behavioral response to dextroamphetamine. *Psychopharm. Bull.*, 18:216–219, 1982.

Jarvaid, J.I., Perel, J.M., and Davis, J.M. Inhibition of biogenic amines uptake by imipramine, desipramine, 20H-imipramine and 20H-desipramine in man. *Life Sciences*, 24:21, 1979.

Jones, M.T. Control of corticotrophin (ACTH) secretion. In: Jeffcoate, S.L., and Hutchinson, J.S. (eds.), *The Endocrine Hypothalamus*. New York: Academic Press, 1978, pp. 385–419.

Laakman, G., Schoen, H.W., Blaschke, D., and Wittman, M. Dose-dependent growth hormone, prolactin and cortisol stimulation after I.V. administration of desipramine in human subjects. *Psychoneuroendocrinology*, 10(1):83–93, 1985.

Meltzer, H.Y., Tricou, B.J., Robertson, A., and Lowy, M. Hormone response to 5-hydroxytryptophan. *Psychiatry Res.*, 10:151–152, 1983.

Modlinger, R.S., Schonmuller, J.M., and Arora, S.P. Adrenocorticotrophin release by tryptophan in man. *J. Clin. Endocrinol. Metab.*, 50:360–363, 1980.

Moore, K.T. Amphetamines: Biochemical and behavioral actions in man. In: Iversen, L.L., Iversen, S.D., and Snyder, S.H. (eds.), *Handbook of Psychopharmacology: Stimulants*, Vol. II. New York: Plenum Press, 1978, pp. 47–98.

Muller, E.E., Nistoco, G., and Scapagnini, U. *Neurotransmitters and Pituitary Function*. New York: Academic Press, 1977.

Murphy, B.E.P. Some studies of the protein-binding of steroids and their application to the routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radioassay. *J. Clin. Endocrinol. Metab.*, 27:973–990, 1967.

Nakai, Y., Imura, H., Yoshimi, T., and Matsukura, S. Adrenergic control mechanism for ACTH secretion in man. *Acta Endocrinol.*, 74:263–270, 1973.

Plonk, J.W., Bivens, C.H., and Feldman, J.M. Inhibition of hypoglycaemia induced cortisol secretion by the serotonin antagonist cyproheptadine. *J. Clin. Endocrinol. Metab.*, 38:836–840, 1974.

Randrup, A., and Braestrup, P. Uptake inhibition of biogenic amines by newer antidepressant drugs: Relevance to the dopamine hypothesis. *Psychopharmacology*, 53:309, 1977.

Sachar, E.J. Neuroendocrine abnormalities in depressive illness. In: Sachar, E.J. (ed.), *Topics in*

Psychoendocrinology. New York: Gruen and Stratton, 1975, pp. 135–156.

Sachar, E.J., Asnis, G.M., Nathan, R.S., et al. Dextroamphetamine and cortisol in depression. *Arch. Gen. Psychiatry*, 37:755–757, 1980.

Sachar, E.J., Halbreich, U., Asnis, G.M., et al. Paradoxical cortisol responses to dextroamphetamine in endogenous depression. *Arch. Gen. Psychiatry*, 38:1113–1117, 1981.

Schildkraut, J.J., and Kety, S.S. Biogenic amines and emotion. *Science*, 156:21–30, 1967.

Spitzer, R.L., Endicott, J., and Robins, E. Research Diagnostic Criteria: Rationale and reliability. *Arch. Gen. Psychiatry*, 35:773–782, 1978.

Westenberg, H.G.M., van Praag, H.M., deJong, J.T.V.M., and Thyssen, J.H.H. Post-synaptic serotonergic activity in depressive patients: Evaluation of the neuroendocrine strategy. *Psychiatry Res.*, 7:361–371, 1982.

Wilcox, C.S., Amiroff, A.J., Millar, J.G.B., et al. Circulating levels of corticotrophin and cortisol after infusion of L-dopa, dopamine and noradrenaline in man. *Clin. Endocrinol.*, 4:191–198, 1975.

Wirz-Justice, A., Puhringer, W., Lacoste, V., et al. Intravenous L-5-hydroxytryptophan in normal subjects: An interdisciplinary precursor loading study. *Pharmakopsychiatr. Neuropsychopharmakol.*, 9:277–288, 1976.

Etiological Theories of Depression: Experimental Paradigms in Animals

Chair:

William T. McKinney, Jr., M.D.

Dept. of Psychiatry
University of Wisconsin Medical School
Madison, WI 53706

A Developmental Perspective on Recurrent Mood Disorders: A Review of Studies in Man

Hagop S. Akiskal, M.D.[1]

Research findings generated during the past decade have generally upheld the multifactional conceptualization of depression deriving from primate (Akiskal & McKinney, 1973) and human studies (Akiskal & McKinney, 1975). Recent findings (reviewed in Akiskal, 1985) also suggest that the predisposition to recurrent mood disorders is developed in childhood and that life events and biological insults in adulthood merely serve as triggering factors. Finally, gender is a nonspecific factor that appears least relevant to the recurrent and bipolar forms of illness (Boyd & Weissman, 1981). In reviewing the clinical literature bearing on the pathogenesis of recurrent mood disorders, I will develop the thesis that the predisposing role of heredity and early life experiences is mediated through personality variables which create the very circumstances that precipitate episodes of mood disorder in adult life.

The Predisposing Role of Heredofamilial Factors

Individuals who have a first-degree biological relative with a mood disorder are at increased risk of developing clinical depression. This risk is highest in the relatives of "schizoaffective" bipolars, followed by those of bipolar I and bipolar II (Gershon et al., 1982). It has been estimated that heredity may contribute 50 percent of the variance in the pathogenesis of *recurrent* mood disorders (Gershon et al., 1971). Although the risk for depression is relatively modest in the relatives of unipolar depressives, many recurrent depressives come from families with bipolar illness. This is best interpreted to mean that some apparently "unipolar" depressions are in fact less penetrant forms of bipolar illness (Akiskal et al., 1983). These depressions typically have early onset, are hypersomnic-retarded in symptom pattern, may exhibit brief switches to hypomania when treated with heterocyclic antidepressants, monoamine oxidase inhibitors, electroconvulsive therapy, or sleep deprivation, and may show preferential responses to lithium carbonate. The heredofamilial risk factor in depression is most dramatically illustrated by comparing the risk in the general population (which approximates the risk for the offspring of unaffected parents) with that of individuals who have one affected parent ("single matings") or both parents affected ("dual matings").

---

[1] Affective Disorders Program, University of Tennessee, Memphis, 66 N. Pauline St., Suite 633, Memphis, TN 38163.

The risk is tripled from the population baseline for single matings and increased at least tenfold for dual matings (Gershon et al., 1982).

Increased familial risk of course is not synonymous with increased genetic risk. Definite evidence for genetic contributions has come principally from adoption studies and monozygotic-dizygotic differences in concordance rates. Adoption studies (e.g., Mendelwicz & Rainer, 1977; Cadoret, 1978; Kety, 1985) have demonstrated increased risk for mood disorders in subjects born to parents with such disorders but raised by normal adoptive parents. However, these findings appear more relevant to recurrent cyclical, rather than pure depressive, disorders (Von Knorring et al., 1983; Cadoret et al., 1985). The wide difference in monozygotic-dizygotic concordance also indicates a strong genetic component (Bertlesen et al., 1977); concordance is the same for monozygotic pairs regardless of whether they are reared together or apart from birth (Price, 1968). The fact that concordance rate is less than 100 percent even in the most genetic (bipolar) forms of mood disorders suggests that nongenetic familial and other environmental factors are of importance in the predisposition to affective episodes. It is also of great theoretical interest that where monozygotic pairs are discordant for affective breakdowns, the unaffected twin often exhibits cyclothymic or dysthymic tendencies (Bertlessen et al., 1977). This suggests that affective illness is not inherited as such, but may be transmitted in the form of temperamental deviations. This was supported in a recent study (Akiskal et al., 1985) that found such deviations in nearly 50 percent of the juvenile offspring of adult bipolars.

The Predisposing Role of Early Home Environment

Although heredity seems to account for a major portion of the variance in the pathogenesis of recurrent mood disorders, nongenetic familial factors appear to modify the actual clinical expression of the disorder. The child reared in a family where one parent suffers from primary mood disorder is exposed to a dual disadvantage: genetic vulnerability to such disorder, as well as separation experiences during childhood through parental illness, suicide, divorce, or more subtle forms of emotional deprivation secondary to conflictual interaction between parents. Such conflict is often aggravated by the fact that the other parent frequently exhibits psychiatric disturbance (assortative mating), ranging from personality and mood disorders to alcoholism (Gershon et al., 1973).

Psychoanalytic theory has long traced adult depressions to early deprivations that preclude adequate mastery of loss situations. According to a specific version of this viewpoint, formulated by Bowlby (1961), the failure to successfully mourn object losses during childhood provides the behavioral sensitization to adult depressions. This notion has found partial support in the high rates of depression in women who have been maternally bereaved in childhood or adolescence (Brown & Harris, 1978). However, the cumulative retrospective evidence has been generally inconclusive regarding the specificity of childhood loss to adult mood disorder (Lloyd, 1980a). Accordingly, in his latest writings, Bowlby (1977) has broadened his formulations to include in the consequences of early loss a large spectrum of adult personality disturbances with mood instability and acting out behavior.

While failing to specifically relate adult depression to childhood object loss, the available research evidence does suggest several interesting links in line with Bowlby's formulations. For instance, we now know from the work of Perris (1966) that unipolar depressives who experienced developmental object loss have an illness onset 10 years earlier than those depressives without such loss. Others (Levi et al., 1966; Hill, 1969) have reported that suicide attempts are more common in depressed subjects who have sustained early separations. Finally, work conducted at the University of Tennessee (Akiskal et al., 1978; Rosenthal et al., 1981) has shown that early losses are associated with the adult occurrence of "unstable" characterologic attributes, such as immaturity, hostile dependency, manipulativeness, impulsiveness, and low threshold for alcohol and drug abuse, rather than overt mood disorders. These findings illustrate how breaks in early object relations could be relevant to certain clinical aspects of depression. While not causing depressive illness, developmental object loss seems to modify the clinical expression of the adult disorder. The characterologic propensity toward hostile dependency may prepare a fertile soil of interpersonal friction that facilitates a depressive onset earlier than that determined by innate genetic factors. Such friction may actually create the life events that trigger the depression. Another possible mechanism whereby early losses can influence the occurrence of adult depression is by creating conditions favorable to the development of character traits associated with what Seligman (1975) refers to as "learned helplessness," or with the self-denigrating depressive mental schemata described by Beck (1967). It is reasonable to assume that situations wherein the individual has failed to master a series of tasks can lead to subsequent helplessness when faced with similar situations. This viewpoint is concordant with classical work at the Wisconsin Primate Laboratory (Harlow, 1975), which demonstrated that coping skills are developed in the context of the contact comfort provided by caring and loving parental objects. Conversely, the loss of this contact comfort often precludes the development of environmental exploration and of coping skills in general. Thus, early separations from parent(s), without adequate substitutes, may prevent the emergence of a sense of mastery of the environment. Such children may become insecure adults who feel unable to face the challenge of new situations. It should be noted that the mere presence of parents, however, does not immunize against the trait of helplessness; developing a sense of mastery requires suitable role models and the opportunity to cope with a series of life events of increasing complexity. Such formulations, while plausible, need verification in prospective designs in clinical populations.

Arguing against the proposed relationship between childhood loss and depression is the fact that history of such loss is not present in two-thirds of adult depressives (Lloyd, 1980a). Furthermore, childhood parental deprivation does not appear to exert *specific* formative influence on depressive illness. It is nevertheless likely that, given specific genetic predisposition to mood disorder, the experience of being raised in an unstable early home environment may contribute to the development of personality disturbances which themselves play a formative role in mood disorder.

The Mediating Role of Temperamental and Characterologic Factors

It is widely believed that affective episodes arise from predisposing personality attributes. This position was most directly articulated by Kretschmer (1936), who believed that "the endogenous psychoses are nothing but accentuation of normal types of temperament." While Kretschmer, as a faithful follower of the Kraepelinian tenets (1921), emphasized constitutionally determined temperamental contributions, much of current theorizing has focused on learned characterologic attributes believed to be a legacy from developmental vicissitudes.

Ideally, the study of personality in a given patient should begin prior to the first onset of affective episodes. Assessing personality during an episode of illness is unsatisfactory because affective states may bias or even mask the patient's personality profile. Even when the affectively ill are examined during a euthymic period, the illness episodes—or the treatments provided for them—significantly alter personality structure. For these reasons, very few studies have succeeded in prospectively assessing the contribution of personality to mood disorders. Despite such thorny methodologic barriers, many interesting findings on the relevance of enduring personality characteristics to mood disorders have been formulated (Akiskal et al., 1983).

Kraepelin (1921) postulated that the various forms of manic-depressive illness often arose from their respective temperamental foundations. For instance, it is fairly well established that certain temperamental disorders—the dysthymic, the hyperthymic, and the cyclothymic—are the precursors of the more serious affective episodes (Akiskal et al., 1977; Akiskal, 1983; Depue et al., 1981). In these temperaments, the genetic potential for affective episodes is considered to be subclinically active at all times and to be easily triggered into clinical illness by environmental characteristics to mood disorders have been formulated (Akiskal et al., 1983).

TABLE 1. Rate of Affective Episodes (Given in Percentages) in Affective Temperaments and Controls During Prospective Observation of 1 to 4 years.*

	(*N*)	Major Depression	Hypomanic/Mania (Spontaneous)	Tricyclic-Hypomania
Cyclothymic	(46)	24	22	35
Subaffective dysthymic	(20)	55	0	33
Nonaffective personality controls	(50)	4	0	0

*Summarized from Akiskal et al. (1977) and Akiskal (1983). Experimental groups significantly higher than controls ($p < .02$).

dysthymic individuals compared with personality controls. It is interesting to note that both temperaments are at highest risk to develop depression; the risk for hypomania is augmented by exposure to tricyclic antidepressants. Recent Italian work (Kukopulos et al., 1980) has shown that tricyclic antidepressants may actually *accelerate* the inherent cyclicity of mood disorders in hyperthymic and cyclothymic individuals. It would therefore appear that certain affective personalities are at high risk of developing depressive states under conditions of environmental challenge; they are also prone to hypomanic and manic states under pharmacologic challenge, as well as under other reactive conditions.

In other words, one mechanism whereby genetic factors may produce episodes is via the instability of the affective temperaments. This viewpoint is strengthened by the recent demonstration of shortened REM latency in individuals with dysthymic and hypomanic temperaments (Akiskal, 1984), very much like the findings in individuals experiencing major full-blown depressions. This sleep neurophysiologic abnormality seems to behave like a trait marker of vulnerability and is not merely a nonspecific stress reaction or a correlate of anxiety (Akiskal et al., 1984). Overall, the sleep findings in affective temperaments suggest that neurophysiologic abnormalities precede full-blown affective episodes.

Temperamental contributions appear to have greater relevance in the recurrent and cyclic forms of mood disorder (Akiskal et al., 1983). In the more purely depressive forms of these disorders, dependency and obsessiveness have long been hypothesized as predisposing factors (Chodoff, 1972); more recent formulations have focused on cognitive-behavioral factors (Lewinsohn, 1974; Kovacs & Beck, 1978). These formulations, which have been developed through retrospective reconstruction of the premorbid characteristics of already depressed subjects, have been based on small clinical populations, have not taken the heterogeneity of mood disorders into consideration, have not used reliable personality measures and, most seriously, have generally tended to confuse state and trait. A recent study (Hirschfeld et al., 1983), which—except for being retrospective—was methodically superior to earlier attempts, reported that introversion, lack of social adroitness, and dependency are the major attributes of recovered depressives. These findings are more consistent with behavioral formulations and suggest the existence of enduring measurable deficits in social skills. Prospective studies are now needed for the more definitive clarification of the characterologic contributions in mood disorders. Despite this limitation, clinical experience suggests mechanisms whereby the postulated characterologic disturbances contribute to major affective episodes. Individuals who are introverted and lack social adroitness do not possess an adequate behavioral repertoire for eliciting rewarding interactions with other people. In particular, they may lack the requisite skills to develop and maintain the supportive relationships that are widely believed to provide a buffer against the depressant impact of aversive life situations (Akiskal, 1985). Passive-dependent individuals can easily exhaust the tolerance of their spouses or lovers and thereby prepare the ground for marital or romantic break-ups. In other words, they may contribute to the very life situations which bring about their depressive breakdowns. Once they become depressed, their dependency needs grow, providing further opportunities for alienating the supportive individuals in their lives. The relationship between personality and mood disorders, however, is not always etiological (Akiskal et al., 1983). Personality may favor the appearance of certain *symptoms*. If and when an affective episode does occur, it may modify the apparent severity of the depressive state and, in many instances, results from recurrently incapacitating episodes of illness (Cassano et al., 1983).

In summary, the individual prone to develop affective episodes is no longer portrayed just in terms of the temperamental traits of cyclothymia, hyperthymia, and dysthymia, but those of related characterologic attributes such as dependency, introversion, and a relative lack of social assertiveness. These traits and attributes, which represent either premorbid personality features or post-episodic complications, appear to be associated with enduring biologic traits, and may serve as a fertile ground for the genesis of major affective episodes.

Precipitating Circumstances

Affective episodes are often temporally related to external and internal circumstances. The preceding discussion suggests that in vulnerable individuals affective disturbance is present subclinically—and that it is activated into overt clinical episodes by environmental challenge. Environmental circumstances may determine the precipitation of the initial episode and, perhaps, the *timing* of subsequent recurrences. These circumstances are extremely varied and include psychosocial, biologic, and seasonal factors.

Although the majority of individuals exposed to losses and other aversive life circumstances do not sink into morbid despair, those predisposed to mood disorders may do so at such times. The lifetime risk for melancholia is about 12 percent (Helgason, 1979), yet no more than 5 percent of those exposed to "exit" type life events decompensate into clinical depression (Paykel, 1976; Clayton, 1979; Lloyd, 1980b). Furthermore, history of previous depressive episodes is a stronger predictor of depression at the face of life stressors than the characteristics of the stressors and their social context (Warheit, 1979). Even individuals predisposed to mood disorders—measured as a function of previous episodes or positive family history—do not develop affective episodes in the face of a major loss; rather, other concurrent or antecedent events seem to mediate the effect of such events (Akiskal, 1985). These include unresolved childhood loss, concurrent life events, impact of life event on life style, symbolic meaning of the life event, inadequate social support, deficient social skills, and personality. Indeed, losses and other aversive events which are common precipitants of depression often result from the affectively unstable personality matrix of the patient (Akiskal, 1984).

The fact that clinically significant depression occurs, on the average, in about 15 percent of the medically ill (Cavanaugh, 1983)—which approximates the lifetime risk for melancholia—is an indication that medical contributions to depression are in the nature of precipitant rather than cause. Reserpine-induced depressions (Goodwin & Bunney, 1971) illustrate this point in that two-thirds of these cases represent "pseudodepressions" secondary to the sedative side effects of the drug, which reverse as medication is discontinued; melancholia persisting in an autonomous fashion despite withdrawal of the offending chemical occurs in the remaining third and is largely limited to those with past personal history or predisposition for depression.

Thus, neither life events nor chemical events appear to be *sufficient* causes for the occurrence of clinical depressions: They seem to exert a depressant influence in the presence of predisposing factors. We know even less about the precipitation of hypomania or mania. The relevance of life events—especially losses—is suggested by Ambelas' study (1979). Obviously such losses can easily result from premorbid cyclothymic or hyperthymic instability in mood (Akiskal, 1984). The best known precipitants of hypomania—and to a lesser extent of mania—are drugs and physiological procedures that increase the central level of catecholamines (Vogel, 1975; Bunney, 1978; Kukopulos et al., 1980). These include the noradrenergic tricyclics, the monoamine-oxidase inhibitors, ephedrine, L-dopa, cocaine, amphetamine-like drugs, REM-deprivation, and total sleep deprivation. These factors, which often represent medically or self-administered treatments—and, in the case of REM-deprivation, a manifestation of the cyclothymic individual's decreased need for sleep—are more consistent in producing a switch from depression to hypomania than from euthymia to hypomania. Thus, the pharmacological switch is largely limited to individuals with a bipolar diathesis—measured as a function of personal or family history of mania (Akiskal et al., 1983). The same applies generally to postpartum affective episodes, whether manic, mixed, or retarded depressive. Another class of precipitating circumstances that has received recent attention is seasonality (Rosenthal et al., 1984), largely relevant to bipolar II disorder.

To summarize, this discussion on precipitating circumstances suggests that the onset of affective episodes is most commonly associated with an interaction between predisposing and triggering factors. Many, though not all, of these triggering factors themselves develop as a result of complex interactions between the environment and the personality of the patient predisposed to mood disorders.

Concluding Remarks

Figure 1 is a diagrammatic representation of the complex interaction between diverse predisposing factors which I have hypothesized lead to the development, during formative years, of biologic and personality attributes that facilitate major affective breakdowns in adult life. Due to space limitations I have deleted a discussion of demographic factors, but as reviewed elsewhere (Akiskal, 1985), gender and age are also associated with certain personality and biologic attributes that favor the circumstances leading to affective dysregulation.

Such a model, to be fully tested in the human, would necessitate detailed prospective observation of children at genetic risk for mood disorders and observed over a period of several decades. Animal models—whether in primates or rodents—provide a convenient approach to examine some of the critical risk factors reviewed in this paper. I would propose that female animals which have been exposed to traumatic separation or aversive stimulation early in life—and which come from genetic strains characterized by severe separation-induced despair responses or repeated failure to escape aversive stimulation—would be at greatest risk for "depressive" behaviors under stressful experimental circumstances. Furthermore, I would predict that exposure to separation or selected chemical stressors in the postpartum period at the early fall or early winter months would be most potent. Finally, I would predict that animals at risk for "depression" would manifest distinct biologic and personality traits *before* the onset of such behavior.

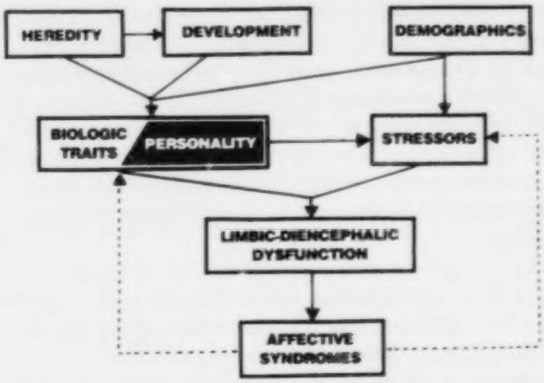


FIGURE 1. Diagrammatic representation of the complex interaction between diverse predisposing factors.

References

Akiskal, H.S. Dysthymic disorder: Psychopathology of proposed chronic depressive subtypes. *Am. J. Psychiatry*, 140:11–20, 1983.

Akiskal, H.S. Characterologic manifestations of affective disorders: Toward a new conceptualization. *Integrative Psychiatry*, 2:83–88, 1984.

Akiskal, H.S. Interaction of biologic and psychologic factors in the origin of depressive disorders. *Acta Psychiatr. Scand.*, 71:131–139, 1985.

Akiskal, H.S., and McKinney, W. T., Jr. Depressive disorders: Toward a unified hypothesis. *Science*, 1982:20–28, 1973.

Akiskal, H.S., and McKinney, W. T., Jr. Overview of recent research in depression: Integration of ten conceptual models into a comprehensive clinical frame. *Arch. Gen. Psychiatry*, 32:285–305, 1975.

Akiskal, H.S., Djenderedjian, A.H., Rosenthal, R.H., Khani, M.D. Cyclothymic disorder: Validating criteria for inclusion in the bipolar affective group. *Am. J. Psychiatry*, 134:1227–1233, 1977.

Akiskal, H.S., Bitar, A.H., Puzantian, V.R., et al. The nosological status of neurotic depression: A prospective three-to-four year examination in light of the primary-secondary and unipolar-bipolar dichotomies. *Arch. Gen. Psychiatry*, 35:756–766, 1978.

Akiskal, H.S., Hirschfeld, R.M.A., and Yerevanian, B.I. The relationship of personality to affective disorders: A critical review. *Arch. Gen. Psychiatry*, 40:801–810, 1983.

Akiskal, H.S., Walker, P.W., Puzantian, V.R., et al. Bipolar outcome in the course of depressive illness. Phenomenologic, familial and pharmacologic predictors. *J. Affective Disord.*, 5:115–128, 1983.

Akiskal, H.S., Lemmi, H., Dickson, H., et al. Chronic depressions: Part 2. Sleep EEG differentiation of primary dysthymic disorders from anxious depressions. *J. Affective Disord.*, 6:287–297, 1984.

Akiskal, H.S., Downs, J., Jordan, P., et al. Affective disorders in referred children and younger siblings of manic-depressives. *Arch. Gen. Psychiatry*, 42:996–1003, 1985.

Ambelas, A. Psychologically stressful events [illegible] the precipitation of manic episodes. *Br. J. Psychiatry*, 135:15–21, 1979.

Beck, A.T. *Depression—Causes and Treatment*. Philadelphia: University of Pennsylvania Press, 1967.

Bertlesen A., Harvald, B., and Hauge, M. A Danish study of manic-depressive disorders. *Br. J. Psychiatry*, 130:338–351, 1977.

Bowlby, J. Childhood mourning and its implications for child psychiatry. *Am. J. Psychiatry*, 118:481–498, 1961.

Bowlby, J. The making and breaking of affectional bonds. I: Aetiology and psychopathology in the light of attachment theory. *Br. J. Psychiatry*, 130:201–210, 1977.

Boyd, H.G., and Weissman, M.M. Epidemiology of affective disorders: A re-examination and future directions. *Arch. Gen Psychiatry*, 38:1039–1046, 1981.

Brown, G.S., and Harris, T. *Social Origins of Depression*. London: Tavistock Publications, 1978.

Bunney, W.E. Psychopharmacology of the switch process in affective illness. In: Lipton, M.A., Dimascio, A., and Killam, K.F (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978, pp. 1249–1259.

Cadoret, R.J. Psychopathology in adopted-away offspring of biologic parents with antisocial behavior. *Arch. Gen. Psychiatry*, 25:1–15, 1978.

Cadoret, R.J., O'Gorman, T.W., Heywood, E., and Troughton, E. Genetic and environmental factors in major depression. *J. Affective Disord.*, 9:155–164, 1985.

Cassano, G.B., Maggini, C., and Akiskal, H.S. Short-term subchronic and chronic sequelae of affective disorders. *Psychiatr. Clin. North Am.*, 6:55–67, 1983.

Cavanaugh, S. The prevalence of emotional and cognitive dysfunction in a medical population. *Gen. Hosp. Psychiatry*, 5:15–24, 1983.

Chodoff, P. The depressive personality: A critical review. *Arch. Gen. Psychiatry*, 27:666–673, 1972.

Clayton, P.J. The sequelae and nonsequelae of conjugal bereavement. *Am. J. Psychiatry*, 136:1530–1534, 1979.

Depue, R.A., Slater, J.F., Wolfstetter-Kausch, H., et al. A behavioral paradigm for identifying persons at risk for bipolar depressive disorders: A conceptual framework and five validating studies. *J. Abnorm. Psychol.*, 90(suppl.): 381–438, 1981.

Gershon, E.S., Dunner, D.L., and Goodwin, F.K. Toward a biology of affective disorders. *Arch. Gen. Psychiatry*, 25:1–15, 1971.

Gershon, E.S., Dunner, D.L., and Sfert, L. Assortative mating in the affective disorders. *Biol. Psychiatry*, 7:63–74, 1973.

Gershon, E.S., Hamovit, J., Guroff, J.J., et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar and normal control probands. *Arch. Gen. Psychiatry*, 39:1157–1167, 1982.

Goodwin, F., and Bunney, W.E., Jr. Depression following reserpine: A reevaluation. *Semin. Psychiatry*, 3:19–53, 1971.

Harlow, H.F. *Learning to Love*. New York: Jason Aronson, 1974.

Helgason, T. Epidemiological investigations concerning affective disorders. In: Schou, M., and Stromgren, E. (eds.), *Origin, Prevention and Treatment of Affective Disorders*. London: Academic Press, 1979, pp. 241–255.

Hendrie, H.C. Organic brain disorders: Classification, the "symptomatic" psychoses, misdiagnosis. *Psychiatr. Clin. North Am.*, 1:3–19, 1978.

Hill, O. The association of childhood bereavement with suicide attempt in depressive illness. *Br. J. Psychiatry*, 115:301–334, 1965.

Hirschfeld, R.M., Klerman, G., Clayton, P., and Keller, M. Personality and depression: Empirical findings. *Arch. Gen. Psychiatry*, 40:993–998, 1983.

Kety, S.S. Interactions between stress and genetic processes. In: Zales, M.R. (ed.), *Stress in Health and Disease*. New York: Brunner/Mazel, 1985, pp. 115–132.

Kovacs, M., and Beck, A.T. Maladaptive cognitive structures in depression. *Am. J. Psychiatry*, 135:525–533, 1978.

Kraepelin, E. *Manic-depressive Insanity and Paranoia*. Edinburgh: Livingstone, 1921.

Kretschmer, E. *Physique and Character* (E. Miller, Trans.). London: Kegan Paule, Trench, Trubner and Co., Ltd., 1936.

Kukopulos, A., Reginaldi, D., Laddomada, P., et al. Course of the manic-depressive cycle and changes caused by treatments. *Pharmacopsychiatrie Neuro-Psychopharmakologie*, 13:156–167, 1980.

Levi, D.L., Fales, C.L., Stein, M., and Sharp, V.H. Separation and attempted suicide. *Arch. Gen. Psychiatry*, 15:158–164, 1966.

Lewinsohn, P.M. A behavioral approach to depression. In: Friedman, R.J., and Katz, M.M. (eds.), *The Psychology of Depression: Contemporary Theory and Research*. New York: Halstead, 1974.

Lloyd, C. Life events and depressive disorder reviewed, I: Events as predisposing factors. *Arch. Gen. Psychiatry*, 32:285–305, 1980a.

Lloyd, C. Life events and depressive disorder reviewed, II: Events are precipitating factors. *Arch. Gen. Psychiatry*, 37:541–548, 1980b.

Mendlewicz, J., and Rainer, J.D. Adoption study supporting genetic transmission in manic depressive illness. *Lancet*, 268:327–329, 1977.

Paykel, E.S. Life stress, depression, and attempted suicide. *J. Human Stress*, 2:3–12, 1976.

Perris, C.A. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. *Acta Psychiatr. Scand.*, 42 (Suppl.): 118–152, 1966.

Price, J. The genetics of depressive behavior. In: Coppen, A., and Walk, A. (eds.), *Recent Developments in Affective Disorders. Br. J. Psychiatry* (spec. publ.), 2:37–54, 1968.

Rosenthal, N.E., Sack, D.A., Gillin, J.C., et al. Seasonal affect. disorder. *Arch. Gen. Psychiatry*, 41:72–80, 1984.

Rosenthal, T.L., Akiskal, H.S., Scott-Strauss, A., et al. Familial and developmental factors in characterological depressions. *J. Affect. Disord.*, 3:183–192, 1981.

Seligman, M.D. *Helplessness: On Depression, Development, and Death*. San Francisco: Freeman, 1975.

Vogel, G.W. A review of REM sleep deprivation. *Arch. Gen. Psychiatry*, 32:749–761. 1975.

Von Knorring, A.L., Cloninger, C.R., Bohman, M., and Sigvardsson, S. An adoption study of depressive disorders and substance abuse. *Arch. Gen Psychiatry*, 40:943–950, 1983.

Warheit, G.J. Life events, coping, stress and depressive symptomatology. *Am. J. Psychiatry*, 136:502–507, 1979.

Developmental Theories of Depression in Nonhuman Primates

Gary W. Kraemer, Ph.D.[1]

Introduction

Theories about depression in nonhuman primates center around the "despair" response of infant monkeys to maternal separation. In this phase monkeys typically become lethargic and curl up into a fetal-like posture for long time periods. Historically, the linkage between despair and human depression was made on the basis of two observations. The first is that despairing monkeys "look" depressed. The second is that the monkey response bears a remarkable resemblance to the response of human infants to maternal separations. Some maternally deprived human infants in turn look and act in ways that clinicians have likened to adult depression. Given this parallel, numerous authors have suggested that despair (monkeys) and anaclitic depression (humans), if not homologous, are at least analogous states. If so, despair in monkeys can be viewed as an animal model of depression.

For a host of reasons this approach is controversial. Without even crossing species one can start a debate about the relationship of anaclitic depression to depressions occurring later in life. Rather than feeding a controversy which alternately focuses on similarities and then differences between despair and a variety of conceptions of the nature of depression, this paper will focus on despair as a biological-behavioral phenomenon that is significant and interesting in its own right, and recount some of the things we have learned about it. Then the reader can be the judge.

Fundamental Drive Systems in Primates

Every mammalian species possesses CNS mechanisms that regulate feeding, aggression, fear, sexual behavior, and rearing and protection of offspring.

In some of the social primates these basic mechanisms have merged with, and are dependent upon, a complex social recognition and cohesion system (attachment). The drive to attach is present at birth, but the full development of infant attachment mechanisms requires maternal and then peer interactions. The primary reinforcers are maternal contact comfort (cuddling) and peer play. To put the system in a hierarchical biological context, it resides slightly above nutrition as a survival goal for the infant primate (Harlow & Mears, 1979). Once the infant has become attached to its mother and peers, behavioral mechanisms exist to prevent separation.

The behavioral response to separation is often biphasic. Frantic activity and vocalization ensue upon separation from an attachment object (protest). Later, some infants become inactive. They adopt a self-enclosed fetal-like body posture (huddling) and are silent (despair).

Kaufman (1977) proposed that both the protest and despair phases are positively selected in the feral environment. Protest behaviors increase the probability that the infant will regain contact. Vocalizations are most prominent as a means of attention-getting behavior, but frantic activity and attempts to search for the mother are evident. If the separation is prolonged, the reduced energy expenditure and lack of attention-getting behavior of the despair phase preserve the infant from exhaustion and predation until it is rediscovered by the mother (conservation-withdrawal). This selective framework ensures that monkeys are socialized in the feral environment. If attachment formation is weak, or the attached infant is separated from its mother and these survival strategies fail, the infant does not survive and procreate. Thus, there are no nonsocially reared

---

[1] University of Wisconsin, Harlow Primate Laboratory, Madison, WI 53715.

monkeys outside of the influence of human husbandry.

While the similarities between the initial responses of infant humans and monkeys to separation from their mothers are profound, in adolescence and adulthood the cross-species parallels are not as clear. This is primarily related to the explosion of human capacity which progressively separates us behaviorally, and perhaps intellectually, from other primates after the initial 5 to 10 percent of expected life span. Monkeys and humans develop attachments to peers, and then to their own offspring. However, humans have diverse cultural differences in social interaction, whereas the rhesus monkey pattern is relatively stereotyped and constant. Humans become attached to a wide array of objects, concepts, and vocations as well as other people. Humans acquire language, a tool used in part to express the depth of their attachments and the devastation of their disruption.

The ubiquitous nature of attachment and the response to attachment disruption makes it so common a phenomenon that many have overlooked the root characteristics of the behavior. Often the point is made clearer by trying to imagine the characteristics of a fellow human who has no response to loss of parents, significant others, children, ideas, goals, morals, or self-esteem, or never develops any of these attachments. Then imagine a society of these individuals, as if such a thing could exist. Therefore, one hypothesis is that this core neurobiological mechanism enables us to maintain a society, a technology, a way of life, and a world view that we are "attached" to. If these attachments are disrupted, or disruption is threatened, then we protest, or we fight. If the loss is sustained, then we despair and adapt. Thus, protest-despair behavior may be a fundamental characteristic of species that can form long-standing attachments. Its associated neurobiological mechanism may have foundations in the primate infant attachment system.

As universal as this genetically based attachment mechanism might be, there are wide individual differences in its expression. Adaptation may be the key to understanding despair. From an ethological standpoint, the despair response is only adaptive if the infant cannot support itself in the environment. Over a prolonged separation it must conserve. In other environments (the laboratory) or at other ages, or in human society, the individual can support itself, or can be adopted and cared for by others. In this context a prolonged despair response is maladaptive because the organism does not function in its environment. It may not react properly to environmental contingencies or sustain itself when there is food and water available. So, why has the response been preserved?

One possibility is that despair is a neurobiological interlude. It may come into play only when all else has failed (behaviorally), and this point would vary with the neurobiological characteristics and previous experience of the individual. Besides conserving energy it could mark a transition in which the organism recasts behavioral strategies to supplant those that have just failed (protest). Under most conditions, neurobiological reorganization and behavioral function which accounts for the loss of the attachment is achieved, and the organism reactivates itself with a behavioral repertoire that is consistent with the prevailing environment. Another consideration relates to pathology. The attachment mechanism is expressed in neurobiological substrate. As with any structural-biochemical system it is possible for something to go wrong. One developmental factor known to be related to predisposition to despair is the nature of the rearing environment.

Persistent Neurobiological Effects of the Early Rearing Environment

If a separation occurs while the mother is the primary attachment object only 10 to 15 percent of human and laboratory housed rhesus infants show life-threatening behavioral despair (Kraemer & McKinney, 1979). In monkeys, significant social separations later in life are usually from peers since maternal attachment is maintained only for the first 9 to 12 months of life. Later separations are rarely life threatening but some juvenile, adolescent, and adult monkeys do become inactive and huddle. Rearing infants with only peer-aged monkeys (maternal deprivation) approximately doubles the proportion of monkeys that become inactive and huddle after separations in adolescence and adulthood

(Kraemer & McKinney, 1979). Some clues as to the neurobiological substrates of the mechanism are surfacing. The increase in vulnerability due to early rearing conditions appears to be associated with changes in brain norepinephrine (NE) systems.

Comparisons have been made between monkeys reared without social-contact comfort (isolation), those reared without mothers (peer-reared), and those reared in socially rich environments with mothers and peers (mother-peer-reared). Long-term effects of these experimentally induced gradations in formation of social attachments will be considered first.

Reductions in locomotor behavior and increases in huddling following administration of catecholamine (CA; collectively referring to both NE and dopamine [DA]) depleting agents occur at different dose levels in differentially reared juvenile (2– to 3-year old) monkeys. Quantity and quality of social stimuli in the rearing environment appear to account for the differences. Alpha-methyl-paratyrosine (AMPT), a tyrosine hydroxylase inhibitor that depletes CNS CA, significantly reduced motor activity in isolated (no social stimuli) monkeys at 200 to 250 mg/kg/day, in separated peer-reared (high-social quantity, low-social quality) monkeys at 12.5 to 25.0 mg/kg/day, and in separated mother-peer reared (high-social quantity and quality) monkeys at doses of 100 mg/kg/day (Kraemer and McKinney, 1979). Thus, maternally deprived peer-reared monkeys are the most sensitive to depressive effects of AMPT, and also most likely to become inactive and huddle following social separation. Isolated monkeys are the least sensitive. They are also not attached to anything. Therefore, it is possible that CA systems in isolated monkeys are not engaged in the regulation of ongoing behavior as they are in socially reared monkeys.

Cerebrospinal fluid (CSF) NE concentration may be affected by rearing environment. Kraemer, Lake, and Suomi (unpublished cross-sectional data) found levels of 379.2 ± 22.7 pg/ml ($N = 11$) in isolation housed monkeys, 675.9 ± 48.3 pg/ml ($N = 11$) in peer-reared monkeys, and 792.4 ± 73.3 pg/ml in mother-peer reared monkeys ($N = 16$) when all monkeys were 2 to 3 years old, and still living in their rearing environments (main effect of rearing condition, $F = 12.2$, $df = 2/35$, $p < .0001$). CSF NE in the isolated monkeys was significantly lower than either of the other groups. CNS NE systems, at least those reflected in CSF, may have reduced output while monkeys are in prolonged isolation.

While these data are limited in scope, the best working hypothesis is that the CNS effects of any degree of social deprivation are reflected, if not mediated, by reductions in NE system activity (reviewed in Kraemer et al., 1985). If the deprivation is prolonged, or occurs during critical developmental periods, then long-standing deficits in the ability of the organism to adapt to changes in the social environment may be produced. In primates, these changes are manifested by effects that resemble denervation supersensitivity and could be due to deprivation induced lesions of the brain NE system (Kraemer, 1985; Kraemer et al., 1984a). Differences in NE system function across individuals may also fit into the hypothesis.

Correlations of CSF NE Levels With Responses to Social Separation

Kraemer et al. (1984b) found that mother-reared monkeys with low CSF NE concentrations (for the group of 8 monkeys examined) were most likely to become inactive and huddle following social separation. This suggested that "low CSF NE" was a risk factor for a depressive response to separation. The reason for individual variation in CSF NE is not known. Clearly, genetic and perinatal factors, as well as the early maternal relationship must be considered. However, the issue is becoming more complicated.

In a recent study (Kraemer, G., Kalin, N., Lake, C.R., McKinney, W.T., unpublished data), CSF was collected from separated monkeys in the morning (9:00) as opposed to the usual afternoon (13:30) collection time. The monkeys that were inactive and huddled the most had the *highest* levels of CSF NE in the morning. The reversal of direction of effect could be because monkeys that cope well with separation maintain a normal diurnal rhythm in CSF NE, whereas the rhythm in despairing monkeys may be blunted or out of phase. A similar situation may prevail in depressed humans. Post et al. (1984) reported that morning CSF NE was increased in depressed patients by comparison to controls.

Mechanisms and Theories

The correlations presented before do not yet relate directly to a brain mechanism or its development. The role, or more likely "roles," of NE in the CNS must be considered. NE systems appear to be involved in at least four levels of adaptation to the environment. They are: 1) Release, reinforcement, and extinction of behavior (Iversen, 1984); 2) Changes in sensory "gating," or tuning of the salience of sensory input in regulating behavioral output (Oades, 1985); 3) Regulation of cyclical rhythms in arousal, i.e., sleep/waking cycle (Kripke, 1984); and 4) Organizational plasticity, or the formation or loss of effective synaptic contact (Kasamatsu et al., 1984). Each mechanism must act within an environmentally adaptive, and yet neurobiologically constrained time frame. Release and reinforcement of behavior occur within seconds, minutes, or hours. Gating changes and cyclical rhythms take minutes, hours, days, or months. Reorganization (a change in the neural structural-biochemical mechanisms underlying all three of the before mentioned processes) takes days to months.

Examination of the behavioral response to social separation suggests that vulnerability factors develop in a long-term time frame (months to years). Precipitating events span days to weeks, while interactions of the response with drug treatment also occur over days to weeks. This suggests three areas in which NE regulated mechanisms could be relevant to the understanding of the substrates of despair. They are:

1) Vulnerability. Deprivation of some classes of early rearing experience can produce vulnerability to both environmental and neurochemical challenges that would otherwise have little effect. While differences in baseline levels of CSF NE bear some relationship to vulnerability to despair, the best hypothesis at this time is that differences found at one time of day or another reflect a regulatory deficit in the NE system. Perhaps the net effect is that individuals who are vulnerable to prolonged despair cannot mobilize the systems (reorganization) which would normally reverse the despair behavior.

It is possible that the neurobiological attachment mechanism, originally selected to maintain social order and survival of primates, has been expanded upon in humans. If so, this system regulates or maintains the sphere of attachments which are common to humans. The expansion of attachment objects or concepts, and potential losses, would leave humans more to despair about. One wonders whether the mechanism is always adequate.

2) Therapeutic lag. Reduced release of NE and/or serotonin has been suggested as both a feature of depression and a state that was counteracted by antidepressant agents. Several well-known effects are incompatible with this "neurotransmitter deficit" hypothesis (reviewed in Stone, 1983). The one most relevant is that antidepressant agents increase neurotransmitter concentration in the synapse within minutes of administration while antidepressant effects take one to three weeks. If NE systems regulate adaptation to the environment through a time-based cascade, then a therapeutic lag is a prerequisite rather than an inconvenience. An example can be given in terms of social separation.

Primates adapt to the mean level of environmental stimulation and avoid social separation. However, the primate social environment is not constant. Brief separations are inevitable. If a prolonged social separation is in progress then efforts must be made to regain contact (protest), and energy must be expended. If this fails, then a number of physiological and behavioral changes must be made to cope with the increased risk to survival (despair and adaptation). On the other hand, if the separation turns out to be transient, then protest and induction of CNS adaptation to the solitary environment may be counterproductive. Therefore, there must be a delay after the perceived separation in order to determine whether adaptive processes must be engaged. The time to fully adapt to the separation environment is the sum of the time required to detect change, the delay to make sure the change is persistent, and the time to make the required physiological and perhaps structural changes in the brain. Completion of the behavioral sequence takes between 3 to 14 days in rhesus monkeys. Changes on a shorter time frame may either be counterproductive in relation to the frequency and duration of transient separations, or exceed the biological limits of the changing mechanisms. Receptor adaptation and then organizational changes may be the focal mechanisms. If antidepressants impact on these basic mechanisms then they also should have a time delay consistent with the function of the mechanisms that they affect.

3) Mechanisms. One mechanism underlying the adaptive capacity of nonhuman primates could be the maintenance of cortical plasticity (Nagatsu et al., 1984) in the sensory-motor and frontal cerebral cortex by NE systems (*see* Levitt et al., 1984). Changes at this level of CNS function probably occur over days to weeks. This time frame is compatible with behavioral responses to social separation and antidepressant treatment. Changes in post-synaptic receptors could signal the induction of these processes. One change in viewpoint from previous theories of depression is that NE systems may not regulate mood (behavioral) states per se, but may regulate the capacity and time necessary to change from one stable mood (behavioral) state to another (*see* Cohen & Campbell, 1984).

Organizational processes are probably intimately linked with biological cycles in arousal, the sleep-wake cycle being primary. Perhaps the simplest mechanistic concept is that you cannot run a railroad and reroute the tracks at the same time. Thus, disrupted sleep cycles could be either a cause or a symptom of deficits in CNS adaptation. Similarly, it is possible that the despair phase reflects a limitation of ongoing behavior so that CNS adaptive processes which alter behavioral programs can be engaged. If the required organizational processes fail, then the behavioral interaction with the environment remains limited.

Conclusion

CNS NE systems appear to be involved in mediating behavioral adaptation to changes in the social environment. Development of NE systems may be promoted by social interactions in the first year of life. These systems may be damaged or fail to develop if the infant is socially isolated, or if it is deprived of a selective class of social stimuli. There are also individual differences that appear to be independent of rearing and could be related to genetic and perinatal factors. One effect of debilitation of these adaptive mechanisms could be the persistent maintenance of behavior patterns that are inappropriate in the prevailing environment. Prolonged despair could be an example.

Acknowledgments

Research and manuscript preparation supported by MH 21892, MH 40748 (NIMH), and the Harry Frank Guggenheim Foundation.

References

Cohen, R.M., Campbell, I.C. Receptor adaptation in animal models of mood disorders: A state change approach to psychiatric illness. In: Post, R.M., Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders*. Baltimore: Williams and Wilkins, 1984, pp. 572–586.

Harlow, H.F., Mears, C. *The Human Model: Primate Perspectives*. Washington, D.C.: V.H. Winston and Sons, 1979.

Iversen, S. Cortical monoamines and behavior. In: Descarries, L., Jasper, H.H. (eds.), *Monoamine Innervation of Cerebral Cortex*. New York: Alan R. Liss, Inc., 1984, pp. 321–349.

Kasamatsu, T., Itakura, T., Jonnson, G., et al. Neuronal plasticity in cat visual cortex: A proposed role for the central noradrenaline system. In: Descarries, L., Jasper, H.H. (eds.), *Monoamine Innervation of Cerebral Cortex*. New York: Alan R. Liss, Inc., 1984, pp. 301–319.

Kaufman, I.C. Developmental considerations of anxiety and depression: Psychobiological studies in monkeys. In: Shapiro, T. (ed.), *Psychoanalysis and Contemporary Science*. New York: International Universities, 1977, pp. 317–363.

Kraemer, G.W. Effects of differences in early social experience on primate neurobiological-behavioral development. In: Reite, M., Field, T. (eds.), *The Psychobiology of Attachment*. New York: Academic Press, 1985, pp. 135–161.

Kraemer, G.W., Ebert, M.H., Lake, C.R., McKinney, W.T. Hypersensitivity to *d*-amphetamine several years after early social deprivation in rhesus monkeys. *Psychopharmacology*, 82:266–271, 1984a.

Kraemer, G.W., Ebert, M.H., Lake, C.R., McKinney, W.T. Cerebrospinal fluid measures of neurotransmitter changes associated with pharmacological alteration of the despair response to social separation in rhesus monkeys. *Psychiatry Res.*, 11:303–315, 1984b.

Kraemer, G.W., McKinney, W.T. Interactions of pharmacological agents that alter biogenic amine metabolism and depression: An analysis of contributing factors within a primate model of depression. *J. Affect. Dis.*, 1:33–54, 1979.

Kripke, D. Does a weak REM-nonREM oscillator cause depression? In: Post, R.M., Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders*. Baltimore: Williams and Wilkins, 1984, pp. 227–233.

Levitt, P., Rakic, P., Goldman-Rakic, P.S. Comparative assessment of monoamine afferents in mammalian cerebral cortex. In: Descarries, L., Jasper, H.H. (eds.), *Monoamine Innervation of Cerebral Cortex*. New York: Alan R. Liss, 1984, pp. 41–60.

Oades, R.D. The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. *Neurosci. Biobehav. Rev.*, 9:261–282, 1985.

Post, R., Jimerson, D., Ballenger, J., et al. Cerebrospinal fluid norepinephrine and its metabolites in manic-depressive illness. In: Post, R.M., Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders*. Baltimore: Williams and Wilkins, 1984, pp. 539–553.

Stone, E.A. Problems with current catecholamine hypotheses of antidepressant agents: Speculations leading to a new hypothesis. *Behav. Brain Sci.*, 6:535–577, 1983.

Biochemical and Functional Studies of D-1 Dopamine Receptors

Co-Chairs:

George Breese, Ph.D.
Biological Sciences Research Center
University of North Carolina School of Medicine
Chapel Hill, NC 27514

Ian Creese, Ph.D.
University of California at San Diego
La Jolla, CA 92093

Multiple Forms of the D_1 Dopamine Receptor: Its Linkage to Adenylate Cyclase and Psychopharmacological Effects

Richard B. Mailman, Ph.D.,[1] David W. Schulz, Ph.D.,[2] Clinton D. Kilts, Ph.D.,[3] Mark H. Lewis, Ph.D.,[4] Hans Rollema, Ph.D.,[5] and Steven Wyrick, Ph.D.[6]

Introduction

It is accepted that antipsychotic drugs act principally by blocking postsynaptic dopamine receptors. The most accepted hypothesis divides dopamine receptors into two classes on the basis of specific biochemical characteristics—the D_1 class is linked to stimulation of cyclic adenosine monophosphate (cAMP) synthesis by dopamine, whereas the D_2 class is not (Kebabian & Calne, 1979). It was the D_2 class that had been believed to mediate both antipsychotic effects in man and various antidopaminergic behavioral effects in laboratory animals (cf. Calne, 1980; Creese et al., 1983). While providing an interesting unifying hypothesis, this scheme (or one of its various permutations) often was not reconcilable with available psychopharmacological data (e.g., Niedzwiecki et al., 1984; Lewis et al., 1983; Mailman et al., 1981; Schulz et al., 1984a). Moreover, it provided no biochemical mechanisms (other than effects of cAMP synthesis) that could be linked with functional changes.

For these reasons, the general hypothesis we have used during the last few years is that there is a functionally relevant microheterogeneity of dopamine receptors throughout the brain, and although the ligand recognition characteristics of these receptors may be different (e.g., catechols act on both sites; ergots only the latter), the functional consequences of receptor occupation also reflect the cellular location of the receptors. Two working hypotheses resulting from these

---

[1] Biological Sciences Research Center, Departments of Psychiatry and Pharmacology, Neurobiology Curriculum, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

[2] Biological Sciences Research Center, Neurobiology Curriculum, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

[3] Department of Psychiatry, Duke University Medical Center, Durham, NC 27710.

[4] Biological Sciences Research Center, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

[5] Department of Medicinal Chemistry, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

[6] Rijksuniversiteit, Laboratorium voor Farmaceutische en Analytische Chemie, 9713 AW Groningen, the Netherlands.

Address all correspondence to: Dr. Richard B. Mailman, Biological Sciences Research Center, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

ideas were: 1) that D_1 dopamine receptors, as well as D_2, can mediate profound antidopaminergic behavioral effects; and 2) that the D_1-dopamine receptors are not always linked to stimulation of cAMP synthesis.

Psychopharmacological Effects of D_1 Dopamine Antagonists

An important tool for investigating the psychopharmacology of dopamine receptors has been SCH23390. The initial report showing biochemical selectivity of this compound suggested that it caused few of the psychopharmacological or neurochemical effects associated with D_2 receptor blockade (Iorio et al., 1981; 1984), consistent with its designation as a selective D_1 antagonist (Cross et al., 1983; Hyttel, 1983). However, our early studies surprisingly showed that SCH23390, administered to rats parenterally, rather than orally, was as potent as haloperidol at antagonizing behaviors induced by direct or indirect acting dopamine agonists (Mailman et al., 1984a; 1984b). These psychopharmacological effects of SCH23390 have since been confirmed and expanded by numerous groups (e.g., Christensen et al., 1984). Of particular interest is the fact that SCH23390 was several-fold more potent than fluphenazine when given directly into the brain. These latter data indicate that it is probably not a metabolite of SCH23390 that is responsible for its behavioral effects, nor does it have antidopaminergic potency simply because it inhibits the entry of amphetamine or other dopamine agonists into the brain.

Unusual Aspects of the Pharmacology of SCH23390

Using a High Performance Liquid Chromatography-based analytical method (Kilts et al., 1985), it was found that the plasma half-life of SCH23390 is less than 1 hour, and it appears that the compound has an extremely large volume of distribution after oral administration. Of greater interest, however, is the fact that after i.p. administration, the brain concentrations of SCH23390 are still near maximal at 2 hours, although the plasma concentrations are almost undetectable at this time. Thus, the persistent biochemical and behavioral effects of SCH23390 seen after clearance of the drug from the circulation (Schulz et al., 1985a) may reflect the prolonged presence of this drug at critical recognition sites in the brain, a pattern that is quite different from classical antipsychotic drugs.

Another interesting contrast between SCH23390 and other dopamine receptor blockers is its relative lack of effect on dopamine synthesis and release, and the firing of dopaminergic neurons. In our early psychopharmacological studies, haloperidol (0.3 mg/kg) caused increases of 150–300 percent in 3, 4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) concentrations (a measure of dopamine turnover), whereas no dose of SCH23390 increased DOPAC or HVA in any region by more than 25 percent. In microdissected dopamine terminal fields throughout brain there was also no evidence of changes in dopamine synthesis and release as estimated by changes in either metabolite concentrations, or rate of dopamine utilization after synthesis inhibition. Conversely, other antipsychotic drugs showed dramatic (and regionally specific) effects using both techniques. Consistent with these data, SCH23390 also failed to affect neurotransmitter release in the electrically stimulated, perfused rabbit striatal slice. It neither reversed apomorphine- or nomifensine-induced inhibition of dopamine release at concentrations of 1 μM. Similarly, in identified dopamine cells in the substantia nigra, behaviorally potent doses of SCH23390 were unable to reverse the apomorphine-induced inhibition of firing (Napier et al., 1986).

Effects of SCH23390 on In Vivo Receptor Binding

Feenstra and coworkers (Feenstra et al., 1983a; 1983b; 1983c; Rollema et al., 1986) have demonstrated that there is saturable accumulation of the dopamine agonist dipropyl-(±)-2-amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (diPrADTN) in striatal membranes, and that the effective dose in 50 percent of subjects (ED_{50}) for this accumulation is similar to the ED_{50} for the induction of stereotyped behavior (Feenstra et al., 1983a; 1983c; Rollema et al., 1986). Moreover, various antipsychotic drugs were found to displace this specific accumulation of dipropyl-5,6-ADTN at the same doses that they inhibited the behavioral effects of the agonist (Feenstra et al., 1983a; 1983c; Rollema et al., 1986). Conversely, the neurochemical changes caused by diPrADTN treatment (i.e., decreases in DOPAC and HVA concentrations) have a lower ED_{50} than for effects on specific binding or induction of stereotypy. A series of experiments was performed to assess the effects of SCH23390 on the *in vivo* binding of diPrADTN, and although SCH23390 blocked the behavioral effects of diPrADTN, it did not displace the specific binding of diPrADTN in striatum (Figure 1). Conversely, in the same experiments *cis*-flupenthixol and haloperidol, but not *trans*-flupenthixol, did cause the expected displacement of diPrADTN. Two hypotheses may explain these data: only a small portion of the high affinity diPrADTN binding sites is directly related to behavioral changes, or, alternately, that SCH23390 can cause blockade of agonist-induced behavioral effects by interacting with sites different from those required to initiate these behaviors.

Biochemical Pharmacology of SCH23390

One hypothesis that was evaluated early in our studies was whether SCH23390 acted via generalized effects on cAMP systems. While it was found that SCH23390 completely antagonized dopamine-stimulated adenylate cyclase in the dorsomedial frontal cortex, in this region it inhibited only that portion of norepinephrine-stimulated adenylate cyclase which could be attributed to stimulation of dopamine receptors. In striatum, adenosine-receptor mediated stimulation of adenylate cyclase was not reversed by SCH23390, nor did SCH23390 have effects in NG108-15 neuroblastoma cells at opiate, muscarinic, or alpha$_2$-adrenergic receptors mediating the regulation of cAMP synthesis. Finally, SCH23390 did not inhibit basal adenylate cyclase activity in any system tested, nor did it inhibit the increase in cAMP synthesis induced by forskolin. Thus, it seems clear that SCH23390 does not act by interfering with the catalytic unit, the nucleotide binding protein, or the processes by which non-dopamine stimulatory ligands couple with adenylate cyclase. Finally, it was also determined that SCH23390 does not affect phosphodiesterase activity.

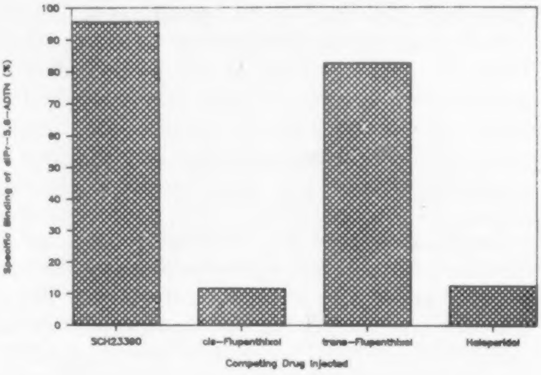


FIGURE 1. The effects of SCH23390 on the *in vivo* binding of dipropyl-5,6-ADTN. Values shown are the specific binding of dipropyl-5,6-ADTN defined per Feenstra et al., 1983. Doses of competing drugs used were: SCH23390—1.07 mg/kg; *cis*- or *trans*-flupenthixol—5 mg/kg; and haloperidol —1 mg/kg.

To provide additional evidence for the hypothesis that SCH23390 acted principally via dopamine receptors, [9-^{3}H]-SCH23390 was synthesized (Wyrick and Mailman, 1985), and its binding characterized (Schulz et al., 1984b; 1985b). The regional distribution of high-affinity, specific [^{3}H]-SCH23390 binding sites in the rat brain correlated well with levels of endogenous dopamine (Figure 2).

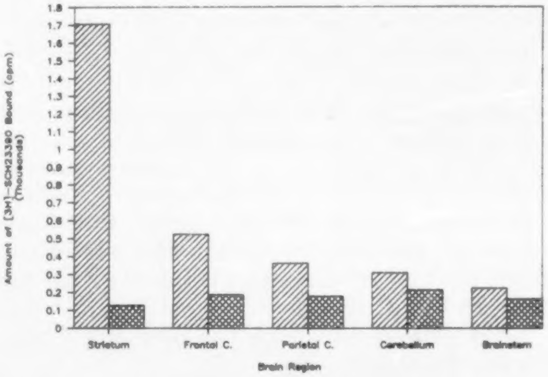


FIGURE 2. The regional distribution of binding of [9-^{3}H]-SCH23390 (3 nM) in several areas of the rat brain. For each region, the left hand bars are total binding, whereas the right hand bar is binding in the presence of 1 µM SCH23390.

Receptor densities were greatest in corpus striatum, nucleus accumbens, and olfactory tubercle; intermediate levels were found in several limbic and cortical areas; while few sites were detectable in cerebellum, brainstem, and olfactory bulb. Specific binding in caudate-putamen was found to be both temperature- and pH-dependent, and appeared to be of a single class of binding sites, or of classes with similar characteristics. Both dopamine and *cis*-flupenthixol altered the slope, but not the intercept, of lines generated by Scatchard analysis. Moreover, the pharmacology of the interactions of [H]-SCH23390 with binding sites in striatal homogenates seemed consistent with an action as a dopamine receptor antagonist (*see* Schulz et al., 1984b; 1985b).

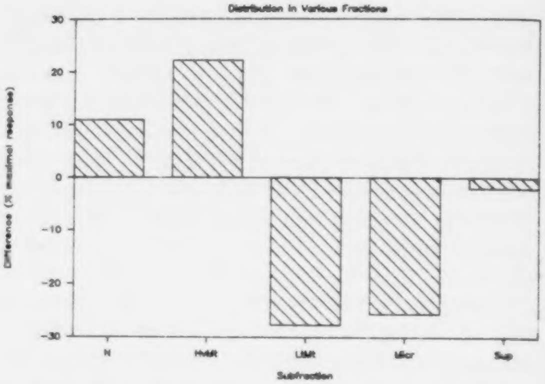


FIGURE 3. Difference in [^{3}H]-SCH23390 binding sites versus dopamine-sensitive adenylate cyclase in cellular subfractions of rat striatum. Values are expressed as percent of maximal concentration of each biochemical parameter. Positive values indicate that relative concentration of dopamine stimulated-adenylate cyclase in that subfraction was higher than the amount of [^{3}H]-SCH23390 binding.

Multiple D_1 Receptors: Differential Distribution of Dopamine–Sensitive Adenylate Cyclase and [^{3}H]-SCH23390 Binding Sites

A critical issue in investigating the biochemical pharmacology of D_1 dopamine receptors is whether all such sites are linked to dopamine-mediated cAMP synthesis (Kebabian and Calne, 1979), or if there are sites with similar recognition characteristics linked to other biochemical events. This latter hypothesis was tested in two ways.

In one series of studies, the rat corpus striatum was subfractionated using differential centrifugation. As can be seen in Figure 3, these studies demonstrated that [^{3}H]-SCH23390 binding sites and dopamine-sensitive adenylate cyclase had significantly different distributions among the various cellular fractions. The [^{3}H]-SCH23390 binding sites tended to be concentrated in lighter cellular fractions relative to dopamine-sensitive adenylate cyclase (Schulz et al., 1985c). These data suggest either that there are spare D_1 dopamine receptors which are localized in cellular structures different than dopamine-sensitive adenylate cyclase, or that the D_1 class of dopamine receptors are actually several populations.

Consistent with the second of these hypotheses, we have found that although basal cAMP synthesis rates are very high in tissue homogenates of rat amygdala, there is no detectable stimulation by addition of dopamine. Dopamine did cause a pronounced dose-dependent increase in cAMP synthesis in tissue from the same animals taken from areas adjacent to the amygdala (i.e., the striatum). SCH23390 alone did not increase or decrease cAMP synthesis in the amygdala (Mailman et al., 1985). Despite the absence of dopamine-stimulated adenylate cyclase in the amygdala, there are significant concentrations of high affinity [^{3}H]-SCH23390 recognition sites in this brain region. Together, these findings suggest that all D_1 receptors (as least as defined by [^{3}H]-SCH23390 binding) are not linked to cAMP synthesis.

Summary

The data summarized above indicate that the psychopharmacological actions of SCH23390 are almost certainly due to interaction of this drug with binding sites that fit the pharmacological characteristics expected of dopamine receptors. Moreover, generalized effects on cAMP systems do not seem to be involved, nor is there evidence that classical neurotransmitters other than dopamine are directly affected by this drug at doses which are psychopharmacologically active. The studies with dipropyl-5,6-ADTN also suggest that functionally important interactions may exist between the D_1 and D_2 classes of receptors, and that the former class may modulate the actions of the latter.

In this regard, it is of particular importance to resolve whether the D_1 dopamine receptor is a single class of sites that always acts via cAMP-dependent mechanisms. Our data suggest there are biochemically distinct sites with similar ligand recognition characteristics that are not linked to cAMP synthesis. A plausible hypothesis may be that much of the psychopharmacological potency of the D_1 class of receptors may be mediated by biochemical mechanisms unrelated to cAMP synthesis. A model consistent with our data is shown in Figure 4.

These biochemical data provide clear evidence that the basis for classification of dopamine receptors into the D_1 and D_2 categories must now be redefined. The impact on both basic and clinical neuropharmacology of verifying such a concept seems obvious. Clinically, it may be possible to design new, truly "atypical," antipsychotic drugs with much greater selectivity, or more selective agonists for uses in neurological disorders such as parkinsonism. Similarly, these data should help in developing new insights into the neurobiology of dopamine-receptive neurons.

Acknowledgments

The authors would like to thank Carl Anderson, Eddie Stanford, and Dr. T.K. Harden for technical assistance. This work was supported in part by PHS grants MH40537, MH37404, HD16834, MH39967, ES01104, and Center Grant HD03110.

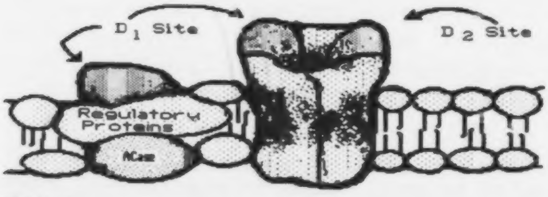


FIGURE 4. Model of dopamine receptors in membrane. This illustrates the lack of identity of some of the [^{3}H]-SCH23390 binding sites and dopamine-sensitive adenylate cyclase. This model also shows how D_1 and D_2 sites might interact to explain the data shown in the paper.

References

Calne, D.B. Clinical relevance of dopamine receptor classification. *Trends Pharmacol. Sci.* 3: 412–414, 1980.

Christensen, A.V., Arnt, J., Hyttel, J., et al. Pharmacological effects of a specific dopamine D_1 antagonist SCH23390 in comparison with neuroleptics. *Life Sci.* 34: 1529–1540, 1984.

Creese, I., Sibley, D.R., Hamblin, M.W., and Leff, S.E. The classification of dopamine receptors: relationship to radioligand binding. *Annu. Rev. Neurosci.* 6: 43–71, 1983.

Cross, A.J., Marshal, R.D., Johnson, J.A., and Owen, F. Preferential inhibition of ligand binding to calf striatal dopamine D1 receptors by SCH 23390. *Neuropharmacol.* 22: 1327–1329, 1983.

Feenstra, M.G.P., Rollema, H., Mulder, T.B.A., et al. *In vivo* dopamine receptor agonist binding in rat brain: Relation with pharmacological effects. *Eur. J. Pharmacol.* 90: 433–436, 1983.

Feenstra, M.G.P., Rollema, H., Mulder, T.B.A., et al. *In vivo* dopamine receptor binding studies with a non-radioactively labelled agonist, dipropyl-5,6-ADTN. *Life Sci.* 32: 1313–1323, 1983.

Feenstra, M.G.P., Rollema, H., Mulder, T.B.A., et al. *In vivo* dopamine receptor binding of a non-radioactively labelled agonist, dipropyl-5,6-ADTN. *Acta Pharm. Sci. Suppl.* 2: 203–210, 1983.

Hyttel, J. SCH 23390—The first selective dopamine D-1 antagonist. *Eur. J. Pharmacol.* 91: 153–154, 1983.

Iorio, L.C., Barnett, A., Leitz, F.H., et al. SCH23390, a potential benzazepine antipsychotic with atypical effects on dopaminergic systems. *Pharmacologist* 23: 137, 1981.

Iorio, L.C., Barnett, A., Leitz, F.H., et al. SCH23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. *J. Pharmacol. Exp. Ther.* 226: 462–468, 1983.

Kebabian, J.W., and Calne, D.B. Multiple receptors for dopamine. *Nature* 277: 93–96, 1979.

Kilts, C.D., Dew, K.L., Ely, T.D., and Mailman, R.B. Quantification of SCH23390 [R-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-methyl-3-benzazepine] in brain and blood by use of reverse phase HPLC with electrochemical detection. *J. Chromatog.* 432: 452–457, 1985.

Lewis, M.H., Widerlov, E., Knight, D.L., et al. N-oxides of phenothiazine antipsychotics: Effects on *in vivo* and *in vitro* estimates of dopaminergic function. *J. Pharmacol. Exp. Ther.* 225: 539–545, 1983.

Mailman, R.B., Kilts, C.D., Beaumont, K., and Breese, G.R. "Supersensitivity" of dopamine systems: Comparisons between haloperidol withdrawal, intracisternal (IC) and unilateral (UNI) 6-hydroxydopamine (6-OHDA) treatments. *Fed. Proc.* 40: 291, 1981.

Mailman, R.B., Rollema, H., Schulz, D.W., et al. Dopamine receptor multiplicity: when the D-1 antagonist is a D-2 antagonist. *Fed. Proc.* 43: 1095, 1984a.

Mailman, R.B., Schulz, D.W., Lewis, M.H., et al. SCH-23390: A selective D-1 dopamine antagonist with potent D-2 behavioral actions. *Eur. J. Pharmacol.*, 101: 159–160, 1984b.

Mailman, R.B., Schulz, D.W., and Kilts, C.D. "D_1-like" dopamine receptors: recognition sites with selectivity for SCH23390 that are not linked to adenylate cyclase. *Soc. Neurosci. Abstr.* 11: 313, 1985.

Napier, T.C., Givens, B.S., Schulz, D.W., et al. SCH23390 effects on apomorphine-induced responses of nigral dopaminergic neurons. *J. Pharmacol. Exp. Ther.* (in press).

Niedzwiecki, D.N., Mailman, R.B., and Cubeddu, L.X. Greater potency for mesoridazine and sulforidazine than thioridazine on striatal dopamine autoreceptors. *J. Pharmacol. Exp. Ther.* 228: 686–689, 1984.

Rollema, H., Feenstra, M.G.P., Grol, C.J., et al. (−)-Dipropyl-5,6-ADTN as an in vivo dopamine receptor ligand: relation between displacement by dopamine agonists and their pharmacological effects. *Naunyn-Schmiedeberg's Arch. Pharmacol.* (in press).

Schulz, D.W., Lewis, M.H., Petitto, J., and Mailman, R.B. Ascorbic acid decreases [^{3}H]-dopamine binding in striatum without inhibiting dopamine-sensitive adenylate cyclase. *Neurochem. Int.* 6: 117–121, 1984a.

Schulz, D.W., Wyrick, S.W., and Mailman, R.B. [^{3}H]-SCH23390 has the characteristics of a dopamine receptor ligand in the rat central nervous system. *Eur. J. Pharmacol.* 106: 211–212, 1984b.

Schulz, D.W., and Mailman, R.B. An improved, automated adenylate cyclase assay utilizing preparative HPLC: Effects of phosphodiesterase inhibitors. *J. Neurochem.* 42: 764–774, 1984.

Schulz, D.W., Staples, L.J., and Mailman, R.B. SCH23390 causes persistent antidopaminergic effects *in vivo*: evidence in longterm occupation of receptors. *Life Sci.* 36: 1941–1948, 1985a.

Schulz, D.W., Stanford, E.J., Wyrick, S.W., and Mailman, R.B. Binding of [^{3}H]SCH23390 in rat brain: regional distribution, inhibition by competing ligands, and effects of assay conditions suggest interactions at D_1-like dopamine receptors. *J. Neurochem.* 45: 1601–1611, 1985b.

Schulz, D.W., Stanford, E.J., and Mailman, R.B. Subcellular localization of the SCH23390 receptor: dissociation from dopamine-stimulated adenylate cyclase. *Soc. Neurosci. Abstr.* 11: 888, 1985c.

Wyrick, S.W., and Mailman, R.B. Tritium-labeled (±) 7-chloro-8-hydroxy-3-methyl-1 phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH23390). *J. Label. Comp. Radiopharm.* 22: 189–195, 1985.

Structural Analogs of SCH 23390 as Discriminators of Dopamine Receptor Subtypes: Behavioral Interactions Between D-1 and D-2 Agonists and Antagonists[1]

Kathy M. O'Boyle, Ph.D.,[2] Anthony G. Molloy, M.Sc.,[2] Marcellina Mashurano,[2] and John L. Waddington, Ph.D.[2]

Recent studies with the first agents to show the characteristics of a selective D-1 dopamine (DA) receptor antagonist, the 7-halogenated benzazepines SCH 23390 (Iorio et al., 1983; Hyttel, 1983; O'Boyle & Waddington, 1984a; Mailman et al., 1984) and SK&F 83566 (O'Boyle & Waddington, 1984b), have revealed a number of unexpected properties. These include the blockade of a variety of responses previously attributed to D-2 receptor function. For example, in the intact rodent, stereotyped behavior induced by the non-selective D-2 agonist apomorphine and by the selective D-2 agonist RU 24213 are potently blocked by SCH 23390 and SK&F 83566. One interpretation of such findings is that D-1 and D-2 receptor systems may be functionally linked and that D-1 dopaminergic function may be necessary to "enable" the expression of responses initiated by D-2 receptor stimulation in the whole animal (Pugh et al., 1985: Molloy & Waddington, 1985b).

The prominent behavioral effects of SCH 23390 and SK&F 83566, apparently resulting from blockade of tonic D-1 dopaminergic activity, might seem at variance with the failure of the selective D-1 agonist SK&F 38393 to induce typical dopaminergic responses such as stereotypy. However, we have noted it to induce more subtle forms of behavior; thus, SK&F 38393 induces, under particular experimental conditions, episodes of non-stereotyped grooming interpolated between episodes of non-stereotyped sniffing, with some rearing and locomotion (*see* Molloy & Waddington, 1984 and 1985a, for descriptions of behaviors).

Presented here is a preliminary account of further efforts to characterize 1) additional selective benzazepine agents potentially able to discriminate between D-1 and D-2 receptors, and 2) behavioral responses to a D-1 agonist using the *R*- and *S*-enantiomers of SK&F 38393 and SK&F 83566. Additionally, we briefly describe some of our initial studies on the concurrent administration of SK&F 38393 and RU 24213.

Studies With Benzazepine Derivatives

SCH 23390 and SK&F 38393 are 8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines, differing only in their 7- and 3-substituents which respectively confer full antagonist and partial agonist activities at D-1 receptors. We have investigated further a series of benzazepine analogs differing only in substituents at these apparently critical 3- and 7- positions (O'Boyle & Waddington, 1985a; *see* Table 1). These drugs and reference dopaminergic compounds were compared for their activity to displace the binding of ^{3}H-SCH 23390 from D-1 receptors in human post mortem putamen (0.3 to 0.8 nM ^{3}H-SCH 23390, specific binding defined by 100 nM piflutixol; O'Boyle & Waddington, 1985b). Results were contrasted with our previous measures of their affinities for rat striatal D-1 and D-2 receptors, assessed using ^{3}H-piflutixol and ^{3}H-spiperone respectively (O'Boyle & Waddington, 1985a).

Our behavioral procedures have been presented in detail elsewhere (Molloy & Waddington, 1984) and involve assessing responses to SK&F 38393 after a period of prolonged habituation using a combined rapid

---

[1] This work was supported by the Medical Research Council of Ireland, the Royal College of Surgeons in Ireland, and the Irish Council for Overseas Students.

[2] Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin 2, Ireland.

Reprint requests: Dr. John L. Waddington, Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin 2, Ireland.

TABLE 1. Displacement of ^{3}H-SCH 23390 in Comparison With ^{3}H-Piflutixol and ^{3}H-Spiperone.

Displacing Agent	K_i (nM)		
	^{3}H-SCH 23390	^{3}H-PIF	^{3}H-SPIP
Flupenthixol	12	0.8	1.0
Fluphenazine	49	19	1.0
Domperidone	2,700	>5,000	0.3
Sulpiride	>50,000	>50,000	109
Dopamine	1,300	23,300	778
SK&F 77174 (7-H-3-H)	898	590	22,900
SK&F 38393 (7-OH-3-H)	735	1,390	12,600
SK&F 83692 (7-H-3-CH_3)	538	165	1,300
SK&F 75670 (7-OH-3-CH_3)	132	1,400	30,600
SK&F 85257 (7-CH_3-3-H)	169	75	7,300
SCH 23390 (R)(7-Cl-3-CH_3)	1.3	0.7	1,080
SK&F 83566 (R)(7-Br-3-CH_3)	2.7	1.4	1,200
SK&F 83566 (S)(7-Br-3-CH_3)	1,470	425	5,100

Data are means of 2 to 5 separate estimations.

time-sampling behavioral checklist technique and conventional stereotypy rating scale. Rats were challenged with *R*- or *S*-SK&F 38393; in characterization studies, *R*-SK&F 38393 was given after 30 min pretreatments with antagonists. Behavioral counts for grooming (Gr), a characteristically intense grooming response (Gr_i), and sniffing (Sn) were obtained by summing the number of observation windows in which these behaviors were recorded, over 20 to 40 min after challenge for grooming responses and over 30 to 60 min after challenge for sniffing. In combination studies, rats were challenged with SK&F 38393, with RU 24213, or with RU 24213 given 10 min after pretreatment with SK&F 38393. The peak score on the stereotypy scale allocated to each animal and the qualitative features of that peak response were analyzed.

Receptor Selectivities of Some Further Benzazepine Derivatives

In human putamen, the binding of ^{3}H-SCH 23390 shows characteristics (O'Boyle & Waddington, 1985b) similar to those previously described for rat striatum (Billard et al., 1984). The D-1 profile for displacement of ^{3}H-SCH 23390 binding over the range of compounds compared in Table 1 was very similar to that for ^{3}H-piflutixol ($r = 0.84$, $p < 0.005$) but distinct from that for ^{3}H-spiperone ($r = 0.41$, NS). Relationships between structure and affinity for D-1 receptors vs. D-2 receptors within this further benzazepine series have recently been discussed in detail in relation to displacement of ^{3}H-piflutixol vs. ^{3}H-spiperone (O'Boyle & Waddington, 1985a). The actions of these analogs to displace ^{3}H-SCH 23390 were similar, with the exception that the 7-OH-3-CH_3 compound (SK&F 75670) appeared to be a somewhat less potent displacer of ^{3}H-piflutixol. Generally, 7-substituents, particularly halogens, were critical determinants of affinity for D-1 but not D-2 receptors, over a range of some three orders of magnitude. Conversely, 3-substituents had somewhat less marked effects, and their influence extended to affinity for D-2 as well as D-1 receptors. In human brain, ^{3}H-SCH 23390 was potently and stereoselectively displaced by *R*- but not by *S*-SK&F 83566. Similarly, we have previously reported that in rat striatum the D-1 affinity of SK&F 38393 and of SK&F 83566 resides stereoselectively in their *R*- but not their *S*-configuration, while weak residual affinity for the D-2 receptor shows negligible enantioselectivity (O'Boyle & Waddington, 1984a,b).

Responses to the Enantiomers of SK&F 38393 and SK&F 83566

The comparative effects of 20 mg/kg of the *R*- and *S*- enantiomers of SK&F 38393, in terms of the induction of behaviors, are shown in Table 2. There appeared to be little induction of Sn by *S*-SK&F 38393, with this effect residing in the *R*-enantiomer. While Gr was also induced by *R*-SK&F 38393, there

TABLE 2. Behavioral Responses to *R*- and *S*- SK&F 38393 and the Influence of Selective Antagonists.

Drug(s)	mg/kg	Sn	Gr	Gr$_l$
Vehicle		2.4 ± 0.5	1.2 ± 0.3	0.1 ± 0.1
S-SK&F 38393	20.0	4.1 ± 0.8	3.2 ± 0.6$^{\wedge}$	0.1 ± 0.1
R-SK&F 38393	20.0	11.1 ± 0.6$^{\wedge}$	4.0 ± 0.3$^{\wedge}$	1.8 ± 0.2$^{\wedge}$
+ SCH 23390	0.1	1.4 ± 0.5*	1.7 ± 0.5*	0.1 ± 0.1*
+ *S*-SK&F 83566	0.2	10.2 ± 1.6	7.3 ± 1.7*	3.5 ± 0.5
+ *R*-SK&F 83566	0.04	7.4 ± 1.6	4.0 ± 0.8	1.8 ± 0.8
	0.2	1.2 ± 0.4*	1.8 ± 0.6*	0.6 ± 0.6*
+ MET	1.0	12.6 ± 0.6	4.3 ± 0.4	0.8 ± 0.4*
	5.0	8.1 ± 1.1	2.9 ± 0.5	0.5 ± 0.3*

Means ± SEM, $n = 4$ to 38; $^{\wedge}p < 0.01$ vs. vehicle; $^{*}p < 0.05$ vs. *R*-SK&F 38393; Mann-Whitney 'U' test.

was some activity in its *S*-antipode; this involved the induction of grooming of the face with forepaws. The induction of Gr$_l$ showed complete enantioselectivity, being induced by *R*- but not by *S*-SK&F 38393.

As shown in Table 2, all three of these behaviors induced by 20 mg/kg *R*-SK&F 38393 were blocked by as little as 100 µg/kg SCH 23390. No such blockade was associated with 200 µg/kg *S*-SK&F 83566, and Gr and Gr$_l$ responses were in fact increased by this pretreatment. However, all three behaviors were dose-dependently blocked by 40–200 µg/kg *R*-SK&F 83566 with complete enantioselectivity. The selective D-2 antagonist metoclopramide (1.0 to 5.0 mg/kg) tended to reduce behavioral counts for Sn and Gr, and antagonized the induction of Gr$_l$.

Responses to SK&F 38393 and RU 24213 Alone and in Combination

When given alone, 15 mg/kg SK&F 38393 failed to induce stereotyped behavior (mean peak scores <2) while 2.5 mg/kg RU 24213 was a threshold dose for the induction of bursts of stereotyped sniffing and locomotion (Table 3). A 10-min pretreatment with 3 to 15 mg/kg SK&F 38393 dose-dependently potentiated responses to this dose of RU 24213. The combination of 15 mg/kg SK&F 38393 and 2.5 mg/kg RU 24213 produced stereotypy scores which significantly exceeded those associated with either drug given alone. In this combination group, 50 percent of animals showed the compulsive stereotypies of fixated sniffing, with or without licking, while these behaviors were not evident in any of the single treatment groups.

The Nature of Behavioral Responses to SK&F 38393

There was significant and substantial separation between the enantiomers of SK&F 38393 for the induction of Sn and Gr$_l$; in the latter case, behavioral activity showed complete enantioselectivity for *R*- but not *S*-SK&F 38393. This parallels the D-1 agonist activity of the enantiomers, which also resides stereoselectively in the *R*- configuration. This is strong evidence that the present behavioral effects have their basis in D-1 receptor stimulation. The activity of *S*-SK&F 38393 to induce some episodes of Gr need not contradict this analysis, as the compound so designated is not enantiomerically pure and contains a modest proportion of its *R*-antipode as contaminant (Kaiser et al., 1982); this would account for some behavioral activity in the *S*-

TABLE 3. Behavioral Responses to SK&F 38393 and RU 24213 Alone and in Combination.

Drug(s)	mg/kg	Stereotypy Score	Compulsive Stereotypy
Vehicle		0.9 ± 0.2	0/8
SK&F 38393	15.0	1.8 ± 0.2	0/8
RU 24213	2.5	2.4 ± 0.2	0/8
RU 2.5 + SK&F	3.0	2.9 ± 0.4	0/8
RU 2.5 + SK&F	15.0	3.4 ± 0.4*	4/8*

Means ± SEM. $^{*}p < 0.05$ vs. RU or SK&F alone; Mann-Whitney 'U' test or Fisher probability test.

sample at such high doses, in terms of low threshold Gr (and occasional Sn) responses, but its inactivity to induce the high threshold Gr$_i$ response.

The ability of as little as 100 µg/kg SCH 23390 to block all behaviors induced by *R*-SK&F 38393 further suggests a primary role for D-1 receptor stimulation in the genesis of these responses. Their antagonism by SK&F 83566 showed complete stereoselectivity for the *R*- but not the *S*- enantiomer, in which D-1 antagonist activity resides. Thus, a primary role for D-1 receptors in the induction of these behaviors is again indicated.

Moderate doses of the selective D-2 antagonist metoclopramide tended to lower counts for Sn and Gr induced by *R*-SK&F 38393 and antagonized Gr$_i$. We have previously noted that metoclopramide does not influence the general prevalence of *R*-SK&F 38393-induced grooming (Molloy & Waddington, 1984); metoclopramide may have some activity to attenuate the overall severity of grooming, or else individual forms of grooming response may be pharmacologically distinct from each other or from other behaviors. Both prevalence and counts for rearing and locomotion induced by *R*-SK&F 38393 are antagonized by metoclopramide as well as by SCH 23390 (Molloy & Waddington, 1985a; Molloy et al., 1986). Such data might also be explained if D-1 and D-2 receptor mechanisms do not invariably constitute functionally independent processes, such that drug effects on D-2 receptor activity may modulate the expression of certain behaviors induced by D-1 receptor stimulation.

D-1: D-2 Receptor Systems and the Regulation of Behavior

Selective D-1 agonists can, under particular experimental conditions, induce episodes of non-stereotyped behaviors, such as prominent grooming, which are sensitive to blockade by selective D-1 antagonists. Stereochemical relationships, revealed using the enantiomers of SK&F 38393 and SK&F 83566, are particularly powerful evidence for a primary role of D-1 receptor stimulation in the initiation of these responses. However, these are clearly not simple processes. The selective D-2 antagonist metoclopramide is able to influence responsiveness to SK&F 38393 (see above) and the selective D-1 antagonists SCH 23390 and SK&F 83566 are able to influence responsiveness to RU 24213, in the latter instance with complete enantioselectivity (Pugh et al., 1985; Molloy & Waddington, 1985b). One interpretation of these data is that there is only one brain DA receptor, such that behavioral responses do not show consistent selectivity for receptor antagonists; this would question the functional relevance of the D-1:D-2 subdivision that is usually made on in vitro considerations (Leff & Creese, 1983). However, selective D-1 and D-2 agonists do induce different forms of behavioral response, even though they are not doubly-dissociable in terms of selective D-1 and D-2 antagonists. Interestingly, the mixed DA agonist apomorphine induces grooming behavior only in animals pre-treated with metoclopramide, perhaps by antagonizing prepotent D-2 activity and unmasking the D-1 component (Molloy & Waddington, 1985a). The status of SCH 23390 and RU 24213 as selective agents, the possible generation of nonselective active metabolites, and the influence of possible nondopaminergic actions have been discussed previously (Pugh et al., 1985) and cannot easily account for such results. In saturation studies of ^{3}H-piflutixol and ^{3}H-spiperone binding, SCH 23390 increases the K_D for the former at sub-nM concentrations, but increases the K_D for the latter only in the µM range, while B_{max} values did not appear to change; thus SCH 23390 shows the properties of a potent, competitive D-1 antagonist with weak residual competitive D-2 antagonist activity. Also, SCH 23390, at a concentration 5-fold greater than was necessary to so influence ^{3}H-piflutixol binding, fails to influence the potent displacement of ^{3}H-spiperone by RU 24213 (O'Boyle et al., 1986). Thus SCH 23390 does not appear to influence D-2 receptor characteristics at the level of the protein recognition site.

If D-1 antagonists block D-2 agonist-induced responses, a corollary would be that D-1 agonists might alter the form of responses to D-2 agents in the direction of fixated stereotypies. We have found it difficult to induce compulsive, fixated stereotyped behavior even with high doses of the selective D-2 agonist RU 24213 (Pugh et al., 1985), although these are a typical response to the mixed D-1/D-2 agonist apomorphine. Perhaps these distinctions reflect the absence and presence of D-1 agonist activity. In preliminary studies, we have found that a threshold dose of RU 24213 for the induction of stereotyped behavior induces a greater compulsive stereotypy response when immediately preceded by SK&F 38393. Thus both decreasing *and* increasing D-1 dopaminergic tone appears able to modulate the intensity of expression of D-2 receptor-stimulated behaviors.

Putative mechanisms for how D-1 agonists and antagonists might influence D-2 agonist responses, such as those discussed above, are conjectural and supported only by indirect data; even less is known about how D-2 antagonists might influence behaviors initiated by D-1 receptor stimulation. Perhaps the situation is somewhat analogous conceptually to the effects of adrenergic antagonists on cardiovascular indices; both α- and β-receptor blockers can induce a reduction in blood pressure, but these effects are mediated via distinct receptor subtypes through which initially distinct mechanisms ultimately influence the same physiological process.

The introduction of these new specific and selective D-1 agonist and antagonist drugs, especially as enantiomeric pairs, has prompted new interest in D-1 receptor function. The notion of concerted D-1: D-2 interplay in the regulation of dopaminergic behaviors (Molloy & Waddington, 1984; Pugh et al., 1985) clearly requires mechanistic support at the neuronal level. Perhaps distinct D-1 and D-2 receptor systems can in some instances each exert an influence over what is ultimately the same efferent pathway, as in a neuronal logic gate. A note of caution is required as these concepts have evolved from studies with only a single class of selective D-1 antagonist.

However, any mechanism must be able to account for the ability of each receptor subtype to select a particular mode of expression of the same behavior, e.g., nonstereotyped vs. stereotyped sniffing, and also to initiate different behaviors such as grooming. Additionally, in animals in whom tonic DAergic function has been removed by 6-hydroxydopamine or reserpine/α-methyl-*p*-tyrosine pretreatment, and in whom adaptive receptor changes are likely, D-1 and D-2 receptors can then be double-dissociated in terms of responses to D-1 or D-2 agonists and their differential responses to selective antagonists (Arnt, 1985; Breese & Mueller, 1985). Thus the extent of tonic DAergic activity appears to be a crucial determinant of the behavioral profile of selective D-1 and D-2 agonists and antagonists.

Acknowledgment

We are most grateful for gifts of experimental drugs from Roussel, Schering, and Smith Kline & French.

References

Arnt, J. Hyperactivity induced by stimulation of separate dopamine D-1 and D-2 receptors in rats with bilateral 6-OHDA lesions. *Life Sci.*, 37:717–723, 1985.

Billard, W., Ruperto, V., Crosby, G., et al. Characterisation of the binding of ^{3}H-SCH 23390, a selective D-1 receptor antagonist ligand, in rat striatum. *Life Sci.*, 35:1885–1893, 1984.

Breese, G.R. and Mueller, R.A. SCH 23390 antagonism of a D-2 dopamine agonist depends upon catecholaminergic mechanisms. *Eur. J. Pharmacol.*, 113:109–114, 1985.

Hyttel, J. SCH 23390: the first selective dopamine D-1 antagonist. *Eur. J. Pharmacol.*, 91:153–154, 1983.

Iorio, L.C., Barnett, A., Leitz, F.H., et al. SCH 23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. *J. Pharmacol. Exp. Ther.*, 226:462–468, 1983.

Kaiser, C., Dandridge, P.A., Garvey, E., et al. Absolute stereochemistry and dopaminergic activity of enantiomers of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine. *J. Med. Chemistry*, 25:697–703, 1982.

Leff, S.E., and Creese, I. Dopamine receptors re-explained. *Trends Pharmacol. Sci.*, 4:463–467, 1983.

Mailman, R.B., Schulz, D.W., Lewis, M.H., et al. SCH 23390: a selective D-1 dopamine antagonist with potent D-2 behavioural actions. *Eur. J. Pharmacol.*, 101:159–160, 1984.

Molloy, A.G., and Waddington, J.L. Dopaminergic behaviour stereospecifically promoted by the D-1 agonist *R*-SK&F 38393 and selectively blocked by the D-1 antagonist SCH 23390. *Psychopharmacology*, 82:409–410, 1984.

Molloy, A.G., and Waddington, J.L. Sniffing, rearing and locomotor responses to the D-1 dopamine agonist *R*-SK&F 38393 and to apomorphine: differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. *Eur. J. Pharmacol.*, 108:305–308, 1985a.

Molloy, A.G., and Waddington, J.L. The enantiomers of SK&F 83566, a new selective D-1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D-1 agonist RU 24213. *Eur. J. Pharmacol.*, 116:183–186, 1985b.

Molloy, A.G., O'Boyle, K.M., Pugh, M.T., and Waddington, J.L. Locomotor behaviours in response to new selective D-1 and D-2 dopamine receptor agonists and the influence of selective antagonists. *Pharmacol. Biochem. Behav.* (in press.)

O'Boyle, K.M., and Waddington, J.L. Selective and stereospecific interactions of *R*-SK&F 38393 with ^{3}H-piflutixol but not ^{3}H-spiperone binding to striatal D-1 and D-2 dopamine receptors: comparisons with SCH 23390. *Eur. J. Pharmacol.*, 90:433–436, 1984a.

O'Boyle, K.M., and Waddington, J.L. Identification of the enantiomers of SK&F 83566 as specific and stereoselective antagonists at the striatal D-1 dopamine receptor: comparisons with the D-2 enantioselectivity of Ro22-1319. *Eur. J. Pharmacol.*, 106:219–220, 1984b.

O'Boyle, K.M., and Waddington, J.L. Structural determinants of selective affinity for brain D-1 dopamine receptors within a series of 1-phenyl-1H-3-benzazepine analogues of SK&F 38393 and SCH 23390. *Eur. J. Pharmacol.*, 115:291–295, 1985a.

O'Boyle, K.M., and Waddington, J.L. Binding of ^{3}H-SCH 23390, a selective D-1 dopamine receptor antagonist, in human brain. *Brit. J. Pharmacol.*, 86:435P, 1985b.

O'Boyle, K.M., Molloy, A.G., and Waddington, J.L. Benzazepine derivatives: nature of the selective and stereospecific interactions of SK&F 38393 and SCH 23390 with brain D-1 receptors. In: Woodruff, G.N., et al. (eds.), *Dopaminergic Systems and their Regulation*. London: Macmillan Press, 1986, pp. 385–386.

Pugh, M.T., O'Boyle, K.M., Molloy, A.G., and Waddington, J.L. Effects of the putative D-1 antagonist SCH 23390 on stereotyped behaviour induced by the D-2 agonist RU 24213. *Psychopharmacology*, 87:308–312, 1985.

Biochemical and Behavioral Studies of D_1 Dopamine Receptors Utilizing SCH23390[1]

Ellen J. Hess, B.A.,[2] and Ian Creese, B.A., M.A., Ph.D.[2]

Previous research has demonstrated the existence of two distinct dopamine receptor subtypes (Creese et al., 1983; Kebabian & Calne, 1979), possessing unique pharmacologic and biochemical properties. D_1 dopamine receptors stimulate adenylate cyclase activity (Hyttel, 1978), while D_2 dopamine receptors inhibit this enzyme (Battaglia et al., 1985; Onali et al., 1984; Stoof & Kebabian, 1981), and have been implicated as the site mediating the antipsychotic and antidopaminergic activity of neuroleptics (Creese et al., 1976; Seeman et al., 1976).

The functional role of D_1 receptors has not been clearly defined due to the lack of *selective*, high-affinity D_1 receptor ligands. To date, the thioxanthenes, [^{3}H]cis-flupentixol and [^{3}H]cis-piflutixol, have been the only suitable radioligands available for labeling D_1 receptors. Since these ligands exhibit similar affinities for both D_1 and D_2 receptors, as well as high nonspecific binding (30 to 50 percent of total binding) (Leff et al., 1985), they have not been ideal tools for investigating D_1 receptor pharmacology, molecular mechanisms, or behavioral function.

Recently, a D_1 selective antagonist, SCH23390, was developed (Iorio et al., 1983) and has since been tritiated, making detailed D_1 receptor characterization possible. This novel benzazepine exhibits nanomolar potency in inhibiting dopamine stimulation of striatal adenylate cyclase activity (Battaglia et al., 1985; Onali et al., 1984), exhibiting a K_i value of approximately 0.5 nM for the striatal D_1 receptor (Billard et al., 1985). In contrast, its affinity for D_2 receptors is orders of magnitude lower (2×10^{-7} M) indicating that SCH23390 is selective for D_1 receptors. Hence, the advent of this first truly selective D_1 receptor antagonist has provided the tool for research into the functional correlates of D_1 receptor activation and antagonism.

Characterization of [^{3}H]SCH23390 Binding to D_1 Dopamine Receptors

We have undertaken a detailed investigation of antagonist and agonist interactions with D_1 receptors labeled by [^{3}H]SCH23390 and the effect of guanine nucleotides on the regulation of agonist interactions with this receptor (Hess et al., in press). In rat striatum, [^{3}H]SCH23390 binding is saturable, monophasic, and exhibits high affinity (K_d = 0.49–nM). Scatchard analyses of saturation data indicate that the site density in striatum, 64 ± 12.9 pmol/g wet weight tissue, corresponds well with densities reported for D_1 receptors labeled by [^{3}H]flupentixol (Hyttel, 1978; Leff et al., 1985). Antagonist competitions for [^{3}H]SCH23390 binding are monophasic, suggesting that [^{3}H]SCH23390 labels a homogeneous population of sites. That the affinities of antagonists' inhibition of [^{3}H]SCH23390 binding correlate well with their respective affinities in both inhibiting D_1 receptor binding of [^{3}H]flupentixol (Figure 1) or antagonizing dopamine-stimulated adenylate cyclase activity indicates that SCH23390 is D_1 receptor selective.

In contrast to the monophasic competitions by antagonists, agonist interactions with [^{3}H]SCH23390 binding were complex, yielding shallow competition curves. Agonist competitions consistently modeled best to two sites composed of a high affinity component (R_H) comprising 30 to 40 percent of the total

---

[1] This study was supported in part by USPHS Grant MH-32990, an RSDA MH-00316 to I.C., and the Scottish Rite Schizophrenia Research Program, NMJ. U.S.A. We would like to thank Drs. George Koob and Neal Swerdlow for discussion, use of their locomotor activity cages, and statistical analyses. Drs. Andrew Norman and George Battaglia are thanked for their collaboration on many of the research papers discussed in this paper.

[2] Department of Neurosciences, M-008, University of California, San Diego, La Jolla, CA 92093.

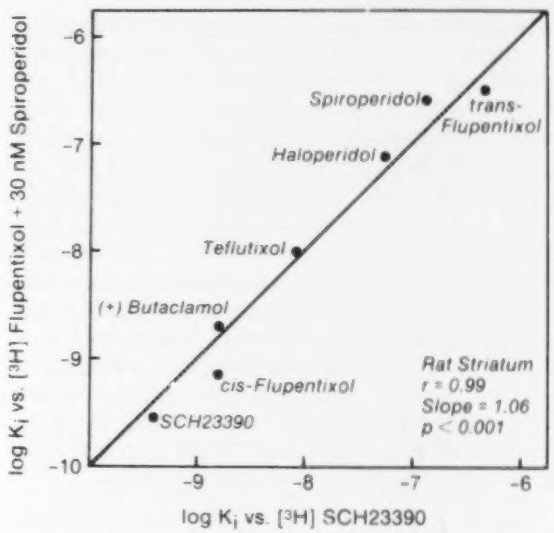


FIGURE 1. Correlation between antagonist inhibition of [^{3}H]SCH23390 and [^{3}H]flupentixol binding in rat striatal homogenates. Log K_i values for [^{3}H]SCH23390 binding and [^{3}H]flupentixol binding were derived from data obtained in this laboratory (Hess et al., in press; Leff et al., 1985).

number of specific binding sites and a low-affinity site (R_L) comprising the remaining 60 to 70 percent of specific binding sites.

In many adenylate cyclase-coupled receptor systems, including D_2 receptors, α-2 and β-adrenoceptors, guanine nucleotides regulate agonist interactions with [^{3}H]antagonist-labeled receptors. The effect of guanine nucleotides, such as GTP, is primarily to reduce the overall affinity of agonists for these receptors (i.e., shift curves to the right) by reducing the percent of agonist high affinity binding (percent R_H). Consistent with these systems, we have found that in the presence of 0.3 M GTP, agonist competitions for [^{3}H]SCH23390 binding were shifted to the right and steepened, resulting in an approximate 50 percent reduction in the high-affinity agonist binding-site density. That guanine nucleotides can promote an apparent shift in agonist competition curves, decreasing the percent R_H without affecting total [^{3}H]SCH23390 binding suggests that the high- and low-affinity agonist components of binding represent partially interconvertible states of a single receptor population. This observation is consistent with the proposed two-state model, modified from the original ternary complex model (Boeynaems & Dumont, 1975). Briefly, this model hypothesizes that both agonists (A) and antagonists bind to the receptor (R) recognition site, but only agonists promote or stabilize the interaction between R and the guanine nucleotide regulatory subunit (N). Thus, a ternary complex is formed (ARN), representing the R_H state of the receptor. In this model, the addition of guanine nucleotides promotes the dissociation of N and R, representing the R_L agonist binding state.

Potential Clinical Utility Of SCH23390

Neuroleptics, administered to rodents *in vivo*, induce catalepsy, suppress conditioned avoidance responses, and antagonize the hyperactivity and stereotypy responses elicited by dopamine agonists. Neuroleptics are also generally antiemetic and have been shown to induce hyperprolactinemia by blocking dopamine receptors in the anterior pituitary. While SCH23390 is a selective D_1 receptor antagonist, this benzazepine surprisingly mimics some of the behavioral effects previously associated with D_2 receptor antagonists—such as blocking agonist-induced stereotypy and hyperactivity, as well as inducing catalepsy (Christensen et al., 1984; Iorio et al., 1983). However, SCH23390 neither antagonizes emesis nor produces hyperprolactinemia—indicating that SCH23390 administered *in vivo* is probably not acting as an antagonist at D_2 receptors.

That SCH23390 can induce these neuroleptic behavioral effects without blockade of D_2 receptors suggests that it may be an effective antipsychotic agent. Because chronic neuroleptic treatment in rodents produces an increase in the number of D_2 receptors (Fleminger et al., 1983), it has been suggested that the side effect of tardive dyskinesia seen following chronic neuroleptic treatment of schizophrenics may result from a selective D_2 receptor up-regulation (Cross et al., 1983). If chronic treatment with the D_1 receptor selective antagonist SCH23390 does not increase D_2 receptor number, it may therefore lack the liability to produce tardive dyskinesia.

Biochemical Effects of Chronic SCH23390 Administration

Indeed, in a preliminary investigation of this hypothesis (Creese & Chen, 1985) we found that after treating rats ($n = 6$) chronically with SCH23390 (0.5 mg/kg/day for 21 days), striatal D_1 receptors were significantly increased as determined by [^{3}H]flupentixol binding (B_{max} control = 56.6 ± 1.5 pmol/g tissue; B_{max} chronic SCH23390 = 70.3 ± 3.5 pmol/g tissue; $p = 0.005$) while no change was observed in the D_2 receptor population. In order to investigate this hypothesis further, we have examined the selectivity of SCH23390 administered *in vivo* for D_1 receptors, the effect of chronic SCH23390 treatment on adenylate cyclase activity as well as on dopamine receptor binding, and tested rats for their locomotor activity and stereotypy responses to selective D_1 and D_2 receptor agonists following chronic treatment with SCH23390.

After chronic treatment with SCH23390, an increase in D_1 receptors, as determined by [^{3}H]SCH23390 binding, was observed, consistent with the previous study by this laboratory (Creese & Chen, 1985). That no increase in D_2 receptors was observed indicates that this effect is D_1 receptor selective; thus, SCH23390 maintains its D_1 receptor specificity *in vivo* even after chronic treatment. This conclusion is supported by studies utilizing *in vivo* N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) treatment.

EEDQ has been shown to be an irreversible pharmacologic antagonist at a variety of neurotransmitter receptors. We recently demonstrated that peripheral administration of EEDQ results in a dose-dependent reduction in both D_1 and D_2 receptor binding (Hamblin & Creese, 1983). Significantly, treatment with SCH23390 (0.5 mg/kg, s.c.) prior to peripheral administration of EEDQ protects D_1 receptors from irreversible blockade by EEDQ, but neither D_2 nor S_2 serotonin receptors are protected from EEDQ-induced modifications by the SCH23390 pretreatment. This indicates that SCH23390, in all probability, interacts *in vivo* exclusively with D_1 receptors at the dose which was chronically administered to rats in our study. These data have been supported by Meller et al. (1985a) using a similar paradigm to examine the specificity of neuroleptics administered *in vivo*. That peripherally administered SCH23390 demonstrates selectivity for D_1 receptors suggests that the behavioral data reported herein are not confounded by any obvious nonspecific effects of this drug.

Interestingly, although the D_1 receptor B_{max} was increased by the chronic SCH23390 treatment, no change was observed in dopamine competition for [^{3}H]SCH23390 binding, nor was any change observed in the rightward shift of these agonist competition curves induced by guanine nucleotides. These data indicate that the coupling of the D_1 receptor to the guanine nucleotide regulatory protein is not perturbed following chronic SCH23390 treatment. That the R_H/R_L ratio remains constant between control and treated animals also suggests that there must exist some mechanism by which this ratio is maintained after receptor upregulation. Theoretically, if the population of N is stoichiometrically limiting (which is likely as 100 percent R_H is never induced by agonists) and R increases, the percent of high affinity agonist binding sites (R_H) should be reduced due to the percent decrease in potential R to N coupling. An excess or spare pool of N, however, would maintain the R_H/R_L ratio after receptor upregulation. Alternatively, if N is stoichiometrically limiting [as we have previously suggested (Battaglia et al., submitted)], N may also undergo concomitant upregulation with D_1 receptors, maintaining a constant R_H/R_L ratio. This may occur either through an increase in the actual population of N subunits or through an increase in the efficacy of the R/N coupling mechanism.

After chronic SCH23390 treatment, adenylate cyclase activity was enhanced by a small (9 to 13 percent) but significant amount. However, not only did dopamine-stimulated cAMP production increase, but guanine nucleotide and forskolin-stimulated adenylate cyclase activity also increased (Figure 2). It is important to note that dopamine-stimulated adenylate cyclase activity was increased by only the same percent as guanine nucleotide-stimulated adenylate cyclase activity. Furthermore, dopamine EC_{50}'s in control and tissue from chronically SCH23390 treated rats were identical. This indicates the increase observed in dopamine-stimulated adenylate cyclase activity most probably reflects the overall increase observed in guanine nucleotide-stimulated enzyme activity. The results of the agonist competition curves plus the adenylate cyclase data suggest that the guanine nucleotide regulatory protein, rather than the adenylate cyclase moiety, is in some manner "upregulated" with the receptor.

That no percentage increase is observed in dopamine-stimulated adenylate cyclase activity after D_1 dopamine receptor upregulation is, at first examination, surprising. However, in other experiments we have demonstrated the existence of "spare" D_1 receptors in the striatum of normal control rats explaining this observation (Hess et al., submitted). In these experiments we again utilized peripheral administration of the irreversible protein-modifying reagent, EEDQ. After *in vivo* EEDQ treatment, no change in adenylate cyclase stimulation above basal activity is observed in the presence of the putative Ns effectors GTP, Gpp(NH)p, and NaF. Likewise, stimulation by forskolin, thought to act directly at the catalytic subunit, is unaltered by EEDQ administration. However, we have found that both the D_1 receptor binding of [^{3}H]SCH23390 and adenylate cyclase stimulation by dopamine are markedly reduced after *in vivo* EEDQ treatment in a dose-dependent manner (Figure 3). Thus, peripherally administered EEDQ acts in a receptor-specific manner, but leaves Ns and the catalytic subunit of adenylate cyclase intact.

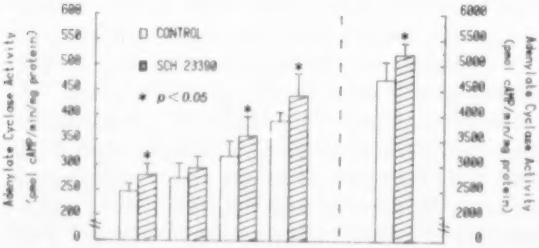


FIGURE 2. Adenylate cyclase activity in control and chronic SCH23390 treated tissue. Bars represent mean + SDs of dopamine and forskolin-stimulated cAMP production in the presence of 100 μM GTP. Asterisks denote adenylate cyclase stimulation in chronic SCH23390 treated tissue significantly greater than control tissue, $p < 0.05$.

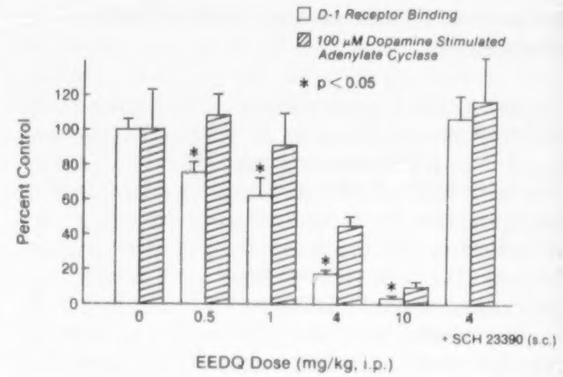


FIGURE 3. Dose-dependent reduction in D_1 receptor binding and receptor-mediated stimulation of adenylate cyclase after peripheral administration of EEDQ. Open bars represent the mean + SEM of [^{3}H]SCH23390 B_{max} values as a percent of the control B_{max} (47 ± 7 pmoles/g tissue) and hashed bars the mean + SEM of the differences between stimulation by 0.1 mM GTP alone and stimulation by 100μM dopamine + 0.1 mM GTP as a percent of stimulation in controls (186 ± 45 pmoles cAMP/min/mg protein). EEDQ-induced reductions were prevented by pretreatment with SCH23390 (0.5 mg/kg s.c.), denoted by bars labeled + SCH23390 (s.c.). Asterisks denote percent B_{max} significantly less than percent dopamine-stimulated adenylate cyclase, $p < 0.05$.

Because the Ns and catalytic moieties are not functionally modified, peripheral EEDQ administration may be used as a tool to assess the stoichiometry of D_1 receptor/effector interactions. That is, by progressively blocking increasing numbers of receptors and monitoring adenylate cyclase activity, the loss of D_1 receptors may be correlated with a decrease in D_1 receptor-mediated stimulation of adenylate cyclase activity. Interestingly, we have found that approximately 40 percent of D_1 receptor binding may be lost with no significant reduction in the V_{max} of dopamine-stimulated adenylate cyclase activity. That is, only approximately 60 percent of the original D_1 receptor population is necessary for full *in vitro* agonist-stimulation of adenylate cyclase activity. Thus, these data suggest that the D_1 receptor population is not a stoichiometrically limiting factor in agonist-stimulation of adenylate cyclase.

This finding has important neurophysiologic implications. Receptor occupancy is determined by transmitter (or drug) concentration. Since only ~60 percent occupancy of the normal D_1 receptor population is required for maximal effector stimulation, the transmitter concentration necessary to elicit full stimulation ($\sim 2 \times K_D$) is considerably less than that concentration necessary for 100 percent receptor occupancy ($100 \times K_D$). The existence of these "spare" receptors, then, potentially enhances neurotransmission by reducing the effective concentration of dopamine required to diffuse across the synaptic cleft to achieve a full response.

In light of this finding, it is not surprising that a ~20 percent increase in D_1 receptors after chronic SCH23390 treatment did not increase the receptor-stimulated adenylate cyclase activity since ~40 percent of the normosensitive D_1 receptor population may be considered "spare." Receptor upregulation, then, probably does not act directly to increase cAMP production but rather supersensitivity is manifested by reducing the effective transmitter (or drug) concentration necessary to induce a maximal response. That is, by increasing receptor number, the percent receptor occupancy necessary to activate a full effector response is reduced. Collectively, these pharmacologic and biochemical data suggest that in addition to a dopamine receptor selective upregulation, an additional upregulation also occurs at the level of either the guanine nucleotide regulatory subunit or perhaps the catalytic subunit of adenylate cyclase, leading to the small overall increase in cAMP production.

Behavioral Effects of Chronic SCH23390 Administration

Unlike chronic neuroleptic treatment, where neither an increase nor decrease in spontaneous locomotor activity was observed (Tarsy and Baldessarini, 1974), rats chronically treated with SCH23390 (0.5mg/kg/day s.c. for 21 days and withdrawn for 2 days) demonstrated a more than twofold higher level of locomotor activity than control animals during habituation to the locomotor cages ($p < 0.02$). Paralleling the habituation results, again in contrast to classic neuroleptics where tolerance develops to their cataleptogenic effects after chronic treatment (Ezrin-Waters & Seeman, 1977), rats receiving chronic administration of SCH23390 for 21 days demonstrated no tolerance to its cataleptogenic action. This suggests that the neuronal network through which chronic SCH23390 elicits its effects is different from and is not regulated in the same manner as the neuronal network through which classic neuroleptics exert their effects.

Other research supports this hypothesis. After treatment with either D_1 or D_2 selective agonists, unilaterally 6-OHDA lesioned rats demonstrate contralateral circling behavior (Arnt & Hyttel, 1985) and reserpinized animals demonstrate hypermotility and oral sterotypy (Arnt, 1985a). In these cases, although similar behaviors were induced by the D_1 and D_2 receptor agonists, behaviors induced by D_2 agonists were blocked only by D_2 antagonists and similarly, D_1 antagonists only blocked D_1 agonist responses. These data suggest that although D_1 and D_2 receptor-mediated behaviors may be overtly similar or even identical, they are independently modulated and can be distinguished from each other through these various pharmacologic treatments.

In concert with these data, the chronically SCH23390 treated rats responded to the selective D_1 receptor agonist, SKF38393, with potentiated locomotor behavior. However, the magnitude and time course of the locomotor activity after SKF38393 administration was identical to the activity response seen in habituation for both groups. Thus, it is unclear from these data whether the chronically SCH23390 treated rats are indeed showing an enhanced response to SKF38393 itself, or simply exhibiting an enhanced spontaneous response to handling. However, the stereotypy observations clearly indicate that chronic SCH23390 does enhance the behavioral response to SKF38393. As seen in Figure 4, chronic SCH23390 treated rats showed a more intense stereotypy response to SKF38393 than did the chronic saline treated rats. Unlike mixed D_1/D_2 agonists, SKF38393 induced stereotyped grooming in both groups of rats. However, grooming quickly diminished in control rats and they demonstrated more locomotor stimulation. The chronic SCH23390 treated rats, how-

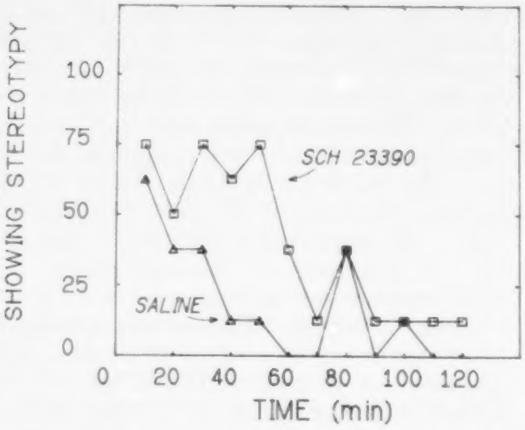


FIGURE 4. Mean stereotypy response to 3.0 mg/kg (s.c.) SKF38393 of rats chronically treated with SCH23390 (0.5 mg/kg/day s.c. for 21 days) or saline. The SCH23390 treated rats demonstrated an overall greater stereotypy response ($p < 0.005$, Information Statistic) as rated on the scale of Creese and Iversen (1975).

ever, continued to groom and/or show stereotyped sniffing and rearing in one location over the first hour in response to SKF38393.

Surprisingly, a similar potentiation in locomotor activity and stereotypy was observed in chronically SCH23390 treated rats after treatment with quinpirole (LY171555), a selective D_2 agonist. The locomotor responses to quinpirole (Figure 5) in both groups was quite different from their habituation response clearly indicating that the locomotor response to quinpirole is enhanced by the chronic SCH23390 treatment. The time course of the response, initially low, peaking and dropping away is explained by the stereotypy ratings (Figure 6). Quinpirole initially induced intense stereotyped sniffing and rearing in one location in both groups. Between 50 and 80 min post injection, some chronic SCH23390 treated rats, but no control rats, also showed stereotyped licking of the cage. The peak in crossovers at 140 min corresponded to the transition from stereotyped behavior in one location to locomotor activity. Surprisingly, locomotor activity was quickly attenuated in the chronically SCH23390 treated rats and each rat "instantaneously" went from "sniff/locomotion" to "freezing" in position. This frozen posture was maintained for 5 to 10 min before the rats closed their eyes and apparently went to sleep. Control rats did not show this freezing behavior. This response may potentially prove to be a useful model for the "on-off" phenomenon seen during dopamine agonist treatment of Parkinson's disease. One might speculate that this troublesome side effect

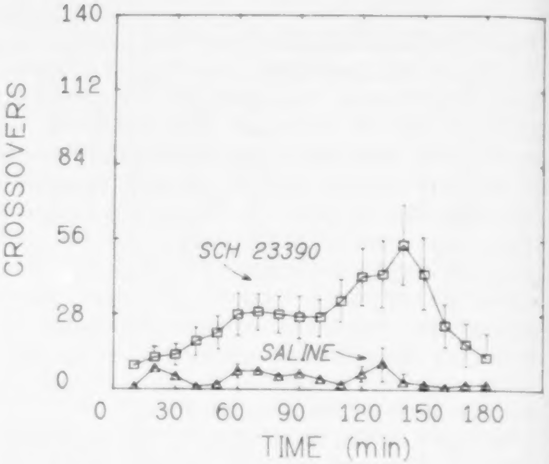


FIGURE 5. Photocell beam crossovers to 0.3 mg/kg (s.c.) quinpirole after habituation in rats chronically treated with SCH23390 or saline. The response of the SCH23390 treated rat was significantly higher ($p <$ 0.005 ANOVA).

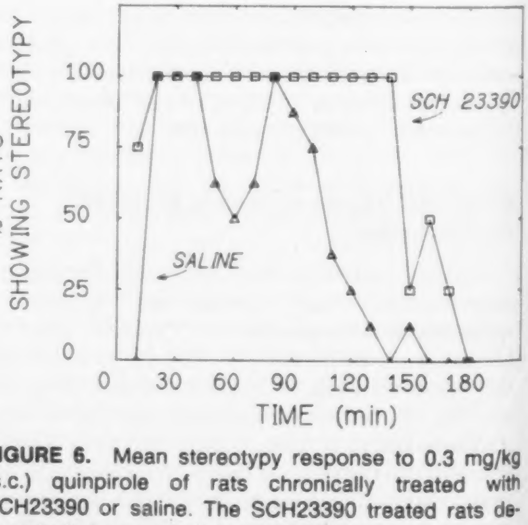


FIGURE 6. Mean stereotypy response to 0.3 mg/kg (s.c.) quinpirole of rats chronically treated with SCH23390 or saline. The SCH23390 treated rats demonstrated an overall greater stereotypy response ($p < 0.005$, Information Statistic).

may result from the upregulation of D_1 receptors in this disease.

Thus, the behavioral effects of a D_2 agonist are potentiated after a selective D_1 receptor upregulation. Certainly this is an anomalous response given that SCH23390 has no *direct* effect on D_2 receptors *in vivo*. Paralleling the results presented herein, it has been demonstrated that although SCH23390 acts as a D_1 receptor antagonist, inducing catalepsy in rats, pretreatment with selective D_2 dopamine receptor agonists prevents this response in a dose-dependent manner (Meller et al., 1985b). Likewise, the behavioral effects of the D_1 receptor agonist, SKF38393 could be partially reversed by the D_2 receptor antagonist metaclopramide (Molloy & Waddington, 1985). These behavioral data, then, suggest that D_1 and D_2 receptor-activated neuronal systems are not functionally isolated. Rather, the behavioral data presented herein suggest that although the networks through which D_1 and D_2 receptors mediate behavioral effects appear to be functionally independent (i.e., separate, parallel systems), these systems are interactive in their modulation of motor function.

Clinical Implications

One must always be careful in drawing conclusions from animal behavioral and biochemical data that pertain to the clinical situation. With this caveat in mind, some points can be made: (1) If SCH23390 proved to be antipsychotic, its chronic use may still lead to tardive dyskinesia since following SCH23390 treatment the behavioral response to both D_1 and D_2 selective agonists is increased—even though there is a selective increase in only D_1 receptors. (2) Classic neuroleptics demonstrate tolerance to their cataleptogenic action and for their induction of acute Parkinsonian extrapyramidal side effects. Since we did not see tolerance to the cataleptic action of SCH23390, it may well continue to induce Parkinsonian side effects during clinical use. However, the validity of these animal models must be questioned for their relevance to the clinical situation. Thus, the study of SCH23390 in clinical trial may be the only tool to determine the validity of these animal models and the utility of this novel drug in the clinical situation.

References

Arnt, J. Behavioural stimulation is induced by separate dopamine D-1 and D-2 receptor sites in reserpine-pretreated but not in normal rats. *Eur. J. Pharmacol.*, 113:79–88, 1985.

Arnt, J., and Hyttel, J. Differential involvement of dopamine D-1 and D-2 receptors in the circling behaviour induced by apomorphine, SK&F 38393, pergolide and LY171555 in 6-hydroxydopamine-lesioned rats. *Psychopharmacol.*, 85:346–352, 1985.

Battaglia, G., Norman, A.B., Hess, E.J., and Creese, I. D-2 dopamine receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in rat striatum. *Neurosci. Lett.*, 59:177–182, 1985.

Battaglia, G., Norman, A.B., Hess, E.J., and Creese, I. Functional recovery of D_1 dopamine receptor-mediated stimulation of rat striatal adenylate cyclase activity following irreversible receptor blockade. (Submitted, 1985).

Billard, W., Ruperto, V., Crosby, G., et al. Characterization of the binding of [^{3}H]SCH23390, a selective D-1 receptor antagonist ligand, in rat striatum. *Life Sci.*, 35:1885–1893, 1984.

Boeynaems, J.M., and Dumont, J.E. Quantitative analysis of the binding of ligands to their receptors. *J. Cyclic Nucleotide Res.*, 1:123–142, 1975.

Christensen, A.V., Arnt, J., Hyttel, J., et al. Pharmacological effects of a specific dopamine D-1 antagonist SCH23390 in comparison with neuroleptics. *Life Sci.*, 34:1529–1540, 1984.

Creese, I., and Chen, A. Selective D-1 dopamine receptor increase following chronic treatment with SCH23390. *Eur. J. Pharmacol.*, 109:127–128, 1984.

Creese, I., Burt, D.R., and Snyder, S.H. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*, 192:481–483, 1976.

Creese, I., and Iversen, S.D. The pharmacological and anatomical substrates of the amphetamine response in rat. *Brain Res.*, 83:419–436, 1975.

Creese, I., Sibley, D.R., Hamblin, M.W., and Leff, S. The classification of dopamine receptors: relationship to radioligand binding. *Ann. Rev. Neurosci.*, 6:43–71, 1983.

Cross, A.J., Crow, T.J., Ferrier, I.N., et al. Dopamine receptor changes in schizophrenia in relation to the disease process and movement disorder. *J. Neural Transm. Suppl.*, 18:265–272, 1983.

Ezrin-Waters, C., and Seeman, P. Tolerance to haloperidol catalepsy. *Eur. J. Pharmacol.*, 41:321–327, 1977.

Fleminger, S., Rupniak, N.M.J., Hall, M.D., et al. Changes in apomorphine–induced stereotypy as a result of subacute neuroleptic treatment correlates with increased D-2 receptors, but not with increases in D-1 receptors. *Biochem. Pharmacol.*, 32:2921–2927, 1983.

Hamblin, M.W., and Creese, I. Behavioral and radioligand binding evidence for irreversible dopamine receptor blockade by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. *Life Sci.*, 32:2247–2255, 1983.

Hess, E.J., Battaglia, G., Norman, A.B., and Creese, I. Differential modification of striatal D_1 dopamine receptors and effector moieties by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) *in vivo* and *in vitro*. (Submitted, 1985).

Hess, E.J., Battaglia, G., Norman, A.B., et al. Guanine nucleotide regulation of agonist interactions at [^{3}H]SCH23390 labeled D_1 dopamine receptors in rat striatum. *Eur. J. Pharmacol.* (In press)

Hyttel, J. Effects of neuroleptics on ^{3}H-haloperidol and ^{3}H-cis(Z)-flupentixol binding and on adenylate cyclase activity *in vitro*. *Life Sci.*, 23:551–556, 1978.

Iorio, L.C., Barnett, A., Leitz, F.H., et al. SCH23390, a potential benzazepine antipsychotic with unique interactions of dopaminergic systems. *J. Pharm. Exp. Ther.*, 226:462–468, 1983.

Kebabian, J.W. and Calne, D.B. Multiple receptors for dopamine. *Nature*, 277:93–96, 1979.

Leff, S.E., Hamblin, M.W., and Creese, I. Interactions of dopamine agonists with brain D_1 receptors labeled by ^{3}H-antagonists: Evidence for the presence of high and low affinity agonist-binding states. *Mol. Pharmacol.*, 27:171–183, 1985.

Meller, E., Bohmaker, K., Goldstein, M., and Friedhoff, A.J. Inactivation of D_1 and D_2 dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline *in vivo*: Selective protection by neuroleptics. *J. Pharmacol. and Exp. Ther.*, 233:656–662, 1985a.

Meller, E., Kuga, S., Friedhoff, A.J., and Goldstein, M. Selective D_2 dopamine receptor agonists prevent catalepsy induced by SCH23390, a selective D_1 antagonist. *Life Sci.*, 36:1857–1864, 1985b.

Molloy, A.G., and Waddington, J.L. Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SKF38393 and to apomorphine: Differential interactions with the selective D-1 and D-2 antagonists SCH23390 and metaclopramide. *Eur. J. Pharmacol.*, 108:305–308, 1985.

Onali, P., Olianas, M.C., and Gessa, G.L. Selective blockade of dopamine D-1 receptors by SCH23390 discloses striatal dopamine D-2 receptors mediating the inhibition of adenylate cyclase in rats. *Eur. J. Pharmacol.*, 99:127–128, 1984.

Seeman, P., Lee, T., Chau-Wong, M., and Wong, K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature*, 261:717–719, 1976.

Stoof, J.C., and Kebabian, J.W. Opposing roles for D_1 and D_2 dopamine receptors in efflux of cyclic AMP from rat striatum. *Nature*, 294:266–268, 1981.

Tarsy, D., and Baldessarini, J. Behavioural supersensitivity to apomorphine following chronic treatment with drugs which interfere with the synaptic function of catecholamines. *Neuropharmacology*, 13:927–940, 1974.

Mixed Mania: Diagnosis and Treatment

Chair:

Stephen H. Koslow, Ph.D.
Neuroscience Research Branch
National Institute of Mental Health
Rockville, MD 20857

Sources of Lithium Resistance in Mixed Mania[1]

Jonathan M. Himmelhoch, M.D.,[2] and
Marc E. Garfinkel, M.D.[2]

> Early learn to appreciate the differences between the descriptions of disease and the manifestations of that disease in an individual, the difference between the composite portrait and one of the component pictures.
>
> Sir William Osler—*Counsels and Ideals and Selected Aphorisms*

In the first half of this century medical students were warned never to invoke more than one diagnosis to explain a given clinical picture, no matter how myriad and complex its presentation. This admonition was known as Osler's Dictum, and represented the first principle of differential diagnosis. The second half of this century has repealed Osler's Dictum. Increased life-span, radical surgeries, long-term maintenance treatments with complex and toxic pharmacological agents, and a host of other modern medical variables have created patient populations who routinely present the physician with the simultaneous effects of two or three concomitant illnesses. Now, untidy problem-oriented methodologies have replaced the pleasing elegance of Osler's Dictum.

Mixed mania, the simultaneous experience of significant symptoms of depression and mania, creates a similar dilemma for modern psychiatric diagnostic systems. These parallel dilemmas exist even though Oslerian diagnoses (and medical diagnoses in general) are inherently hypothetical, whereas psychiatric diagnoses, with their reliance on operational criteria, are antihypothetical and descriptive. Indeed any illness that meets operational, descriptive criteria for manic-depressive illness *is* manic-depressive illness and complicating factors can be, and usually are, separated off onto another diagnostic axis, as if they "Lethe ward had sunk." All that is left is a peculiar, psychiatric distillation of Osler's Dictum.

Mixed mania, however, does not tolerate this distillation process very well. In this paper we will present evidence derived from 130 subjects with mixed mania (84 reported in two earlier papers, and 46 new cases) which will show that mixed mania is a phenomenologic entity that occurs frequently enough to considerably complicate both the diagnosis and treatment of manic-depressive illness. Mixed mania has a major impact on the biological theories of bipolar disorders; it reflects the influence of a host of neurological, pharmacological, medical, and characterological factors on the clinical manifestation

---

[1] Supported by the NIMH grant number MH37266.

[2] University of Pittsburgh, School of Medicine, Western Psychiatric Institute & Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

of manic-depressive illness; it is, diagnostically speaking, chameleon-like in presentation—appearing in some people like schizophrenia, in others like psychotic depression, and in still others like labile, hysteroid states—thereby creating a set of differential diagnostic conundra. And, finally, it resists treatment intervention with any pharmacologic agent, particularly lithium salts.

Our data will allow us to hypothesize some of the sources of mixed mania and of lithium resistance. We will also demonstrate the relative effectiveness of carbamazepine regimina in the treatment of mixed mania. Of special interest is the frequent incidence of both mixed mania and lithium resistance in adolescent bipolar populations (age 12–19) discovered by the second author of this paper (M.G.), as part of a larger systematic study of carbamazepine treatment of adolescents with manic-depressive illness (Garfinkel et al., 1985).

Methods

Our early investigation was carried out on 84 bipolar patients taken from 143 consecutive admissions to Affective Disorders Clinics at Yale University Medical Center and at the University of Pittsburgh (Himmelhoch et al., 1976; Himmelhoch, 1979). Diagnoses were made according to the criteria of Feighner (1972) and data were collected and analyzed by use of the Kupfer-Detre System (KDS) (Kupfer & Detre, 1970). Those patients who in their initial episode demonstrated simultaneous significant mania (score greater than 12) and depressive (score greater than 18) symptom clusters were considered to be experiencing a mixed manic episode. Our recent study focused on 46 lithium resistant bipolar patients. These patients were diagnosed according to the Diagnostic and Statistical Manual-III criteria. Patients from this group with a simultaneous 21-item Hamilton Depression Score of greater than 16 and a KDS-mania score of greater than 12 were designated as mixed manic. Thirty-seven of the 46 met these criteria. Treatment outcome in both groups was considered good if both manic and depressive scores returned within 2 months to the normal range for the given measurement instrument and stayed within the normal range during the entire follow-up period. Response was considered poor if the patient's original mood swing (manic, depressed, or mixed) did not return to the normal range within 2 months or if at any time during the follow-up period the patient experienced a significant new mood swing as scored on the same measurement instruments. Follow-up periods ranged from 6 months to 14 years, and were greater than 18 months in 88/130. Both diagnosis and treatment outcome were carefully correlated in all 130 patients with standard demographic variables and the presence or absence of sedative and alcohol abuse. In addition the second group of 46 were carefully studied to ascertain the presence or absence of neuropsychiatric factors such as seizures, paroxysmal electroencephalograms (EEG), severe head injuries, migraine, perinatal insults, hyperactivity and learning disorders.

The Incidence and Significance of Mixed Mania in a Bipolar Population

Mixed mania was first described by Kraepelin:

> You see here before you a student of music aged nineteen, who has been ill for about a year. . . without any tangible cause he became depressed, felt ill at ease and lonely, made all manner of plans, which he always gave up, changing his place of residence and his profession, for he could come to no fixed resolution. During a visit to Munich, he felt as if people in the street had something to say to him, and as if he were talked about everywhere. He heard an offensive remark in an inn, which he answered angrily. Next day, he was seized with the apprehension that his remark might be taken as *lèse majestè*. . . . Since then he overheard people in the street who threatened to shoot him, and to set fire to his house, and on that account he burned no light in his room. In the streets, voices pointed out the way he ought to go so as to avoid being shot. He also heard long conversations of not very flattering purport as to his person. . . . After about six months he felt more free, comfortable, enterprising, and cheerful, began to talk a lot, to compose, criticized everything, concocted great schemes, and was insubordinate to his teacher. . . . The interpretation of this condition is not easy at first glance. Of the diseases hitherto considered, dementia praecox would perhaps come first and foremost under consideration. But the exceedingly fresh and active mood of the patient, his interest in his surroundings, his sociability and his press of occupation are de-

> cidedly opposed to this supposition. . .[all] points to the relationship of the condition with maniacal-depressive insanity. *And this opinion would be justified by the joyless irresolute manifestations of the first stage, passing into the comfortable but active states, so noticeable in the second stage.* (Kraepelin, 1968)

As is often the case there is little new one can add to a Kraepelinian *Urfall* (original case description). His depiction of underlying intense dysphoria, of rapid, unpredictable shifts in motor activity, and of oscillations in the efficiency of information processing nicely catch the heteronymous nature (Kleist, 1926) of mixed mania. If the clinician fails to note the *marche* of a mixed manic episode, that merging of an anhedonic first stage into a manic second stage, but concentrates instead on the signs and symptoms present at any one point in time (on a *tranche du mal*, as it were) schizophrenia would indeed come first and foremost to mind. Mixed mania can be equally misleading in its non-psychotic presentation. In our initial investigation (Tables 1, 2, 3), 26 of 84 patients (31 percent) were admitted with mixed mania (Himmelhoch et al., 1976). Fourteen presented the psychotic picture described by Kraepelin. The remaining manifested variable neurotic syndromes made up of unpredictably occurring turns of dysphoria, irritability, elation and anergia, appearing in one patient like atypical depression, in another like hysteriod dysphoria and, surprisingly, in a few like panic disorder (Himmelhoch, 1984). Kraepelin never described these low-grade forms of mixed mania. The distinction between Kraepelin's *Urfälle* and these non-psychotic disorders may have considerable theoretical importance, because our subsequent findings indicate that the non-psychotic syndrome may have different origins from the psychotic presentation of mixed mania.

TABLE 1. Frequency of Mixed States in Manic-Depressive Illness.

Type	Number of Patients	Percent
Mixed states	26	31 percent
Non-mixed states	58	69 percent

TABLE 2. Drug Abuse in Incidence of Mixed States in Manic-Depressive Illness.

	Drug Abuse	No Drug Abuse
Mixed states	12	14
Non-mixed states	11	47

$\chi^2 = 13.95$, $p < .001$.

The 31 percent incidence of mixed manic presentations (Table 1) in our population is similar to the incidences reported by Winokur et al. (1969) and Nunn (1979). Subjects with mixed mania differed from subjects presenting with pure depression or with pure elation in two ways. First, the incidence of alcohol and sedative abuse was significantly higher in the mixed patients (Table 2). Alcohol and sedative abuse were defined according to criteria given in earlier papers (Himmelhoch et al., 1976; 1980; 1983). Second, mixed manics had significantly worse treatment outcome than did typical bipolar subjects (Table 3). Part of this lesser treatment outcome was explained by the deleterious impact of alcohol and sedative abuse on the mixed patients treatment response. However, first order, partial correlation showed that mixed mania still had a significant negative effect on outcome even after the negative effects of alcoholism and sedativism had been partialled out. Fifteen of 26 mixed subjects had poor treatment outcome. Only 4 of these

TABLE 3. The Relative Effects of Mixed Mania and Drug Abuse on Treatment Outcome.

Treatment Response	Mixed States	Non-Mixed States
Poor	15	11
Good	11	47

$\chi^2 = 12.60$, $p < .001$.

Treatment Response	Drug Abuse	No Drug Abuse
Poor	21	5
Good	2	56

$\chi^2 = 53.89$, $p < .001$.

First Order Partial Correlations

	Drug Abuse	Mixed States
Outcome	.778	.333
Drug Abuse		.052

$p < .01$.

15 did not abuse sedatives or alcohol. Of the 14 with psychotic features similar to those described in Kraepelin's *Urfall*, 10 had a good response to treatment. Conversely, only 1 of 12 non-psychotic mixed manics had good outcome on lithium based treatment regimina. These findings suggest that there are two clinical parameters important to the production of mixed mania; the first, severity of illness; the second, the presence of a complicating neuropsychiatric variable that lends a significant dysphoric coloration to a manic or hypomanic episode. It is only the severely ill, uncomplicated, bipolar patients whose illness follows the process described by Kraepelin as generative of mixed mania, i.e., an anhedonic first stage of illness merging into a hypomanic-manic second stage. By no means do all manic-depressive patients repeatedly follow this sequence as they become manic. Nevertheless, Court (1968) and Bunney et al. (1972) have used this two-stage process, along with the existence of mixed states themselves, as evidence for what has become known as the continuum hypothesis of manic-depressive illness.

The continuum theory denies the usual notion that mania is a polar opposite state to depression, as is implied by the term "bipolar illness," so often used as a synonym for manic-depressive illness. Instead the continuum hypothesis posits that depression and mania are closely related entities that are, in all likelihood, only *quantitatively* different. Depression represents mild to moderate illness, and mania severe illness. Mania is viewed as a state with a depressive core. Therefore, any given patient, as he gets more severely ill, passes from depression through a mixed manic phase into pure mania. Bunney et al. (1972) feel that the rapid switch from depression to mania usually includes a brief normal period, often overlooked because there is usually no opportunity to continuously observe these patients. They offer a variation of Court's continuum, an extension of Prange's (1973) "serotonin-permissive" hypothesis: ". . . which includes both an underlying dysfunction and a superimposed dysfunction. The underlying dysfunction, present during both depressive and manic phases, may not be related to catecholamine function."

Court's hypothesis, however, seems preferable because it explains both mixed states and rapid cycling. But in all variations of this hypothesis mania is viewed as a state with a depressive core: mixed mania represents a transitional phase occurring as depression "switches" to mania (the switch process) and the patient becomes trapped in the switch phase. The whole continuum is a complex psychobiological restatement of the psychoanalytic observation that mania is the pathological extension of the very human process of denying depression (Himmelhoch, 1979). Elation can represent a failing organism's last gasp attempt at adaptation and survival, when all that is left to it is a frail tissue composed of absolute denial, cheerful delusion, exaggerated religiosity, and desperate drivenness (Himmelhoch, 1986). Sometimes, the *masque* succeeds: Solshenitzen observed in *Gulag Archipelago* that any given Zek's (shortened Russian form of the word zaklyuchennye or prisoner) survival depended directly on his abilities to mobilize hypomanic denial and no wise physician would interfere if he saw this same maneuver employed by a cancer patient undergoing chemotherapy. But just as often the defense mechanism fails, and then the psychotic and delusional nature of the organism's denial becomes readily apparent, and worse yet, underlying protest and despair, the depression at denial's core, wells up through cracks and crazes of an imperfect defensive structure. Here, perhaps, is an ethological source of mixed mania. And there exists a fair amount of biochemical (Coppen, 1965; Dunner et al., 1971), endocrinologic (Sachar et al., 1971; 1970), genetic (Winokur, 1970), perceptual-motor (Buchsbaum et al., 1971; Court & Mai, 1970; Beigel & Murphy, 1971), clinical (Rosenfield, 1973), and psychopharmacological (Prange, 1973; Dyson & Mendels, 1968) evidence that mania and bipolar depression are, in many ways, similar psychophysiologic states. Mixed mania is the phenomenologic *sine qua non* of all these fascinating theorizations.

But, although the continuum hypothesis and its variations seem helpful in explaining mixed mania in some manic-depressive patients, the incidence and clinical correlates of this phenomenon imply heterogeneity, not only of mixed mania but of manic-depressive illness itself. In the first place the incidence of mixed mania is 40 percent at most, and even assuming that certain patients who have not experienced mixed mania eventually will at some time during the course of their illness, one can readily deduce that at least 50 percent of manic-depressive patients will only experience pure episodes. Moreover, in a recent investigation, Nunn (1979) has demonstrated that the sequence described by Kraepelin, where anhedonia switches into mania, is not experienced by every patient in whom mixed mania develops; nor does a manic patient always pass backwards through the phases of the continuum when he recovers. Nunn hypothesizes that some mixed states arise from the impingement of another illness (in his thinking another type of depression) on core manic-depressive illness. Himmelhoch et al. (1976) had already suggested this mechanism, but described sedative abuse as the "second factor" necessary to the provocation of a mixed affective state. "Drug abuse (particularly alcohol and sedatives) alters the clinical presentation of manic-depressive swings, and . . . the impact of over-sedation or withdrawal or both on a 'pure elation' is to make it dysphoric or mixed."

Our most recent investigation of 46 lithium resistant bipolar patients not only shows that mixed mania is a major clinical correlate of lithium resistance, but that a second neuropsychiatric factor is a consistent correlate of mixed mania. In addition to alcoholism and sedativism (15/46 patients) demonstrated in our earlier work, second factors such as seizures, paroxysmal EEG's, classical migraine, history of severe head injury, significant perinatal insults, hyperactivity, or clear-cut learning disorders were demonstrated in a preponderant majority of these patients. Indeed, it became evident from our second investigation that alcoholism and sedativism are only representative of the many forms of cerebral insufficiency which serve as the substrate for the development of mixed mania. Thirty-seven of the 46 lithium resistant patients had mixed mania and 31/37 had significant second neuropsychiatric factors. The distribution of these factors is shown in Table 4. Although only 9/46 lithium resistant patients had "pure" presentations, the association of a second neurological condition with mixed mania was still highly significant ($\chi^2 = 13.83, p < .001$).

TABLE 4. Distribution of Second Neuropsychiatric Factors.*

	Mixed	Non-Mixed
Seizure disorder	5	1
Paroxysmal EEG		
General	7	0
Focal	13	0
Non-paroxysmal EEG		
General	2	0
Focal	1	0
Classical migraine	6	0
Significant head injury	4	1
Developmental disorders	8	2
Neurological illness**	2	0
Alcohol/Drug abuse	12	3

*Numerous subjects had greater than one second factor.
**Benign adenoma of the pituitary and Sydenham's Chorea.

When both investigations are combined, a total of 63 patients had mixed manic presentations. Eighteen (14 from the original study and 4 in the second group) had uncomplicated bipolar illness that fit the continuum model and 10 of these responded to lithium plus an antidepressant. Forty-five had second neuropsychiatric factors (albeit, in the first investigation drug abuse was the only complicating factor recorded). Only 1/45 such patients responded to a lithium based treatment regimen. This difference in outcome ($\chi^2 = 25.38, p > .001$) is highly significant.

Thus, lithium resistance in mixed mania can be seen to rise from two sources; first, from the greater severity of bipolar illness that fits the continuum model; and, second, from superimposed neuropsychiatric illnesses that greatly complicate treatment. It is important to note that the majority of patients (34/45) who have mania correlated with second neurological factors, had non-psychotic clinical presentations. Under ordinary circumstances their manic-depressive illness would have been mild and easily treatable. In general, such patients have milder illnesses which do not fit the continuum model. They do not experience rapid cycling and only rarely exhibit psychotic elation. Usually they enjoy productive hypomanic periods which are separated from their depressive episodes by long spells of euthymia. *There is no depressive core to their hypomania* (Himmelhoch, 1986). Their lesser prognosis is generated by a second illness, because it is a geometrically more difficult task to effectively treat two coexisting illnesses. On the other hand, continuum model manic-depressive illness, which spontaneously generates mixed mania through the organism's last gasp mobilization of denial, is, under ordinary circumstances, a completely different and more severe kind of manic-depressive illness than the milder, interrupted, "true bipolar" syndrome. Indeed, continuum model illness is much akin to a neurological disorder such as temporal lobe epilepsy or a mild dementia. In attempting to explain the difference between the neurologically normal and the neurologically abnormal organism, Kurt Goldstein (1971) concluded:

> . . . whenever anxiety, as the mainspring of an organism comes into the foreground, we find that something is awry in the nature of that organism. To put it conversely, an organism is normal and healthy when its tendency toward self-actualization issues from within and when it overcomes the disturbance arising from its clash with the world, not by virtue of anxiety but through the joy of coming to terms with the world.

In the end, both sources of mixed mania may boil down to relative cerebral insufficiency.

Mixed Mania and Adolescence

Twenty-three of the 46 lithium resistant patients were adolescents (between ages 12 and 19). A detailed report about their clinical characteristics already has been presented. Table 5 shows the relationship, first of drug abuse then of "second neuropsychiatric factors," to mixed mania in this adolescent population. Unlike adults, adolescents showed no significant association of drug abuse with mixed mania (although 8/23 were addicted to sedatives and/or street drugs). This association is evidently washed out by the almost inevitable presence of concomitant neuropsychiatric disorders. As with the 23 adult lithium-resistant patients, the correlation of second factors to mixed mania was powerful (Fishers two-tailed, $p = .002$), even though only six adolescents presented with pure affective episodes. Six mixed adolescents had two "second factors" (10/45 of the total patients with mixed mania had two or more "second factors"). The severity of illness and the lithium resistance shown by these patients is reflective of our general experience with manic-depressive illness in adolescent populations. The developmental immaturity and inadequate defensive structure of adolescents interact in some way with the genetic *anlage* of manic-depressive illness to foster both the mixed mania and lithium resistance. A few adolescents respond well to lithium regimina, although almost none respond to lithium alone. A majority, moreover, require complex pharmacologic treatment programs involving carbamazepine and lithium salts. Antipsychotics, tricyclics, and/or monoamine oxidase inhibitors are often necessary adjuncts. On occasion, unusual interventions including clonidine, clonazepam, calcium channel blockers, sodium valproate, phenytoin, etc., are indicated. Severe, dysphoric mixed manias often give rise to suicidality and may require electroconvulsive therapy. Patience, empirical tinkering, frequent clinical contact, and the careful monitoring of critical blood levels and other related laboratory variables are the *sine qua non* of successful management.

Treatment of Mixed Mania

Mixed mania represents the rare situation where poor prognostic bipolar patients do better on lithium regimina, because better prognostic bipolar patients with mixed mania actually present the clinician with two illnesses—a good prognosis, true bipolar ill-

TABLE 5. Second Neuropsychiatric Factors in Adolescents (Age <20) With Mixed Mania—Sedative and Alcohol Abuse

	Abuser	Non-Abuser
Mixed	6	11
Non-mixed	2	4
Total	8	15

Other Neuropsychiatric Factors

	Presence	Absence
Mixed	17	0
Non-mixed	2	4
Total	19	4

ness, and a second neurological condition which simultaneously decreases cognitive abilities and increases dysphoria. Ten of 18 "continuum model" manic-depressives, therefore, responded to lithium based treatments (all needed adjunctive antidepressant and some needed adjunctive neuroleptics). Forty-four of the 45 mixed manias with concomitant neuropsychiatric disorders, and the 8 lithium resistant, continuum-model patients required treatment regimina based on anticonvulsant therapy (all but 4 carbamazepine-based). In our second study, 21/46 mixed manics had a good response to anticonvulsant based therapy, as compared to 8/9 patients with "pure" presentations ($\chi^2 = 3.2$, $p < .07$) showing that even in a lithium-resistant population the presence of mixed mania produces a trend towards a worse outcome. However, six of our carbamazepine failures were found in the adolescent population. These six had an initial slow and incomplete response to carbamazepine plus lithium, but stabilized on this regimen after 6 to 12 months. Although they failed to meet our research definition for a good response, it is likely they were carbamazepine responders. The management of adolescents on carbamazepine is a complicated situation, requiring frequent dosage changes. Adjunctive lithium is almost always necessary. Indeed, the management of any patient with mixed mania is a challenge to the persistence and to the pharmacological skill and imagination of the clinician.

Conclusion

Mixed mania occurs either in severely ill, continuum-model, manic-depressive patients (uncomplicated mixed mania) or in "true bipolar" patients whose illness has been complicated by a second neuropsychiatric condition, especially sedative abuse or epileptic changes (complicated mixed mania). All mixed manias tend to be lithium resistant, but uncomplicated mixed mania responds significantly better to lithium regimina than does complicated mixed mania. Mixed mania often responds well to anticonvulsants, especially carbamazepine, as might be deduced from the clinical correlates of mixed mania. However, as reported by Ballenger and Post (1980) and Okuma and Kishimoto (1977) in a majority of cases, carbamazepine must be combined with other psychopharmacologic agents—especially lithium and/or antidepressants—to obtain optimal clinical response. Early onset manic-depressive illness seems particularly prone to manifest itself as severe, lithium resistant, and mixed. Here again, carbamazepine-lithium combination is the most effective pharmacological intervention—but it often takes 6 to 12 months of careful follow-up and frequent drug adjustment to stabilize adolescent patients. The findings of both of our investigations seem to suggest that any phenomenon which significantly compromises central nervous system integrity, including developmental immaturity, frank neurological illness, or substance abuse and addiction, may result in the production of mixed mania.

References

Ballenger, J.C., and Post, R.M. Carbamazepine in manic-depressive illness: A new treatment. *Am. J. Psychiatry*, 137:782–790, 1980.

Beigel, A., and Murphy, D. Unipolar and bipolar affective illness: Differences in clinical characteristics accompanying depression. *Arch. Gen. Psychiatry*, 24:215–220, 1971.

Buchsbaum, M., Goodwin, F., Murphy, D., et al. AER in affective disorders. *Am. J. Psychiatry*, 128:19–22, 1971.

Bunney, W., Murphy, D., Goodwin, F., et al. The 'switch process' in manic-depressive illness: I. A systematic study of sequential behavior change. *Arch. Gen. Psychiatry*, 27:295–302, 1972.

Coppen, A. Mineral metabolism in affective disorders. *Brit. J. Psychiatry*, 11:1133–1142, 1965.

Court, J. Manic-depressive psychosis: An alternative conceptual model. *Brit. J. Psychiatry*, 114:1523–1530, 1968.

Court, J.H., and Mai, J.H. A double-blind intensive crossover design trial of methysergide in mania. *Med. J. Aust.*, 2:526–529, 1970.

Dunner, D., Cohn, C., Gershon, E., et al. Differential catechol-o-methyl-transferase activity in unipolar and bipolar illness. *Arch. Gen. Psychiatry*, 25:348–353, 1971.

Dyson, W., and Mendels, J. Recurrent depressions and the lithium ion. *Am. J. Psychiatry*, 125:544–548, 1968.

Feighner, J.P., Robins, E., Guze, B., et al. Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiatry*, 26:57–63, 1972.

Garfinkel, M.E., Himmelhoch, J.M., Garfinkel, L.S., and McHugh, T.R. Lithium carbonate and carbamazepine: Treatment for manic or mixed bipolar adolescents. Abstract of the 32nd Annual Meeting of The American Academy of Child Psychiatry, San Antonio, Texas, 1985.

Goldstein, K. *Human Nature in the Light of Psychopathology*. New York: Schocken, 1971, pp. 112–113.

Himmelhoch, J.M. Mania: The dual nature of elation. In: Giannini, A.J. (ed.), *The Biological Foundations of Clinical Psychiatry*. New York: Medical Examination Publishing Company, 1986, pp. 116–130.

Himmelhoch, J.M. Major mood disorders related to epileptic changes. In: Blumer, D. (ed.), *Psychiatric Aspects of Epilepsy*. Washington, D.C.: American Psychiatric Press, Inc., 1984, pp. 271–294.

Himmelhoch, J.M. Mixed states, manic-depressive illness, and the nature of mood. *Psychiatric Clin. North Am.*, 2(1):449–459, 1979.

Himmelhoch, J.M., Hill, S., Steinberg, B., and May, S. Lithium, alcoholism and psychiatric diagnosis. *J. Psychiatric Treatment Eval.*, 5:83–88, 1983.

Himmelhoch, J.M., Mulla, D., Neil, J.F., et al. Incidence and significance of mixed affective states in a bipolar population. *Arch. Gen. Psychiatry*, 33:1062–1066, 1976.

Himmelhoch, J.M., Neil, J.F., May, S.J., et al. Age, dementia, dyskinesia, and lithium response. *Am. J. Psychiatry*, 137(8):941–945, 1980.

Kleist, K. *Episodische Dämmerzustande*. Leipzig, 1926, pp. 1–80.

Kraepelin, E. *Lectures on Clinical Psychiatry* (a facsimile of the 1904 edition). New York: Hafner Publishing Company, 1968.

Kupfer, D., and Detre, T. Development and application of the KDS-1 in inpatient and outpatient settings. *Psychol. Rep.*, 29:607, 1970.

Nunn, C.M. Mixed affective states and the natural history of manic-depressive psychosis. *Brit. J. Psychiatry*, 134:153–160, 1979.

Okuma, T., and Kishimoto, A. Anti-manic and prophylactic effects of Tegretol. Abstracts of the Sixth World Congress of Psychiatry, Honolulu, Hawaii, 1977.

Prange, A. The use of drugs in depression: Its theoretical and practical basis. *Psychiatry Ann.*, 3:2, 1973.

Rosenfield, H. Notes on the psychopathology and psychoanalytic treatment of depressive and manic-depressive patients. In: Azima, H., and Glueck, B.C. (eds.), *Psychotherapy of Schizophrenic and Manic-Depressive States. Psychiatric Research Report 17*. Washington, D.C.: American Psychiatric Association, 1973.

Sachar, E., Finkelstein, J., and Hellman, L. Growth hormone responses in depressive illness. *Arch. Gen. Psychiatry*, 25:263–269, 1971.

Sachar, E., Hellman, L., Fukushima, D., et al. Cortisol production in depressive illness: A clinical and biochemical clarification. *Arch. Gen. Psychiatry*, 23:289–298, 1970.

Winokur, G. Genetic findings and methodological considerations in manic-depressive disease. *Brit. J. Psychiatry*, 117:267–274, 1970.

Winokur, G., Clayton, P., and Reich, T. *Manic-Depressive Illness*. St. Louis: C.V. Mosby Company, 1969.

Expressed Emotion of Relatives, Maintenance Drug Treatment, and Relapse in Schizophrenia and Mania

Chair:

Michael J. Goldstein, Ph.D.

Department of Psychology
University of California
Los Angeles, CA 90024

Expressed Emotion, Maintenance Pharmacotherapy, and Schizophrenic Relapse Among Mexican-Americans[1]

Janis H. Jenkins, Ph.D., Marvin Karno, M.D., Aurora de la Selva. M.Ed.Psych., Felipe Santana, Ph.D., Cynthia Telles, Ph.D., Steven Lopez, Ph.D., and Jim Mintz, Ph.D.[2]

While there is a pressing need for valid epidemiological studies, current evidence suggests that schizophrenia afflicts persons the world over (Kennedy, 1974; Murphy, 1982; World Health Organization, 1979). However, a growing body of literature has documented significant cross-cultural variations in the course and outcome of schizophrenia. The most systematically collected data for this observation has been gathered by the World Health Organization's International Pilot Study of Schizophrenia (IPSS). In that study, 1,202 patients from Nigeria, India, Colombia, Taiwan, the United Kingdom, the United States, the U.S.S.R., Czechoslovakia, and Denmark were followed for a 5-year period. Findings at the time of 2-year followup indicated a markedly superior course of illness for patients from the developing countries relative to outcomes observed for patients residing in more industrialized nations (World Health Organization, 1979).

There has been some speculation that pharmacological influences might explain these findings. For example, in a review of the IPSS data collected for Nigeria—the African nation where the most favorable of outcomes were observed—anthropologist Robert Edgerton (1980) has drawn our attention to several possible sources of explanation for the IPSS results, including pharmacological and sociocultural factors. Edgerton observed that

> [i]n addition to receiving phenothiazines during treatment at a Western psychiatric center, patients in the Ibadan sample may have received psychoactive medications, including neuroleptics, from native healers either before admission to a treatment center, or after release. Rauwolfia alkaloids are still used by Yoruba native heal-

---

[1] Presented at the annual meetings of the American College of Neuropsychopharmacology, Maui, Hawaii, December 9–13, 1985. This study was supported by National Institute of Mental Health Research grant MH 33502 and by National Institute of Mental Health research grant MH 30911 (Mental Health Clinical Research Center for the Study of Schizophrenia, R.P. Liberman, M.D., Principal Investigator).

[2] Drs. Jenkins, Karno, Santana, Telles, Mintz, and Ms. de la Selva, University of California, Department of Psychiatry and Biobehavioral Sciences, 760 Westwood Plaza, Los Angeles, CA 90024. Dr. Lopez, University of Southern California, Department of Psychology, Los Angeles, CA 90089–1061. Requests for reprints should be directed to the first author.

> ers, as are many other drugs . . . which could have neuroleptic properties. . . . (1980:175–176).

Since the IPSS investigators did not provide specific data concerning the use of drugs by the Nigerian patients, however, it is not possible to ascertain the effects of such pharmacological influences. While drug information available for the other IPSS developing countries is sketchy, the available data would seem to indicate that the variance in outcome cannot be explained by unexamined neuroleptic effects (World Health Organization, 1979:104–106). Rather, as the IPSS investigators concluded, it is possible that the observed differences in course and outcome can be explained by features of the sociocultural environment (Sartorius, Jablensky, & Shapiro, 1978).

Moreover, the existence of other (albeit less rigorous) reports of favorable schizophrenic outcome in non-Western settings supports the plausibility of the IPSS conclusion. Such additional observations have been recorded for China (Rin & Lin, 1962), Africa (Jilek & Jilek-Aall, 1970; Kennedy, 1974), Mauritius (Murphy & Raman, 1971), and Sri Lanka (Waxler, 1977). These researchers, along with investigators of the IPSS, have suggested that familial and societal patterns of response to an ill individual may influence the course of illness. For example, it has been hypothesized that families who respond to an ill family member with tolerance and acceptance might contribute to a more benign course for schizophrenic illness.

Our research was undertaken to examine this hypothesis concerning family influences on the course of schizophrenia among Mexican-Americans. The study was designed to further British research initiated by George Brown and his colleagues. Their work represents the most systematic and significant line of research documenting the importance of family life on the course of psychiatric illness (Brown, Birley, & Wing, 1972). While these investigators are careful to point out that they make no etiological assumptions about the familial emotional climate and schizophrenic onset, a high degree of "expressed emotion" (EE)—as indexed by criticism, hostility, or over-involvement on the part of family members toward their schizophrenic relatives—was found to be significantly associated with a poor course of illness.

Subsequent studies of EE among British and Anglo-American families have replicated the initial British findings (Vaughn & Leff, 1976; Vaughn et al., 1984). While such studies have provided necessary corroboration of the British results, the question of the cross-cultural validity of the EE index and its prognostic importance for other culturally distinct groups remained unanswered. Our work has attempted to shed light on the relationship of EE and schizophrenic illness within a Mexican-American family context, one which is culturally and linguistically quite distinct from those of the British and Anglo-American samples. Given the potential importance of sociocultural factors for schizophrenic outcome, it seems essential for reasons both theoretical and applied that we study a range of culturally diverse populations. Mexican-Americans, as well as the myriad of other culturally distinct populations in the United States, continue to be notably under-represented in clinical studies, including schizophrenia research.

In our research project entitled "The Course of Schizophrenia Among Mexican-Americans" (COSAMA), patients were followed for 9 months subsequent to hospitalization for an acute psychotic episode. The major findings of this study will be reported upon here in abbreviated fashion. (For more detailed reports of the study and these data, the reader is referred to lengthier publications by Karno et al., in press; Jenkins et al., 1986; Jenkins, in press. Additional reports are forthcoming.)

Sample and Methods

The patients included in the study met the following selection criteria: (1) of Mexican birth or bilateral Mexican descent; (2) between 18 and 50 years of age; (3) hospitalized for an acute psychotic episode; (4) diagnosed as suffering from schizophrenia according to Present State Examination (PSE) and DSM-III criteria; (5) living with a family before and after hospital admission.

Assessment Procedures

Patients were diagnostically assessed using the Present State Examination (PSE), the Brief Psychiatric Rating Scale (BPRS), and a brief Psychiatric Assessment Scale (PAS). Bilingual Hispanic clinicians were formally trained to administer these instruments. Key relatives of the patients were interviewed by Spanish-speaking researchers trained to administer and reliably rate the Camberwell Family Interview (CFI) schedule (Vaughn & Leff, 1976). Several other procedures were also completed with relatives and patients; however, this report will focus only on expressed emotion and medication compliance in relation to clinical outcome at 9 months post-hospital discharge.

The Rating of Outcome

The ratings for clinical outcome were made on the basis of integration of clinical information from records at treatment facilities, monthly telephone log sheets, notes from household return visits by CFI interviewers, and initial and final PSE, BPRS, and PAS ratings. All the available information for a case was reviewed by bilingual clinical psychologists who then made a final clinical status rating. These raters did not categorize outcome for patients they themselves had interviewed and were also "blind" to the EE ratings. Outcome ratings were made employing the following three categories:

1) *Sustained Remission*. This rating required a continuous absence of positive psychotic symptoms beginning no later than three months after index hospitalization and extending at least to the time of 9-month followup.

2) *Psychotic Relapse*. This rating was made only in cases in which subjects had entered a prior period of clear remission as just described, followed by decompensation.

3) *Sustained Psychoticism*. This category was defined as a failure of positive psychotic symptoms to remit for a continuous period of at least three months, beginning within three months after discharge from index hospitalization.

Reliability checks of the outcome categories were made by randomly selecting 16 cases for independent "blind" ratings by the 2 rating psychologists. An overall agreement of 88 percent (14/16) was obtained. Subsequent to careful review and discussion of the first 6 cases rated for outcome, 100 percent agreement was reached for the final 10 of these cases.

Results

Tables 1 and 2 provide basic sociodemographic and clinical characteristics for the 70 patients and the 109 key relatives assessed for their "expressed emotion." The degree of acculturation of patients and key relatives was ascertained through use of an Acculturation Rating Scale for Mexican-Americans designed by Cuellar, Harris, and Jasso (1980). As Tables 1 and 2 indicate, both key relatives and patients were relatively unacculturated. The five-point scale ranges from one ("wholly Mexican") to five ("wholly Anglo-American") in cultural orientation. The scale is based upon domains of language use, ethnic identity, and cultural participation. The majority of the patients and key

TABLE 1. Sociodemographic and Clinical Characteristics of Mexican-American Patient Sample ($N = 70$).

Variable	*N*	%
Sex		
Females	30	43
Males	40	57
Mean Age (SD)	26.1 (7.2)	
Marital Status		
Never Married	52	71
Married	10	14
Separated, Divorced, Widowed	8	11
Mean Years Ill (SD)	4.5 (3.6)	
Mean Number of Hospitalizations (SD)	3.3 (2.7)	
Family Type		
Parental	49	70
Sibling	10	14
Marital	10	14
Other	1	1
Socioeconomic Status (Hollingshead two-factor index)		
III	4	6
IV	27	39
V	39	56
Mean Acculturation Score (SD)	2.36 (0.95)	

Due to rounding error, percentages do not necessarily equal 100 percent.

TABLE 2. Demographic Characteristics of Key Relatives ($N = 109$).

Variable	*N*	%
Kinship Relationship to Patient		
Mother	48	44
Father	26	24
Sister	12	11
Brother	11	10
Wife	2	2
Husband	7	6
Other	3	3
Sex		
Female	66	61
Male	43	39
Mean Age (SD)	46.7 (13.6)	
Mean Acculturation Score (SD)	1.84 (0.85)	

relatives were Spanish-speaking, Catholic, and first generation immigrants, i.e., born in Mexico.

TABLE 3. Expressed Emotion Profiles of Anglo-American, British, and Mexican-American Households.

	Low EE		High EE	
	N	%	*N*	%
Anglo-American ($N = 69$, from Vaughn et al., 1984)	23	33.3*	46	66.7
British ($N = 138$, from Brown, Birley, & Wing, 1972; Vaughn & Leff, 1976)	72	52.2	66	47.8
Mexican-American ($N = 70$)	41	58.6	29	41.4

Overall $\chi^2 = 9.90$, d.f. 2, $p < .02$; Anglo-American vs. British Yates corrected $\chi^2 = 5.84$, d.f. 1, $p < .02$; Mexican-American vs. British Yates corrected $\chi^2 = .530$, N.S.; Anglo-American vs. Mexican-American Yates corrected $\chi^2 = 7.92$, d.f. 1, $p < .01$.

TABLE 4. Individual Expressed Emotion Profiles for Mexican-American Key Relatives ($N = 109$).

	N	%
Low Expressed Emotion	78	71.6
High Expressed Emotion	31	28.4
Totals	109	100.0

The household EE ratings for the Mexican-American sample are presented in Table 3, as are results from the British and Anglo-American studies. (The presence of only one high EE relative will result in the household designation of "high.") This cross-cultural view of expressed emotion illustrates that the Mexican-American households were lowest in criticism, hostility, and over-involvement concerning their ill relatives. The finding of significant cross-cultural differences in levels of expressed emotion among Mexican-American families compared to Anglo-American households constitutes one of the major findings of the study. As can be noted in Table 3, there were no significant differences between the Mexican-American and British samples in this regard. While these scores may be similar, it should be evident that the nature and meaning of family expressed emotion is culturally specific. (This subject will be discussed more fully in a forthcoming publication.) Individual profiles obtained for the key relatives are illustrated in Table 4, revealing that high levels of expressed emotion characterize only a little more than one-fourth (28 percent) of the Mexican-American relatives.

Clinical Outcome

From the original sample of 70 patients, 16 cases were lost to final followup for a variety of reasons: several patients and their families ($N = 7$) moved and left no indication of how they could be located; several ($N = 5$) were continuously hospitalized in a state hospital on a long-term basis subsequent to initial recruitment and were resident too short a time in their family households to be rated. One family refused further contact with the study; one patient left her household after a short stay at home to live with other relatives; one (the only) key relative moved out of a patient's household; and one patient died. The 54 cases for whom full followup data were collected were followed for 9 months after hospital discharge and resided continuously in the household from which the EE ratings were obtained. There was only one statistically significant difference in the clinical, sociodemographic, and expressed emotion characteristics of the 54 patients for whom complete data were available compared with the 16 patients lost to followup.[1]

Results for the 9-month outcomes for the final sample of 54 cases are presented in Table 5. Table 6 illustrates the total schizo-

---

[1] Only one household characteristic significantly differed. Among the group for whom full followup data were available, patients were more likely to be living with parents than with spouses or siblings ($p = .01$). This difference may reflect a greater stability in parental households as compared with others included in the study.

TABLE 5. Outcome Status at 9-Month Followup of 54 Schizophrenic Patients ($N = 54$).

Outcome Category	N	%
Stable Remission	27	50.0
Psychotic Relapse	17	31.5
Sustained Psychosis	10	18.5
Totals	54	100.0

phrenic symptom scores derived from PSE ratings for each outcome category at the time of initial and followup assessments. While all patients displayed a decrease in the severity of symptomatology, it is clear that patients in the sustained remission group demonstrated the most significant change ($p < .001$).

Relapse and Expressed Emotion

The relapse rates were analyzed for those patients who experienced some period of non-psychotic stabilization. A total of 10 patients (5 from low EE families), who remained continuously psychotic (and therefore could not "relapse"), were excluded from these analyses, as were such cases in the Anglo-American study. Results for the remaining 44 cases are presented in Table 7. As illustrated, remitted patients from low EE households relapsed at a significantly lower rate than did those from high EE households. This result replicates previous findings (Brown, Birley, & Wing, 1972; Vaughn & Leff, 1976; Vaughn et al., 1984) on the relationship of EE and schizophrenic relapse for the Mexican-American sample.

It is also important to note that in the Mexican-American sample, as in the Anglo-American study, total PSE schizophrenic symptom scores were not significantly correlated with EE ratings (household or individual profiles). Therefore, it appears that expressed emotion cannot be explained simply as family members' responses to varying levels in the severity of schizophrenic symptomatology.

TABLE 6. PSE* Schizophrenic Mean Symptom Scores for Each Outcome Group.

Outcome Group	Initial	Final	Diff	t
Sustained Psychoticism	13.00	8.15	4.85	2.9**
Sustained Remission	10.46	1.13	9.33	7.2**
Psychotic Relapse	9.00	5.53	3.47	1.9(n.s.)

*PSE indicates Present State Examination.
**$p < .05$.
***$p < .001$.

TABLE 7. Relationship of Families' EE Score to Outcome in the 9 Months After Discharge (Total Patient Sample, $N = 44$).

	Outcome Category		
Families' EE	Sustained Remission	Psychotic Relapse	Totals
Low	20 (74%)	7 (26%)	27
High	7 (41%)	10 (59%)	17

$p = .031$ by Fisher's Exact Test.

Medication Compliance, Expressed Emotion, and Clinical Outcome

Medication compliance was rated according to the criteria employed in the British and Anglo-American studies. A patient was considered to have adhered to neuroleptic medication regimens "regularly" if he or she had been taking drugs continuously during the 9-month followup period with no time of up to 4 consecutive weeks without medication. For those cases in which 4 consecutive weeks had passed without taking prescribed medications, medication use was rated as "irregular." Twenty-four (56%) of the 43 available cases (one of the 44 cases could not be confidently rated for medication compliance) were rated "regular" in use of medication; 19 (44%) were considered "irregular."

Table 8 presents the varying contributions of medication and expressed emotion for outcome. As indicated, there is no confounding of the effects of these two variables. Moreover, this analysis shows the effect of EE on outcome as stronger than that of medication. The most favorable clinical outcome was observed for patients who resided in low EE homes and regularly took anti-psychotic medications; 88 percent of these patients experienced sustained remissions.

It should be pointed out that all 10 (100%) of the patients in the "sustained psychoticism" outcome category (excluded from the relapse analyses) were rated as "irregular" in their compliance with medication. A separate discriminant function analysis of all three outcome categories (including sustained psychoticism) revealed medication compliance to be predictive of outcome for patients

TABLE 8. Relationship of Families' EE Score, Patients' Medication Compliance and Clinical Outcome (Total Patient Sample, $N = 43^*$).

	Medication Compliance			
	Irregular		Regular	
Families' EE	Sustained Remission	Psychotic Relapse	Sustained Remission	Psychotic Relapse
Low	6 (60%)	4 (40%)	14 (88%)	2 (12%)
High	3 (33%)	6 (67%)	4 (50%)	4 (50%)

From Log-Linear Analysis:

Effect	χ^2	*d.f.*	*p*
EE × Medication	0.08	1	(n.s.)
EE × Relapse	4.85	1	0.028
Medication × Relapse	2.70	1	(n.s.)

$^*N = 43$. Data on medication compliance missing for one patient.

in states of sustained psychosis ($p = .002$) and stable remission ($p = .004$), but non-significant ($p = .70$) among those patients who remitted and subsequently relapsed.

Summary and Conclusion

The basic findings of the study can be summarized as follows: 1) Expressed emotion is significantly lower among Mexican-Americans than Anglo-Americans. 2) Expressed emotion significantly predicted schizophrenic outcome among Mexican-Americans, as for British and Anglo-American samples. 3) The expressed emotion index appears to be independent of patient morbidity. 4) For those patients who experienced a period of remission during the 9 months following hospitalization for a psychotic episode, expressed emotion appears to have a greater predictive utility than does medication compliance; moreover, there is no confounding of the effects of these two variables. 5) Analyses of outcome for patients in either sustained psychosis or stable remission revealed medication to be significantly related to clinical outcome. 6) The best clinical outcome is observed when patients resided in low EE home environments and regularly adhered to maintenance pharmacotherapy.

The finding that "expressed emotion" significantly predicts the course of schizophrenic illness for Mexican-American, Anglo-American, and British patients requires explanation. It may be that the expression of angry or hostile affects in family settings constitutes a highly stressful situation for patients across a range of diverse sociocultural contexts, and that such environments often portend a poor course for schizophrenic illness. While this relationship has held up for culturally distinctive groups, it is important to point out that the nature and meaning of "expressed emotion" among these three groups varies in qualitatively important ways. However, while the symbolic and emotional meaning of family interactions are culturally and individually specific, a patient's general perception of an absence of love, acceptance, or support may be similarly experienced as distressing. Such perceptions on the part of the patient, along with the daily difficulties inherent in coping with a home environment marked by asperity and tension, may prove inimical to sustained recovery. (This point, however, deserves discussion beyond the scope of the current report.)

It is also critical to note a host of other life stressors that are likely to also impact upon patterns of relapse among Mexican-American patients, including such factors as immigrant, minority, and lower socioeconomic status; a severe lack of culturally and linguistically appropriate mental health facilities; and continuing prejudice and discrimination. It is our hope that further analyses and research results from the COSAMA Project will contribute toward the formulation of culturally meaningful psychosocial and pharmacotherapeutic interventions for Hispanic-American patients and their families.

Acknowledgments

The authors wish to gratefully acknowledge the research assistance of Richele Bettencourt, Mariana Lopez, and Martha Magana. We also acknowledge the assistance in training procedures provided by Karen Snyder, Ph.D., Christine Vaughn, Ph.D., David Lukoff, Ph.D., and Joseph Ventura, M.A. Editorial assistance was generously provided by Sharon Sabsay, Ph.D.

References

Brown, G.W., Birley, J., and Wing, J. Influence of Family Life on the Course of Schizophrenic Disorders: A Replication. *Br. J. Psychiatry*, 121:241–258, 1972.

Cuellar, I., Harris, L.C., and Jasso, R. An Acculturation Scale for Mexican-American Normal and Clinical Populations. *Hispanic J. Behavioral Science*, 2:199–217, 1980.

Edgerton, R.B. Traditional Treatment for Mental Illness in Africa: A Review. *Cult., Med., and Psychiatry*, 4:167–189, 1980.

Jenkins, J.H. Ethnopsychiatric Interpretation of Schizophrenic Illness: The Problem *Nervios* within Mexican-American Families. *Cult., Med., and Psychiatry*, in press.

Jenkins, J.H., Karno, M., de la Selva, A., and Santana, F. In: Goldstein, M., Hand, I., and Hahlweg, K. (eds.), *Treatment of Schizophrenia: Family Assessment and Intervention*. Springer Verlag, in press.

Jilek, W. and Jilek-Aall, L. Transient Psychoses in Africans. *Psychiatric. Clin.*, 3:337–364, 1970.

Karno, M., Jenkins, J., de la Selva, A., et al. Expressed Emotion and Schizophrenic Outcome Among Mexican-American Families. (Submitted, 1986)

Kennedy, J.G. Cultural Psychiatry. In: Honigmann, J. (ed.), *Handbook of Social and Cultural Anthropology*. New York: Rand McNally College Publishing Co., 1974.

Murphy, J. Cultural Shaping and Mental Disorders. In: Gove, W.R. (ed.), *Deviance and Mental Illness*. Beverly Hills, California: Sage Publications, 1982.

Murphy, H.B.M., and Raman, A.C. The Chronicity of Schizophrenia in Indigenous Tropical Peoples: Results of a 12-year follow-up on Mauritius. *Br. J. Psychiatry*, 118:489–497, 1971.

Rin, H., and Lin, T.-Y. Mental Illness among Formosan Aborigines as Compared to Chinese in Taiwan. *J. Ment. Sci.*, 108:134–146, 1962.

Sartorius, N., Jablensky, A., and Shapiro, R. Cross-Cultural Differences in the Short-Term Prognosis of Schizophrenic Psychosis. *Schizophr. Bull.*, 4:102–113, 1978.

Vaughn, C.E., and Leff, J. The Influence of Family and Social Factors on the Course of Psychiatric Illness: A Comparison of Schizophrenic and Depressed Neurotic Patients. *Br. J. Psychiatry*, 129:125–137, 1976.

Vaughn, C.E., Snyder, K.S., Jones, S., et al. Family Factors in Schizophrenic Relapse: A California Replication of the British Research on Expressed Emotion. *Arch. Gen. Psychiatry*, 41:1169–1177, 1984.

Waxler, N. Is Mental Illness Cured in Traditional Societies? A Theoretical Analysis. *Cult., Med., and Psychiatry*, 1:233–254, 1977.

World Health Organization. *Schizophrenia: An International Followup Study*. Chichester, New York, Brisbane and Toronto: John Wiley and Sons, 1979.

Expressed Emotion, Affective Style, Lithium Compliance, and Relapse in Recent Onset Mania[1]

David J. Miklowitz, Ph.D., Michael J. Goldstein, Ph.D., Keith H. Nuechterlein, Ph.D., Karen S. Snyder, M.A., and Jeri A. Doane, Ph.D.[2]

Two family communication factors have been identified that appear to have predictive utility for the course of schizophrenia: expressed emotion (EE), a measure of the degree to which a key relative (usually a parent) holds highly critical, hostile, and/or emotionally overinvolved *attitudes* toward the patient, and affective style (AS), a measure of the emotional-verbal *behavior* of relatives in direct interaction with the patient. Schizophrenic patients from families judged to be high EE are at approximately a fourfold greater risk for relapse in the 9 months following hospital discharge than are patients from families rated low EE (Brown et al., 1972; Vaughn & Leff, 1976: Vaughn et al., 1984). Similarly, schizophrenic patients from families rated as negative AS during the postdischarge period are at far greater risk for relapse in the first 9 months of followup than are patients from families who demonstrate AS behaviors that are emotionally benign (Doane et al., 1985). High-EE intrafamilial attitudes and negative-AS behaviors, while often coexisting in the same family, are not isomorphic to one another (Miklowitz et al., 1984).

There has been interest in recent years in studying the applicability of these family measures to other psychiatric populations. In their original study of schizophrenic patients and their parents, Vaughn & Leff (1976) included a comparison group of nonpsychotic depressed patients and their spouses, and found that high-EE attitudes in spouses were predictive of depressive relapse in the patient. This finding was later replicated by Hooley et al. (in press). However, the predictive utility of EE attitudes has never been studied in psychotic populations other than schizophrenia, and the above-mentioned replication studies were based on spousal, rather than parental families. Furthermore, the predictive utility of negative intrafamilial AS behaviors has never been studied in a nonschizophrenic or schizophrenic spectrum population.

The present study was designed to test the applicability of intrafamilial EE and AS to the parental families of patients with another psychotic illness, bipolar affective disorder. Bipolar illness, like schizophrenia, follows a relapse-remission course, and can be quite disruptive to the family environment. Further, it is estimated that a large proportion of bipolar patients (i.e., 47%) require rehospitalization or show exacerbations during a 1-year period despite following recommended lithium regimens (O'Connell & Mayo, 1981). It was hypothesized that the emotional climate of the family to which a recently episodic bipolar patient returns following hospitalization may be one factor accounting for a proportion of the variability in patient illness outcome.

Method

Subjects

Patients in this sample were 24 recently episodic bipolar–manic patients recruited from inpatient wards at the UCLA Neuropsychiatric Hospital in Los Angeles. Patients were interviewed by a trained research staff member using an extended version of the Present

---

[1] This research was supported by a grant from the MacArthur Foundation on Risk and Protective Factors in the Major Mental Disorders, and NIMH grants MH–30911, MH–08744, MH–37705, and MH–14584.

[2] Department of Psychology, University of California, Los Angeles, CA 90024.

Reprint requests: David J. Miklowitz, UCLA Family Project, Dept. of Psychology, Univ. of Calif., Los Angeles, CA 90024.

State Examination (PSE; Wing, Cooper, & Sartorius, 1974), and were diagnosed using the Research Diagnostic Criteria (RDC; Spitzer et al., 1978). Patients met RDC criteria for manic episode (n = 13) or schizoaffective, mainly affective, manic episode (n = 11). Diagnoses were later confirmed by an independent clinician on the basis of case summaries describing the patient's current episode. Exclusionary selection criteria for the sample are described in detail elsewhere (Nuechterlein, 1982).

The mean age of the 24 patients (13 male, 11 female) was 21.45. Age of onset of bipolar illness tended to be early (mean = 19.88 years), and the average duration of illness since onset was 9.42 months. The sample was primarily Caucasian and of high socioeconomic status. Nine patients were living with or in significant contact with one parent, 14 had two parents, and 1 was living with a spouse.

Procedure

Expressed emotion. Patients were first interviewed and diagnosed during the inpatient phase. If a patient met the diagnostic and exclusionary criteria, his/her relatives were administered the Camberwell Family Interview (CFI; Vaughn & Leff, 1976) by a trained staff member. The CFI is a 1½-hour interview focusing on the patient's most recent psychiatric episode and its impact on the family environment. Following the interview, the number of *critical* comments made by the relative, or statements of dislike or resentment regarding the patient with accompanying voice tone, were counted by a trained judge on the basis of audiotapes of the interview. In addition, ratings were made of the degree to which the relative showed evidence of *emotional overinvolvement*, or markedly overconcerned, self-sacrificing, overprotective attitudes toward the patient. Emotional-overinvolvement ratings were based on a 0 (absent) to 5 (high) scale. Camberwell judges had attained minimum interrater reliability coefficients of .80 on these two EE subscales prior to participation in the present study, and were blind as to any other information about the patient and his/her family.

Relatives were rated high EE if they made at least 6 criticisms and/or were rated as moderately high (4) or higher on emotional overinvolvement. Relatives who did not meet these criteria were classified as low EE. *Families* were rated high EE if one or more key relatives were so rated.

Affective style. Approximately 3 weeks after the patient's hospital discharge, a 2-hour family-assessment session was conducted with each patient and his/her parents or spouse. Family members were first interviewed about their current family environment, and conflict issues within the family were identified. The family was then brought together and asked to discuss two such issues for 10 minutes each while the experimenter was out of the room. Typed transcripts were generated from audiotapes of these interactions, and the transcripts were coded on dimensions of affective style (AS; Doane et al., 1985).

For the present study, relative-to-patient statements during the interactions were coded along two major dimensions: (1) critical statements, which could be of a benign, situational type (e.g., "You have a bad attitude about school, Tom"), a harsh, severely negative type ("You have an arrogant, stupid attitude"), or of a guilt-inducing type ("You are making life miserable for us"); (2) neutral-intrusive statements, which imply that the relative has a special knowledge about the patient's attitudes or feeling states, beyond what the patient has stated explicitly (e.g., "You always feel guilty when you're around Dad"). Families were rated as negative AS if at least one relative made (a) one or more severely critical or guilt-inducing statements during either 10-minute interaction, or (b) 6 or more neutral-intrusive statements (Doane et al., 1985).

Transcripts were rated by one of two raters who were blind to the other family assessment and patient outcome data. Interrater reliability for AS codes was .78 (kappa statistic).

Patient followup. Patients were followed for a 9-month period following discharge. Every 3 months, the patient was interviewed on a face-to-face basis and was rated on an extended version of the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962; Nuechterlein, 1982). In addition, an abbreviated version of the scale was administered on a monthly basis over the telephone. The BPRS interviewer had completed a workshop on the administration and scoring of the scale, and interrater reliability, calculated across each subscale, averaged .80. In addition, the rater was blind to the baseline family assessment data.

Patients were judged to have relapsed (total $n = 14$) if they showed a significant clinical exacerbation (i.e., a rise to BPRS scale point 5, 6, or 7) following a minimum 1-month period of remission (i.e., all BPRS scales at 3 or below) or near remission on at least one of 10 subscales judged to be relevant to manic or depressive relapse. Patients were classified as nonrelapsers ($n = 7$) if they retained a state of clinical remission or near remission for the majority of the 9-month followup period, with no exacerbations. Patients were judged to be clinically unchanged if they retained a state of moderately severe, severe, or extremely severe (i.e., scale points 5, 6, or 7) symptomatology for at least 6 of the 9 months of followup ($n = 2$; Nuechterlein, Miklowitz, & Ventura, 1985).

Assessments of the patients' level of medication (usually lithium) compliance were also conducted every 3 months. Ratings of compliance were based on self-report information from the patient, data obtained from key relatives and the patient's physician, and serum lithium levels (Cochran, 1982). Patients were judged to be noncompliant (total $n = 16$) if they demonstrated at least one 3-month period in which they were missing at least one dosage per week. More typically, these patients were ingesting less than 50 percent of their prescribed medication. Compliant patients were those who missed a maximum of one or two dosages per month throughout the 9-month followup period (total $n = 7$). Interrater agreement on ratings of compliance vs. noncompliance was .92 (kappa statistic).

Results

The first question posed by the current study concerned the relative utility of intrafamilial affective attitudes (EE) and behavior (AS) in predicting the longitudinal course of manic disorder. Results are presented in Table 1. For these analyses, patients with relapsing and unchanged outcomes were combined due to the small number of subjects in the unchanged cell. All χ^2values were calculated using the likelihood ratio method.

TABLE 1. Family Expressed Emotion Status and Affective Style Profiles as Predictors of 9-Month Clinical Outcome.

Family EE Status	No Relapse	Relapse/Unchanged
Low EE	6	7
High EE	1	9

$\chi^2 (1) = 3.82, p = .05$

Family AS Profile	No Relapse	Relapse/Unchanged
Benign AS	5	6
Negative AS	1	10

$\chi^2 (2)=3.92, p < .05.$

Conjoint Prediction Family Pattern	No Relapse	Relapse/Unchanged
Low EE/Benign AS	5	1
Negative on One	0	11
Negative on Both	1	4

$\chi^2 (2) = 15.37, p < .0005.$

Note: Outcome data were unavailable for one patient who refused the longitudinal followup. In addition, one family consented to the Camberwell Family Interview (EE) procedure but declined to participate in the direct interaction (AS) exercise.

High-EE attitudes in relatives were moderately associated with poor clinical outcomes, with 90 percent of patients from high-EE homes demonstrating recurrences at followup ($p = .05$). Similarly, as indicated in Table 1, negative family AS profiles were moderately associated with poor outcomes ($p < .05$).

The finding that family EE status and AS profiles were unrelated in this sample ($p > .10$) suggested that family affective attitudes and behavior might be usefully combined and treated as conjoint predictors of patient outcome. As indicated at the bottom of Table 1, this combination of predictive factors accurately identified 91 percent of the good and poor clinical outcomes in this sample ($p < .0005$). This improved level of prediction occurred because the two family factors appeared to be associated with different types of patient outcome: High-EE intrafamilial attitudes were most common in cases where the patient achieved a state of full remission following discharge and then evidenced a significant clinical relapse or exacerbation, whereas patients from negative-AS homes either (a) showed high levels of persisting symptomatology throughout followup, and then manifested a clinical exacerbation on top of this ongoing residual illness, or (b) remained unchanged and highly symptomatic throughout followup.

Medication compliance was not in itself a significant predictor of clinical outcome in this sample [χ^2 (1) = .71, $p > .10$], nor was this variable associated with level of intrafamilial EE or AS (ps $> .10$). However, both EE and AS interacted to some degree with medication compliance in predicting manic outcome (Table 2). Patients from high-EE or negative-AS homes tended to relapse regardless of whether they were compliant with their medication regimens. However, patients from low-EE or benign-AS homes tended to have positive outcomes only when they were medically compliant. Those who were noncompliant demonstrated rates of relapse similar to those noted in the high-EE and negative-AS cells.

TABLE 2. Expressed Emotion, Affective Style, Medication Compliance, and Patient Illness Outcome.

Expressed Emotion and Medication Compliance	No Relapse	Relapse/ Unchanged
Low EE		
Compliant	3	1
Noncompliant	3	6
High EE		
Compliant	0	3
Noncompliant	1	6

χ^2 (3) = 6.57, $p = .09$.

Affective Style and Medication Compliance	No Relapse	Relapse/ Unchanged
Benign AS		
Compliant	3	1
Noncompliant	2	5
Negative AS		
Compliant	0	3
Noncompliant	1	7

χ^2 (3) = 6.88, $p < .08$.

Discussion

The present study tested the utility of two measures of family affective communication, intrafamilial expressed emotion and affective style, in predicting the course of recent onset mania. Both EE and AS were individually, though moderately, predictive of 9-month clinical outcome in this sample. Results are consistent with those of Doane et al. (1985) and Vaughn & Leff (1976) in suggesting that the intrafamilial environment to which a psychiatrically disturbed patient returns following hospitalization is an important influence on the subsequent course of the disorder.

Prediction of outcome was optimal when intrafamilial EE and AS were combined and treated as conjoint predictors: 91 percent of the clinical outcomes were accurately identified in this manner. This level of prediction was achieved due to the finding that EE and AS were associated with different types of clinical outcome at followup. Therefore, in a bipolar sample, it may be necessary to have information on both family attitudes and actual interactional behavior in order to confidently predict the subsequent course of the patient's illness.

Medication compliance was not by itself significantly associated with illness course in this sample, but did tend to mediate the relations between family factors and 9-month clinical outcome. Specifically, when the family environment to which the patient returned following hospitalization was negative, patients were at high risk for a poor clinical outcome regardless of whether they were medically compliant. However, a neutral or benign family environment was associated with a good clinical outcome only when the patient consistently adhered to his/her medication regimen. These findings contrast to some degree with those of Vaughn & Leff (1976), who reported that, in a schizophrenic sample, medication compliance was to some degree a protective factor against relapse for patients from high-EE homes, whereas patients from low-EE homes had positive outcomes regardless of their medication-taking habits. The present findings indicate that some manic patients, unlike schizophrenics, may benefit from a consistent medication regimen only when the family environment is affectively benign.

Due to the small number of subjects utilized in the present study, the findings should be viewed as tentative and in need of replication. However, the results do suggest that the affective climate of the family following hospitalization may be an important factor contributing to the subsequent course of bipolar disorder. Further, treatment of the family as a unit during the outpatient phase may be a useful adjunct to medication management for these patients.

Acknowledgments

The authors would like to thank Sibyl Zaden, Ana Magana, Portia Loughman, Joe Ventura, Sandra Rappe, and Sandra Malik for their assistance in this study.

References

Brown, G.W., Birley, J.L.T., and Wing, J.F. Influence of family life on the course of schizophrenic disorders: A replication. *Br. J. Psychiatry,* 121:241–258, 1972.

Cochran, S.D. "Strategies for preventing lithium noncompliance in bipolar affective illness." Unpublished doctoral dissertation, University of California, Los Angeles, 1982.

Doane, J.A., Falloon, I.R.H., Goldstein, M.J., and Mintz, J. Parental affective style and the treatment of schizophrenia: Predicting course of illness and social functioning. *Arch. Gen. Psychiatry,* 42:34–42, 1985.

Hooley, J.M., Orley, J., and Teasdale, J.D. Levels of expressed emotion and relapse in depressed patients. *Br. J. Psychiatry.* (In press.)

Miklowitz, D.J., Goldstein, M.J., Falloon, I.R.H., and Doane, J.A. Interactional correlates of expressed emotion in the families of schizophrenics. *Br. J. Psychiatry,* 144:482–487, 1984.

Nuechterlein, K.H. *Developmental processes in schizophrenic disorders.* NIMH Research Grant MH37705, 1982.

Nuechterlein, K.H., Miklowitz, D.J., and Ventura, J. "Manual for assessing outcome in schizophrenic and bipolar-manic patients." Unpublished manuscript, 1985.

O'Connell, R.A., and Mayo, J.A. Lithium: A biopsychological perspective. *Compr. Psychiatry,* 22(1):87–93, 1981.

Overall, J.E., and Gorham, D.R. The Brief Psychiatric Rating Scale. *Psychol. Rep.,* 10:799–812, 1962.

Spitzer, R.L., Endicott, J., and Robins, E. Research diagnostic criteria: Rationale and reliability. *Arch. Gen. Psychiatry,* 35:773–782, 1978.

Vaughn, C.E., & Leff, J.P. The influence of family and social factors on the course of psychiatric illness. *Br. J. Psychiatry,* 129:125–137, 1976.

Vaughn, C.E., Snyder, K.S., Jones, S., et al. Family factors in schizophrenic relapse: Replication in California of British research on expressed emotion. *Arch. Gen. Psychiatry,* 41:1169–1177, 1984.

Wing, J.K., Cooper, J.E., & Sartorius, N. *The Description and Classification of Psychiatric Symptoms: An Instruction Manual for the PSE and CATEGO System.* London: Cambridge University Press, 1974.

Expressed Emotion, Fixed-Dose Fluphenazine Decanoate Maintenance, and Relapse in Recent-Onset Schizophrenia[1]

Keith H. Nuechterlein, Ph.D.,[2] Karen S. Snyder, M.A.,[2] Michael E. Dawson, Ph.D.,[2] Sandra Rappe, M.S.W.,[2] Michael Gitlin, M.D.,[2] And David Fogelson, M.D.[2]

The presence of high levels of critical comments, hostility, or emotional overinvolvement, as expressed by family members during the Camberwell Family Interview (CFI; Brown & Rutter, 1966; Rutter & Brown, 1966; Vaughn & Leff, 1976b), has been shown to be highly predictive of psychotic relapse during the 9, 12, or 24 months following hospital discharge after an acute schizophrenic episode (Brown et al., 1962; Brown et al., 1972; Leff & Vaughn, 1981; Vaughn & Leff, 1976a; Vaughn et al., 1984). The term "expressed emotion" is used to describe the set of CFI measures that quantify the attitudes, feelings, and behaviors concerning the patient that are expressed or reported by a relative. Although there are numerous scales of expressed emotion, only the scales involving 1) the number of critical comments, 2) the presence of hostility, and 3) the level of emotional overinvolvement have been predictive of psychotic relapse (Brown et al., 1972; Vaughn et al., 1984).

In the CFI scoring procedure, a critical comment is a statement of unambiguous dislike, disapproval, or resentment of the patient's actions, attitudes, or feelings. Hostility is rated as present based on remarks that spell out an all-encompassing rejecting attitude toward the patient and/or generalized negative comments about the person himself or herself rather than about selected behaviors or characteristics. In practice, hostility is rarely found in interviews in which critical comments are not numerous. For the emotional overinvolvement rating, the most important information is the amount and degree of self-sacrificing and devoted behavior or overprotective behavior demonstrated by the relative. Expression of a high number of critical comments, hostility, or a high level of emotional overinvolvement by a family member in relationship to the patient has come to be summarized as "high expressed emotion" (EE)* and has been associated with a 3- to 8-fold increase in the rate of psychotic relapse.

Although the studies of EE conducted by Brown et al. (1972) and Vaughn and Leff (1976a) in Great Britain and by Vaughn et al. (1984) in California reported patients' outpatient medication adherence, they did not involve experimental control for medication effects. Examination of data within these initial studies indicated that patients who were maintained on regular antipsychotic medication had lower relapse rates than those who had irregular or no antipsychotic maintenance medication (Vaughn & Leff, 1976a; Vaughn et al., 1984), but suggested that familial EE had a predictive role that was not statistically accounted for by the regular/irregular medication dichotomy (Vaughn et al., 1984). The reduction of relapse rate in chronic schizophrenia by maintenance antipsychotic medication is well established (e.g., Hogarty, Goldberg, & the Collaborative Study Group, 1973; Leff & Wing, 1971; Rifkin, Quitkin, Rabiner, & Klein, 1977). Because the earlier EE studies did not experimentally control medication administration or dosage, the varying medication practices of the treating physicians, unreliable reporting of compliance with oral medications, and patient self-selection for regular/irregular medication may have had unknown effects on the results. The present study examines the predictive role of familial EE for psychotic relapse under conditions in which patients are administered a standardized dosage of antipsychotic medication in a reliable injectable fashion and are followed in a common manner in the same aftercare clinic.

---

[1] This research was supported by NIMH Research Grants MH-37705 to K.H. Nuechterlein, Ph.D., and MH-30911 (Clinical Research Center for the Study of Schizophrenia) to R.P. Liberman, M.D. The authors gratefully acknowledge the dedicated efforts of Portia Loughman, B.A., and Mariana Lopez, B.A., in collection of the Camberwell Family Interview data, and of David Lukoff, Ph.D., Joseph Ventura, M.A., Margie Stratton, M.S., and Deborah Gioia-Hasick, M.S.W., in recruitment and outpatient treatment and assessment of the patients. Michael J. Goldstein, Ph.D., Robert P. Liberman, M.D., and Christine E. Vaughn, Ph.D., have offered valuable consultation to this project.

[2] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, CA 90024

Reprint requests: Keith H. Nuechterlein, Ph.D., UCLA Neuropsychiatric Institute, Box 18, 760 Westwood Plaza, Los Angeles, CA 90024.

*This categorization of a family member as high vs. low in "expressed emotion" is somewhat a misnomer, as it is based only on negative attitudes and extreme overconcern. This misnomer has occurred because other initial dimensions of expressed emotion, the expression of warmth and positive remarks, were found to bear no linear relationship to the patient's outcome (Brown et al., 1972; Leff & Vaughn, 1985) and have, therefore, not been used in the summarizing dichotomy for familial level of expressed emotion.

A second major feature of the conditions of the present study involves the restriction of the sample to schizophrenic patients with a recent onset of psychosis. The earlier studies included patients who varied widely in chronicity, ranging from many years of illness to a smaller number who were experiencing their first episode. Increased experience with a schizophrenic patient's repeated episodes might have elicited increased critical comments, hostility, or emotional overinvolvement in family members, thereby leading to a predictive relationship between these family attitudes and higher relapse rates that did not involve any causal role for the family attitudes. Restriction of the present sample to patients who had experienced their first psychotic episode in the previous 2 years allows an opportunity for the predictive role of familial EE to be examined in a situation in which the attitudes of family members are not confounded with experience of established chronicity of illness.

Another important feature of the current study is the use of objective, quantitative criteria for psychotic relapse based on Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) evaluations completed every 2 weeks. This intensive, ongoing monitoring of symptomatology by reliable, carefully trained raters had allowed more precise criteria for psychotic relapse to be developed, thereby taking one additional step in the progressive improvements in psychotic relapse criteria that had characterized the Brown et al. (1972), Vaughn and Leff (1976a), and Vaughn et al. (1984) investigations. This study continues the primary focus on return or exacerbation of psychotic symptoms. Thus, as in the Brown et al. (1972), Vaughn and Leff (1976a), and Vaughn et al. (1984) studies, psychotic relapse is not mixed with nonpsychotic forms of symptomatic excerbation and with rehospitalizations based on breakdowns of social support systems that do not involve significant exacerbation of psychotic symptoms.

The data reported here summarize the EE results from analyses for the first 30 patients to finish a 1-year, fixed-dose, fluphenazine (Prolixin) protocol within an ongoing project, Developmental Processes in Schizophrenic Disorders (Principal Investigator: Keith H. Nuechterlein, Ph.D.), in which the predictive roles of several key social, psychological, and biological factors in the early course of schizophrenic disorders are being evaluated.

Methods

Subjects

The schizophrenic patients were selected from the Los Angeles metropolitan region during an index hospitalization at one of four public hospitals (UCLA Neuropsychiatric Institute & Hospital, Camarillo State Hospital, Harbor/UCLA Medical Center, Olive View Medical Center) or, in a few cases, at one of the local private hospitals. These subjects were required to have the following characteristics: 1) a diagnosis of schizophrenia or of schizoaffective disorder, mainly schizophrenic, by Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978), determined by trained research personnel based on an expanded version of the Present State Examination (PSE; Wing et al., 1974) administered to the patient and consideration of any additional data gathered from relatives; 2) a recent onset of major psychosis lasting at least 2 weeks (first psychotic episode not longer than

2 years before project contact); 3) age between 16 and 45 years; and 4) Caucasian, acculturated Asian, or acculturated Hispanic in ethnic background. Subjects with any of the following were excluded: 1) evidence of an organic central nervous system disorder (e.g., epilepsy, traumatic brain injury, infectious or toxic cerebrovascular disease); 2) significant and habitual drug or alcohol abuse in the 6 months prior to the current episode, or past drug or alcohol abuse that clouded the diagnostic picture; or 3) mental retardation (premorbid IQ less than 70).

To be included in these analyses, patients needed to be maintained in the medication protocol for 1 year or until they relapsed. Three patients who relapsed after discontinuation of their antipsychotic medication were eliminated from analyses. To qualify for inclusion in the EE portion of the larger project, patients were required to have been in contact at least weekly with a family member during at least 1 of the 3 months prior to the index hospitalization. Twenty-seven of the initial 30 schizophrenic patients who finished the fixed-dosage medication protocol met this criterion. One additional patient who was maintained on oral fluphenazine due to refusal of injections was excluded from analyses for this report of patients maintained on fluphenazine decanoate. The 26 participating schizophrenic patients (20 male, 6 female) had a mean study-entry age of 22.6 years (SD = 3.4; range = 19 to 32 years). The mean educational level was 12.1 years (SD = 1.9, range = 9 to 16 years). Twenty-three of the patients were Caucasian, two were acculturated Hispanic, and one was acculturated Asian. For 22 of 26 patients, the index period was the first psychotic episode, and for 19 of 26 patients, the index hospitalization was the first psychiatric hospitalization.

Procedure

Expressed emotion. The family members who had significant contact with the patient were administered the abbreviated version of the Camberwell Family Interview (CFI; Vaughn & Leff, 1976b) within 1 month of the patient's hospital admission. The CFI is a standardized, semi-structured interview that focuses on the onset and development of the present illness episode and its impact on family life in the 3 months before hospitalization. Spontaneous expressions of feelings and self-reports of emotions are noted, with emphasis on the former. The entire interview is tape-recorded for later scoring.

Ratings of critical comments, hostility, and emotional overinvolvement were completed by the interviewers shortly after the CFI according to procedures established in the original British work. Interviewer/raters were trained to reliability by Christine E. Vaughn, Ph.D., and Karen S. Snyder, M.A., and were required to achieve interrater reliability with the criterion judges of at least $r = .80$ (Pearson correlation) prior to study participation. Randomly selected interviews were also co-rated by one of the authors (K.S.S.) and other trained raters to ensure maintenance of high interrater reliability.

The family environment was rated as high in EE if any family member made six or more critical comments, was rated as high or marked 4 or 5 on emotional overinvolvement, and/or was rated as showing hostility. In the absence of these features, it was rated low in EE.

Outpatient treatment. All of the patients were seen regularly at the Aftercare Clinic of the UCLA Mental Health Clinical Research Center (MHCRC) for the Study of Schizophrenia, which is located at the UCLA Neuropsychiatric Institute. Patients were placed on a standardized dosage of fluphenazine decanoate, 12.5 mg every 2 weeks, as soon as their clinical state could be stabilized during the first 2 to 3 months of outpatient treatment. (One patient who developed intolerable side effects on this dosage was maintained on a fixed dosage of 10 mg every 2 weeks.) Two psychiatrists (M.G. and D.F.) on the research team maintained the medication protocol. Individual case management and supportive therapy were provided by clinic therapists. Clinic staff involved in a patient's treatment were blind to the EE level of the family.

The 1-year period of outcome evaluation began when a patient completed a battery of information-processing, psychophysiological, and personality measures, which occurred 1 month after the standardized medication was initiated.

Evaluation of outpatient outcome. The individual case manager completed a rating of patient symptomatology every 2 weeks, using an expanded form of the BPRS that was developed by David Lukoff, Ph.D., Keith H. Nuechterlein, Ph.D., and Joseph Ventura, M.A. This BPRS version includes behavioral anchors and a structured interview format to standardize rating levels. Before rating the study patients, the BPRS raters were required to complete a training program that included rating a set of audiotaped interviews as well as conducting and rating their own interviews. A median interrater reliability (intraclass correlation coefficient) of at least .80 for all subscales was required of each rater. Median interrater reliabilities across raters on the three key symptoms used to evaluate psychotic relapse, Unusual Thought Content, Hallucinatory Behavior, and Conceptual Disorganization, were .93, .97, and .73 (intraclass correlation coefficients), respectively.

A nine-category system for evaluating psychotic relapse was modeled after the system used by Vaughn et al. (1984), but was keyed to the BPRS rather than the Psychiatric Assessment Scale (Krawiecka et al., 1977) and PSE to take advantage of the more differentiated seven-point scales and to allow easier application by the large number of investigators who are familiar with the BPRS. The category definitions are based on initial and subsequent outpatient symptomatology on the three psychotic scales (Nuechterlein et al., 1985). Three subtypes of psychotic relapse are (initial status—subsequent status): Remission—Relapse; Remission—Significant Exacerbation; and Persisting Symptoms—Significant Exacerbation. Five subtypes of outcomes without relapse are: Remission—Remission; Persisting Symptoms—Remission; High Persisting Symptoms—Improvement; Persisting Symptoms—Persisting Symptoms; and Remission—Mild Exacerbation. Finally, a category for patients who never improve sufficiently to allow room for a Relapse or Significant Exacerbation is called High Persisting Symptoms—High Persisting Symptoms.

Space does not allow the details of the nine-category outcome system to be described here. However, the criteria for the first two psychotic relapse sub-categories can be summarized as requiring an increase to a rating of 6 (severe) or 7 (extremely severe) for Relapse or a rating of 5 (moderately severe) for Significant Exacerbation on the Unusual Thought Content, Hallucinatory Behavior, or Conceptual Disorganization scales, preceded by an initial Remission period [at least 1 month of BPRS ratings on the three psychosis scales of 3 (mild) or below]. The third subcategory of psychotic relapse concerns patients who show Persistent Symptoms [continuing ratings of 4 (moderate) or above on at least one of the psychotic scales]. To be classified as having a Significant Exacerbation, these patients must show an increase to a rating of 6 or 7 that involves a 2-point change on one of the psychotic scales. Patients are classified as nonrelapsers if they show neither Relapse nor Significant Exacerbation, unless their psychotic symptoms persist at such a high level as to preclude these states. Patients are classified as showing Unchanged High Persisting Symptoms if they maintain a rating of 5 or above on any of the psychotic scales for at least two-thirds of the followup period and never meet criteria for Improvement (ratings of 4 or less on psychotic scales sustained over 3 months).

Two independent judges placed each of the patients into one of the nine categories of outcome based on the BPRS scores, without knowledge of the EE status of the family environment. Interrater agreement on placement of cases into the nine categories was 93 percent, and agreement for the three groupings of relapse, no relapse, and unchanged high persisting symptoms categories was 100 percent. In two cases, these two judges disagreed on the subcategory of relapse to be assigned. For these cases, a third independent judge rated outcome and a consensus rating was used.

Results

Table 1 presents the distribution of 1-year outcomes for the 26 patients available for these analyses of the predictive value of familial expressed emotion under controlled, fixed-dose fluphenazine decanoate medication conditions. The overall 1-year relapse rate is 27 percent (7 of 26), which is within

TABLE 1. 1-Year Outcomes of Schizophrenic Patients Maintained on Standardized Dosage of Fluphenazine Decanoate

Initial Status	Later Status	*n*
Relapse categories		
Remission	Relapse	4
Remission	Signif. Exacerbation	3
Persisting Symptoms	Signif. Exacerbation	0
No-relapse categories		
Remission	Remission	16
Persisting Symptoms	Remission	2
High Persisting Symptoms	Improvement	0
Persisting Symptoms	Persisting Symptoms	0
Remission	Mild Exacerbation	1
Unchanged high persisting symptoms		
High Persisting Symptoms	High Persisting Symptoms	0

the expected range based on past studies of schizophrenic patients maintained on antipsychotic medication (Hogarty et al., 1973; Hogarty et al., 1979; Leff & Wing, 1971; Davis, 1985).

As shown in Table 2, the 1-year relapse rate for patients from high EE environments was 37 percent, whereas none of the patients from low EE environments relapsed. Thus, for the first 26 patients who have finished the 1-year, standardized fluphenazine decanoate period in this ongoing study, high familial EE already predicts psychotic relapse at a statistically significant level (likelihood ratio chi-square = 5.28, $p < .03$; Hays, 1973). The correlation (phi coefficient) between EE level and psychotic relapse is .37. [If the patient maintained on oral fluphenazine is included, the relapse rate for patients from high EE environments is 40 percent (8 of 27), which strengthens further the differential relapse rate for patients in high vs. low EE environments.]

To examine the possibility that relatives' high EE may be partially a reaction to experience with duration of the patient's schizophrenic illness or psychiatric hospitalization, even within the period preceding chronic schizophrenia [by the American Psychiatric Association's *DMS-III* (1980), the first 2 years of illness], the association of high EE with indices of illness duration was examined. In addition, the relationship of EE level to the inpatient overall severity of symptomatology (sum of the standard 18 BPRS scales) and to key demographic factors was determined. As shown in Table 3, in this sample of recent-onset schizophrenic patients, the EE level of the family was not related to the duration of the patient's illness, the duration or number of past hospitalizations, severity of inpatient overall symptomatology, patient age, patient

TABLE 2. Prediction of Psychotic Relapse From Relatives' Expressed Emotion Level Rated From CFI at the Index Hospitalization

EE of Relatives	No Relapse	Relapse	1 Yr. Relapse Rate
High (6 or more Critical Comments, Emotional Overinvolvement rating of 4 or 5, or Hostility)	12	7	37%
Low (0-5 Critical Comments; no marked Emotional Overinvolvement; and no Hostility)	7	0	0%

Note. $p < .03$, likelihood ratio χ^2.

TABLE 3. Illness Duration, Past Hospitalization, Inpatient Symptomatology Level, and Demographic Characteristics of Recent-Onset Schizophrenic Patients From Families With High vs. Low Expressed Emotion

Background Factor	High EE ($n = 19$) *M* (*SD*)	Low EE ($n = 7$) *M* (*SD*)	*t*	*p*
Total months of illness, including prodromal period	12.3 (9.9)	14.7 (5.9)	−.60	NS
Total weeks of hospitalization including index hospitalization	6.2 (3.7)	4.3 3.9)	1.14	NS
Number of previous hospitalizations	0.4 (0.8)	0.3 (0.5)	.40	NS
Inpatient BPRS total psychopathology score (18 scales)	31.9 (7.3)	33.0 (7.2)	−.34	NS
Age (years)	22.2 (2.7)	23.6 (4.9)	−.69	NS
Educational level (years)	11.9 (1.8)	12.6 (2.1)	−.81	NS
Sex	14 M, 6 F	5 M, 1 F	.45^a	NS
Hollingshead-Redlich social class (rearing family)	2.8 (1.4)	3.3 (1.1)	−.74	NS

^{a}Likelihood ratio χ^2.

educational level, patient sex, or rearing-family socioeconomic status. The direction of these nonsignificant differences is as would be expected by this familial reactivity hypothesis for total duration of hospitalization, but not for total length of illness. Thus, although these relationships will need to be re-examined as the sample size increases in this ongoing project, these data offer no support for the view that family EE may be a reaction to duration of experience with the patient's illness or severity of inpatient symptomatology.

Discussion

Consistent with a vulnerability/stress model of schizophrenic psychotic relapses (Nuechterlein & Dawson, 1984), the EE level of the family environment is a significant predictor of psychotic relapse during a 1-year period of maintenance on standardized, fixed-dose fluphenazine decanoate within this ongoing study of patients who have had a recent onset of schizophrenic disorder. The presence of a significant predictive role for familial EE despite standardization and guaranteed administration of antipsychotic medication indicates that results from earlier naturalistic studies (Brown et al., 1962; Brown et al., 1972; Vaughn & Leff, 1976a; Vaughn et al., 1984) were not due to the lack of experimental control over medication administration. The 1-year relapse rates of 37 percent and 0 percent for schizophrenic patients from high EE and low EE family environments, respectively, are in the same range as would be expected from the data of Brown et al. (1972), Vaughn and Leff (1976a), and Vaughn et al. (1984) for patients who were judged to have maintained regular outpatient antipsychotic medication.

The results also indicate that the predictive role of relatives' EE is not limited to chronic schizophrenic patients, because the present sample contains only patients whose psychosis developed relatively shortly before entry into the study. In 22 of 26 cases, the index period was the first psychotic episode. Furthermore, the lack of association between relatives' EE level and length of patient's illness (including prodromal period), number of previous hospitalizations, and total length of hospitalization indicates that any residual differences in these factors among patients within this sample do not account for these familial attitudes and behaviors. Similarly, familial EE level is not associated with overall severity of inpatient symptomatology. Thus, although these data do not demonstrate directly that familial EE level has a causal influence on psychotic relapse, the predictive relationship between EE level and psychotic relapse in these data cannot be explained by an association between EE level and the patient attributes examined here.

The focus on recent-onset schizophrenic patients is shared with another current study of EE and relapse by MacMillan, Gold, Crow, Johnson and Johnstone (1986), in which statistically significant predictive effects of familial EE were found before, but not after, treatment. Duration of illness preceding admission and neuroleptic treatment following discharge were employed as covariates. The present study differs from that study in at least three important ways. First, standardized, injectable medication was employed to provide better control over medication conditions, including dosage and compliance assessment. Second, objective, quantitative criteria for psychotic relapse, applied in a uniform way based on symptom ratings by trained research staff with demonstrated interrater reliability, were used to define relapse. For their statistical analyses, MacMillan et al. (1986) defined relapse by less specific criteria of clinically judged relapse that did not demand presence of psychotic symptoms, that emphasized instead the need for hospital readmission, and that were applied by the responsible clinician in multiple participating hospitals. Finally, assessment of family EE in the present study involved all relatives with whom the patient had a significant amount of contact, rather than assessment of a single relative as was employed in all but six cases by MacMillan et al. (1986). Assessment of all key relatives should yield much more accurate determination of familial EE level, because presence of any relative who is rated above the individual scale cutoff points leads to classification of the family environment as high in EE (Leff & Vaughn, 1985). These factors may explain the stronger predictive relationship between EE level and relapse in the present study than in the MacMillan et al. (1986) report.

References

American Psychiatric Association. *DSM–III: Diagnostic and Statistical Manual of Mental Disorders.* 3d ed. Washington, DC: The Association, 1980.

Brown, G.W., Birley, J.L.T., and Wing, J.K. Influence of family life on the course of schizophrenic disorders: A replication. *Br. J. Psychiatry,* 121:241–258, 1972.

Brown, G.W., Monck, E.M., Carstairs, G.M., and Wing, J.K. Influence of family life on the course of schizophrenic illness. *Br. J. Prev. Soc. Med.,* 16:55–68, 1962.

Brown, G.W., and Rutter, M. The measurement of family activities and relationships: A methodological study. *Human Relations,* 19:241–263, 1966.

Davis, J.M. Maintenance therapy and the natural course of schizophrenia. *J. Clin. Psychiatry,* 11:18–21, 1985.

Hays, W.L. *Statistics for the Social Sciences.* (2nd ed.). New York: Holt, Rinehart, and Winston, Inc., 1973.

Hogarty, G.E., Goldberg, S.C., and the Collaborative Study Group. Drug and sociotherapy in the aftercare of schizophrenic patients: One-year relapse rates. *Arch. Gen. Psychiatry,* 28:54–64, 1973.

Hogarty, G.E., Schooler, N.R., Ulrich, R.F., et al. Fluphenazine and social therapy in the aftercare of schizophrenic patients. *Arch. Gen. Psychiatry,* 36:1283–1294, 1979.

Krawiecka, M., Goldberg, D., and Vaughn, M. A standardized psychiatric assessment scale for rating chronic psychotic patients. *Acta Psychiatr. Scand.,* 55:299–308, 1977.

Leff, J., and Vaughn, C. The role of maintenance therapy and relatives' expressed emotion in relapse of schizophrenia: A two-year follow-up. *Br. J. Psychiatry,* 139:102–104, 1981.

Leff, J., and Vaughn, C. *Expressed Emotion in Families.* New York: Guilford Press, 1985.

Leff, J.P., and Wing, J.K. Trial of maintenance therapy in schizophrenia. *Br. Med. J.,* 3:599-604, 1971.

MacMillan, J.F., Gold, A., Crow, T.J., et al. The Northwick Park Study of first episodes of schizophrenia. IV. Expressed emotion and relapse. *Br. J. Psychiatry,* 148:133–143, 1986.

Nuechterlein, K.H., and Dawson, M.E. A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin,* 10:300–312, 1984.

Nuechterlein, K.H., Miklowitz, D.J., and Ventura, J. "Manual for Assessing Outcome in Schizophrenic and Bipolar-Manic Patients." Unpublished manuscript, 1985.

Overall, J.E., and Gorham, D.R. The brief psychiatric rating scale. *Psychol. Rep.,* 10:799–812, 1962.

Rifkin, A., Quitkin, F., Rabiner, C.J., and Klein, D.F. Fluphenazine decanoate, fluphenazine hydrochloride given orally, and placebo in remitted schizophrenics. I. Relapse rates after one year. *Arch. Gen. Psychiatry,* 34:43–47, 1977.

Rutter, M., and Brown, G.W. The reliability and validity of measures of family life and relationships in families containing a psychiatric patient. *Soc. Psychiatry,* 1:38–53, 1966.

Spitzer, R.L., Endicott, J., and Robins, E. Research Diagnostic Criteria: Rationale and reliability. *Arch. Gen. Psychiatry,* 35:773–782, 1978.

Vaughn, C.E., and Leff, J.P. The influence of family and social factors on the course of psychiatric illness: A comparison of schizophrenic and depressed neurotic patients. *Br. J. Psychiatry,* 129:125–137, 1976a.

Vaughn, C.E., and Leff, J.P. The measurement of expressed emotion in the families of psychiatric patients. *Br. J. Soc. Clin. Psychol.,* 15:157–165, 1976b.

Vaughn, C.E., Snyder, K.S., Jones, S., et al. Family factors in schizophrenic relapse: Replication in California of British research on expressed emotion. *Arch. Gen. Psychiatry,* 41:1169–1177, 1984.

Wing, J.K., Cooper, J.E., and Sartorius, N. *The Measurement and Classification of Psychiatric Symptoms: An Instruction Manual for the PSE and Catego Program.* London: Cambridge University Press, 1974.

best copy available

The Benzodiazepine/GABA Receptor: From Molecular Structure to Function in Man

Chair:

Steven M. Paul, M.D. *National Institute of Mental Health*
Bethesda, MD 20896

Molecular Aspects of Benzodiazepine Receptor Function

Paul Sweetnam, Ph.D.[1]
Peter Gallombardo, M.A.[1] and
John Tallman, Ph.D.[1]

The benzodiazepines (BDZ) are among the most widely prescribed drugs in the world today. While the clinical importance of these drugs is unquestioned, the molecular interactions underlying their effects are not fully characterized. Over the past 20 years, a number of possible mechanisms of action have been proposed (Costa & Greengard, 1975) and have been reviewed (Tallman et al.). Today with the rapid advances in biochemistry, immunology, and genetics these mechanisms will be more rigorously investigated. This should ultimately lead to an increased understanding of the molecular aspects of BDZ function.

The existence of a high affinity binding site in brain tissue for the BDZs was first documented in 1977 (Squires & Braestrup, 1977). These sites show all of the properties ascribed to other pharmacological receptors including binding that is rapid, reversible, stereospecific, and saturable. Studies in animals and man have shown a high correlation between binding ability and the potency of benzodiazepines as anxiolytics and anticonvulsants (Braestrup & Squires, 1978).

In 1978, Tallman and others (Tallman et al., 1978) showed that BDZ agonist binding is enhanced by γ-aminobutyric acid (GABA), the major inhibitory-neurotransmitter in the brain. This phenomenon of allosteric facilitation of BDZ binding, the "GABA shift," and the known electrophysiological interaction of BDZ with GABA suggests a close physical association between the BDZ and GABA receptors. It now appears likely that a supramolecular complex exists composed of the BDZ receptor, the GABA$_A$ receptor, the chloride channel, and the picrotoxin/barbiturate binding site (Figure 1) (Olsen, 1981).

BDZ agonists function within the complex to increase the efficacy of GABA, thus facilitating the inhibitory actions of GABA. This binding interaction can be inferred from the GABA shift, and has proven useful in the classification of BDZ receptor ligands. The BDZ antagonist, Ro15-1788, shows little GABA shift. Ro15-1788 is pharmacologically inactive but it can reverse the sedative and anticonvulsant actions of BDZ agonists. In contrast, inverse agonists, such as the β-carbolines, show decreased binding in the presence of GABA (Braestrup & Nielson, 1981). These compounds are anxiogenic and proconvulsant. Partial agonists, such as the

---

[1] Yale University School of Medicine, Department of Psychiatry, Connecticut Mental Health Center of Abraham Ribicoff Research Facilities, 34 Park Street, New Haven, CT 06508.

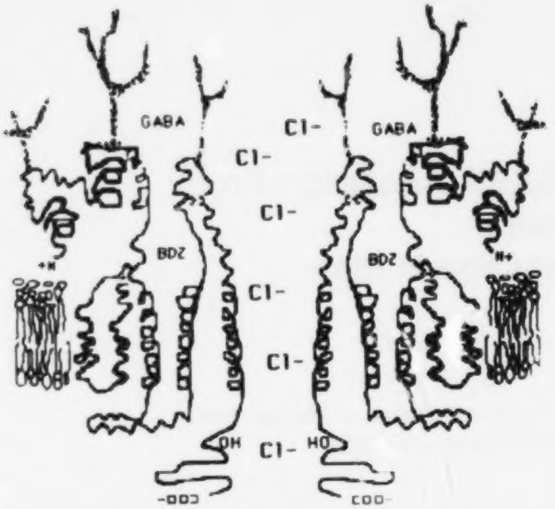


FIGURE 1. Hypothetical conformation of the GABA$_A$ complex in a neuronal cell membrane. This proposed model suggests that the GABA and benzodiazepine (BDZ) receptor proteins may form part of the chloride (Cl$^-$) anion channel. The proteins of the complex also appear to be glycosylated. These carbohydrate moieties may serve an important role in neuronal development and also alter ligand/receptor interactions.

triazolopyridazines, exhibit only a small GABA shift. These different interactions between BDZ ligand binding and GABA further support the notion that the two receptors are closely coupled.

In 1980 Mohler discovered that certain benzodiazepines with a nitro group in the 7 position could act as photoaffinity labeling reagents. Upon exposure to ultraviolet light these compounds become covalently linked to the BDZ receptor (Mohler et al., 1980). Photolabeling studies of membrane bound BDZ receptors revealed that for every receptor labeled, four agonist binding sites are converted to a very low affinity state (Thomas & Tallman, 1983). This study, and radiation inactivation studies (Braestrup, 1985) suggest that the stoichiometry of GABA and BDZ receptors is more complicated than a one to one pairing. The ability to incorporate a radiolabeled BDZ into the receptor has afforded a simple and sensitive method for monitoring biochemical manipulations and purification of the receptor.

By photolabeling membranes prior to discontinuous SDS gel electrophoresis it is possible to obtain differential labeling of proteins in various brain regions (Thomas & Tallman, 1981; Sieghart & Karobath, 1980). All investigators have demonstrated the labeling of a 50K protein; and some studies have also labeled higher molecular-weight species. The labeling of these higher molecular-weight species varies between brain regions. Attempts have been made to correlate this regional distribution with the pharmacological differences between BDZ agonists (Sieghart et al., 1983). Recently immunochemical staining using monoclonal antibodies directed against the BDZ receptor has shown a homogeneous distribution of these higher molecular-weight species (Haring et al., 1985).

Our group and others have been able to purify the BDZ receptor to near homogeneity. The receptor is initially solubilized from brain tissue with the detergent Lubrol-PX. The binding kinetics of the solubilized receptor indicate a relatively intact active site (Yousufi et al., 1979). After the solubilization the receptor is then affinity purified on an agarose matrix containing bound Ro7-1986, a BDZ agonist (Tallman & Gallager, 1979). Recovery of the receptor from the affinity gel is accomplished by a competitive ligand elution using 10^{-5}M flurazepam. High receptor yields utilizing this type of affinity elution require that an agarose bead with a long spacer arm be used for coupling. At present, the use of a 15 carbon spacer arm with a cationic charge appears to allow for the most efficient receptor recovery. The receptor after purification has a molecular weight of 50,000 and like the soluble receptor has an intact active site which can be photolabeled.

Enzymatic manipulation of the receptor has been made possible by the production of purified proteolytic and glycosidic enzymes that reliably cleave specific peptide bonds and glycosidic linkages. Subjecting photolabeled receptors to proteolytic digestion has resulted in the purification of a single limiting peptide bearing the radioligand tag (Klotz et al., 1984). Because this peptide contains the radioligand it seems probable that it also contains the agonist binding domain. Sequencing this peptide should yield valuable information about the origins of the BDZ receptor. This information could also be used to construct a genetic probe that would lead to furthering our knowledge of the molecular biology of the BDZ receptor.

The BDZ receptor, like many cell surface proteins, is heavily glycosylated. Exposure of the receptor to the glycosidases neuraminidase and endoglycosidase H specifically removes sialic acids and asparagine linked carbohydrates, respectively. This treatment reduces the apparent molecular weight of the receptor from all brain regions. However, the reduction was not uniform across all regions suggesting regional differences in post translational glycosylation. Deglycosylation also alters the apparent number of agonist and antagonist binding sites (Table 1) (Sweetnam & Tallman, 1986).

Recently our laboratory has developed monoclonal antibodies directed against the BDZ receptor. These antibodies were initially developed in mice inoculated with affinity purified BDZ receptor. Spleen cells from these mice were fused with myeloma cells to create hybridoma cells. After cloning, individual clones were injected into the peritoneum of syngenic mice for the production of ascites fluid.

Six monoclonal antibodies (mAb) have been developed. The specificity of these mAb's has been confirmed by immunoblotting them to BDZ receptor immobilized on nitrocellulose after SDS electrophoresis. The results demonstrate that the 50K protein is the major protein recognized by these mAb's (Figure 2). Currently we are immunoblotting mAb's to proteins from separate brain regions, in order to identify heterogeneous receptor regions.

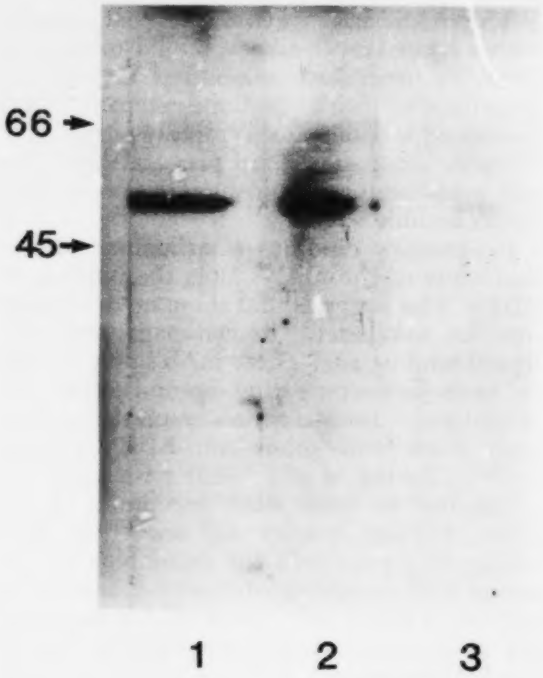


FIGURE 2. Immunoblotting monoclonal antibody 6BE9 onto a purified BDZ receptor preparation. Following separation with SDS/polyacrylamide gel, electrophoresis proteins were electrophoretically transferred to a sheet of nitrocellulose. The sheet was washed for 30 min in phosphate buffered saline containing 0.05% Tween-20 to block further binding of protein to the nitrocellulose. The sheet was cut into strips and each strip was incubated with monoclonal antibody in PBS/Tween or buffer alone (control) overnight at 4°C. The strips were washed and incubated in ^{125}I-labeled antibody to mouse IgG for 1 hr at room temperature. The strips were washed again, dried, and prepared for autoradiography. (1) monoclonal 6BE9 diluted 1:1000 (2) monoclonal 6BE9 diluted 1:100 (3) control strip incubated without monoclonal.

TABLE 1. The Effects of Glycosidase Treatment on Brain Region Specific Benzodiazepine Receptors.

Brain Region	Glycosidase Treatment	Molecular Weight	Agonist		Antagonist	
			K_D	B_{max}	K_D	B_{max}
Cortex	Control	50 K	3.2	535	1.7	520
	Endo-H	40 K	4.7	290	1.1	919
	Neur-Ase	42 K	5.2	250	1.2	840
Cerebellum	Control	50 K	3.9	143	2.9	180
	Endo-H	46 K	4.7	135	2.6	260
	Neur-Ase	50 K	5.2	104	2.1	215

Note. These data suggest a brain regional heterogeneity in carbohydrate moieties as indicated by differing molecular weight changes following enzyme treatment and by the differing Scatchard analysis (K_D expressed as nM and B_{max} as fmol/10 mg tissue).

The mAb's have been used in conjunction with a secondary antibody bound to agarose beads to precipitate solubilized membranes photolabeled with ^{3}H-flunitrazepam. This technique will allow us to rapidly purify BDZ receptor from solubilized preparations. This will make sensitive phosphorylation experiments feasible.

Preliminary binding experiments indicate that some of the mAb's alter the binding of BDZ's. This suggests that these mAb's recognize an antigenetic determinant near the ligand binding site. These mAb's may be useful tools for investigating ligand-receptor interactions. Immunohistochemical studies with these and other anti-BDZ receptor mAb's (Haring et al., 1985) have used the antibodies to stain BDZ receptors in the brain. Further studies will use these antibodies to screen cells for recombinantly inserted BDZ receptors. Monoclonal antibodies will play a major role in elucidating the pharmacology, anatomy, and molecular biology of the BDZ receptor.

Our knowledge of the molecular aspects of the benzodiazepine receptor function is incomplete. The experimental approaches mentioned briefly in this review will make it possible to study the benzodiazepine ligand/receptor interaction at a level which can help us to understand how benzodiazepines induce specific changes in the GABA$_A$ complex and how these changes result in the manifestation of the drugs' actions in the central nervous system. This knowledge will aid in the design of specific drugs to treat anxiety free of unwanted side effects or tolerance. In the future, benzodiazepine receptor research at the molecular level could help define the neurochemical etiology of anxiety.

Acknowledgments

Work funded by NIMH Grant MH 38813 and the State of Connecticut, Abraham Ribicoff Facilities.

References

Braestrup, C. Symposium. Molecular Insights Into GABA-Receptor Function. *Soc. for Neurosci.*, 11:Abstr. 277 (1985).

Braestrup C., and Nielson, M. GABA reduces binding of 3H-methyl beta-carboline-3-carboxylate to brain benzodiazepine receptors. *Nature*, 294:472–474 (1981).

Braestrup, C., and Squires, R.F. Pharmacological characterization of benzodiazepine receptors in the brain. *Eur. J. Pharmacol.*, 48:263–270 (1978).

Costa, E., and Greengard, P. *Advances in Biochemical Psychopharmacology*. Vol. 14. New York: Raven Press, 1975.

Costa, T., Rodbard, D., and Pert, C.B. Is the benzodiazepine receptor coupled to a chloride anion channel? *Nature*, 277:315–317 (1979).

Haring, P., Stahli, C., Schoch, P., Takaos, B., and Mohler, H. Monoclonal antibodies reveal structural homogeneity of gamma-aminobutyric acid/benzodiazepine receptors in different brain areas. *Proc. Natl. Acad. Sci. USA*, 82:4837–4841 (1985).

Klotz, K.L., Bocchetta, A., Neale, J., Thomas, J.W., and Tallman, J.F. Proteolytic degradation of neuronal benzodiazepine binding sites. *Life Sci.*, 34:293–299 (1984).

Mohler, H., Battersby, M.K., and Richards, J.G. Benzodiazepine receptor protein identified and visualized in brain tissue by a photo-affinity label. *Proc. Natl. Acad. Sci. USA*, 77:1666–1670 (1980).

Mohler, H., and Okada, Ta. Benzodiazepine receptor: Demonstration in the central nervous system. *Science*, 198:849–851 (1977).

Olsen, R.W. GABA-benzodiazepine-barbiturate receptor interactions. *J. Neurochem.*, 37:1–13 (1981).

Sieghart, W., and Karobath, M. Molecular heterogeneity of benzodiazepine receptors. *Nature*, 286:285–287 (1980).

Sieghart, W., Mayer, A., and Drexler, G. Properties of [3H] flunitrazepam binding to different benzodiazepine binding proteins. *Eur. J. Pharmacol.*, 88:291-299 (1983).

Squires, R.F., and Braestrup, C. Benzodiazepine receptors in rat brain. *Nature*, 266:732–734 (1977).

Sweetnam, P.M., and Tallman, J.F. Regional difference in brain benzodiazepine receptor carbohydrates. *Mol. Pharm.*, 29:299–306, 1986.

Tallman, J.F., and Gallager, D.W. Modulation of benzodiazepine binding site sensitivity. *Pharmacol. Biochem. Behav.*, 10:809–813 (1979).

Tallman, J.F., Paul, S.M., Skolnick, P., and Gallager, D.W. Receptors for the age of anxiety: Pharmacology of the benzodiazepines. *Science*, 207:274–281 (1980).

Tallman, J.F., Thomas, J.W., and Gallager, D.W. GABAergic modulation of benzodiazepine binding site sensitivity. *Nature*, 274:383–385 (1978).

Thomas, J.W., and Tallman, J.F. Characterization of photoaffinity labeling of benzodiazepine binding sites. *J. Biol. Chem.*, 256:9838–9842 (1981).

Thomas, J.W., and Tallman, J.F. Photoaffinity labeling of benzodiazepine receptors causes altered agonist-antagonist interactions. *J. Neurosci.*, 3:433–440 (1983).

Yousufi, M., Thomas, J.W. and Tallman, J.F. Solubilization of benzodiazepine binding site from rat cortex. *Life Sci.* 25:463–469 (1979).

Neurochemical Correlates of Suicide

Co-Chairs:

Michael J. Stanley, Ph.D.

Department of Psychiatry
New York State Psychiatric Institute
New York, NY 10032

J. John Mann, M.D.

New York Hospital
Cornell Medical Center
New York, NY 10021

Postmortem Serotonergic and Adrenergic Receptor Binding to Frontal Cortex: Correlations With Suicide

J. John Mann, M.D.,[1,2] P. Anne McBride, M.D.,[1] and Michael Stanley, Ph.D.[3]

The demonstration that receptor binding studies are feasible in human postmortem brain tissue (Mann et al., 1986) permitted another approach to the evaluation of the functional status of monoaminergic systems in the human central nervous system. In earlier postmortem studies (Shaw et al., 1967; Pare et al., 1969; Beskow et al., 1976; Bourne et al., 1968; Lloyd et al., 1974), levels of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were found to be slightly lower in the brainstem of suicide victims compared to controls. However other studies failed to find any alteration in 5-HT or 5-HIAA levels in frontal cortex (Stanley & Mann, 1983) and one study (Cooper et al., in press) reported increased 5-HIAA levels in hippocampus (although postmortem delays were significantly longer in this study). Results from studies (Mann et al., in press) of levels of 5-HIAA in cerebrospinal fluid (CSF) have more consistently demonstrated lower levels in suicide attempters compared to controls. Furthermore violent suicide attempts were more strongly associated with lower levels of CSF 5-HIAA than nonviolent attempts.

Postsynaptic receptor sensitivity generally bears a reciprocal relationship with levels of transmitter exposure. Hence, up- or down-regulation of postsynaptic receptors relative to control values permits inferences to be drawn regarding the presence of reduced or increased presynaptic activity, respectively. Moreover, absolute levels of transmitter or metabolite may be a poor guide to functional status because much of the transmitter may be located in a storage pool not readily available for synaptic release and there may be rapid fluctuations in transmitter turnover during the agonal process. We therefore undertook a study of postsynaptic monoamine receptor binding in the frontal cortex of suicide victims compared to matched controls to assess the functional status of the serotonergic and noradrenergic systems.

---

[1] Laboratory of Psychopharmacology, Department of Psychiatry, Cornell University Medical College, 1300 York Avenue, New York, NY 10021.

[2] Address all correspondence to Dr. Mann.

[3] Department of Psychiatry, Columbia College of Physicians and Surgeons, New York, NY 10032.

Methods and Subjects

Samples were collected from suicide victims who had died by nonpharmacological means and from controls matched for age, gender ratio, postmortem delay, and violence of death. Beta-adrenergic receptors were assayed using ^{3}H-dihydroalprenolol (DHA) and ^{125}I-iodopindolol (PIN). Serotonin-2 receptors (5-HT$_2$) were assayed using ^{3}H-spiroperidol and 1 μM ketanserin to define specific binding. Details of brain collection, storage, dissection, and assays have been described elsewhere (Mann et al., 1986).

Results

A statistically significant 28 percent increase was found in the number of 5-HT receptor (B_{max}) in frontal cortex (Brodmann's area 9) of the suicide group. No differences were found in binding affinity (K_D). Beta-adrenergic binding in suicide victims was increased 78 percent over control values ($p < 0.05$, 2-tailed t test). Beta-adrenergic agonist binding was assessed using ^{125}I-iodopindolol as a ligand and 1 μM isoproterenol. Agonist binding, particularly high affinity agonist binding, is a more sensitive indicator of functionally relevant changes in receptor binding. Both overall beta-adrenergic binding and high affinity agonist binding were increased in tissue pooled from a subgroup of three subjects in the suicide victims compared to three controls.

Discussion

Two other laboratories have assessed 5-HT$_2$ binding in suicide victims and depressed patients. Cooper et al. (in press) found no change in 5-HT$_2$ binding in a series of suicide victims; however, most of these patients were on either antipsychotics or antidepressants which would have lowered 5-HT$_2$ binding. Moreover the postmortem interval was over twice as long as in our study and no saturation binding isotherms were carried out—resulting in reduced accuracy of assay results as well as providing less information regarding binding kinetics. In contrast, Ferrier et al. (in press) controlled for the effects of medication and found a trend for an increase in 5-HT$_2$ binding in the frontal cortex of depressed patients.

Beta-adrenergic binding has been studied by three laboratories. In agreement with our results Zanko and Biegon (1983) reported an increase in B_{max} and no change in K_D in several brain regions in suicide victims. Meyerson et al. (1982) found no change in ^{3}H-DHA binding, but this study did not involve well-matched controls in terms of age, postmortem delay, or method of death. Ferrier et al. (in press) found no change in beta-adrenergic binding in a series of patients dying with a history of MDD.

Our findings indicate upregulation of both 5-HT$_2$ and beta-adrenergic binding. These results would be consistent with reduced serotonergic and noradrenergic transmission. Data from CSF studies, neuroendocrine challenge tests, and assay of 5-HT and 5-HIAA in brainstem generally indicate reduced serotonergic function that would explain upregulation of the postsynaptic 5-HT$_2$ receptors in suicide victims (Mann et al., in press). There are few data regarding noradrenergic indices in suicide and these are inconclusive (Mann et al., in press). Future studies must examine the status of the noradrenergic system in conjunction with the serotonergic system in this condition and should address their correlations with suicide separately from those with depressive illnesses.

Antidepressant drugs downregulate beta-adrenergic and/or 5-HT$_2$ receptors in animal studies after chronic but not acute administration. This effect is in the opposite direction to that observed in suicide victims. Therefore, it may be hypothesized that the antidepressant *and* antisuicidal action of these drugs is mediated via one or both of these receptor populations. This hypothesis may be tested by prospective controlled studies of antidepressants in suicidal patients who are suffering from a psychiatric disorder other than a major depressive disorder. Studies of brain samples from patients on antidepressants antemortem will enable evaluation of the effect of antidepressant treatment on monoamine receptors in patients since findings in animals are not necessarily generalizable to the brain of depressed patients.

Acknowledgments

The technical assistance of Ms. Joanie Chin and typing of Ms. Isadora Johnson and Mary Ruth Goodley are acknowledged. This work was supported by PHS grant MH40210 and an Irma T. Hirschl Research Scientist Award to Dr. Mann.

References

Beskow, J., Gottfries, C.G., Roos, B.E., et al. Determination of monoamine and monoamine metabolites in the human brain: postmortem studies in a group of suicides and in a control group. *Acta Psychiatrica. Scand.*, 53:7–20, 1976.

Bourne, H.R., Bunney, W.E., Colburn, R.W., et al. Noradrenaline, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid in hindbrains of suicidal patients. *Lancet*, ii:805–808, 1968.

Cooper, S.J., Owen, F., Chambers, D.R., et al. Postmortem neurochemical findings in suicide victims and depression: a study of the serotonergic system and imipramine binding in suicide victims. *Brit. J. Psychiatry* (in press).

Ferrier, I.N., McKeith, I.G., Cross, A.J., et al. Postmortem neurochemical studies in depression. *Ann. N.Y. Acad. Sci.* (In press.)

Lloyd, K.G., Farley, I.J., Deck, J.H.N., et al. Serotonin and 5-hydroxyindoleacetic acid in descrete areas of the brain stem of suicide victims and control patients. *Adv. Biochem.*, II:387–398, 1974.

Mann, J.J., McBride, P.A., and Stanley, M. Aminergic receptor binding correlates of suicide: Methodological issues. *Psychopharmacology Bulletin*, 22(3):741–743, 1986.

Mann, J.J., Stanley, M., McEwen, B.S., and McBride, P.A. Postmortem studies of central nervous system adrenergic and serotonergic receptors in suicide victims. *Ann. N.Y. Acad. Sci.* (In press.)

Meyerson, L.R., Wennogle, L.P., Abel, M.S., et al. Human brain receptor alterations in suicide victims. *Pharmacol. Biochem. Behavior*, 17:159–163, 1982.

Pare, C.M.B., Young, D.P.H., Price, K., et al. 5-Hydroxytryptamine, noradrenaline, and dopamine in brain stem, hypothalamus and caudate nucleus of controls and patients committing suicide by coal-gas poisoning. *Lancet*, ii:133–135, 1969.

Shaw, D.M., Camps, E.F., and Eccleston, E.G. 5-Hydroxytryptamine in the hindbrain of depressive suicides. *Brit. J. Psychiatry*, 113:1407–1411, 1967.

Stanley, M., and Mann, J.J. Serotonin-2 binding sites are increased in the frontal cortex of suicide victims. *Lancet*, i:214–216, 1983.

Zanko, M.T., and Biegon, A. Increased β-adrenergic receptor binding in human frontal cortex of suicide victims. Abstract, Annual Meeting, Society for Neuroscience, Boston (1983), p. 719.

Suicide and Adrenocortical Function

James H. Kocsis, M.D.,[1] Sara Kennedy, M.D.,[1] Richard P. Brown, M.D.,[1] J. John Mann, M.D.,[1] and Barbara Mason, Ph.D.[1]

Twenty years ago Bunney and Fawcett reported that elevation of urinary 17-hydroxycorticoids was a specific test for prediction of future suicidal behavior in depressed patients who did not communicate suicidal intent (Bunney & Fawcett, 1965).

Several subsequent studies have examined relationships between abnormalities of the hypothalamic-pituitary-adrenocortical (HPA) axis and occurrence of suicide attempts and the results are summarized in Table 1. Three investigations have found elevated levels of 24-hour urinary 17-hydroxycorticosteroids or urinary free cortisol in patients who had been severely suicidal or who later completed suicide (Bunney & Fawcett, 1965; Bunney et al., 1969; Ostroff et al., 1982) although two other studies involving small numbers of subjects have not confirmed this (Levy & Hansen, 1969; Krieger, 1970). Investigations of relationships between suicidal behavior and plasma cortisol levels, both before and after administration of dexamethasone, have mostly found higher rates of non-suppression on the Dexamethasone Suppression Test (DST) in patients who have attempted or completed suicide compared to non-suicide attempters (Carroll et al., 1981; Coryell & Schlesser, 1981; Targum et al., 1983; Banki & Arato, 1983).

Only one study to date has assessed the relationship between cerebrospinal fluid (CSF) cortisol and suicidal behavior (Traskman et al., 1980). Increased CSF cortisol levels were found in depressed patients; however, levels in depressed patients who had made a suicide attempt were not significantly higher than depressed non-attempters. Normal CSF cortisol values were present in non-depressed suicide attempters.

The purpose of the current report is to summarize results of two additional investigations (Secunda et al., in press; Brown et al., unpublished) of relationships between suicidal behavior and HPA function, to relate these findings to results of prior studies and to discuss practical and theoretical implications.

TABLE 1. Studies of Suicide and Adrenal Activity.

Authors	Year	*N* in Suicide Group (Completers)	Diagnosis	Measure	Association
Bunney and Fawcett	1965	3(3)	Depressed	U17–OHCS	Significant
Levy and Hansen	1969	2(2)	Mixed	U17–OHCS	No
Bunney et al.	1969	9(9)	Mixed	U17–OHCS	Significant
Krieger	1970	6(6)	Mixed	U17–OHCS	Trend
Traskman et al.	1980	12(0)		Morning plasma cortisol	Trend
			Depressed		No
			Mixed	CSF Cortisol	No
Carroll et al.	1981	5(5)	Depressed	DST	Significant
Coryell and Schlesser	1981	4(4)	Depressed	DST	Trend
Ostroff et al.	1982	3(2)	Mixed	UFC	Significant
Targum et al.	1983	17(0)	Depressed	DST	Significant
Banki and Arato	1983	14(0)	Mixed	DST	Trend

---

[1] Department of Psychiatry, New York Hospital—Cornell Medical Center, 525 East 68th Street, New York, NY 10021.

NIMH Study Methods

One hundred thirty-two hospitalized patients with a diagnosis of Major Depressive Disorder as determined by the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer & Endicott, 1978) and the Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) were selected for inclusion in the NIMH-Clinical Research Branch Collaborative Study—Biology of Depression. Eighty-five were classified as unipolar depressives and forty-seven as bipolar depressives. Patients were admitted to one of six university hospital centers participating in the Collaborative Study between 1975–80. Full details about the rationale and methods of the study have been published. (Maas et al., 1980; Secunda et al., 1980).

Specific SADS items were used to assess suicidal thoughts and the number, seriousness, and lethality of previous suicide attempts during the current episode. On the basis of SADS data, patients were assigned to one of three groups: (1) a suicide attempter group (SA), defined as those patients who had made at least one suicide attempt during the current episode which could be considered significant with regard to the seriousness of its intent and/or its medical lethality; (2) a non-attempter group (NA), defined as those patients with no history of suicide attempts for either the current or past episodes; and (3) an unclassified group (UC) consisting of patients who had made a suicide attempt during the current episode which did not meet the established "significant" criteria and patients who had a history of suicide attempts during prior episodes. Except where noted, the UC group was excluded from data analyses. Severity of depression was assessed using the Hamilton Depression Rating Scale (HRS-D) and the Global Assessment of Severity (Endicott et al., 1976), a measure of coping mechanism and degree of impairment.

Within 2 weeks of admission three successive morning and one evening plasma cortisol levels, 24-hour urine collection for urinary free cortisol, and a CSF cortisol level were obtained. Subsequently, 1 mg of dexamethasone was given orally in liquid solution, under observation of a nurse at 10:40 p.m. The following day, post-DST plasma cortisol levels were obtained at 8:30 a.m., 4 p.m., and 10 p.m. During the 24-hour period following dexamethasone administration, urine was collected to measure urinary cortisol. DST nonsuppression was defined as an a.m. post-dexamethasone plasma cortisol of 5 μg/dl or more. Urine free cortisol hypersecretion was defined as more than 133 mg/24 hour (Stokes et al., 1984).

Cornell Study Methods

Sixty-six inpatients, who participated in depression research protocols on the clinical research unit at the Payne Whitney Psychiatric Clinic during 1982–84 and also met *DSM-III* criteria for primary Major Depressive Disorder (American Psychiatric Association, 1980), were included. Patients were categorized as attempters if a suicide attempt requiring medical intervention or hospitalization had been made within 4 weeks prior to hospitalization. Ten patients had a past history but no recent history of suicide attempts, and were dropped from the analysis. A further evaluation of suicidal ideation was completed at the time of the administration of dexamethasone and at the time of drawing cortisol levels. Severity of depression was assessed using the HRS-D. Blood samples were collected at 9 a.m. and 4 p.m. on the day before and the day after administration of 1 mg of dexamethasone orally at 11 p.m. under observation by a nurse. DST nonsuppression was defined as either the 9 a.m. or 4 p.m. plasma cortisol greater than 5 μg/dl (Brown et al., unpublished).

No patient in either sample had major medical illnesses or was taking medication known to affect cortisol levels or DST results. Patients were not treated with antidepressant medication until after cortisol measures were obtained. CSF plasma and urinary free cortisol for both studies were measured in one laboratory by radioimmunoassay by methods previously described in detail (Stokes et al., 1984).

Results from the NIMH Study

The demographic and clinical characteristics of the suicide attempters and non-attempters have been reported (Secunda et al., in press). No differences were found with regard to sex, polarity, duration of current episode, number of previous episodes, presence of psychotic features, or recovery status. Suicide attempters were significantly younger and had an earlier age at onset than non-attempters. Non-attempters showed more depressive symptoms, higher levels of anxiety, agitation, and somatization and greater psychomotor retardation than did the suicide attempter group.

Analyses of covariance performed on the various HPA measures revealed few differences between the attempter and non-attempter group (Table 2). Among the plasma, CSF, and urinary cortisol comparisons made, only the pre-DST evening plasma cortisol sample was significantly different, being lower in the suicide attempter group. The results of statistical analyses performed on the post-DST plasma cortisol levels (i.e., suppressors versus non-suppressors) and on urine free cortisol hypersecreters versus normal secreters did not reveal significant differences between attempters and non-attempters (see Table 2).

Pearson product moment correlations between the HPA variables and scores on the SADS Suicidal Ideation and Behavior Scale and the individual items which comprise the scale were performed on the entire depressed population (including the UC group). None of these achieved the .05 level of significance.

Results from the Cornell Study

The mean age of attempters was 63 ± 11 (SD) and of non-attempters was 61 ± 14. Female:male ratios were approximately two to one for attempters and non-attempters. Baseline mean HRS-D scores were 34 ± 11 for attempters and 32 ± 9 for non-attempters. None of these differences were significant.

Morning and evening cortisol levels before and after dexamethasone did not differ significantly between groups (Table 3). There was also no significant difference between attempters and non-attempters in frequency of cortisol suppression in the morning or afternoon following dexamethasone. Furthermore, no significant differences were found in cortisol levels between those patient groups rated as currently having active suicidal intent, passive suicidal ideation, or no suicidal ideation.

Correlations among cortisol levels and other variables possibly related to suicidality were also calculated. Significant positive correlations included the following: presence of delusions and both pre- and post-dexamethasone morning and afternoon cortisol levels ($r = .41$, $p = .001$; $r = .43$, $p = .001$, respectively); and age and morning and afternoon post-dexamethasone cortisols ($r = .39$, $p = .001$; $r = .84$, $p = .001$, respectively).

Discussion

The possibility that hyperactivation of the pituitary-adrenal axis might have a special relationship to suicidal behavior was initially suggested by the empirical observation of elevated urinary corticosteroids in patients who later committed suicide (Bunney & Fawcett, 1965). Several subsequent studies investigating this association have yielded mixed results

TABLE 2. Results of NIMH Study—Adrenal Function of Depressed Attempters and Non-Attempters.

Adrenal Measure	Attempters ($N = 28$)	Non-Attempters ($N = 60$)
$\bar{X}$ *CSF Cortisol (ng/ml)	.89 ± .07	1.04 ± .05
$\bar{X}$ Urinary Free Cortisol	111.7 ± 16.5	147.9 ± 19.7
$\bar{X}$ AM Plasma Free Cortisol (ug/dl)	15.6 ± 1.1	18.4 ± .77
$\bar{X}$ 10 PM Plasma Cortisol (ug/dl)	5.2 ± 1.3	7.0 ± .66**
% DST nonsuppression (>5 ug/dl in AM)	28	43
% UFC Hypersecretion (>133 ug/ 24 hr)	32	48

* ± SEM. ** $p<.05$.

TABLE 3. Results of Cornell Study—Adrenal Function of Depressed Attempters and Non-Attempters.

Adrenal Measure	Attempters ($N = 13$)	Non-Attempters ($N = 43$)
$\bar{X}$* AM Plasma Cortisol	20 ± 9	21 ± 9
$\bar{X}$ 4 PM Plasma Cortisol	11 ± 4	14 ± 6
% DST Nonsuppression (> 5 ug/dl)		
9 A.M.	59	65
4 P.M.	73	79

* ± SD.

(Levy & Hansen, 1969; Bunney et al., 1969; Krieger, 1970; Traskman et al., 1980; Carroll et al., 1981; Coryell & Schlesser, 1981; Ostroff et al., 1982; Targum et al., 1983; Banki & Arato, 1983). Thus, further research was merited to clarify these issues.

The current report summarizes findings from two additional studies done in hospitalized depressed patients comparing results of measures of HPA function in suicide attempters versus non-attempters (Secunda et al., in press; Brown et al., unpublished). The main findings are a lack of significant HPA differences in these two subgroups. One significant difference was found in the two studies and this was in the direction opposite of what was predicted. Evening plasma cortisol concentrations in the Collaborative Study were higher in non-attempters on the day prior to administration of dexamethasone ($p <$ .05 by ANCOVA).

Relationships between HPA function and suicidal acts are clearly not simple. Clinical research in this area is likely to have been confounded by numerous interacting variables, which are difficult to control in any single study. These would include age, presence or absence of psychosis, recent weight loss, levels of anxiety and agitation, psychiatric diagnosis, method of suicide attempt, and proximity of the biological sampling to the suicidal act.

The Cornell study patient ages were similar in the attempter and non-attempter groups. However, in the NIMH study attempters were younger than non-attempters. The latter situation would work against finding increased HPA activity in the attempter sample, because increased age is a known correlate of higher HPA activity (Kocsis et al., 1985). Presence of psychosis in depression has also been associated with both HPA activation and suicidality in some but not all previous studies (Schatzberg et al., 1983; Kocsis et al., unpublished). The current study from New York did find an association between delusions and higher cortisol levels. However, neither study reported significant differences in suicidality between delusional and non-delusional patients. HPA studies conducted separately in psychotic and non-psychotic depressed patients will help to resolve these questions.

Weight loss, anxiety, and agitation were all found to correlate with HPA measures in the NIMH study (Kocsis et al., 1985). Unfortunately data on these possibly confounding variables were not compared between attempters and non-attempters in the present studies. Such analyses are suggested for future research.

Psychiatric diagnoses were carefully established in both of the current studies by research psychiatrists who had established diagnostic reliability. All subjects were diagnosed as having Major Depressive Disorders by RDC or *DSM-III* criteria. It is possible that suicide attempters and non-attempter samples in other studies have contained either mixed or unreliable diagnoses. Such samples might create a bias for both suicide and abnormal HPA function to cluster in the subgroups with major depressive disorders, and thus yield a spurious impression that suicidal behavior has a special association with the endocrine findings.

Method of suicide attempt may also be an important variable because previous research has suggested links between inwardly and outwardly directed aggression and brain serotonin systems in humans, based on CSF studies in patients who used violent methods of attempting suicide (Asberg & Traskman, 1981). Although prior studies of suicide and HPA function have not reported linkage with method of suicide act, this remains at least a theoretical possibility.

Whether associations between suicidal behavior and biology are confounded by the proximity between the times of the biological sampling and the suicide attempt would depend on whether the putative biological marker is state or trait-related. For example, low CSF serotonin has been suggested as a trait marker for aggressive acts and violent suicide attempts (Asberg & Traskman, 1981) because the altered biochemistry appears to persist long after a suicide act. On the other hand behavioral assessments performed in suicidal subjects before and after their attempts have demonstrated distinctive patterns prior to suicidal behavior with reversion back toward patterns seen in non-suicidal patients following an attempt (Mason et al., in press). This kind of observation raises important questions about the longitudinal patterns of potential biological markers for suicidality. Specifically, in the case of HPA function, increased activation associated with state of arousal prior to a suicide attempt could theoretically revert to normal following the attempt. All of HPA measures in the current studies were obtained in subjects who had attempted suicide earlier during their current illness episode. Thus, some prior studies, which have evaluated HPA function in patients who later committed suicide, might have their discrepant findings explained on the basis of different temporal sequences between biological sampling and the suicidal act.

In conclusion, this brief review has summarized results from two recent studies of relationships between suicidal behavior and adrenocortical activity in depressed psychiatric inpatients. Hopefully a consideration of these findings and the discussion of previous studies and of factors which can influence these relationships will help to alert investigators in the biology of suicide to methodological considerations and important unresolved questions to be answered in future studies.

References

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders.* 3d ed. Washington, DC: The Association, 1980.

Asberg, M., and Traskman, L. Studies of CSF 5-HIAA in depression and suicidal behavior. *Exp. Med. Biol.*, 133:739–752, 1981.

Banki, C.M., and Arato, M. Amine metabolites and neuroendocrine response related to depression and suicide. *J. Affective Dis.*, 5:223–232, 1983.

Brown, R.P., Mason, B., Stoll, P., et al. Hypothalamic-pituitary-adrenal axis function and suicidal behavior in depressed patients. (Unpublished manuscript.)

Bunney, W.E., Jr., and Fawcett, J.A. Possibility of a biochemical test for suicidal potential. *Arch. Gen. Psychiatry*, 13:232–239, 1965.

Bunney, W.E., Jr., Fawcett, J.A., Davis, J.M., and Gifford, S. Further evaluation of urinary 17-Hydroxycorticosteroids in suicidal patients. *Arch. Gen. Psychiatry*, 21:138–150, 1969.

Carroll, B.J., Greden, J.F., and Feinberg, M. Suicide, neuroendocrine dysfunction and CSF 5-HIAA concentrations in depression. In: Angrist, B. (ed.), *Recent Advances in Neuropsychopharmacology*. Oxford and New York: Pergamon Press, 1981, pp. 307–313.

Coryell, W., and Schlesser, M.A. Suicide and the dexamethasone suppression test in unipolar depression. *Am. J. Psychiatry*, 138:1120–1121, 1981.

Endicott, J., Spitzer, R., Fleiss, J.L., et al. The Global Assessment Scale, a procedure for measuring overall severity of psychiatric disturbance. *Arch. Gen. Psychiatry*, 33:766–771, 1976.

Kocsis, J.H., Davis, J.M., Katz, M.M., et al. Depressive behavior and hyperactive adrenocortical function. *Am. J. Psychiatry*, 142:1291–1298, 1985.

Kocsis, J.H., Croughan, J.L., Katz, M.M., et al. Clinical and biological features of psychotic depression. (Unpublished manuscript.)

Krieger, G. Biochemical predictors of suicide. *Dis. Nerv. System*, 31:478–482, 1970.

Levy, B., and Hansen, E. Failure of the urinary test for suicidal potential. *Arch. Gen. Psychiatry*, 20:415–418, 1969.

Maas, J.W., Koslow, S.H., Davis, J., et al. Biological component of the NIMH clinical research branch collaborative program on the psychobiology of depression I. Background and theoretical considerations. *Psychol. Med.*, 10:759–776, 1980.

Mason, B.J., Exner, J.E., and Cohen, J.B. The fallacy of studying suicide potential after the attempt. *J. Pers. Assess.* (In press.)

Ostroff, R., Giller, E., Bonese, K., et al. Neuroendocrine risk factors of suicide. *Am. J. Psychiatry*, 139:1323–1325, 1982.

Schatzberg, A.F., Rothchild, A.J., Stahl, J.B., et al. The dexamethasone suppression test: Identification of subtypes of depression. *Am. J. Psychiatry*, 140:88–91, 1983.

Secunda, S.K., Cross, C., Kocsis, J.H., et al. Biochemical predictors of suicide. *Biol. Psychiatry*. (In press.)

Secunda, S., Koslow, S.H., Redmond, D.E., et al. Biological component of the NIMH clinical research branch collaborative program on the psychobiology of depression II: Methodology and data analysis. *Psychol. Med.*, 10:777–793, 1980.

Spitzer, R.L., and Endicott, J. Collaborative depressive study — clinical SADS — RDC, NY State Psychiatric Inst., New York, 1978.

Spitzer, R.L., Endicott, J., and Robins, E. Research diagnostic criteria for a selected group of functional disorders. NY State Psychiatric Inst., New York, 1978.

Stokes, P.E., Stoll, P.M., Koslow, S.H., et al. Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups. *Arch. Gen. Psychiatry*, 41:257–267, 1984.

Targum, S.D., Rosen, L., and Capodanno, A.E. The dexamethasone suppression test in suicidal patients with unipolar depression. *Am. J. Psychiatry*, 140:877–879, 1983.

Traskman, L., Tybring, G., Asberg, M., et al. Cortisol in the CSF of depressed and suicidal patients. *Arch. Gen. Psychiatry*, 37:761–767, 1980.

Suicidal Potential in Depression: Focus on CSF Monoamine and Purine Metabolites

Hans Ågren, M.D., Ph.D.,[1] and Frank Niklasson, M.D., Ph.D.[2]

Introduction

Biochemical differences between depressed individuals who have or who have not committed suicidal acts were proposed already in 1965 by Bunney and Fawcett, suggesting that suicidal patients have an elevated 17-hydroxycorticosteroid output. A broader interest in the field did not develop until Åsberg and her colleagues reported lower levels of 5-hydroxyindoleacetic acid (5HIAA) in the cerebrospinal fluid (CSF) of depressed patients who made violent suicide attempts when compared with non-suicidal depressives (Åsberg et al., 1976). Focus on serotonin is now established in biochemical research on suicide (Träskman et al., 1981; van Praag, 1982), and post-mortem findings of altered serotonin receptors in suicides add to its importance (Stanley and Mann, 1984).

A growing number of reports state that changes in CSF monoaminergic indices other than 5HIAA also are or become deranged in suicidal states. At least three studies have found a reduction in CSF homovanillic acid (HVA) in suicidal depression that is more pronounced than that of 5HIAA (Montgomery and Montgomery, 1982; Ågren, 1983; Roy et al., 1986). Furthermore, we have reported low concentrations of the purine metabolites xanthine and hypoxanthine (Ågren et al., 1983) as well as CSF creatinine, a marker of cerebral metabolism (Niklasson et al., 1983) to correlate with suicidal ideation. The significant intercorrelations between all these CSF indices of monoamine and purine metabolism raise statistical problems of collinearity that must be addressed before a specific neurotransmitter system can be singled out to play a major role in the biochemical substrate of suicidal mood states. The present study attempts to compare the relative contributions of a number of CSF monoaminergic and purinergic indices as well as psychoendocrinological variables in retrospectively "accounting" for previous suicidal acts in a large sample of patients with major depressive disorders.

Methods

Patients

Table 1 shows the composition of the patient sample, all inpatients at the Department of Psychiatry, University Hospital at Uppsala, Sweden, and suffering from major depressive disorders. They were diagnosed according to Research Diagnostic Criteria using the Schedule of Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1979). Scores for the Hamilton Depression Rating Scale (HRS-D) were deduced by converting appropriate SADS items following rules laid down by Endicott et al. (1981).

TABLE 1. Composition of the Patient Sample.

	Males	Females
n	66	85
Age ± SD	42.7 ± 12.5	40.1 ± 12.7
HRS-D ratings for worst week ± SD	25.5 ± 6.6	25.2 ± 6.8
HRS-D ratings for past week ± SD	18.2 ± 9.0	18.8 ± 9.1

HRS-D = Hamilton Depression Rating Scale extracted from the SADS (Endicott et al., 1981).

---

[1] Department of Psychiatry, University Hospital, S-751 85 Uppsala, Sweden.

[2] Department of Clinical Chemistry, University Hospital, S-751 85 Uppsala, Sweden.

Address correspondence to Dr. Ågren.

Biochemical Analyses

Monoamine metabolites HVA, 5HIAA, and 3-methoxy-4-hydroxyphenylglycol (MHPG) in CSF and MHPG in 24-hour urinary samples were assessed by gas chromatography–mass spectrometry by L. Svennerholm (Andersen et al., 1981). CSF purine metabolites xanthine and hypoxanthine as well as creatinine were analyzed by high pressure liquid chromatography (Niklasson and Ågren, 1983). Analyses of plasma cortisol for dexamethasone suppression tests, urinary free cortisol (UFC), and plasma thyroid-stimulating hormone (TSH) for thyroid-releasing hormone (TRH) stimulation test were carried out using radioimmunological assays as described by Ågren and Wide (cortisol: 1982; TSH: 1986).

Statistics

Ordinary *t* tests were used for comparisons of means in the previous-suicide-attempts and no-previous-suicide-attempts groups. Multiple regression analyses were done with ranked independent variables, permitting common parametric test procedures to be used in a non-parametric application (Conover and Iman, 1981). Statistical Analysis System, Inc., procedures were used.

Results

Univariate Differences in Means

Table 2 shows statistically significant differences between the suicidal and non-suicidal groups in six variables considered (the suicide group includes disproportionately more bipolar patients; patients are shorter in stature; patients are marked by lower CSF HVA, CSF MHPG, urinary MHPG, and CSF xanthine). Differences at trend probability were found in two variables (lower CSF 5HIAA and CSF creatinine). Non-significant differences were seen in seven other variables (weight, CSF hypoxanthine and five psychoendocrine measures).

Multivariate Analyses With Suicide Measures as Dependent Variables

All variables listed in Table 2 were ranked and used as independent variables in stepwise multiple regressions employing the forward maximum R^2 improvement technique. Analyses were run for the whole patient group as well as separately for unipolar and bipolar patients. The HRS-D score for the week preceding tests was forced to be included first. The suicide/non-suicide dichotomy and SADS item 247 (Suicidal Tendency and Ideation for past week) were used in turn as independent, "predicted" variables.

TABLE 2. Comparisons Between Patients Not Having *vs.* Having Committed Suicidal Acts at Some Time. Means ± SEM.

	No History of Suicide Attempts	History of Suicide Attempts	Test of Significance
Males/Females	46/54	20/31	(*)
Unipolars/Bipolars	76/23	27/24	$\chi^2 = 8.81$, $p = 0.0029$
Height, cm	172.0 ± 0.8	168.8 ± 1.3	$t = 2.12$, $p = 0.040$
Weight, kg	68.3 ± 1.2	65.4 ± 1.7	(*)
CSF HVA	180.1 ± 8.7	153.0 ± 9.1	$t = 2.15$, $p = 0.034$
CSF 5HIAA, nmol/l	95.7 ± 3.8	84.0 ± 4.9	$t = 1.86$, $p = 0.066$
CSF MHPG, nmol/l	42.9 ± 0.9	39.0 ± 1.3	$t = 2.48$ $p = 0.014$
Urinary MHPG, nmol/24 hr	13.6 ± 0.5	11.4 ± 0.6	$t = 2.57$, $p = 0.011$
CSF Xanthine, μmol/l	1.85 ± 0.05	1.68 ± 0.06	$t = 2.00$, $p = 0.048$
CSF Hypoxanthine, μmol/l	2.41 ± 0.08	2.38 ± 0.11	(*)
CSF Creatinine, μmol/l	59.6 ± 1.4	55.9 ± 1.5	$t = 1.82$, $p = 0.072$
ΔTSH, mU/l	9.2 ± 1.1	8.0 ± 1.0	(*)
DST cortisol at 8 a.m., mmol/l	126 ± 22	121 ± 24	(*)
DST cortisol at 11 a.m., mmol/l	122 ± 18	133 ± 30	(*)
DST cortisol at 8 p.m., mmol/l	143 ± 18	135 ± 19	(*)
Urinary Free Cortisol, mmol/24 hr	394 ± 16	389 ± 26	(*)

*$p > 0.10$.

TABLE 3. Final Selection of Ranked Independent Variables "Predicting" Previous Suicidal Acts.

Dependent variable: Ever Attempted Suicide (Yes/No)				
All patients:	$R^2 = 0.136$;	$F = 5.64$;	df = 4,144;	$p = 0.0003$
Unipolars:	$R^2 = 0.145$;	$F = 4.12$;	df = 4,97;	$p = 0.0040$
Bipolars:	$R^2 = 0.189$;	$F = 2.39$;	df = 4,41;	$p = 0.066$
Independent variables:				
(Type III Sums-of-Squares)		*F*		*p*
Hamilton scores Past Week	All	6.35 +[a]		0.013
	Unip	3.38 +		0.069
	Bip	5.64 +		0.022
Body height	All	6.66 −		0.011
	Unip	2.15 −		NS
	Bip	2.66 −		NS
CSF HVA	All	5.59 −		0.020
	Unip	6.99 −		0.0096
	Bip	0.01 −		NS
CSF MHPG	All	3.01 −		0.085
	Unip	3.11 −		0.081
	Bip	0.00 −		NS

[a] This sign indicates the direction of the regression coefficient.

Table 3 shows high HRS-D scores for past week, a short body stature, and low CSF concentrations of HVA and MHPG to retrospectively "predict" the existence of previous suicidal acts, but only in the context of unipolar depression. For the undivided group, short stature and low CSF HVA significantly "predict" earlier suicidal acts even when influence of severity of current depression has been covaried out. Low CSF MHPG contributed at trend significance. When only unipolars were considered, the importance of CSF HVA strengthened. Among bipolar patients, only current depressive severity was of any significant importance. Adding multiplicative terms checking for interactions between the independent variables did not reveal any significant increases of overall degree of explanation.

A discriminant analysis using the above four variables to "predict" previous suicidal acts classified 86/100 non-suicide attempters and 16/51 suicide attempters correctly (χ^2 = 7.55, df = 1, p <0.01). Thus, specificity was 86 percent but sensitivity only 31 percent.

Table 4 shows the result from a stepwise analysis "predicting" current suicidal tendency. Adding a multiplicative term [(CSF 5HIAA) times (post-DST plasma cortisol at 8 p.m.)] yielded a significant increase in R^2 for

TABLE 4. Current Suicidal Ideation "Predicted" by a Selection of Ranked Independent Variables.

Dependent variable: Suicidal tendency past week				
All patients:	$R^2 = 0.561$;	$F = 28.79$;	df = 4,90;	$p < 0.0001$
Unipolars:	$R^2 = 0.573$;	$F = 20.76$;	df = 4,62;	$p < 0.0001$
Bipolars:	$R^2 = 0.638$;	$F = 9.68$;	df = 4,42;	$p < 0.0001$
Independent variables:				
(Type III Sums-of-Squares)		*F*		*p*
Hamilton scores Past Week	All	83.51 +[a]		0.0001
	Unip	46.94 +		0.0001
	Bip	33.91 +		0.0001
CSF 5HIAA	All	7.99 −		0.0029
	Unip	7.04 −		0.010
	Bip	2.05 −		NS
DST Cortisol 8 p.m.	All	9.08 −		0.0034
	Unip	7.04 −		0.010
	Bip	3.03 −		0.096
5HIAA × Cortisol	All	4.77 +		0.032
	Unip	3.57 +		0.064
	Bip	1.85 +		NS

[a] This sign indicates the direction of the regression coefficient.

the whole sample. As could be expected, results indicate that current severity of depression is overwhelmingly important in accounting for current suicidal thoughts, but that even when this factor is under control, low CSF concentrations of 5HIAA and a more effective cortisol suppression by dexamethasone are highly significant predictors among unipolar patients. Again, in bipolar patients, CSF 5HIAA and the cortisol variable did not reach individual significance.

Discussion

This study of multiple biochemical sources of variance for suicidal parameters in clinically depressed patients offers arguments to modify the serotonin deficiency hypothesis for suicidal acts. First, certain CSF metabolites other than 5HIAA are associated with previous suicidal acts, especially HVA. A conjecture that the signals from the suicide source actually originate from a disturbed CSF flow or spinal reuptake mechanism needs to be addressed in future studies. The highly significant positive correlation between CSF HVA and 5HIAA presents intricate statistical problems of collinearity. We have dealt with the implications of this association elsewhere (Ågren et al., 1986). Furthermore, the very notion of "low" CSF 5HIAA in suicidal depression has been challenged by Roy et al. (1986), who report a non-significant difference between suicidal depressed patients and normal controls. The well-known negative association between body height and CSF HVA and 5HIAA (discussed by Ågren et al., 1986) is apparently reflected in the form of short stature paradoxically reaching importance as a "suicide predictor." In a short individual, low CSF HVA and 5HIAA would conceivably carry a purer suicide signal since shortness per se would tend to "increase" the metabolite levels.

Second, the specificity issue of disturbed monoamine metabolite regulation in suicidal behavior needs attention. Low CSF 5HIAA has been argued to differentiate impulsive from non-impulsive behavior irrespective of affective diagnosis (Brown et al., 1982; Linnoila et al., 1983). Low CSF 5HIAA was associated with suicidality in schizophrenic patients in one NIMH study (Ninan et al., 1984) but not in another (Pickar et al., personal communication). Contrasting against this broader view of the importance of low CSF 5HIAA stand reports that the associations only hold in unipolar, not bipolar depression (Ågren, 1983; Post et al., personal communication; this study). In a negative study of CSF 5HIAA and suicide in affective disorder (Roy-Byrne et al., 1983), 32 out of the 45 patients investigated were bipolars. We found, however, that bipolar patients had more often tried to commit suicide than unipolar depressives. This possible difference needs more work before anything specifically can be stated about subdiagnostic differences in suicidal potential: bipolars are likely to have experienced more depressive episodes and thus to have been subjected to a more intense wearing-out effect of depression as such.

Third, psychoendocrine variables (DST, UFC, ΔTSH) in isolation failed to relate to the suicide variables in focus. However, in combination with CSF monoamine metabolites, DST status helped increase the power of CSF 5HIAA and HVA to "predict" current suicidal tendencies. Similar conclusions concerning interactions between hypercortisolism, CSF HVA, and suicidality have been reached earlier on a smaller sample of Swedish patients (Ågren, 1983) and in a recent NIMH study (Roy et al., 1986).

In conclusion, several measures, mainly monoamine metabolite concentrations in lumbar CSF, have been related to setting the stage for a suicide act. The degree of significance of the correlations and the question of which one is the strongest candidate to reach the status of a specific suicide marker differs between studies. These inconsistencies suggest a common denominator that lies behind both suicidality and the lumbar CSF metabolite levels. Partly for this reason, renewed attention should focus on the dynamics of CSF flow and its implications for concentrations of small molecules in lumbar CSF.

Summary

Low levels of monoamine metabolites in lumbar CSF, especially 5HIAA, have repeat-

edly been linked with previous suicidal acts in depressive and other psychiatric patients. This study compared the relative contribution of a number of monoamine and purine metabolites in CSF and DST and TRH stimulation tests on 151 patients with RDC major depressive disorders. Restricted to unipolar patients, we found that low CSF HVA and short stature best "predicted" previous suicidal acts and did so better than CSF 5HIAA and that low CSF 5HIAA and DST status predicted current suicidal ideation, even when current depressive severity was accounted for. Collinearity between indices creates problems in singling any one out as a suicide marker, and possible unaccounted sources of variance lying behind both alterations in CSF indices and suicidality may confuse correlational analyses.

Acknowledgments

Support from the National Institute of Mental Health, Bethesda, MD, the Swedish Medical Research Council (grant #6604), and the Fredrik and Ingrid Thuring Foundation is gratefully acknowledged.

References

Ågren, H. Symptom patterns in unipolar and bipolar depression correlating with monoamine metabolites in the cerebrospinal fluid: II. Suicide. *Psychiat. Res.*, 3:225–236, 1980.

Ågren, H. Life at risk: markers of suicidality in depression. *Psychiat. Devel.* (Oxf), 1:87–104, 1983.

Ågren, H., Niklasson, F., and Hällgren, R. Brain purinergic activity linked with depressive symptomatology: hypoxanthine and xanthine in CSF of patients with major depressive disorders. *Psychiat. Res.*, 9:179–190, 1983.

Ågren, H., and Wide, L. Patterns of depression reflected in pituitary—thyroid and pituitary—adrenal endocrine changes. *Psychoneuroendocrinology*, 7:309–327, 1982.

Ågren, H., and Wide, L. TRH test with analyses of TSH, prolactin, and GH in subgroups of patients with major depressive disorders. *Acta Psychiat. Scand.* (1986, in press).

Andersen, O., Johansson, B., and Svennerholm, L. Monoamine metabolites in successive samples of spinal fluid. *Acta Neurol. Scand.*, 63:247–254, 1981.

Åsberg, M., Träskman, L., and Thorén, P. 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? *Arch. Gen. Psychiat.*, 33:1193–1197, 1976.

Conover, W.J., and Iman, R.L. Rank transformations as a bridge between parametric and non-parametric statistics. *Am. Statistician*, 35:124–129, 1981.

Endicott, J., and Spitzer, R.L. Use of the Research Diagnostic Criteria and the Schedule for Affective Disorders and Schizophrenia to Study Affective Disorders. *Am. J. Psychiat.*, 136:52–56, 1979.

Endicott, J., Cohen, J., Fleiss, J., and Sarantakos, S. Hamilton depression rating scale. Extracted from regular and change versions of the Schedule for Affective Disorders and Schizophrenia. *Arch. Gen. Psychiat.*, 38:98–103, 1981.

Linnoila, M., Virkkunen, M., Scheinin, M., et al. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sci.*, 33:2609–2614, 1983.

Montgomery, S.A., and Montgomery, D.B. Pharmacological prevention of suicidal behaviour. *J. Affect. Disord.*, 4:291–298, 1982.

Niklasson, F., Ågren, H., and Hällgren, R. Purine and monoamine metabolites in cerebrospinal fluid: parallel purinergic and monoaminergic activation in depressive illness? *J. Neurol. Neurosurg. Psychiat.*, 46:255–260, 1983.

Ninan, P.T., van Kammen, D.P., Scheinin, M., et al. CSF 5-hydroxyindoleacetic acid levels in suicidal schizophrenic patients. *Am. J. Psychiat.*, 141:566–569, 1984.

Roy, A., Ågren, H., Pickar, D., et al. Cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid and homovanillic acid and suicidal behavior in depressed patients: relationship to dexamethasone suppression. *Arch. Gen. Psychiat.*, in press.

Roy-Byrne, P., Post, R.M., Rubinow, D.R., et al. CSF 5HIAA and personal and family history of suicide in affectively ill patients: a negative study. *Psychiat. Res.*, 10:263–274, 1983.

Stanley, M., and Mann, J.J. Suicide and serotonin receptors. *Lancet*, i:349, 1984.

Träskman, L., Åsberg, M., Bertilsson, L., and Sjöstrand, L. Monoamine metabolites in CSF and suicidal behavior. *Arch. Gen. Psychiat.*, 38:631–636, 1981.

Van Praag, H. Depression, suicide and the metabolism of serotonin in the brain. *J. Affect. Disord.*, 4:275–290, 1982.

Monoamines, Glucose Metabolism, Suicidal and Aggressive Behaviors

Alec Roy, M.B., Matti Virkkunen, M.D., Sally Guthrie, Pharm.D., Russell Poland, Ph.D., and Markku Linnoila, M.D., Ph.D.[1]

In 1976 Asberg et al. reported a bimodal distribution of levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the lumbar cerebrospinal fluid (CSF) of depressed patients. Significantly more of the patients in the low CSF 5-HIAA mode had attempted suicide in comparison with those in the high mode. Since then there have been other studies in personality-disordered, schizophrenic, and depressed patients also reporting an association between low levels of CSF 5-HIAA and aggressive and suicidal behaviors (reviewed by Asberg et al., 1986). It is of note that some investigators have associated low CSF 5-HIAA levels particularly with violent suicide attempts (Banki et al., 1984). In fact, in an early study Traskman et al. (1981) reported that CSF 5-HIAA levels were significantly lower only among those patients who had made a violent suicide attempt and that levels were not reduced among those who had made a nonviolent suicide attempt.

Violent Offenders

Initial studies of CSF 5-HIAA levels and aggressive behaviors were reported by Brown et al. (1979, 1982). Recently Linnoila et al. (1983) examined CSF 5-HIAA levels among 36 male murderers and attempted murderers. Twenty-seven of them formed a group of impulsive offenders, 20 had an intermittent explosive disorder, and 7 an antisocial personality disorder; all also met criteria for borderline personality disorder and alcohol abuse. Nine violent offenders who had premeditated their crimes formed the non-impulsive group and had paranoid or passive-aggressive personality disorders. The authors found that CSF 5-HIAA levels were significantly lower among the group of impulsive violent offenders than among the non-impulsive violent offenders (Figure 1). Also, the 17 offenders who had committed more than one violent crime had CSF 5-HIAA levels significantly lower than those who had committed only one violent crime (mean 67.9 ± 12.1 vs. 87.1 ± 23.7 nM, $p < 0.02$). Furthermore,

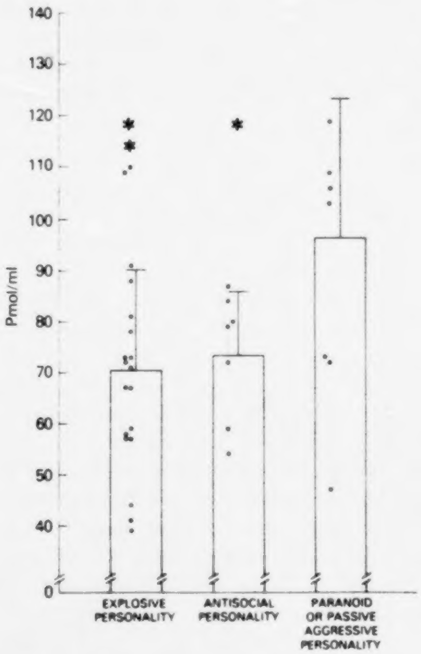


FIGURE 1. CSF 5-HIAA concentration in three diagnostic subgroups of violent offenders. The explosive personality ($n = 20$) and antisocial personality ($n = 7$) subgroups are classified as impulsive offenders, whereas the paranoid or passive-aggressive personality subgroup ($n = 9$) is classified as nonimpulsive. ANOVA $p < .01$ between the groups. Two-tailed, students *t*-tests compare the two impulsive subgroups with the nonimpulsive subgroup; ** = $p < .01$, * = $p < .05$.

---

[1] From Laboratory of Clinical Studies, DICBR, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD (Drs. Roy, Guthrie and Linnoila), Department of Psychiatry, University Central Hospital, Helsinki, Finland (Dr. Virkkunen), and Harborview Hospital, Torrance, CA (Dr. Poland).

Address for correspondence: Markku Linnoila, M.D., Ph.D., National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3B19, 9000 Rockville Pike, Bethesda, MD 20892.

the impulsive offenders who at some time had attempted suicide were found to have significantly lower CSF 5-HIAA levels than violent offenders who had never attempted suicide (Figure 2). There were no significant differences for CSF levels of free testosterone (Figure 3). The power to detect a significant difference ($p < 0.05$) in the mean free testosterone levels of these three groups was only 25 percent. However, for this comparison to have an 80-percent probability of finding a significant difference (should such a difference exist) each group would have to contain in excess of 700 subjects.

Because of these findings Linnoila et al. suggested that low CSF 5-HIAA levels may be associated with a tendency towards impulsive violent behavior which may manifest itself either as violence towards others or as suicide attempts. The authors cautioned that the implications of their study are presently limited as the number of subjects was relatively small and consisted of offenders who had exhibited extreme forms of impulsive violent behavior. However, they speculated that there may be individuals who have a defect in their central serotonin metabolism who, at an early age start to abuse alcohol, and later manifest impulsive violent behavior towards themselves and others. Furthermore, they suggested that experimental prospective prophylactic studies with serotonergic drugs should be considered, particularly for impulsive individuals who also have a family history of impulsive behavior.

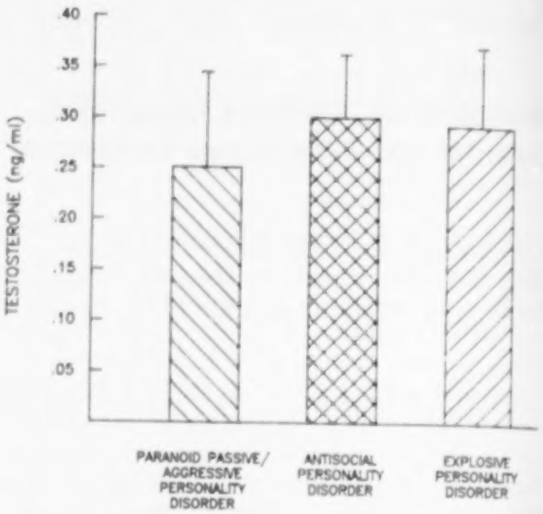


FIGURE 3. CSF free testosterone concentrations in paranoid or passive-aggressive personality disorder ($n = 12$), explosive personality disorder ($n = 19$), and antisocial personality disorder ($n = 10$) subgroups. There were no significant differences between group means.

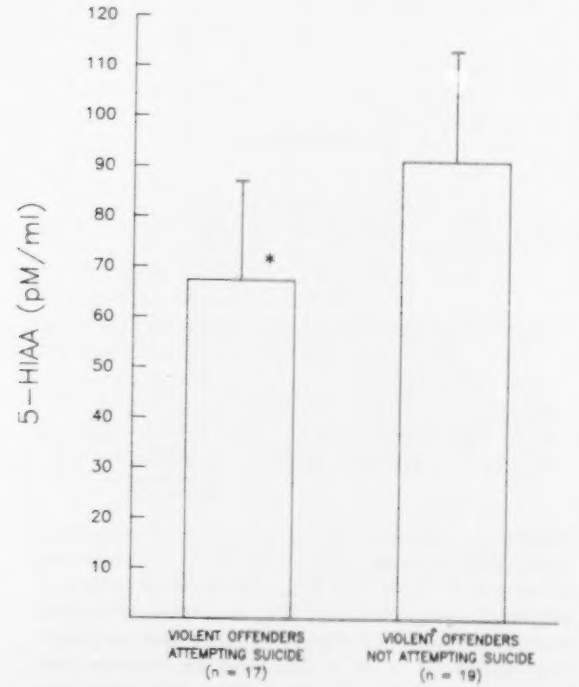


FIGURE 2. CSF 5-HIAA concentrations in violent offenders who had or had not attempted suicide. Two-tailed, student's *t*-test; * = $p < .05$.

Arsonists

In a later study Virkkunen et al. (1986) performed lumbar punctures on 20 male arsonists matched with a subgroup of the previously studied violent offenders and also compared with 10 normal controls. CSF 5-HIAA levels were significantly lower among the arsonists than the other two groups (Figure 4). When patients who had made past violent suicide attempts were excluded, arsonists again showed significantly lower CSF 5-HIAA and CSF MHPG levels than the other two groups (Figure 5).

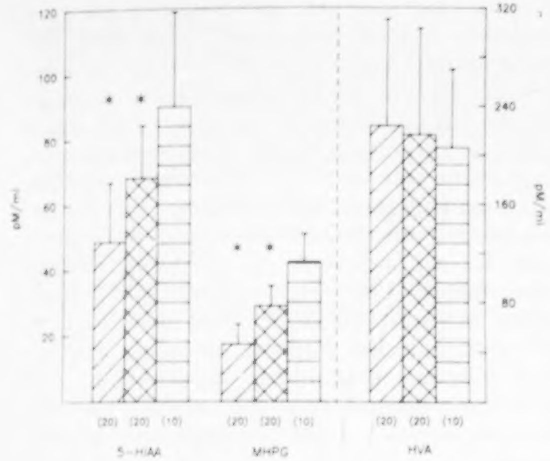


FIGURE 4. CSF monoamine metabolites in arsonists ($n = 20$), violent offenders ($n = 20$), and normal controls ($n = 10$). Post hoc student's t-tests comparing violent offenders or arsonists to normal controls; * = $p < .001$.

All of the arsonists also met DSM-III criteria for borderline personality disorder and many of them had exhibited occasional explosive behavior, usually after consuming alcohol. Thus, Virkkunen et al. argued that these results also suggest that low brain serotonin turnover, as indicated by low CSF 5-HIAA levels, may be associated with poor impulse control.

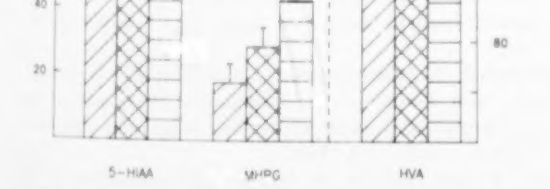


FIGURE 5. CSF monoamine metabolites in arsonists ($n = 9$), violent offenders ($n = 11$), and normal controls ($n = 10$), who had not attempted suicide. Post hoc student's t-tests comparing violent offenders or arsonists to normal controls; * = $p < .001$, + = $p < .05$.

Reactive Hypoglycemic Tendency

Virkkunen (1982, 1983, 1984, 1985a,b) also investigated glucose metabolism among these violent and impulsive offenders, half of whom had exhibited suicidal behavior. Blood-glucose levels fell below the basal level to a nadir of 2.4 ± 0.5 mmol/l in the antisocial personality group ($n = 37$) and to 2.3 ± 0.4 mmol/l in the intermittent explosive disorder group ($n = 31$). The blood-glucose nadir for controls ($n = 29$) was 3.1 ± 0.5 mmol/l, which was significantly higher than that found in both impulsive, violent offender groups ($p < .001$). A long duration of hypoglycemia correlated with a low verbal IQ, the presence of tattoos and slashing scars, and behavioral and sleeping problems. There were also significant positive correlations between the duration of hypoglycemia and truancy, stealing, number of crimes against property, having multiple sentences, and having a father who was violent under the influence of alcohol. Also, among 59 arsonists 27 (45.8 percent) had a glucose nadir under 3.0 mmol/l compared with only 5 of 29 male controls (17 percent; $p < .01$).

Among 23 young violent offenders with antisocial-personality disorder, insulin secretion during the GTT was found to be greater in those who also had an early undersocialized aggressive-conduct disorder. Day-night rhythm disturbances, sleeping difficulties, and behavioral problems during the evaluation were also more characteristic of subjects who developed high insulin peak values. In rats lesions of the suprachiasmatic nucleus abolish circadian rhythms of sleep and feeding, hyperglycemic responses to intracranial injection of 2-deoxy-D-glucose, and produce hyperinsulinaemia and enhanced-insulin secretion similar to that seen in impulsive violent offenders and arsonists after an oral or intravenous glucose load (Yamamoto et al., 1985). As the suprachiasmatic nucleus has a major serotonergic input from the raphe nuclei, one might speculate that deficient brain serotonin systems in impulsive violent offenders produce the insomnia and changes in feeding and glucose metabolism through a dysfunction of suprachiasmatic regulatory mechanisms.

Alcoholics

It is estimated that approximately 15 percent of alcoholics die by committing suicide and a high percentage attempt suicide (reviewed by Roy and Linnoila, 1986). Takahashi et al. (1974) reported that alcoholics with delirium tremens and other florid abstinent symptoms had significantly lower CSF 5-HIAA levels than controls and that after 4 weeks of supervised abstinence CSF 5-HIAA levels remained low. Takahashi et al. speculated that abnormality of brain serotonin metabolism might be a factor causing the psychiatric symptoms, including suicidal ideation, that are commonly found among alcoholics. Later, Ballenger et al. (1979) found that CSF 5-HIAA levels were significantly lower in alcoholics during the abstinent phase than in the postintoxication phase, or when compared to levels found in personality-disordered controls free of drinking problems. Moreover, Banki (1981) found a significant negative correlation between the number of days abstinent and CSF 5-HIAA levels. Also, depressed patients, themselves free of drinking problems, but with a positive family history of alcoholism, had significantly lower CSF levels of both 5-HIAA and of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MGPG) (Rosenthal et al., 1980) than depressed patients without a family history of alcoholism.

Ballenger et al. (1979) suggested that alcoholics may have a low brain serotonin turnover rate, which is transiently elevated by alcohol consumption. This in turn eventually leads to further depletion of brain serotonin. They speculated that a pattern may become established where the alcoholic drinks repeatedly in order to pharmacologically modify a serotonin deficiency in the brain.

Conclusion

A number of reports suggest that a deficiency of the serotonin system may be associated with disorders characterized by episodic deficits of impulse control and alcoholism. Furthermore, hypoglycemia during the oral glucose tolerance test and insomnia are very common among individuals with poor impulse control and a low CSF 5-HIAA concentration. Recent animal research has implicated the suprachiasmatic nucleus, which has a dense serotonergic innervation, as playing an important role in controlling both circadian rhythms and glucose metabolism. The insomnia of individuals with poor impulse control may be an indicator of circadian rhythm disturbance. Thus, we postulate that a functional serotonergic deficit may be conducive of poor impulse control, circadian rhythm and glucose metabolism disturbances, and that these disturbances are conducive of violent outbursts, suicide attempts, and alcohol abuse.

References

Asberg, M., Traskman, L., and Thoren, P. 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor. *Arch. Gen. Psychiatry*, 33:93–97, 1976.

Asberg, M. Biological factors in suicide. In: Roy, A. (ed.), *Suicide*. Baltimore: Williams and Wilkins, 1986.

Ballenger, J., Goodwin, F., Major, L., and Brown, H. Alcohol and central serotonin metabolism in man. *Arch. Gen. Psychiatry*, 36:224–227, 1979.

Banki, C. Factors influencing monoamine metabolites and tryptophan in patients with alcohol dependence. *J. Neural Transmission*, 50:98–101, 1981.

Banki, C., Arato, M., Papp, Z., and Kurcz, M. Biochemical markers in suicidal patients: investigations with cerebrospinal fluid amine metabolites and neuroendocrine tests. *J. Affective Disord.*, 6:341–350, 1984.

Brown, G., Ebert, M., and Goyer, P., et al. Aggression, suicide, and serotonin. *Am. J. Psychiatry*, 139:741–746, 1982.

Brown, G., Goodwin, F., Ballenger, J., et al. Aggression in human correlates with cerebrospinal fluid amine metabolites. *Psychiatry Res.*, 1:131–139, 1979.

Linnoila, M., Virkkunen, M., and Scheinin, M., et al. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non-impulsive violent behavior. *Life Sci.*, 2:2609–2614, 1983.

Rosenthal, N., Davenport, Y., Cowdry, R., Webster, M., and Goodwin, F. Monamine metabolites in cerebrospinal fluid of depressive subgroups. *Psychiatry Res.*, 2:113–119, 1980.

Roy, A., and Linnoila, M. Suicide and alcoholism. *J. of Life Threatening Behaviours*. (In press.)

Takahashi, S., Yamane, H., Kondo, H., and Tani, N. CSF monoamine metabolites in alcoholism, a comparative study with depression. *Folia Psych. Neurol. Japan*, 28:347–354, 1974.

Traskman, L., Asberg, M., Bertilsson, L., and Sjostrand, L. Monoamine metabolites in CSF and suicidal behavior. *Arch. Gen. Psychiatry*, 38:631–636, 1981.

Virkkunen, M. Reactive hypoglycemic tendency among habitually violent offenders: A further study by means of the glucose tolerance test. *Neuropsychobiology*, 8:35–40, 1982.

Virkkunen, M. Insulin secretion during the glucose tolerance test in antisocial personality. *Brit. J. Psychiatry*, 142:598–604, 1983.

Virkkunen, M. Reactive hypoglycemic tendency among arsonists. *Acta Psychiatrica Scandinavica*, 69:445–452, 1984.

Virkkunen, M. Insulin secretion during the glucose tolerance test among habitually violent and impulsive offenders. *Aggressive Behavior*, 1985a.

Virkkunen, M. Reactive hypoglycemic tendency among habitually violent offenders. *Nutrition Reviews*, 1985b.

Virkkunen, M., Nuutila, A., Goodwin, F., and Linnoila, M. CSF monoamine metabolites in male arsonists. *Arch. Gen. Psychiatry*, in press, 1986.

Yamamoto, H., Nagai, K., and Nakagawa, H. Lesions involving the suprachiasmatic nucleus eliminate the glucagon response to intracranial injection of 2-deoxy-D-glucose. *Endocrinology*, 117:468–473, 1985.

Genetic Factors in Suicide

Alec Roy, M.B.[1]

Suicide is a multidetermined act (Roy, 1985a) and evidence about genetic factors comes from a wide range of studies.

Clinical Studies

A family history of suicide has been noted in a small but significant percentage of individuals who commit suicide (Farberow & Simon, 1969; Roy, 1982; Shaffer et al., 1974; Stengel, 1964). Also, significantly more psychiatric patients with a family history of suicide themselves attempt suicide than patients without such a family history (Roy, 1983; 1985b). Linkowski et al. (1985), examining a consecutive series of psychiatric inpatients with affective disorders, also found that a family history of suicide significantly increased the frequency of violent suicide attempts in both depressed women and men.

A family history of suicide is associated with attempts at suicide throughout the life cycle. Among the young, Garfinkel et al. (1982) found that a family history of suicidal behavior was found significantly more frequently among 443 adolescents who presented to hospital having attempted suicide than among 442 adolescent controls who had not attempted suicide (37 vs. 5, $p<0.01$). Among adults, Murphy et al. (1982) reported that 14 percent of 127 patients admitted after an attempt at suicide had a family history of suicide. Among the elderly, Batchelor and Napier (1953) studying individuals over 60 years of age who had attempted suicide, noted that 12.5 percent had a family history of suicide.

How commonly a family history of suicide is found among psychiatric inpatients can be determined from the data in the studies of Pitts and Winokur (1964) and Roy (1983). These two studies found that approximately 4 to 5 percent of psychiatric inpatients have a family history of suicide and that between 50 percent to 66 percent of inpatients with such a history have a diagnosis of affective disorder (Roy, 1985b). Approximately 10 percent of manic-depressive patients have a family history of suicide (Roy, 1985c).

Twin Studies

In 1967, Haberlandt examined all the reports in the world literature concerning a twin who had committed suicide. He identified 149 reports since 1830. There were 9 twin pairs where both twins had committed suicide. All 9 of these twin pairs were found among the 51 identical twin pairs (17.7%) and none among the 98 nonidentical twin pairs. This is a highly significant difference between identical and nonidentical twin pairs ($p<0.0001$) and is strong evidence that there are genetic factors in suicide. Furthermore, in several other of the 149 twin pairs the living twin had attempted suicide—again in all cases this was found among identical twin pairs. It should be noted that 4 of the 9 twin pairs concordant for suicide were also concordant for psychiatric disorder—in 3 twin pairs this was for affective disorder while the fourth pair was concordant for schizophrenia.

The Iowa 500 Study

The 30- to 40-year follow-up study of the 685 selected psychiatric patients and surgical controls admitted to hospital in Iowa City between 1934 and 1955 revealed that there had been 30 suicides—29 among the 727 psychiatric patients (5.5%) and 1 among the 160 controls (0.6%) ($p<0.001$). Tsuang (1983) recently reported the follow up of the 5,721 first-degree relatives of this cohort. He found that the risk of suicide in the relatives of the psychiatric patients (2.3%) was nearly eight times greater than the risk among the relatives of the surgical controls ($p<0.01$). Furthermore, the relatives of patients who had committed suicide had a four times greater risk themselves of committing suicide than the relatives of patients who had not committed suicide (7.9% vs. 2.1%, $p<0.05$). These findings support "the presence of a genetic element in suicide." Interestingly, the increased risk of suicide for relatives of patients who had committed suicide was confined to the relatives of the bipolar and unipolar patient suicides.

---

[1] Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20205.

Amish Study

Suicide among the Old Order Amish of Lancaster County in Pennsylvania has been studied by Egeland and Sussex (1985). This community is of particular interest, as some of the sociodemographic correlates of suicide derived from general population studies are not found among the Amish. This is because they are a pacifist, nonviolent, agrarian society, alcohol is prohibited, there is no unemployment, no social isolation, and there is no lack of social support as three generations live together under the same roof.

However, during the hundred years between 1880 and 1980 there were 26 suicides in this community. Detailed psychological autopsies indicate that 92 percent of the individuals who committed suicide suffered from affective disorder. Furthermore, three-quarters of the suicides clustered in four pedigrees, each of which contained a heavy loading of affective disorders and suicide. Egeland and Sussex concluded that individuals with a major affective disorder and a family history of suicide themselves have an increased risk of suicide.

Adoption Studies

The strongest evidence that there are genetic factors in suicide comes from the Danish Adoption Studies of Schulsinger et al. (1979). The Psykologisk Institut in Copenhagen has a register of the 5,483 adoptions that occurred in the greater Copenhagen area between 1924 and 1947. A screening of the registers of causes of death revealed that 57 of these adoptees had committed suicide. These 57 suicides were matched with adopted controls for sex, age, social class of the adopting parents, and time spent both with their biological relatives and in institutions before being adopted. Searches of the registers of causes of death revealed that 12 of the 269 biological relatives (4.5%) of these 57 adopted suicides had themselves committed suicide compared with only 2 of the 269 biological relatives (0.7%) of the 57 adopted controls ($p<0.01$). None of the adopting relatives had committed suicide. Also, 6 of the 12 biological suicide relatives of the adopted suicide victims had a psychiatric history.

In another study this group compared the 71 adoptees known to have suffered from depressive disorder with 71 matched adopted controls. Fourteen of the 407 biological relatives (3.7%) of the adoptees with depression were found to have committed suicide compared with only 1 of the 360 (0.3%) biological relatives of the controls ($p<0.01$). Of particular interest was the finding that the type of depressive disorder among the adoptees most significantly associated with suicide among their biological relatives was the diagnosis of "affective reaction." This is a diagnosis often given in Denmark to individuals who have attempted suicide and who have associated affective symptoms.

These findings led Kety and associates to suggest that there may be a genetic factor in suicide independent or additive to depression, psychosis, or the other psychiatric disorders associated with suicide. They suggested that such a genetic factor for suicide may be involved in the control of impulsive behavior and that depression and stress may serve to trigger or foster impulsive suicidal behavior (Kety, 1986).

Conclusions

This review suggests that suicide, like so much else in psychiatry, tends to run in families. The clinical, Iowa, Amish, twin, and adoption studies show that a family history of suicide is associated with an increased risk of suicidal behavior. There are three possible reasons for this. First, the genetic factors in suicide may be the genetic transmission of psychiatric disorders per se—particularly affective disorders. Second, the Copenhagen adoption studies suggest that there may be a genetic factor for suicide that is additive to psychiatric disorders and that this genetic factor may be related to the control of impulsive behavior. Third, a family member who has committed suicide may serve as a role model for a disturbed individual.

References

Batchelor, I., and Napier, M. Attempted suicide in old age. *Br. Med. J.*, 1186–1190, 1953.

Egeland, J., and Sussex, J. Suicide and family loading for affective disorders. *JAMA*, 254:915–918, 1985.

Farberow, N., and Simon, M. Suicide in Los Angeles and Vienna: An intercultural study of two cities. *Public Health Rep.*, 84:389–403, 1969.

Garfinkel, B., Froese, A., and Hood, J. Suicide attempts in children and adolescents. *Am. J. Psychiatry*, 139:1257–1261, 1982.

Haberlandt, W. Aportacion a la genetica del suicidio. *Folia Clin. Int.*, 17:319–322, 1967.

Kety, S. Genetic factors in suicide. In: Roy, A. (ed.), *Suicide*. Baltimore, Md.: Williams & Wilkins, 1986.

Linkowski, P., de Maertelaer, V., and Mendlewicz, J. Suicidal behaviour in major depressive illness. *Acta Psych. Scand.*, 72:233–238, 1985.

Murphy, G., and Wetzel, R. Family history of suicidal behaviour among suicide attempters. *J. Nerv. Ment. Dis.*, 170:86–90, 1982.

Pitts, F., and Winokur, F. Affective disorder. Part 3 (Diagnostic correlates and incidence of suicide). *J. Nerv. Ment. Dis.*, 139:176–181, 1964.

Roy, A. Risk factors for suicide in psychiatric patients. *Arch. Gen. Psychiatry*, 39:1089–1095, 1982.

Roy, A. Family history of suicide. *Arch. Gen. Psychiatry*, 40:971–974, 1983.

Roy, A. Suicide: A multidetermined act. *Psychiatr. Clin. N. Am.*, 8:243–250, 1985a.

Roy, A. Family history of suicide in manic-depressive patients. *J. Affective Disord.*, 8:187–189, 1985b.

Roy, A. Family history of suicide in affective disorder patients. *J. Clin. Psychiatry*, 8:317–319, 1985c.

Schulsinger, R., Kety, S., Rosenthal, D., et al. A family study of suicide. In: M. Schou & E. Stromgren (eds.), *Origins, Prevention and Treatment of Affective Disorders.* New York: Academic Press Inc., 1979, pp. 277–287.

Shaffer, D. Suicide in childhood and early adolescence. *J. Child Psychol. Psychiatry*, 15:275–291, 1974.

Stengel, E. *Suicide and Attempted Suicide*. New York: Viking Penguin Inc., 1964.

Tsuang, M. Risk of suicide in the relatives of schizophrenics, manics, depressives, and controls. *J. Clin. Psychiatry*, 44:396–400, 1983.

(Auto)Aggression and CSF 5-HIAA in Depression and Schizophrenia

Herman M. van Praag, M.D., Ph.D.[1]

This paper is divided into two parts. The first part discusses methodological flaws in present day biological suicide research. In the first section previous observations are summarized. In the subsequent two sections new data are added. The second part describes a study adding new supportive evidence to the hypothesis relating aggression-regulation (or impulse control) to central serotonergic functioning.

Methodological Flaws in Biological Suicide Research

Previous Observations

In previous publications we called attention to some untenable assumptions on which present day biological suicide research is based. Most research is related to serotonin (5-hydroxytryptamine: 5-HT) and I will limit myself to that variable.

1. The observation that low CSF concentration of 5-hydroxyindoleacetic acid (5-HIAA) in depression is correlated with suicide attempt, in particular if committed with violent means, led to the conclusion of a relationship between decreased 5-HT metabolism and strong auto-destructive impulses. This conclusion is premature. The risk of violent suicide attempt appeared to be not evenly distributed over different forms of depression but to be increased in the group of endogenous depression (Major Depression, Melancholic type, according to DSM-III criteria) (van Praag & Plutchik, 1984). It is therefore impossible to decide whether low CSF 5-HIAA relates to violent suicide attempt or to the depression type in which the chance of that behavior happens to be increased.

2. The hypothesis that low CSF 5-HIAA relates to suicidal behavior rather than to the affective disorder as such, is based on low CSF 5-HIAA having been observed not only in depressed but also in non-depressed suicide attempters. The latter diagnosis however was based on *post*-suicidal assessment and is therefore unreliable. We demonstrated in a group of hospitalized suicide attempters that depression is extremely common in the 2 months prior to the attempt (van Praag, 1982), while during the first week of hospitalization the depression ratings drop significantly (van Praag & Plutchik, 1985). The diagnosis nondepressive suicide attempter therefore should be based on *pre*-suicidal assessment.

3. Method used in the suicide attempt has been used as a measure of strength of suicidal impulses. This is not justified. First, suicide method pertains to seriousness of the *attempt*, not to the seriousness of *intent*. These two variables should be assessed independently. Second, seriousness of attempt is not only determined by risk factors, among which method is the most significant one, but by the chance of being rescued as well. Weisman and Worden (1973) constructed a scale measuring lethality of the attempt as a risk/rescue ratio. We demonstrated that suicide attempters using violent means have the same risk/rescue scores as those using nonviolent means (van Praag et al., 1986). Obviously suicide method alone is not a reliable measure of lethality of the suicide attempt.

The Flaw of Equalizing Various Types of Suicidal Behaviors in Schizophrenia

5-HT studies in suicide have included three types of suicidal behavior: recent suicide attempt, life-time history of suicidal behavior with no recent attempt, and suicidal ideation. These behaviors have been regarded as equivalent and so have the biological data. They have simply been pooled and averaged. We obtained data making this procedure untenable.

---

[1] Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY 10461.

In a group of schizophrenic patients with recent suicide attempts, prompted by "voices," but without an affective disorder, CSF 5-HIAA was found to be lowered compared to a matched group of schizophrenics without suicidal history and a non-psychiatric control group (van Praag, 1983). These observations were confirmed by Ninan et al. (1984). Subsequently we compared the findings in schizophrenics with recent suicide attempt with those obtained in two other groups: The first consisted of 13 schizophrenics with life-time history of at least 1 and on the average 1.6 suicide attempts but no recent attempts. The second group comprised 12 schizophrenics with suicidal ideation at the time of the lumbar puncture but no recent or past attempts. The various groups of patients were comparable in terms of symptomatology, age, and sex.

The only group of schizophrenics in which CSF 5-HIAA was lowered in comparison to the nonpsychiatric control group was the group with recent suicide attempts. In the others the concentrations were within normal limits (Figure 1).

We *concluded* that in schizophrenia low CSF 5-HIAA is related to recent suicide attempt.

The Flaw of Equalizing Various Types of Suicidal Behaviors in Depression

The situation is different in the group of affective disorders. We measured CSF 5-HIAA in 52 patients suffering from nonpsychotic major depression, melancholic type. Fifteen of them had attempted suicide recently, i.e., 3 to 7 days prior to the lumbar puncture. The second group comprised 19 patients with life-time history of at least 1 suicide attempt and on the average 1.9 suicide attempts. The third group, consisting of 18 patients, displayed suicidal ideation at the time of the lumbar puncture but had made no attempts either recently or in the past. All patients had been hospitalized.

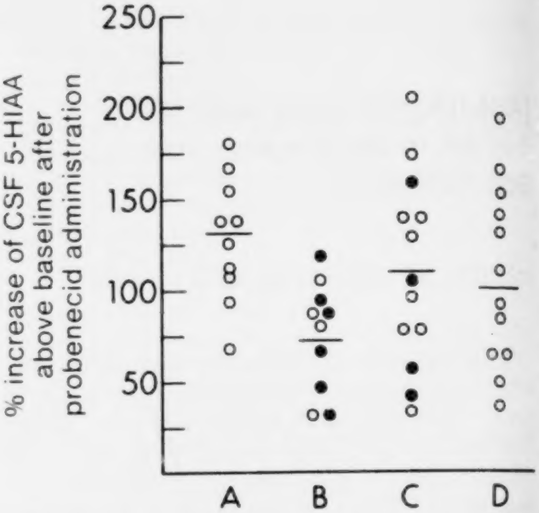


FIGURE 1. Percentage increase of post-probenecid CSF 5-HIAA above baseline concentration, in 4 groups of individuals. *Group A*: 10 controls without psychiatric symptoms or history. *Group B*: 10 schizophrenics with recent suicide attempts prompted by "voices." The lumbar puncture was carried out within 1 week after the attempt. *Group C*: 13 schizophrenics with life-time histories of suicide attempts but no recent attempts. *Group D*: 12 schizophrenics with suicidal ideation at the time of the lumbar puncture but no recent or past suicide attempts.

CSF 5-HIAA was measured before and 8 hours after the beginning of a probenecid load of 5 g/5 h.

In comparison with a nonpsychiatric control group, CSF 5-HIAA was lower in the group having made recent attempts and in the group with life-time histories of suicide attempts. In the group of patients with suicidal ideation, CSF 5-HIAA concentration was within normal limits (Figure 2).

We *concluded* that in affective disorder, low CSF 5-HIAA is apparently a trait marker related to increased risk of suicide. Moreover, it appears that suicidal ideation, intent, and attempt should be differentiated biologically, as they have to be, of course, in psychopathological terms. Attempts are obviously preceded or accompanied by suicidal ideation. Suicidal ideation on the other hand can occur without a marked drive to implement the idea. In other words, the intentional "load" of suicidal ideas does vary markedly.

The *general conclusion* is that in biological suicide research, recent attempt, life-time his-

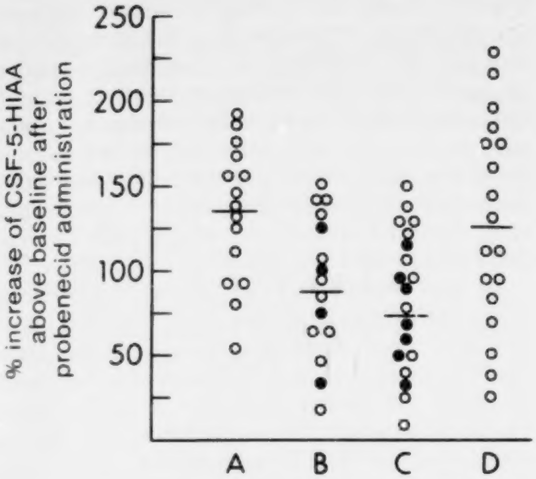


FIGURE 2. Percentage increase of post-probenecid CSF 5-HIAA above baseline concentration in 4 groups of individuals. *Group A*: 15 controls without psychiatric symptoms or history. *Group B*: 15 depressed patients with recent suicide attempts. Lumbar puncture was performed within 1 week after the attempt. *Group C*: 19 depressed patients with life-time history of suicide attempts but no recent attempts. *Group D*: 18 depressed patients with suicidal ideation at the time of the lumbar puncture but no recent or past suicide attempts. All depressed patients were suffering from major depression, melancholic type, according to DSM-III criteria.

CSF 5-HIAA was measured before and 8 hours after the beginning of a probenecid load of 5 g/5 h.

tory of suicide attempt, and suicidal ideation should be regarded and treated as separate categories.

New Evidence in Favor of a Relationship Between 5-HT and Aggression Regulation

Hypothesis

Low CSF 5-HIAA has been reported to occur in suicidal schizophrenic patients without affective disorder (Ninan et al., 1984; van Praag, 1983) as well as in nondepressed individuals with disregulated outward directed aggression (Bioulac et al., 1980; Brown et al., 1979, 1982; Lindberg et al., 1985; Linnoila et al., 1983). These findings prompted the hypothesis that lowered 5-HT metabolism is related not so much to depression or to suicidal behavior, but to disordered aggression regulation or disturbed impulse control. Based on this hypothesis, one would expect depressed patients with low CSF 5-HIAA, compared to similar patients with normal 5-HIAA levels, to display not only more suicidal behavior but more hostile behavior as well.

Methods

In order to verify this hypothesis, we compared 25 depressed patients with lowered CSF 5-HIAA and 25 depressed patients with normal 5-HIAA levels in terms of suicidal acts and acts of hostility in interpersonal functioning. CSF 5-HIAA was measured after probenecid administration (van Praag, 1977). 5-HIAA concentration was called lowered, if two standard deviations or more below the normal mean. The average number of previous admission for depression numbered 2.4 in the low 5-HIAA and 2.7 in normal 5-HIAA group. In both groups, the majority of patients was unipolar: 19 in the low 5-HIAA group, 17 in the normal-level-group.

By means of a semistructured interview, emotion-laden events, including hostility in interpersonal functioning which occurred in the preceding 6 months, were recorded. In addition, the occurrence of previous suicide attempts was explored. A suicide attempt was defined as any intentionally self-inflicted injury (including ingestion) with self-destructive intent. Only those attempts were counted that had led to medical intervention. Besides the patient, at least one "significant other" was interviewed. Finally, signs of hostility in interpersonal functioning during the interview were recorded.

Results

We were able to confirm previous observations indicating preponderance of suicide attempts in the low CSF 5-HIAA depressives compared to their normal 5-HIAA counterparts. In addition, the former group surpassed the latter in all signs of outward directed aggression that were studied (Table 1).

TABLE 1. Comparison of Patients With Major Depression, Melancholic Type (DSM–III) With Low Post-Probenecid CSF 5-HIAA ($n = 25$), and Those With Normal CSF 5-HIAA Post-Probenecid ($n = 25$).

Suicide Attempts and Signs of Interpersonal Hostility	$p \leq$
More suicide attempts	0.01
Greater number of contacts with police	0.05
Increased arguments with	
—relatives	0.05
—spouse	0.01
—colleagues	0.05
—friends	0.05
More hostility at interview	0.05
Impaired employment history (arguments)	0.05

Discussion and Conclusion

The high concordance of inward and outward directed aggression has been established in purely psychopathological studies as well. Weissman et al. (1973), comparing a group of suicide attempters with a group of depressed patients, found increased hostility in the suicide group to be the single most important distinguishing characteristic between the two groups. Another case in point is the high incidence of suicide in murderers amounting to more than 30 percent in some European countries (West, 1965). Psychoanalysts of old, of course, underlined the trivariate relationship between aggression, depression, and suicide (Freud, 1956). In conformity with our findings, Rydin et al. (1982) reported that depressed patients with low CSF 5-HIAA showed on Rorschach testing more hostility than comparable patients with normal 5-HIAA.

In conclusion, in depressives with low post-probenecid CSF 5-HIAA, suicide attempt and outward directed aggression are more frequent than in normal CSF 5-HIAA depressives. These data support the hypothesis of diminished central 5-HT metabolism being related to disordered aggression regulation or diminished impulse control.

Summary

Two issues are being discussed. In the first part of this paper methodological shortcomings of present day biological suicide research are discussed. Previous data are summarized and one flaw is added, i.e., the inadmissability of putting on a par different forms of suicidal behavior—such as suicidal ideation, recent suicide attempt and life-time history of suicide attempts—and generalizing about the biological findings. Evidence is presented that these behaviors are biologically heterogeneous, as they are psychopathologically.

In the second part evidence is presented that depressives with low CSF 5-HIAA show not only more signs of suicidal behavior than their normal 5-HIAA counterparts but more evidence of hostile behavior as well. These findings support the hypothesis that diminished central 5-HT metabolism and disordered aggression regulation (or impulse control) are interrelated, a hypothesis with which we have dealt in more detail elsewhere (van Praag, in press).

References

Bioulac, B., Benezich, M., Renaud, B., et al. Serotonergic functions in the 47, XYZ syndrome. *Biol. Psychiatry*, 15:917, 1980.

Brown, G.L., Ebert, M.E., Goyer, P.F., Jimerson, D.C., Klein, W.J., Bunney, W.E., Goodwin, F.K. Aggression, suicide, and serotonin: Relationships to CSF amine metabolites. *Am. J. Psychiatry*, 139:741, 1982.

Brown, G.L., Goodwin, F.K., Ballenger, J.C., et al. Aggression in humans correlates with cerebrospinal fluid metabolites. *Psychiatry Res.*, 1:131, 1979.

Freud, S. Mourning and melancholia. In: London, J.E. (ed.), *Collected Papers*. New York: Hogarth Press, 1956.

Lindberg, L., Tuck, J.R., Åsberg, M., et al. Homicide, suicide, and CSF 5-HIAA. *Acta Psychiatr. Scand.*, 71:230–236, 1985.

Linnoila, M., Vikkunen, M., Scheinin, M., et al. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non-impulsive violent behavior. *Life Sci.*, 33:2609–2614, 1983.

Ninan, P.T., van Kammen, D.P., Scheinin, M., et al. CSF 5-hydroxyindoleacetic acid levels in suicidal schizophrenic patients. *Am. J. Psychiatry*, 141:566–569, 1984.

Rydin, E., Schalling, D., and Åsberg, M. Rorschach ratings in depressed and suicidal patients with low levels of 5-hydroxyindoleacetic acid in cerebrospinal fluid. *Psychiatry Res.*, 7:229–243, 1982.

Van Praag, H.M. Affective disorders and aggression disorders. Evidence for a common biological mechanism. In: *Suicide and Life-Threatening Behavior*. (In press.)

Van Praag, H.M. CSF 5-HIAA and suicide in non-depressed schizophrenics. *Lancet*, I:977–978, 1983.

Van Praag, H.M. Depression, suicide, and the metabolism of serotonin in the brain. *J. Affect. Disord.*, 4:275–290, 1982.

Van Praag, H.M. *Depression and Schizophrenia. A Contribution on Their Chemical Pathologies*. New York: Spectrum Press, 1977.

Van Praag, H.M. Biological suicide research. Outcome and limitations. *Biol. Psychiatry* (In press).

Van Praag, H.M., and Plutchik, R. An emperical study on the "cathartic effect" of attempted suicide. *Psychiatry Res.*, 16:123–130, 1985.

Van Praag, H.M., and Plutchik, R. Depression-type and depression-severity in relation to risk of violent suicide attempt. *Psychiatry Res.*, 12:333–338, 1984.

Van Praag, H.M., Plutchik, R., and Conte, H. The serotonin hypothesis of (auto)aggression. Critical appraisal of the evidence. *Ann. N.Y. Acad. Sci.* (In press.)

Weisman, A.D., and Worden, J.W. Risk/rescue rating in suicide assessment. *Arch. Gen. Psychiatry*, 26:553–560, 1972.

Weissman, M., Fox, K., and Klerman, G.L. Hostility and depression associated with suicide attempts. *Am. J. Psychiatry*, 130:450, 1973.

West, D.J. (ed.). *Murder Followed by Suicide*. London: Heinemann, 1965.

Acquired Immunodeficiency Syndrome (AIDS): Neuropsychologic and Psychoimmunologic Aspects

Co-Chairs:

T. Peter Bridge, M.D
Office of the Administrator
Alcohol, Drug Abuse, and Mental Health Administration
Rockville, MD 20857

Allan F. Mirsky, Ph.D.
National Institute of Mental Health
Bethesda, MD 20892

Introduction

T. Peter Bridge, M.D.,[1] and Donald I. Macdonald, M.D.[1]

Although considerable public preoccupation with the Acquired Immunodeficiency Syndrome (AIDS) presently exists, inclusion of a panel on AIDS by the American College of Neuropsychopharmacology reflects our recent awareness of the neuropsychiatric aspects of this illness. As we would expect, any fatal illness such as AIDS would have psychologic parameters. Some of these are unique to AIDS and have been addressed elsewhere (Holland & Tross, in press). What the papers in this panel demonstrate, however, is that neuropsychologic consequences, presumably secondary to a direct viral infection of the brain by the Human Lymphotropic Virus, Type III (HTLV-III) (Levy et al., 1985; Ho et al., 1985; Resnick et al., 1985), the etiologic agent for AIDS, are also present. As background, then, for the papers in this panel three points need to be stated:

1) AIDS is a medical problem of the highest priority to the American medical research community;

2) AIDS is an illness whose sequelae are likely to remain with us for a considerable period of time;

3) AIDS is an illness presenting the fields of neuroscience and behavioral research with challenges and opportunities compelling to pursue.

Few remain to be convinced of the importance of AIDS. The epidemiologic facts speak for themselves:

- 16,000 cases of AIDS in the United States have been reported to the Centers for Disease Control as of January 1986, with the number of cases doubling every 6 to 12 months in many areas. One half of these cases are already dead. No one is known to have recovered from AIDS (CDC Update: AIDS—USA, 1986).
- Estimates are that as many as 1 million people have been infected by HTLV-III (Curran et al., 1985).
- Current estimates are that at least 10 percent of those infected with HTLV-III will develop the full blown AIDS diagnosis during the 5 or more years of incubation period (Curran et al., 1985). This could translate to 100,000 dead by the end of this decade.

---

[1] Office of the Administrator, Alcohol, Drug Abuse and Mental Health Administration, Rockville, MD 20857.

- Among some high risk groups in metropolitan areas, prevalence rates for infection by HTLV-III approach 60 to 70 percent sampled (Fauci et al., 1985; Marmor et al., 1984).
- While AIDS has been an illness appearing first in certain high risk groups in this country [sexually active gay and bisexual men, intravenous (i.v.) drug users, recipients of blood products contaminated with HTLV-III, and sexual partners or infants born to these groups] (Curran et al., 1985), the likelihood of its spread to other groups (i.e., sexually active, non-i.v. drug using heterosexuals) in this country remains unknown.
- Data from central Africa, where the AIDS epidemic hypothetically originated, make clear the point that transmission of the virus among sexually active persons is male to male, male to female, and female to male (Fauci et al., 1985).

These facts make the point that AIDS is a present public health imperative. What data do we have that speak to whether AIDS will remain an imperative? It would be an all too easy leap of faith to observe that medical researchers have made extraordinary progress since AIDS was first described in late 1981. We know the etiologic agent for the illness (Fauci et al., 1985). We have serologic screening tests that can detect blood products contaminated with HTLV-III as well as processes to render clotting factors free from the virus (Curran et al., 1985). In 3 years medical research has accomplished what took decades with prior infectious illnesses. Unfortunately, the next phases of medical research do not appear likely to move so quickly.

- Antibodies to HTLV-III detected in enzyme linked immunosorbent assay or the ELISA test do not neutralize the virus (Fauci et al., 1985).
- Characteristic of the retroviruses, to which HTLV-III belongs, is the capacity to mutate frequently and spontaneously. Most of the mutations occur in the protein envelope surrounding the virus, to which vaccines are normally developed. To date more than 200 separate isolates of HTLV-III have been made (Benn et al., 1985). There may be, however, constant segments on the viral envelope to which a vaccine might be developed (Gallo, 1985).
- There are no currently effective treatments for AIDS. Treatment regimens must address both antiviral approaches as well as restoring immune function. Antiviral agents, while effective in reducing viral counts in AIDS patients, are extremely toxic and require ongoing administration to continue their antiviral action (Fauci et al., 1984). Effective immunostimulant treatments do not presently exist, although recent findings with Interleukin-2 may prove useful for AIDS patients eventually (Lane et al., 1984).

One does not wish to sell short the possibility of dramatic advances in the treatment and prevention of AIDS. They occur and hopefully they will happen and happen soon for those infected with HTLV-III. Our colleagues in cancer and immunologic research caution us, however, not to expect either effective vaccines or treatments soon (Gallo, 1985).

The papers in this panel make the point that neuropsychiatric symptoms—behavioral, affective, cognitive, and motoric—are part of the AIDS picture. Of course, there are sample to sample variations, but a consistent picture nonetheless emerges. Not only is there evidence of a global, and to date untreatable, brain disease present in AIDS patients, but this may also be one of the most critical issues determining choices in clinical care. The course of AIDS is characterized by intermittant infections, some of which are amenable to medical intervention. Between episodes of infection, these patients generally remain outside the hospital. When cognitive impairment appears, decisions about chronic institutionalization are generally made. Future research must address the issue of cognitive impairment from HTLV-III infection. Efficacious treatment for the immune defects in AIDS which do not act in the central nervous system (CNS) will likely result in a population of healthy, but demented, AIDS patients. As papers in this panel indicate, neuroreceptor and neurotransmitter research offer a most intriguing opportunity for AIDS research. At this point we must conclude that HTLV-III exhibits tissue specificity both for the T4 lymphocyte, perhaps the monocyte, and white matter in the CNS. Speculatively, data presented in these papers might lead us to consider the role of neuroreceptor and neurotransmitter research in the development of effective treatment and prevention strategies for AIDS.

While the development of vaccines and antiviral therapies generally are outside the purview of neuropsychopharmacologic research, many agents which have immunosuppressant actions do typically fall within this research area. We do need to learn much more about the role of cofactors in the progress of a viral illness such as AIDS. Various psychoactive agents including alcohol, nitrites, marijuana, heroin, as well as stressful life experience and affective illness have all been reported to be associated with immunosuppression (Morahan et al., 1979; Orangio et al., 1983; MacGregor & Gluckman, 1979; Ader, 1981). In an illness marked by progressive health deterioration secondary to impaired immunoresponsivity, we might speculate that agents which worsen immune function would hasten the course of this illness. More speculative would be the extent of such an effect or whether compromised immune function observed in many members of AIDS high risk groups is causally linked to the onset of HTLV-III infection. Research needs to replace speculation.

AIDS research represents one example of many illnesses which fall at the intersection of neuroscience, immunology, and endocrinology. Both predisposition and illness outcome may be expressed in behavioral terms. These are concepts and methodologies familiar to those in the field of neuropsychopharmacology. The progress that has been made to date in AIDS research is the result of rapid utilization of technologies already in place. The application of other technologies and the development of new technologies are needed to move the field of AIDS research forward. It is time to make use of the neuroscience and behavioral science technologies to advance AIDS research.

References

Ader, R. *Psychoneuroendocrinology*. New York: Academic Press, 1981.

Benn, S., Rutledge, R., Folks, T., et al. Genomic heterogeneity of AIDS retroviral isolates from North America and Zaire, *Science*, 230:949–951, 1985.

CDC update:Acquired Immunodeficiency Syndrome—United States. *MMWR*, 35:17–20, 1986.

Curran, J.W., Morgan, W.M., Hardy, A.M., et al. The epidemiology of AIDS: Current status and future prospects. *Science*, 229:1352–1357, 1985.

Fauci, A.S., Macher, A.M., Longo, D.M., et al. Acquired Immunodeficiency Syndrome:Epidemiologic, clinical, immunologic, and therapeutic considerations. *Annals of Internal Medicine*, 100:92–106, 1984.

Fauci, A.S., Masur, H., Gelmann, E.P., et al. The Acquired Immunodeficiency Syndrome:An update. *Annals of Internal Medicine*, 102:800–813, 1985.

Gallo, R.C. AIDS:An update; presentation to the Institute of Medicine, October, 1985.

Ho, D.D., Rota, T.R., Schooley, R.T., et al. Isolation of HTLV-III from cerebrospinal fluid and neuronal tissues of patients with neurologic syndromes related to the Acquired Immunodeficiency Syndrome. *New England Journal of Medicine*, 313:1493–7, 1985.

Holland, J.C., and Tross, S. Psychosocial and neuropsychiatric Sequelae of AIDS and AIDS-related disorders: An overview. *Annals of Internal Medicine* (in press).

Lane, H.C., Siegal, J., Rook, A.H., et al. Use of Interleukin-2 in patients with Acquired Immunodeficiency Syndrome. *Journal of Biologic Response Modifiers*, 3:512–516, 1984.

Levy, J.A., Shimabukuro, J., Hollander, H., et al. Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. *Lancet*, 2:586–8, 1985.

Marmor, M., DesJarlais, D.C., Friedman, S.R., et al. The epidemic of Acquired Immunodeficiency Syndrome (AIDS) and suggestions for its control in drug abusers. *Journal of Substance Abuse Treatment*, 1:237–247, 1984.

Morahan, P.S., Klykken, P.C., and Smith, S.H. Effect of cannabinoids on host resistance to *Listeria monocytogenes* and herpes simplex virus. *Infection and Immunity*, 23:670–674, 1979.

MacGregor, R.R., and Gluckman, S.G. Effect of acute alcohol intoxication on granulocyte mobilization and kinetics. *Blood*, 52:551–559, 1979.

Orangio, G.R., Latta, P.D., Marino, C., et al. Infections in parenteral drug abusers. *American Journal of Surgery*, 146:738–741, 1983.

Resnick, L., diMarzo-Veronese, F., Schupbach, J., et al. Intra-blood-brain-barrier synthesis of HTLV-III-specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex. *New England Journal of Medicine*, 313:1498–1504, 1985.

Psychosocial Aspects of AIDS Risk

David G. Ostrow, M.D., Ph.D.,[1] Jill Joseph, Ph.D.,[2] Andrew Monjan, Ph.D.,[3] Ronald Kessler, Ph.D.,[4] Carol Emmons, Ph.D.,[2] John Phair, M.D.,[5] Robin Fox, M.S.,[6] Lawrence Kingsley, D.P.H.,[7] Janice Dudley, D.P.H.,[8] Joan S. Chmiel, Ph.D.,[9] and Mark Van Raden, M.S.[10]

Introduction

Since its discovery in 1981 (Centers for Disease Control, 1981, 1981a) there have been approximately 20,000 cases of acquired immunodeficiency syndrome (AIDS) reported to the Centers for Disease Control (Centers for Disease Control, 1986). Central to all considerations of this usually fatal syndrome has been the concentration of cases in several specific risk groups, most notably homosexual or bisexual men (73 percent) and intravenous drug abusers (17 percent). Given the recency of AIDS and its varied clinical presentations and course, the National Institutes of Health (NIH) in collaboration with the National Cancer Institute (NCI) in 1983 set about the establishment of a series of natural history and epidemiology studies of immune function in homosexually active men in four cities including those with both very high and relatively low AIDS incidence rates. The Multicenter AIDS Cohort Study (MACS), as that cooperative research program has come to be known, began to enroll subjects early in 1984 in Los Angeles, Chicago, Pittsburgh, and Baltimore. The goal of the MACS is to investigate, in a relatively large cohort of homosexual men, the natural history of infections and other problems leading to the development of AIDS with particular attention to the sequelae of HTLV-III infection, early medical manifestations of AIDS, and transmissability of HTLV-III within subpopulations of the cohort. However, we also are focusing on the identification of potential cofactors or modulators associated both with the risk of developing HTLV-III infection once exposed to the virus and the subsequent development of specific medical endpoints such as AIDS and AIDS related illness in an individual. Between April of 1984 and March 1985, the full MACS cohort of over 1,000 men in each MACS center were enrolled and subjected to a medical history interview, physical examination, immunological and viral laboratory testing, specimen acquisition, and lengthy epidemiological investigation. Since then, each subject has returned on a 6-month basis for follow-up evaluation. In addition, those individuals showing recent seroconversion to a positive HTLV-III antibody test are currently being enrolled in a quarterly examination protocol to determine the sequence of immunological consequences of HTLV-III infection and, by attempting to isolate virus from various bodily tissues, to determine more precisely the infectivity and routes of transmission of the HTLV-III virus. Preliminary retrospective findings from the baseline MACS protocol have been summarized elsewhere (Multicenter AIDS Cohort Study, 1985). However, it is important to note that approximately 40 percent of the MACS cohort was HTLV-III antibody positive at baseline. The degree of seropositivity correlated with

---

[1] Biological Psychiatry Programs, Northwestern University Medical School, 259 E. Erie St., Chicago, IL 60611.

[2] Department of Epidemiology, University of Michigan School of Public Health, 109 Observatory, Ann Arbor, MI 48109.

[3] NIA-NIH, BRCM, PAB, Building 31 Room 5C27, 9000 Rockville Pike, Bethesda, MD 20205.

[4] ISR, University of Michigan, 426 Thompson St. Ann Arbor, MI 48106.

[5] Section of Infectious Diseases, Northwestern University School of Medicine, 320 E. Superior St., Chicago, IL 60611.

[6] Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, MD 21205.

[7] Pitt Men's Study, P.O. Box 7319, Pittsburgh, PA 15213.

[8] UCLA School of Public Health, Center for Health Sciences, Los Angeles, CA 90024.

[9] Epidemiology-Biometry Section, Northwestern Cancer Center, 330 E. Chicago Ave., Chicago, IL 60611.

[10] Epidemiology-Biometry Section, NIH-NIAID, 5333 Westbard Ave., Bethesda, MD 20892.

Paper presented at the American College of Neuropsychopharmacology Annual Meeting, Maui, Hawaii, December 10, 1985.

clinical status: in asymptomatic men with no extrainguinal lymphadenopathy or other signs or symptoms of AIDS related complex (ARC), the positivity rate was only 20 percent. In contrast, in subjects with lymphadenopathy with or without other constitutional symptoms of ARC, the positivity rate ranged from 65 to 85 percent.

Methods

Because of the enormous psychological and social consequences accompanying being at risk for AIDS and the belief that psychological and other factors may be involved in determining disease course following HTLV-III infection, a group of investigators from the University of Michigan and the Chicago MACS team have undertaken a psychosocial study of the participants in the Chicago cohort of the MACS study. The "Coping and Change" study has as its principal objectives the determination of the psychological and social characteristics of the AIDS crisis as experienced and perceived by homosexual men participating in the MACS. We are assessing, using previously validated self-administered questionnaires, a broad set of psychosocial variables, including: perceived risk of AIDS, causal attributions, personality, lifestyle, life events, social support networks, and coping mechanisms (Joseph et al., 1984). As outcomes, we are studying behaviors which may place one at increased risk for acquiring HTLV-III infection, social functioning in a variety of settings, and various measures of psychological distress and symptomatology (Joseph et al., 1985). In addition, we are ultimately interested in examining the relationship between these psychological measures, immunological changes and clinical outcomes (AIDS, ARC, lymphadenopathy) taking place both independently and as the result of HTLV-III infection in the study population.

Results

The basic characteristics of our population are presented in Table 1. Our subjects are upper middle class, predominantly white, with at least 4 years of college and postgraduate education. The majority of subjects described themselves "exclusively homosexual" on the Kinsey sexual preference scale (Kinsey et al., 1948) and at least 20 percent have had a close sexual or social contact with an AIDS patient. An overview of the extent to which specific high-risk sexual behaviors were reported to have changed in our cohort at the time of baseline evaluation is shown in Table 2. We must caution that subsequent waves of analysis are indicating further behavioral change. We focus here on three specific high-risk behaviors, namely receptive oral-genital, receptive anal-genital, and insertive oral-anal intercourse. From 11 to 60 percent of subjects ever having performed a specific sexual behavior reported not having engaged in that behavior during the month prior to baseline evaluation. Of the remaining individuals, approximately half avoided exchange of ejaculate during oral-genital intercourse in line with recommended sexual practices modifications for the avoidance of transmission of HTLV-III infection. These modifications of either condom use or avoidance of ejaculation were less frequently used by persons continuing to engage in receptive anal intercourse. Pilot data indicated that this period of 1 month prior to questionnaire completion provides a valid and accurately remembered indication of current sexual activity.

The difficulty of completely eliminating high-risk sexual behavior is also indicated by the response to questions directly asking the subject to assess the extent and significance of their sexual behavioral changes. While three-quarters of our subjects replied that they feel they have changed a specific aspect

TABLE 1. Chicago Psychosocial Study Cohort Characteristics ($N = 947$).

Mean age	34.6 years
Percent white	96.7%
Mean annual income	$24,611
Mean education	16.2 years
Percent professional occupation	47.5%
Percent currently working	89.5%
Percent religious affiliation	31.5% Protestant 23.3% Catholic
Percent "exclusively homosexual" identity	61.8%
Mean time since first homosexual experience	16.0 years

TABLE 2. Prevalence of Risk-Related Behaviors During the Past Month Among 947 Homosexual Chicago Men: June 1984–August 1985.

		Behavior in the Past Month (% of those ever engaging in behavior)				
			Continued Behavior With Modification*		Continued Behavior Without Modification*	
Behavior	*N* Who Ever Engaged in Activity	Did not Engaged in Activity	With Single Steady Partner Only	With Other Partners	With Single Steady Partner Only	With Other Partners
Receptive Oral-Genital Sex (Partner's penis put in respondent's mouth)	921	11.2	4.3	34.3	9.8	40.3
Receptive Anal-Genital Sex (Partner's penis put in respondent's rectum)	893	42.2	1.0	10.0	8.0	38.9
Insertive Oral-Anal Sex (Respondent's tongue put in partner's anus)	812	60.2	—	—	6.9	32.9

*Modification defined as behaviors which potentially interrupt exposure to semen such as condom use or withdrawal before ejaculation

of their behavior and made an effort to reduce the total number of sexual partners, only one-half of the cohort at baseline felt that they had changed "medically important things and been fairly consistent in those changes." This pattern of some behavioral change coupled with difficulty in maintaining that change is what we would expect for relatively established sexual behaviors for which rapid elimination is urged in order to reduce the risk of disease, a largely negative inducement. This is shown when we look at the degree of psychological stress associated with these changes. Subjects reported modest amounts of perceived stress in terms of making those behavioral changes that they had already accomplished. While the thought of eliminating the most frequently persistent behavior, oral-genital intercourse, was associated with the highest level of anticipated stress, over half of the subjects rated the anticipated stress of making further changes which would bring them into a low- or no-risk situation as either very stressful or fairly stressful.

Further examination of our data indicates that the pattern of behavioral change is creating subgroups within our cohorts. When we look at average number of sexual partners or frequency of any specific activity, we see a very skewed distribution with the mean numbers much higher than the mode (e.g., 6.0 vs. 1.0). Examination of the actual distribution of numbers of sexual partners (Figure 1) very clearly shows that the majority of our subjects have reduced the number of sexual contacts to relatively low numbers whereas a few subjects remain with very high numbers of sexual partners indicating two distinct patterns of sexual behavior in our cohort.

Examination of the reasons given for continued high-risk sexual behavior indicates several patterns of rationalization for persistent high risk behavior. Most frequent (75 to 80 percent) is the assertion that the individual feels he is at low risk by "limiting the number of sexual partners." However, almost as frequently given are statements that the activity is too enjoyable to stop despite prior resolutions. Between 30 to 40 percent also report that peer pressure and expectations by sexual partners are determining factors in the continuation of that activity. Finally, 25 percent of the cohort expresses some form of a sense of invulnerability—either they do not believe that their sexual activities place them at risk or that they believe that many more sexual exposures than they are having are necessary to develop AIDS. This is in spite of information given to the cohort stating very clearly that any sexual contact involving the exchange of bodily fluids places one at high risk of transmitting or contracting infection.

We have just begun to examine the psychological outcomes associated with the various behavioral and social consequences of being at risk for AIDS. We here present some ini-

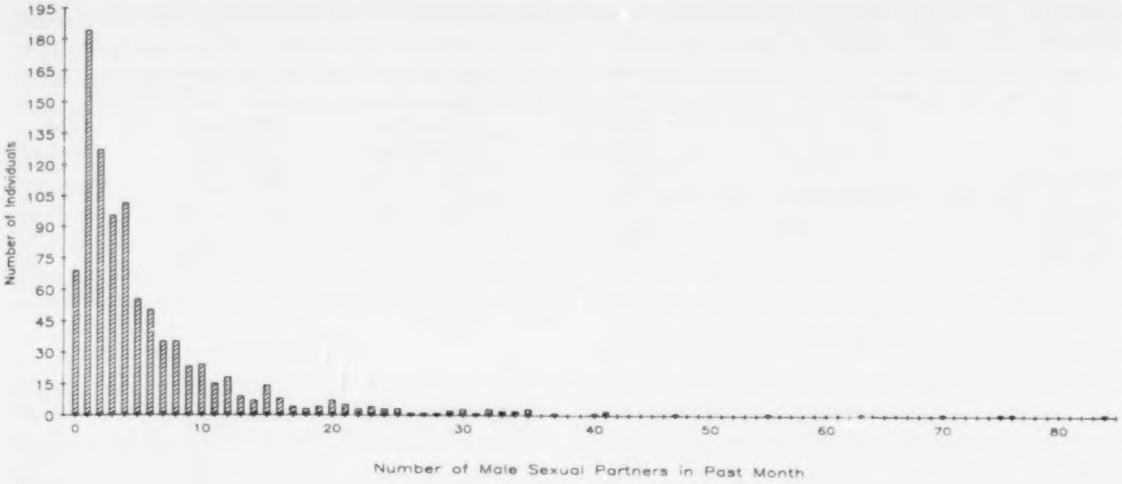


FIGURE 1

tial data utilizing the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977) which has been and continues to be administered to all 5,000 members of the MACS cohort in all four cities. The baseline CES-D data indicates a remarkable degree of consistency in the patterns of responses in our cohorts between the four cities, indicating that at least in terms of this very broad measure of psychological function there is little difference between the cohorts whether they reside in Los Angeles, Chicago, Pittsburgh, or Baltimore. In comparing the overall responses of the MACS cohort to a published study of 680 married men (Ross & Mirowsky, 1984) we see that the former is more highly educated (16.3 vs. 13.1 years) and has a modest elevation in total CES-D score (9.75 vs. 8.88, $p < .01$). Table 3 shows the distribution of CES-D scores in our population as compared to the Ross and Mirowsky sample of married men with the MACS population separated on the basis of whether they were HTLV-III antibody negative or positive at the time of evaluation. Our subjects are elevated primarily in the depressed affect subscale of the CES-D when compared to the married male cohort. Differences between HTLV-III negative and positive members of the MACS cohort are seen only in the depressed affect and enervation subscales of the CES-D. Examination of the specific items endorsed more frequently by HTLV-III positive subjects in our cohort indicated a cluster of items (feeling blue, difficulty concentrating, poor sleep, lack of energy, and difficulty communicating to others) which suggested a higher level of anergy in HTLV-III exposed individuals. These symptoms are similar to those found by investigators looking at AIDS patients with CNS complications of HTLV-III infection (Perry & Tross, 1984). Univariate analysis of the relationship between a broad set of predictor variables (sex-

TABLE 3. CES-D Scores in 3,058 MACS Subjects With Available HTLV-III Antibody Data.

CES-D Factor	MACS Subjects HTLV-III Neg	 HTLV-III Pos	 Married Men*
Depressed Affect	3.11	3.36	1.96
Enervation	3.17	3.49	3.48
Positive Affect	2.71	2.66	2.96
Interpersonal Functioning	0.45	0.46	0.48
Total CES-D Score	9.55	10.08	8.88
Overall CES-D Score	9.75		

*Data extracted from Ross and Mirowsky, *Am. J. Epid.*, 119:997, 1984.

TABLE 4. Effects of HTLV-III Antibody Status and Lymphadenopathy Status on CES-D Scores in MACS Cohort.

	HTLV-III Neg				HTLV-III Pos			
	Exam Neg Perceived		Exam Pos Perceived		Exam Neg Perceived		Exam Pos Perceived	
CES-D Factor	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
Depressed Affect	3.02*	5.43	3.02**	6.87	3.11*	4.58	3.26*	4.30
Enervation	3.03	5.00	3.07*	5.61	3.17	4.97	3.40	4.25
Total CES-D	9.15*	15.49	9.25**	17.77	9.22	13.63	9.93*	12.24
No. of subjects	1701	47	1100	76	495	34	1054	284

*$p < .01$. **$p < .001$.

ual and drug use behaviors, health, history and physical examination findings) revealed that self-reported lymphadenopathy was strongly associated with increased CES-D scores.

The effect of perceived lymphadenopathy on self-reported depression and anergy can be seen in Table 4 where CES-D scores are given for the eight subgroups according to HTLV-III serology status, lymphadenopathy observed on physical exam, and perceived lymphadenopathy. In almost all comparisons, subjects who denied the presence of swollen lymph nodes had CES-D scores as low as persons without actual and perceived lymphadenopathy. While the highest CES-D scores were obtained in seronegative subjects with recognized lymphadenopathy, in the seropositive group persons who reported lymphadenopathy which was not confirmed on physical examination had higher CES-D scores than those with examiner confirmed lymphadenopathy ($p < .05$). It is interesting that the three specific symptoms which were most elevated in healthy seropositive subjects who worried that they had lymphadenopathy were restless sleep, fearfulness, and "difficulty getting going."

The final data presented in Figure 2 show the relationship between the pattern of perception and actual presence of lymphadenopathy and an overall measure of cellular immune function, the T-helper: T-suppressor lymphocyte ratio. The higher the T-helper:T-suppressor ratio, the more likely that an individual has an adequately functioning cellular immune system. Looking at the left side of the figure, there was an effect of perception of lymphadenopathy in HTLV-III seronegative individuals with those perceiving themselves as having lymphadenopathy having significantly lower helper:suppressor ratios than those who did not ($p < .001$). However in the HTLV-III antibody positive portion of our cohort (right side of figure) only the effect of HTLV-III infection on this cellular immune parameter is seen. Any differences based on perception or presence of lymph nodes seen in the antibody negative group are lost once the overriding effect of this virus on the helper:suppressor ratio has taken place. These findings suggest that if we are to look for psychoimmunological correlates in cohorts at risk of AIDS, we must look for situations where we can factor out the overwhelming effect of virus infection from the more modest effects of psychological functioning upon the immune system.

In conclusion, this overview of the psychological and behavioral consequences of AIDS risk illustrates some of the profound changes taking place in the male homosexual population as the result of this health crisis. Coupled with the psychological consequences of the threat of developing AIDS are the secondary stresses of the behavioral change itself and the social isolation and stigmatization of the

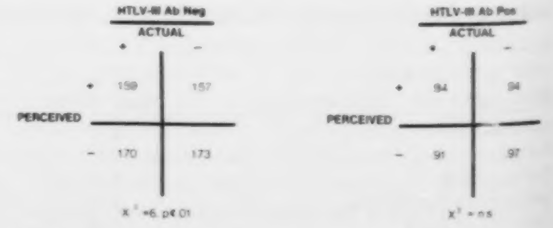


FIGURE 2. T-helper/T-suppressor ratio and lymphadenopathy status.

disease. We must now add the effects of CNS HTLV-III infection to the list of factors potentially contributing to the depression and anergy seen in our study population (Shaw et al., 1985; Ho et al., 1985). Carefully designed prospective examinations of psychological, cognitive, and neurological functioning in persons infected with HTLV-III are necessary if we are to sort out the relative contributions of these various factors to the overall mental health impact of AIDS.

References

Centers for Disease Control. Pneumocystis Pneumonia-Los Angeles. *Mortal. Morbid. Weekly Rep.*, 30:250–252, 1981.

Centers for Disease Control. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men—New York City and California. *Mortal. Morbid. Weekly Rep.*, 30:305–358, 1981a.

Centers for Disease Control. AIDS Activity Section. Monthly AIDS surveillance report, April 1986. Multicenter AIDS Cohort Study. Prevalence and correlates of HTLV-III antibodies among 5,000 gay men in four cities. *Program Abstracts 25th Intersci. Conf. Antimicrobial Agents Chemother.*, 25:229, 1985.

Ho, D.D., Rota, T.R., Schooley, R.T., et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N. Eng. J. Med.*, 313:1493–1497, 1985.

Joseph, J.G., Emmons, C.A., Kessler, R.C., et al. Coping with the threat of AIDS: An approach to psychosocial assessment. *Amer. Psychol.*, 39:1297–1302, 1984.

Joseph, J.G., Emmons, C.A., Kessler, R.C., et al. Changes in sexual behavior of gay men: Relationship to perceived stress and psychiatric symptomatology. Presented at the First International Conference on AIDS, Atlanta, GA, April 14–17, 1985.

Kinsey, A.C., Pomeroy, W.B., and Martin, C.E., *Sexual Behavior in the Human Male*. Philadelphia: W.B. Saunders, 1948.

Perry, S.W., and Tross, S. Psychiatric problems of AIDS patients at the New York Hospital: Preliminary report. *Pub. Health Rep.*, 99:200–205, 1984.

Radloff, L.S. The CES-D Scale: A self-report depression scale for research in the general population. *Appl. Psychol. Meas.*, 1:385–401, 1977.

Ross, C.E., and Mirowsky, J. Components of depressed mood in married men and women. *Am. J. Epid.*, 119:997–1004, 1984.

Shaw, G.M., Harper, M.E., Hahn, B.H., et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science*, 227:177–182, 1985.

Neuropsychiatric Aspects of AIDS

Russell T. Joffe, M.D.,[1] David R. Rubinow, M.D., [2] Kathleen Squillace, B.S.,[3] Clifford H. Lane, M.D.,[4] Connie C. Duncan, Ph.D.,[3] and Anthony S. Fauci, M.D.[4]

Neurological complications are a commonly observed feature of acquired immune deficiency syndrome (AIDS) (Snider et al., 1983). Several case reports have described AIDS patients, particularly those with subacute encephalitis, who present with clinical manifestations of a rapidly progressive delirium or dementia (Ochitill et al., 1984; Loewenstein & Sharfstein, 1983–84; Snider et al., 1983). There have also been reports of adjustment disorders with altered mood in patients after they have been diagnosed with AIDS (Ochitill et al., 1984). However, these case studies describe either patients with gross central nervous system dysfunction or patients who have been referred for psychiatric consultation specifically because of behavioral disorders or alteration in mental state. Therefore, very little is known about the neuropsychiatric characteristics of patients with AIDS unselected for psychiatric disorders or neurological complications.

In this paper, we report preliminary data from a systematic investigation of the neuropsychological functioning and occurrence of psychiatric disorders in a group of AIDS patients who had no clinical evidence of neurological disease.

Subjects

Thirteen male homosexual AIDS patients, who were electively admitted to the National Institute of Allergy and Infectious Disease for various study protocols, gave oral and written informed consent to participate in this study. All subjects were free of acute illness and had no clinical or laboratory evidence of systemic infection; three patients did have residual Kaposi skin lesions. Most patients were medication-free, and none had recently received psychoactive drugs.

Ten males were recruited by the volunteer office at the National Institutes of Health from the local homosexual community to serve as a control group. All were screened clinically and by routine laboratory tests for the absence of medical illness.

Method

A standardized psychiatric interview, using a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS—L) (Spitzer & Endicott, 1978*a*) was performed on 10 patients and all the controls. Psychiatric diagnoses for the subjects and their first-degree relatives were derived from the interview according to Research Diagnostic Criteria (RDC) (Spitzer et al., 1978*b*). All subjects, at the time of interview, completed the Beck Depression Inventory (Beck et al., 1961) and the Symptom Checklist 90—Revised (SCL-90R) (Derogatis, 1984).

A neuropsychological test battery that evaluated general intelligence as well as specific cognitive functions was performed on all patients and controls. The specific cognitive functions tested include abstraction and categorization, visual-spatial organization and visual-motor performance, and attention and concentration. These tests included:

1) The Wechsler Adult Intelligence Scale—Revised (WAIS—R),
2) Trail Making Test,
3) Rey Osterreith Complex Figure Test,
4) Halstead Category Test,
5) Wisconsin Card Sort,

---

[1] Department of Psychiatry, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, M5B 1W8, Canada.

[2] Psychiatric Consultation Service and Biological Psychiatry Branch, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, MD 20205.

[3] Laboratory of Psychology and Psychopathology, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, MD 20205.

[4] Laboratory of Immunoregulation, National Institute of Allergy and Infectious Disease, 9000 Rockville Pike, Bethesda, MD 20205.

6) Cancellation Test,
7) Wechsler Memory Scale,
8) The Test of Selected Reminding and Restricted Reminding (Buschke),
9) Stroop Color-Word Test,
10) Continuous Performance Task (CPT),
11) Raven's Progressive Matrices,
12) Babcock Story Recall Test,
13) Harris Hand Dominance Test.

In addition a personality profile was obtained with the Minnesota Multiphasic Personality Inventory (MMPI).

Details of these tests and their references are available from the authors on request.

Statistical analysis was by group *t*-tests and Fisher Exact Tests.

Results

a) *Psychiatric Interview.* Three patients (1—substance abuse disorder, 2—adjustment disorder with depressed mood) and three controls (adjustment disorders with mixed mood) fulfilled RDC criteria for current psychiatric disorders. Eight patients and six controls had a history of past psychiatric disorder (p = NS, Fisher Exact Test). Past major depressive disorder tended to be more common in patients (5 of 10) than controls (1 of 10) ($p = 0.07$, Fisher Exact Test). However, a history of past adjustment disorder tended to be significantly more common in controls (5 of 10) than patients (1 of 10) ($p = 0.07$, Fisher Exact Test). A family history of psychiatric disorder was evident in four patients and four controls.

AIDS patients had significantly higher scores on the Beck Depression Inventory than controls (14.4 ± 2.7 vs. 4.9 ± 1.2, $t = 2.90$, $p < .02$). There was also a nonsignificant trend for patients to have higher scores on the Depression Scale of the SCL-90R (1.16 ± .04 vs. 0.33 ± 0.2, $t = 2.01$, $p < .1$). However, only the two patients with adjustment disorder with depressed mood scored in the depressed range (more than 15) (Beck et al., 1961) on the Beck Depression Inventory.

b) *Neuropsychological Test Battery.* Patients and controls were well-matched for age (34.8 ± 7.0 years vs. 35.3 ± 6.9 years, $t = 0.20$, $df = 21$, p = NS), years of education (14.2 ± 0.6 years vs. 14.3 ± 0.7 years, $t = 0.02$, $df = 21$, p = NS), and right handedness (11 patients and 9 controls, p = NS, Fisher Exact Test).

All mean scores on the WAIS-R were within the normal range. However, AIDS patients had significantly lower scores than controls on Full Scale IQ ($t = 2.26$, $p < .05$), and Verbal IQ ($t = 2.30$, $p < .05$). (*See* Table 1.) There was a trend for performance IQ to be lower in AIDS patients as compared with controls ($t = -1.65$, $p < .1$). AIDS patients also scored significantly lower than controls on the following subtests: Vocabulary ($t = -3.05$, $p < .01$), Similarities ($t = -2.45$, $p < .05$), and Digit Symbol ($t = -2.93$, $p < .05$).

On the Halstead Category Test, patients, as compared with controls, had a significantly higher mean number of errors ($t = 2.61$, $p < .05$). Moreover, 5 of 8 patients as compared with 2 of 10 controls scored above 50, the upper limit of normal performance ($p = 0.07$, Fisher Exact Test). On the other hand, no difference was noted between patients and controls in either mean or perseverative error scores on the Wisconsin Card Sort, a test of categorization and abstraction that is particularly sensitive to frontal lobe dysfunction.

On the Cancellation Tests, timed vigilance and attention tasks which also measure motor skills, patients completed significantly fewer items and had significantly fewer correct responses than controls on each of the three sections, although no significant difference in number of errors committed was observed. On the CPT, however, a test of sustained visual attention, no significant difference was observed between subjects and controls in variables measured, including percentage of correct responses, omission errors, commission errors, and mean reaction time. Furthermore, AIDS patients did not differ from controls in their performance on the other test of attention and concentration, the Stroop Color-Word Test.

AIDS patients took significantly longer than controls to complete Trial B of the Trail Making Test ($t = 2.69$, $p < .05$). However, their mean score was within the normal range on Trial B, and there was no difference in performance on Trial A between patients and controls. The Trail Making Test is a measure of visual-conceptual and motor performance.

TABLE 1. Significant Differences in Neuropsychological Test Scores Between AIDS Patients and Controls.

Test	Description	AIDS Patients[1]	Controls	t^2	df
1. Wechsler Adult Intelligence Scale—Revised:	General Intelligence				
Full Scale IQ		102.8 ± 3.2	113.0 ± 3.0	-2.26^{*}	21
Verbal IQ		102.6 ± 3.4	113.0 ± 2.6	-2.30^{*}	21
Performance IQ		101.8 ± 2.9	109.5 ± 3.7	-1.65	21
Vocabulary Subtest		11.0 ± 0.6	13.6 ± 0.5	-3.05^{**}	21
Similarities Subtest		9.9 ± 0.6	12.0 ± 0.5	-2.45^{*}	21
Digit Symbol Subtest		9.0 ± 0.6	11.5 ± 0.7	-2.93^{*}	21
2. Halstead Category Test	Abstraction and Categorization	54.4 ± 5.1	31.5 ± 6.7	2.61^{*}	18
3. Trail Making Test: Trial B	Visual conceptual and motor performance	77.6 ± 4.4	59.8 ± 4.9	2.69^{*}	21
4. Rey Osterreith Complex Figure Test:	Visual-spatial organization				
Copying Percentile Score		80.4 ± 6.0	57.9 ± 9.3	2.12^{*}	21
5. Minnesota Multiphasic Personality Inventory:	Personality Profile				
Hysteria Scale (Hs)		69.4 ± 4.3	50.4 ± 2.4	3.6	21
Hypochondriasis Scale (Hy)		68.8 ± 2.7	61.7 ± 2.1	1.9	21
6. Cancellation Test	Timed Vigilance and attention task; motor skills				
Section 1: Number completed		229.1 ± 12.1	282.1 ± 9.7	-3.1	21
Number correct		62.1 ± 3.3	76.4 ± 2.4	-3.2	21
Section 2: Number completed		302.5 ± 14.5	363.7 ± 23.0	-2.3	21
Number correct		60.4 ± 2.7	74.3 ± 3.9	-3.0	21
Section 3: Number completed		154.8 ± 6.7	198.1 ± 12.0	-3.4	21
Number correct		63.8 ± 2.4	81.4 ± 4.2	-3.8	21

[1] Values equal mean ± SEM.
[2] Group t-tests.
$^{*}p < .05$.
$^{**}p < .01$.

In contrast to the other tests, patients did better than controls on the copying but not the recall part of the Rey Osterreith Complex Figure Test, a test of visual-spatial organization. Patients as compared with controls had a higher percentile score on the copying component ($t = 2.12, p < .05$), but there was no significant difference in scores on immediate and 40 minute recall.

On all memory tests, The Wechsler Memory Scale, Buschke and Babcock, as well as the Raven's Progressive Matrices, the performance of patients was not different from that of controls and all mean scores were within normal limits.

On the MMPI, AIDS patients, as compared with controls, had significantly higher scores on only the hysteria (Hs) scale ($t = 3.63, p < .01$), although they tended to also have a higher score on the hypochondriasis (Hy) scale ($t = 1.99, p < .1$). With the exception of the hysteria and hypochondriasis scales, which were markedly elevated in the patients, scores for both subjects and controls were similar to those previously reported for homosexuals (Horstman, 1975).

Discussion

Our data show that a group of AIDS patients unselected for psychiatric morbidity are more likely to have a history of past depressive illness than a group of medically well homosexual controls. The implications of this finding are uncertain. However, depression has been associated with several measures of immune system dysfunction, and depressed patients have been reported to have increased susceptibility to cancer, infections, and allergic disorders, all of which may be associated with disorders of immune function (Kronfol et al., 1983). Speculation must clearly be limited pending replication of this observation in a larger group of patients.

Our neuropsychological test data show that AIDS patients, in the absence of evidence of active neurological disease, when compared with medically well homosexual controls matched for age and educational level, show reduced levels of general intellectual and specific cognitive function.

On the WAIS-R, the significantly lower Full Scale and Verbal IQ and the trend towards significantly lower Performance IQ is suggestive of lower general cerebral functioning in the AIDS patients compared with controls. In addition, the significantly reduced Similarities and Digit-Symbol subtest scores in the patients are consistent with other evidence of diffuse cerebral impairment (Lezak & Glaudin, 1972). On the other hand, the significantly reduced Vocabulary subtest score in the AIDS patients may be more consistent with lateralized, particularly dominant hemisphere, cerebral dysfunction, as this subtest is usually the least affected by diffuse brain dysfunction or psychiatric disorders (Lezak & Glaudin, 1972). Therefore, the Vocabulary subtest data, if not due to a sampling error, may suggest a dominant hemisphere dysfunction in the AIDS patients, and the significantly reduced Similarities subtest score, while suggestive of diffuse cerebral dysfunction, may also be consistent with such a reduction in dominant hemisphere function (Lezak & Glaudin, 1972).

The significantly fewer total and correct items on the Cancellation Test, the significantly longer time to complete part B of the Trail Making Test, and the reduced Digit-Symbol subtest scores in the AIDS patients as compared with controls are all suggestive of a slowing of visual-motor performance. On the other hand, on the CPT, also a timed test, no difference between patient and control groups were evident. However, the CPT differs from the Trail Making Test, Cancellation Test and Digit Symbol subtest in that items are presented at a steady rate determined by the test, not the subject, whereas the latter three tests are self-paced with speed rewarded. It is, therefore, possible that impairment on these tests may represent diminished motivation.

The mean score on the Halstead Category Test was in the abnormal range in the AIDS patients as compared with the controls. The abnormal Halstead Test scores are suggestive of abnormalities of abstraction and conceptualization as well as being a sensitive measure of general brain dysfunction (Halstead, 1947).

The significance of our neuropsychological data is unclear. It is possible that depressed mood could account for these abnormal findings, as depression can have an effect on all these tests, particularly on the more effortful, self-paced tasks such as the Cancellation Test, Trail Making Test, and Digit Symbol subtest. However, when the data were reanalyzed excluding the two patients who scored in the depressed range on the Beck Depression Inventory, significant differences between patients and controls remained the same. Obviously, reduced motivation may exist despite the absence of clinically evident depression.

The absence of differences in memory tests between the AIDS patients and controls suggests that there was preservation of memory function in the patient group despite evidence of general and specific cognitive dysfunction.

With the exception of the hysteria and hypochondriasis scales, the scores on the MMPI did not differ significantly between patient and control groups. Furthermore, the scores in both groups were not substantially different from those reported for both homosexual and heterosexual males (Horstman, 1975). The significantly elevated scores on the hysteria and the nonsignificantly elevated hypochondriasis and depression scales in the AIDS patients are similar to the elevated "neurotic triad" which has been described in neurological patients with no psychiatric disease (Lezak & Glaudin, 1972).

Our preliminary data, although requiring replication in larger samples, are similar to the data reported by Tross and Holland in this volume. Nonetheless, longitudinal, prospective studies of cognitive functioning in a larger group of AIDS patients are necessary to ascertain whether general cerebral and dominant hemisphere function in AIDS patients is impaired and if it progressively declines over the course of the illness. Further studies should also include a non-neurological medically ill control group to clarify whether the neuropsychological impairments are specific to AIDS or to medical illness in general. Finally, although the number of *t*-

tests performed in our data analysis increased the likelihood of observing significant differences on the basis of chance, the significant differences observed were almost uniformly (15/16) in the direction of greater cognitive impairment in the patients, thus suggesting that AIDS patients do perform more poorly than controls on at least some cognitive measures.

In conclusion, our findings suggest that AIDS patients, in the absence of clinical evidence of neurological complications, as compared with medically well homosexual controls, are more likely to have a history of past major depressive illness and to have evidence of reduced general and specific cognitive function. Our data are intriguing in the light of the recent report that the HTLV-III virus is trophic to brain tissue, perhaps in a site-specific manner (Shaw et al., 1985). Our findings, although preliminary, raise some important clinical issues. These include the potential prognostic importance of these neuropsychological findings, the extent to which their longitudinal course may parallel that of the illness, their potential reversibility if an effective treatment for AIDS is found, and their impact on the long-term rehabilitation of the AIDS patients. Further study of neuropsychological function in HTLV-III positive patients, with and without AIDS, will also advance our understanding of the relationship between immune system and central nervous system dysfunction.

References

Beck, A.T., Ward, C.H., and Mendelson, M. An inventory for measuring depression. *Arch. Gen. Psychiatry*, 41:561–571, 1961.

Derogatis, L.R. *SCL-90-R Manual*. Towson: Clinical Psychometric Research, 1984.

Halstead, W.C. *Brain and Intelligence*. Chicago: University of Chicago Press, 1947.

Horstman, W.R. MMPI responses of homosexual and heterosexual male college students. *Homosexual Counselling J.*, 2:68–76, 1975.

Kronfol, Z., Silva, J., Jr., Greden, J., et al. Impaired lymphocyte function in depressive illness. *Life Sci.*, 33:241–247, 1983.

Lezak, M.D., and Glaudin, V. Differential effects of physical on MMPI profiles. *Newsletter Res. Psychol.*, 11:27–28, 1969.

Loewenstein, R.J., and Sharfstein, S.S. Neuropsychiatric aspects of acquired immune deficiency syndrome. *Int'l. J. Psychiatry Med.*, 13:255–260, 1983-84.

Ochitill, H.N., Perl, M., Dilley, J., and Volberding, P. Case reports of psychiatric disturbance in patients with acquired immune deficiency syndrome. *Int'l. J. Psychiatry Med.*, 14:259–263, 1984.

Shaw, G.M., Harper, M.E., Hand, B.H., et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science*, 227:177–181, 1985.

Snider, W.D., Simpson, D.M., Nielsen, S., et al. Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. *Ann. Neurol.*, 14:403–418, 1983.

Spitzer, R.L., and Endicott, J. *Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L)* (3rd edition). New York: Psychiatric Institute, 1978*a*.

Spitzer, R.L., Endicott, J., and Robins, E. Research diagnostic criteria: rationale and reliability. *Arch. Gen. Psychiatry*, 34:773–782, 1978*b*.

Localization of the T4 Antigen/AIDS Virus Receptor in Monkey and Rat Brain: Prominence in Cortical Regions

Joanna M. Hill, Ph.D.,[1] William L. Farrar, Ph.D.,[2] and Candace B. Pert, Ph.D.[1]

Introduction

The acquired immune deficiency syndrome (AIDS) is a recently described cellular immunodeficiency disorder which is characterized by malignancies and opportunistic infections with a variety of pathogens (Gottlieb et al., 1981; Masur et al., 1981; Siegal et al., 1981).

Central nervous system involvement, as evidenced by intellectual and cognitive impairment (Joffe et al., 1986), language disorders, movement dysfunction, stroke symptoms (Wolcott et al., 1986), and delirium and dementia (Snider et al., 1983; Loewenstein and Sharfstein, 1983–84), is a common feature in AIDS patients and neuropathological complications, such as encephalitis, neoplasms, and vascular lesions, frequently occur (Snider et al., 1983).

The retrovirus, HTLV-III/LAV (human T lymphotropic virus type III/lymphadenopathy virus) has been implicated as the causative agent in AIDS (Barre-Sinoussi et al., 1983; Popovic et al., 1984; Levy et al., 1984). AIDS infection is found to deplete the helper/inducer T lymphocyte subset which is characterized by the presence of the T4 surface antigen (Klatzmann et al., 1984). HTLV-III/LAV binding, absorption, and replication in human (Klatzmann et al., 1985; McDougal et al., 1985; Dalgleish et al., 1985) and squirrel monkey (Ruscetti et al., in press) T cells can be inhibited by anti-T4 mab; therefore, it appears that the T4 antigen complex acts as the viral entry protein or receptor.

Spurred by the realization that immune cells and brain cells frequently share common antigens (Pert et al., 1985), as well as the report that HTLV-III/LAV associated retrovirus has been isolated from brain tissue (Shaw et al., 1985), we recently demonstrated that similar T4 antigen structures are present on lymphoid and brain structures (Ruscetti et al., in press). In contrast to the suggestion that the neurological/psychiatric symptoms of AIDS are the secondary results of opportunistic infections and/or reactions to the disease, we have suggested that the virus interacts with brain cells via an entry protein (receptor) shared in common with T cells, thus directly causing psychiatric and neuropathological dysfunctions (Ruscetti et al., in press).

Using a novel autoradiographic method, the present study visualizes the distribution of the T4 antigen/AIDS virus receptor on sections of squirrel monkey brain. We now also report that the T4 antigen is present on rat brain and is distributed in a manner analogous to that of the primate. Interestingly, the HTLV-III/LAV virus receptor is generally confined to cortical regions, a distribution consistent with the suggestion that AIDS dementia is the result of direct viral modulation.

Methods

As described by Herkenham and Pert (1982) adult squirrel monkeys, one male and one female, and male Sprague-Dawley rats (200 to 250 g) were decapitated and their brains were frozen and cut on a cryostat at 36 μm in the coronal or horizontal plane. Sections were thaw mounted on gelatin-coated microscope slides and stored under vacuum at 4°C until used.

---

[1] Section on Brain Biochemistry, Clinical Neuroscience Branch, National Institute of Mental Health, Bethesda, MD 20892.

[2] Laboratory of Molecular Immunoregulation, Biological Response Modifiers Program, Division of Cancer Treatment, NIH, Frederick Cancer Research Facility, Frederick, MD 21701-1240.

Send correspondence to: Candace B. Pert, Ph.D., Chief, Section on Brain Biochemistry, Clinical Neuroscience Branch, National Institute of Mental Health, Building 10, Room 3N256, 9000 Rockville Pike, Bethesda, MD 20892.

Sections were incubated in RPMI-1640 with or without a 1:600 dilution of T4 monoclonal antibody (10 mg/ml, Ortho Diagnostics) at 0°C overnight. The following day the sections were rinsed in four 1-min washes of RPMI-1640 and crosslinked by immersion into phosphate buffered saline (PBS) plus 1 mM disuccinylsuberate (DDS) dissolved in dimethyl sulfoxide (DMSO) 45 min on ice. The sections were then rinsed in two 2-min washes of PBS, 2 min in 100 mM Tris in PBS and 3 min in RPMI-1640. Sections were then incubated in RPMI-1640 containing about 100,000 cpm ^{125}I-goat anti-mouse immunoglobulin (New England Nuclear) overnight at 0°C. Following incubation the sections were rinsed in four 1-min washes of PBS, dipped into deionized water, dried rapidly under a stream of cold air and fixed in paraformaldehyde vapors for 2 hrs at 80°C. Slides were exposed to LKB ultrofilm for 3 to 7 days after which the film was developed in Kodak D-19. Some sections were defatted in xylene and dipped into liquid emulsion (Kodak NTB-2) and exposed for 2 weeks. After exposure they were developed in D-19 and stained with thionine. Microscopic examination of these slides facilitated the identification of receptor distribution in brain microregions.

Results

T4 binding was widespread and detected in discrete areas in both monkey and rat brain forming a distinctive pattern of distribution (Figures 1 and 2). The highest density of binding occurred in the molecular layer of the dentate gyrus in both the monkey (Figure 1,D,E) and rat brain (Figure 2,B,C,D) followed by the hippocampus (Figure 1,D,E—monkey, Figure 2,B,C,D—rat). Receptors were prominent in the nuclei of the amygdala of both monkey (Figure 1,C,D) and rat (Figure 2,B) and in the superficial layers of the primate cortex especially in the cingulate (Figure 1,A,C,D,E), insular (Figure 1,A,C,D), opercular (Figure 1,A,C,D), temporal (Figure 1,C,D,E), medial temporal (Figure 1,A,C,D,E) and striate cortex (Figure 1,F). In the rat the frontal cortex (Figure 2,D), pyriform cortex (Figure 2,B) (especially near the rhinal fissure), cingulate cortex (Figure 2,D), and striate cortex had a higher density of binding than other cortical areas. A moderate density of binding occurred in the deep layers of the cortex, claustrum (Figure 1,A,C,D), caudate (Figure 1,A,C,D), putamen (Figure 1,A,C,D), hypothalamus (Figure 1,C,D), and substantia nigra (Figure 1,D) of the monkey and the accumbens, caudate/putamen (Figure 2,B), claustrum, and lateral septum of the rat. Among ancillary brain structures the choroid plexus (Figure 1,A,C,D—monkey and Figure 2,B,C—rat) and hypophysis (Figure 1,C,D) had a high density of binding.

Rat and monkey sections incubated in radiolabeled secondary antibody without prior incubation in the anti-T4 monoclonal antibody show no pattern and merely a low level of "background" optical density (Figure 1,B). Specificity is further demonstrated by our previous work in which a monoclonal antibody to the transferrin receptor revealed a different distribution pattern in rat brain using similar methods (Hill et al., 1985).

Most of the brain regions with a high density of T4 antigen are laminated cortical structures in which the prominent binding occurs in the superficial layers. This is evident in the hippocampal formation where binding is greatest in the molecular layer of the dentate gyrus and hippocampus (Figure 1,D,E—monkey; Figure 2,B,C,D—rat) and in the olfactory bulb (Figure 2,A), where binding is greatest in the external plexiform layer. In addition, in the neocortex of the monkey greatest binding is localized to superficial layers (Figure 1,A,C,D,E,F). These superficial layers are composed primarily of the dendritic and axonal branches of neurons, the cell bodies of which are in different lamina or structures. Consistent with this observation, microscopic examination of emulsion-coated slides revealed that receptor binding sites occur primarily throughout the neuropil; however, they were also observed over neurons and glial cells.

Discussion

The binding of T4 antibody to both the monkey and rat brain outlines the distinctive pattern of distribution of the T4 antigen in brain. The T4 antigen, initially known as a

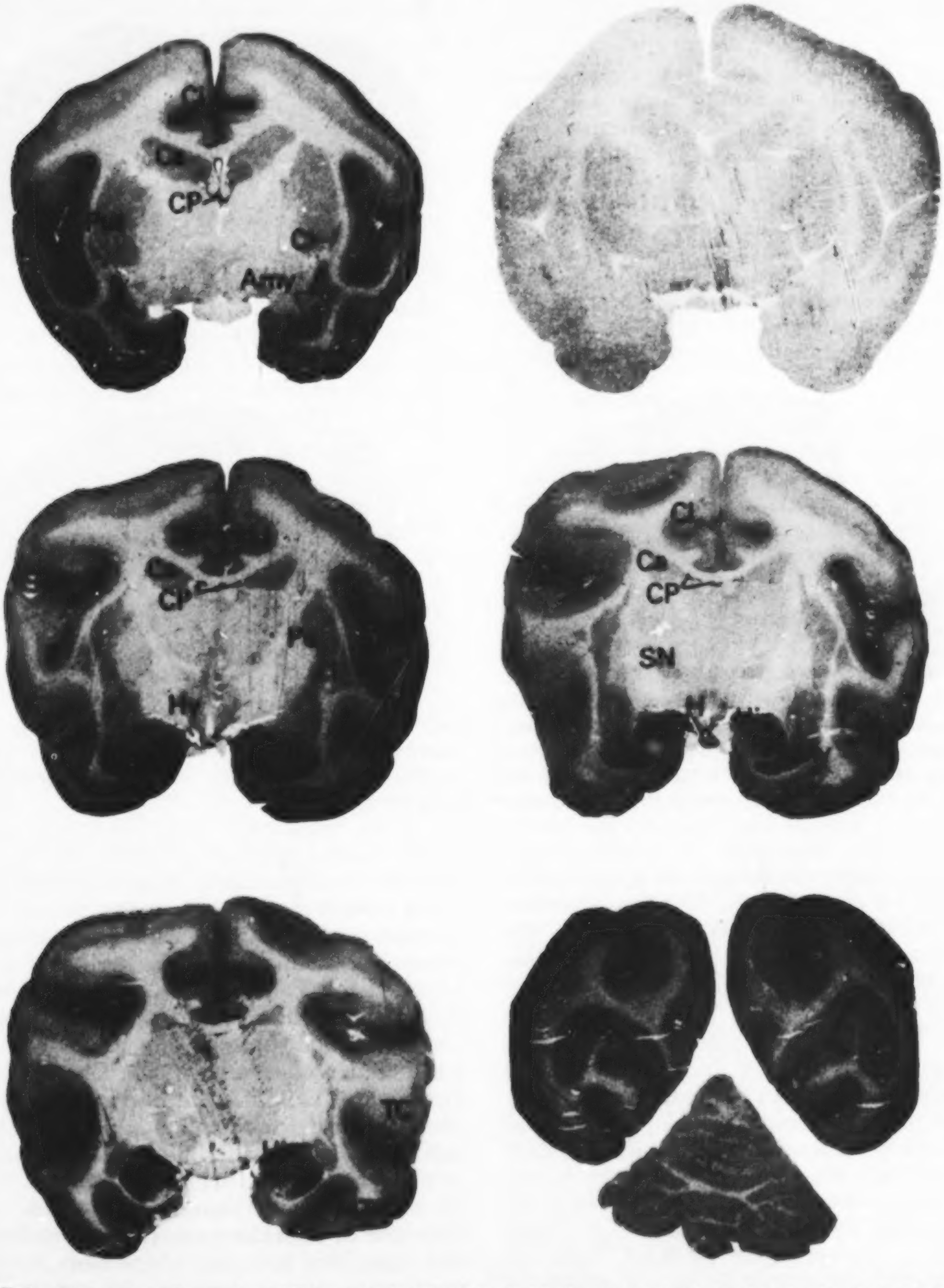


FIGURE 1. Film autoradiographs of T4 monoclonal antibody binding in squirrel monkey brain. A: C, D, E, and F sections incubated in T4 monoclonal antibody in RPMI-1640 followed by ^{125}I goat anti-mouse immunoglobulin; B: brain section at the same level as A incubated in ^{125}I goat anti-mouse immunoglobulin following RPMI-1640 alone. Amy, amygdala; Ca, caudate; CC, cerebellar cortex; Ci, cingulate cortex; Cl, claustrum; CP, choroid plexus; EC, entorhinal cortex; H, hypophysis; Hip, hippocampal formation; Hy, hypothalamus; I, insula; MTC, medial temporal cortex; OC, occipital cortex; Put, putamen; SN, substantia nigra; TC, temporal cortex.

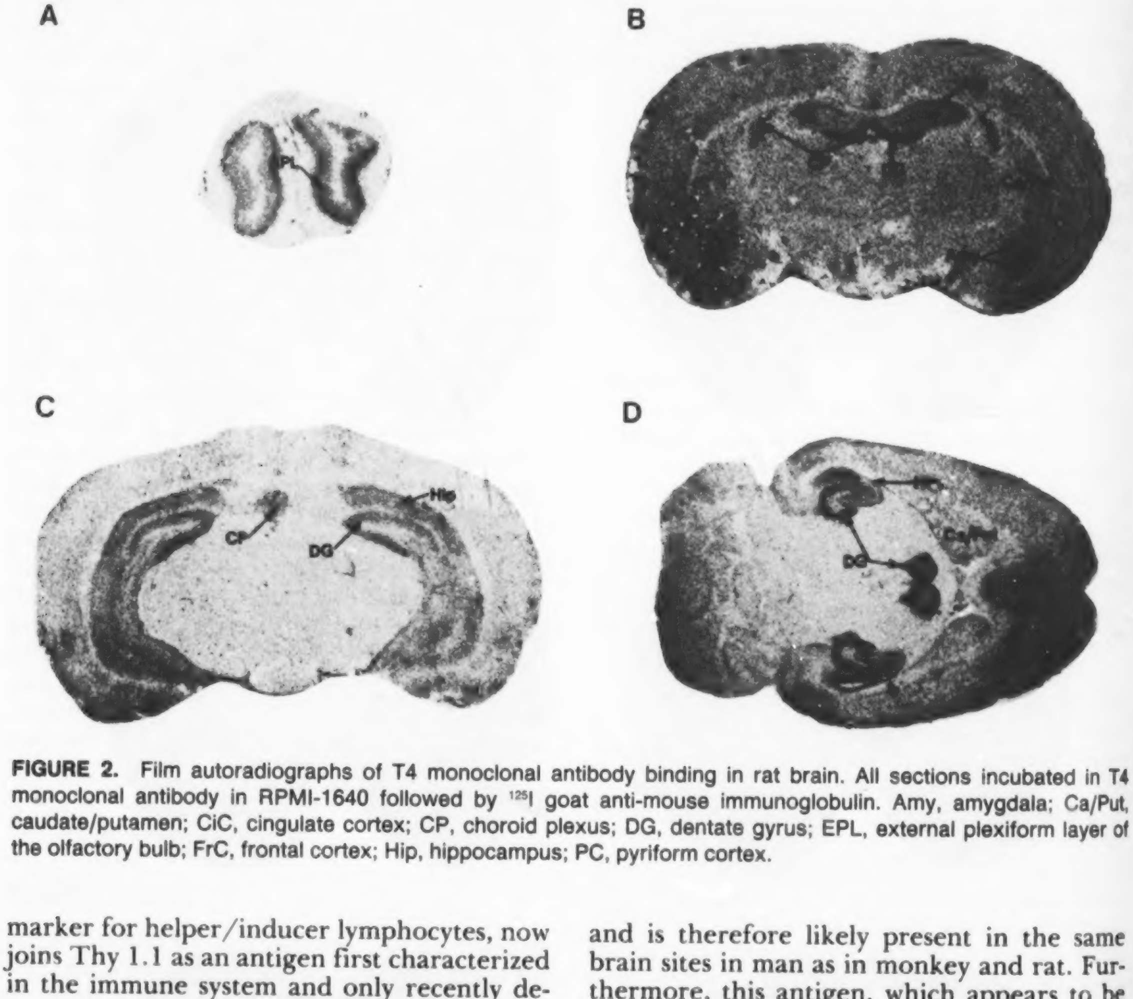


FIGURE 2. Film autoradiographs of T4 monoclonal antibody binding in rat brain. All sections incubated in T4 monoclonal antibody in RPMI-1640 followed by ^{125}I goat anti-mouse immunoglobulin. Amy, amygdala; Ca/Put, caudate/putamen; CiC, cingulate cortex; CP, choroid plexus; DG, dentate gyrus; EPL, external plexiform layer of the olfactory bulb; FrC, frontal cortex; Hip, hippocampus; PC, pyriform cortex.

marker for helper/inducer lymphocytes, now joins Thy 1.1 as an antigen first characterized in the immune system and only recently demonstrated to be present in the nervous system (Williams and Gagnon, 1982; Weber et al., 1986).

With few exceptions the T4 antigen is found in the same brain areas and with the same relative density in both monkey and rat. This, surprisingly, contradicts immunological theory which emphasizes the species-specificity of antibody reagents. However, immunological methodology such as cell sorting detects antibody binding only if very high affinity binding occurs. Our method, with its covalent cross-linking of primary antibody to antigen, can efficiently detect antibody-antigen binding with relatively low (10 nM) affinity. The similarity in distribution of the T4 antigen in the brain of two diverse mammals suggests that the pattern is stable in mammals and is therefore likely present in the same brain sites in man as in monkey and rat. Furthermore, this antigen, which appears to be conserved structurally as well as in its neuroanatomical organization, resembles in its pattern of distribution receptors for other "informational substances" which function in intercellular communication (Schmitt, 1984; Pert et al., 1985). An endogenous signal neuropeptide for the T4 antigen/receptor subserving nervous/immune system communication has not yet been described but might be expected on theoretical grounds. The presence of abundant receptors in molecular and superficial laminae, where neuronal communication occurs, supports this notion.

Since the T4 antigen acts as the receptor for the AIDS retrovirus, those brain areas with high densities of T4 antigen are targets for virus-induced behavior changes. T4 antigen is especially prominent in the cortical areas of the brain, being abundant in the hippocampus, amygdala, and many subdivisions of the neocortex. The area of highest binding, the hippocampal formation, plays an important role in learning and memory and, in addition, is a major component of the limbic system, which functions in the mediation of emotion. The amygdala, a second limbic structure, is also especially enriched with T4 antigen and is concerned with a variety of behaviors including agonistic behavior, feeding activities and sexual behavior (Kaada, 1972). Other limbic sites which have a moderate to high density of T4 antigen include the cingulate cortex, reported to be involved in maternal behaviors and vocalization (see review by MacLean, 1985); the hypothalamus, a center for the coordination of visceral functions; and the insular cortex, which functions in gustatory integration as well as being the highest way station of somatosensory integration (Friedman et al., 1986).

A moderately high concentration of T4 antigen is also found in the temporal and occipital cortices, which are involved in auditory and visual integration and in the caudate, putamen, and substantia nigra, brain areas which govern motor functions.

It should be emphasized that dense concentrations of T4 antigen are localized in all of the several cortical areas specialized for processing information from each sensory modality, i.e., olfactory, gustatory, visual, somatosensory, and auditory. Generally, it is the regions subserving "higher" cortical functions, i.e., progressively more highly processed sensory information (Turner et al., 1980), which we would predict would be most susceptible to viral modulation.

The predominantly cortical brain areas characterized by the presence of T4 antigen are thus involved in extensive and varied brain functions. The fact that these areas are the potential sites for AIDS virus infection could explain the variety of psychiatric and neuropathological abnormalities seen in AIDS patients.

Acknowledgments

We thank Nicole Jelesoff and Robert Berman for superb technical assistance and Mrs. Sharon Morgan for her careful preparation of the manuscript.

References

Barre-Sinoussi, F., Chermann, J.C., Rey, F., Nageyre, M.T., et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*, 220:868–871, 1983.

Dalgleish, A.C., Beverley, P.C.L., Clapham, P.R., Crawford, D.H., et al. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature*, 312:763–767, 1985.

Friedman, D.P., Murray, E.A., O'Neill, J.B., and Mishkin, M. Cortical connections of the somatosensory fields in the lateral sulus of macaques: evidence for a cortico limbic pathway for touch. *J. Comp. Neurol.* (In press.)

Gottlieb, M.S., Schroff, R., Schanker, H.M., Weisman, J.D., et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men. *N. Engl. J. Med.*, 305:1425–1431, 1981.

Herkenham, M., and Pert, C.B. Light microscopic localization of brain opiate receptors: a general autoradiographic method which preserves tissue quality. *J. Neurosci.*, 2:1129–1149, 1982.

Hill, J.M., Ruff, M.R., Weber, R.J., and Pert, C.B. Transferrin receptors in rat brain: neuropeptide-like pattern and relationship to iron distribution. *Proc. Natl. Acad. Sci. USA*, 82:4553–4557, 1985.

Joffe, R.T., Rubinow, D.R., Squillace, K., Lane, C.H., et al. Neuropsychiatric manifestations of acquired immune deficiency syndrome (AIDS). *Psychopharm. Bull.*, 22. (In press.)

Kaada, B.R. Stimulation and regional ablation of the amygdaloid complex with reference to functional representations. In: Eleftheriou, B.E. (ed.), *The Neurobiology of the Amygdala*. The proceedings of a symposium on the neurobiology of the amygdala (1971; Bar Harbor, ME). New York: Plenum Press, 1972, pp. 205–281.

Klatzmann, D., Barre-Sinoussi, F., Nageyre, M.T., Dauguet, C., et al. Selective tropism of lymphadenopathy associated virus (LAV) for helper-inducer T lymphocytes. *Science*, 225:59–63, 1984.

Klatzmann, D., Champagne, E., Chamaret, S., Gruest, J., et al. T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature*, 312:767–768, 1985.

Levy, J.A., Hoffman, A.D., Kramer, S.M., Landis, J.A., et al. Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science*, 225:840–842, 1984.

Loewenstein, R.J., and Sharfstein, S.S. Neuropsychiatric aspects of acquired immune deficiency syndrome. *Int'l. J. Psychiatry in Med.*, 13:255–260, 1983–84.

MacLean, P.D. Brain evolution relating to family, play and the separation call. *Arch. Gen. Psychiatry*, 42:405–417, 1985.

Masur, H., Michelis, M.A., Greene, J.B., Ororato, I., Vande Stouwe, R.A., et al. An outbreak of community acquired *Pneumocystis carinii* pneumonia. *N. Engl. J. Med.*, 305:1431–1438, 1981.

McDougal, J.S., Mawle, A., Cort, S.P., Nicholson, J.K.A., et al. Cellular tropism of the human retrovirus HTLV-III/LAV. Role of T cell activation and expression of the T4 antigen. *J. Immunol.*, 135:3151–3162, 1985.

Pert, C.B., Ruff, M.R., Weber, R.J., and Herkenham, M. Neuropeptides and their receptors: a psychosomatic network. *J. Immunol.*, 135:820S–826S, 1985.

Popovic, M., Sarngadharan, M.G., Read, E., and Gallo, R.C. Detection, isolation and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science*, 224:497–500, 1984.

Ruscetti, F.W., Farrar, W.L., Hill, J.M., and Pert, C.B. Visualization of the human helper T lymphocyte related antigen (T4) in primate brain: implications for HTLV-III/LAV infection. *Peptides*, in press 1986.

Schmitt, F.O. Molecular regulation of brain function: A new view. *Neuroscience*, 13:991–1001, 1984.

Siegal, F.P., Lopez, C., Hammer, G.S., Brown, A.E., et al. Severe acquired immunodeficiency in male homosexuals manifested by chronic perianal ulcerative *Herpes simplex* lesions. *N. Engl. J. Med.*, 305:1439–1444, 1981.

Shaw, G.M., Harper, M.E., Hahn, B.H., Epstein, L.G., et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science*, 227:177–181, 1985.

Snider, W.D., Simpson, D.M., Nielsen, S., Gold, S.W.M., et al. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann. Neurol.*, 14:403–418, 1983.

Turner, B.H., Mishkin, M., and Knapp, M. Organization of the amygdalopetal projections from modality-specific cortical association areas in the monkey. *J. Comp. Neurol.*, 191:515–543, 1980.

Weber, R.J., Hill, J.M., and Pert, C.B. Regional distribution of the Thy 1.1 antigen in rat brain. (Submitted, 1986.)

Williams, A.F., and Gagnon, J. Neuronal cell Thy 1 glycoprotein: homology with immunoglobulin. *Science*, 216:696–703, 1982.

Wolcott, D.L., Fawzy, F.I., and Pasnau, R.D. Acquired immune deficiency syndrome (AIDS) and consultation-liaison psychiatry. *Gen. Hosp. Psychiatry*. (In press.)

Methionine Enkephalin: Enhancement of T-Cells in Patients With Kaposi's Sarcoma (AIDS)

N.P. Plotnikoff, Ph.D.,[1] J. Wybran, Ph.D.,[2] N.F. Nimeh, M.D.,[3] and G.C. Miller, Ph.D.[4]

Introduction

The enkephalins were originally described as endogenous opiate peptides modulating perception of pain (Hughes et al., 1975). Other behavioral functions for the peptides were identified including antidepressant and antianxiety actions (Plotnikoff et al., 1976).

More recently we reported that the enkephalins were immunomodulators, resulting in very significant activation of the T-cells in mice and men (Plotnikoff & Miller, 1983; Plotnikoff et al., 1983; Miller et al., 1983; Miller et al., 1984; Faith et al., 1984; Wybran, 1985). Based on the latter studies we started a series of *in vivo* studies in cancer patients.

Patient 1 (age 27) was admitted to Oral Roberts University School of Medicine with swollen lymph nodes, fever, and suspected Kaposi's sarcoma and pneumocystitis. Initially he was placed on Pentamidine therapy for suspected Pneumocystis carinii pneumonia. After the initial treatments with Pentamidine, the patient was placed on methionine enkephalin treatment. The schedule employed was daily infusion the first week for 5 days and twice a week thereafter. The dose employed was 10 μg/kg prepared in a normal saline solution and infused over a 30-minute time course. Twenty-four hours after infusion, blood samples were withdrawn and analyzed for T-cells (E rosettes), OKT 3 T lymphocytes, mature thymocytes, OKT 11 T lymphocytes-early development stage thymocytes, T helper cells (OKT 4), T suppressor cells (OKT 8), blastogenesis or mitogen stimulated proliferation, phytohemagglutinin (T helper cell mitogen), concanavalin A (a T helper and T suppressor cell mitogen), pokeweed (a T dependent B cell mitogen), and Staph A (a B cell mitogen). NK cell assay (natural killer cells) was conducted against the K-562 tumor cell line labeled with ^{51}Cr (7).

This patient received infusions of methionine enkephalin (10 micrograms per kilogram) each day of the first week (5 days, Monday through Friday). Blood samples were taken each day before infusion of methionine enkephalin. The data in Table 1 indicate that absolute number of T helper cells increased (57 to 94/mm^3) and the absolute number of suppressor cells (OKT 8) decreased from 382 to 264 per mm^3 on the fifth day. There was a slight increase in OKT 3 and OKT 11 cells. The T helper/T suppressor ratio rose from 0.149 to 0.354. The total lymphocyte count dropped from 516 on day one to 368 on day four and rose again to 550 on day five. Active T-cells rose significantly from 201 on day one to 396/mm^3 on day five.

No methionine enkephalin was infused on day six or day seven. On day eight blood samples were withdrawn followed by methionine enkephalin infusion (dose of 25 μg/kg) corresponding to one-half of the first week total dose. The T-cells were still elevated on day eight compared to day five. T helper cells were 119 compared to 94; T suppressor cells increased to 409 from 264; OKT 3 increased from 341 to 491/mm^3; and OKT 11 increased from 429 on day five to 558 on day eight. The active T-cells increased to 565/mm^3 on day eight compared to 396/mm^3 on day five. Furthermore, the total lymphocytes increased to 774/mm^3 on day eight compared to 550/mm^3 on day five. The NK cell assay on day eight was slightly decreased compared to day one values. Finally, there was a significant increase in interleukin 2 receptors.

---

[1] Department of Pharmacology, Oral Roberts University School of Medicine, Tulsa, OK.

[2] Hospital Erasme, Université Libre de Bruxelles, Brussels, Belgium.

[3] Department of Medicine, Oral Roberts University School of Medicine, Tulsa, OK.

[4] Immuno-Diagnostics Laboratory, Inc., Tulsa, OK.

TABLE 1. Methionine enkephalin treatment of Patient 1.

Assays	Day 1 10 μg/K/da	Day 2 10 μg/K/da	Day 3 10 μg/K/da	Day 4 10 μg/K/da	Day 5 10 μg/K/da	Day 8 25 μg/K/da	Day 11 25 μg/K/da
WBC	4300/mm^3	2600/mm^3	2300/mm^3	2300/mm^3	2500/mm^3	3100/mm^3	2950/mm^3
Lymphocytes	516/mm^3	442/mm^3	391/mm^3	368/mm^3	550/mm^3	774/mm^3	738/mm^3
Active T cells							
Percent	39%	83%	79%	72%	72%	76%	26%
Absolute	201/mm^3	367/mm^3	309/mm^3	265/mm^3	396/mm^3	565/mm^3	192/mm^3
T Lymphocytes & subsets							
T lymphocytes (OKT 3)							
Percent	60%	80%	82%	82%	62%	66%	76%
Absolute	310/mm^3	354/mm^3	321/mm^3	302/mm^3	341/mm^3	491/mm^3	561/mm^3
T lymphocytes (OKT 11)							
Percent	79%	88%	80%	80%	78%	75%	81%
Absolute	408/mm^3	389/mm^3	313/mm^3	294/mm^3	429/mm^3	558/mm^3	598/mm^3
T lymphocytes (OKT 4)							
Percent	11%	13%	14%	17%	17%	16%	17%
Absolute	57/mm^3	58/mm^3	55/mm^3	63/mm^3	94/mm^3	119/mm^3	125/mm^3
T lymphocytes (OKT 8)							
Percent	74%	63%	53%	53%	48%	55%	61%
Absolute	382/mm^3	278/mm^3	207/mm^3	195/mm^3	264/mm^3	409/mm^3	450/mm^3
T helper/T suppressor ratio	0.149	0.209	0.264	0.321	0.354	0.291	0.278
Blastogenesis							
Phytohemagglutinin	20X	—	—	—	—	134X	—
Concanavalin A	11X	—	—	—	—	49X	—
Pokeweed	12X	—	—	—	—	18X	—
Staph A	1X	—	—	—	—	3X	—
Interleukin-2 Receptor	14%	—	—	—	—	48%	—
NK cell Assay							
100:1	26%	—	—	—	—	16%	—
33:1	11%	—	—	—	—	8%	—
11:1	5%	—	—	—	—	3%	—
Slope of killing	0.237	—	—	—	—	0.156	—

On day 11 blood samples were taken once again followed by methionine enkephalin infusion. All of the T-cell subsets increased except active T-cells. The total lymphocyte count diminished slightly.

The patient was discharged from the hospital with signs of subjective improvement. Of great interest was that the original lesion of the sarcoma, including biopsy hole, was crusting and healing. Lymph nodes in the axillary and groin area were palpably smaller.

AIDS Patient Study*

Methionine enkephalin was given to Patient 2 (a 26-year-old male Caucasian AIDS patient from Zaire, Africa) whose clinical manifestations included resected cerebral lymphoma and opportunistic infections (Candida albicans and Mycobacteriumbovis). Methionine enkephalin (UCB, Brussels) was administered at a dose of 20 μg/kg in saline perfusion over a period of 30 minutes. Lymphocyte populations were studied using monoclonal antibodies (Ortho, Raritan, NJ, and Becton-Dickinson, Mtn. View, CA). After incubation with the monoclonal antibodies, the cells were further incubated with goat antimouse coupled particles of colloidal gold (Janssen Life Science Products, Beerse, Belgium) and the smears were put in a silver developer and counter-stained with May-Grunwald-Giemsa (Romasco et al., in press). This smear method allows morphology and is about 20 times more sensitive than immunofluorescence.

---

*By Dr. J. Wybran (Brussels, Belgium).

Results

Lymphocytes	Before (%)	After 2 h (%)	After 24 h (%)
OKT 3	30	26	27
OKT 10	45	53	49
OKT 11	31	34	31

Blood T-cells increased in number slightly as judged by the OKT 10 and OKT 11 antisera. Of special interest is the increase in OKT 10 which is similar to *in vitro* data obtained by incubating human lymphocytes with methionine enkephalin (Seligmann et al., 1984).

Discussion

The patient with Kaposi's sarcoma was diagnosed as an AIDS patient on the basis of defective T helper cell levels compared to T suppressor cell levels. Seligmann et al. have indicated that AIDS is characterized by a decreased OKT 4 lymphocyte subset (Seligmann et al., 1984).

The present study with methionine enkephalin is based on our earlier findings that methionine enkephalin stimulates PHA-induced blastogenesis (a T helper cell antigen) in mice and also markedly stimulated OKT 4 (T helper cell) production in normal volunteers (Plotnikoff & Miller, 1983; Plotnikoff et al., 1983). Similar elevation of T helper cells by methionine enkephalin was seen in the present AIDS patient with Kaposi's sarcoma. In addition there is a marked elevation of interleukin-2 receptors to 48 percent of the lymphocytes compared to 14 percent on day one. Recently Wybran reported that methionine enkephalin stimulated production of interleukin-2. In addition, the primary sarcoma lesion appears to be healing. Similar findings on T-cell subsets were seen in the AIDS patient studied by J. Wybran.

References

Faith, R.E., Liang, H.J., Murgo, A.J., and Plotnikoff, N.P. Neuroimmodulation with enkephalins: Enhancement of human natural killer (NK) cell activity *in vitro*. *Clin. Immunol. Immunopathol.*, 31:412, 1984.

Hughes, J., Smith, T.W., Kosterlitz, H.W., et al. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature*, 258:577, 1975.

Miller, G.C., Murgo, A.J., and Plotnikoff, N.P. Enkephalins: Enhancement of active T-cell rosettes from normal volunteers. *Clin. Immunol. Immunopathol.*, 31:132, 1984.

Miller, G.C., Murgo, A.J., and Plotnikoff, N.P. Enkephalins: Enhancement of active T-cell rosettes from lymphoma patients. *Clin. Immunol. Immunopathol.*, 26:446, 1983.

Plotnikoff, N.P., and Miller, G.C. Enkephalins as immunomodulators. *Int. J. Immunopharm.*, 5:437, 1983.

Plotnikoff, N.P., Murgo, A.J., and Faith, R.E. Neuroimmunomodulation with enkephalins: Effects on thymus and spleen weights in mice. *Clin. Immunol. Immunopathol.*, 26:446, 1983.

Plotnikoff, N.P., Kastin, A.J., Coy, D.H., et al. Neuropharmacological action of enkephalins after systemic administration. *Life Science*, 19:1283, 1976.

Romasco, F., Rosenberg, J., and Wybran, J. An immunogold silver staining method for the light microscopical analysis of blood lymphocyte subsets with monoclonal antibodies. *Amer. J. Clin. Pathol.* (In press.)

Seligmann, M., Chess, L., Fahey, J.L., et al. AIDS: An immunologic re-evaluation. *N. Engl. J. Med.*, 311:1286, 1984.

Wybran, J. Enkephalins and endorphins as modifiers of the immune system: Present and future. *Fed. Proc.*, 44:92, 1985.

Wybran, J., and Schandene, L. (In preparation.)

Molecular Biology: Relevance to Neuropsychopharmacology and Psychiatry

Chair:

Samuel H.Barondes, M.D.

University of California at San Diego
La Jolla, CA 92093

Introduction

It is now established that brain function depends, in large part, on the synthesis, processing, and degradation of many of its constituent proteins. There is also evidence that modification of a single brain protein can have dramatic structural and functional consequences. These general conclusions came from studies using classical molecular and genetic techniques.

Like the rest of biology, studies of brain function are being greatly facilitated by recent advances in molecular biology. These have, for example, dramatically increased our ability to detect new proteins that are critical for brain function. They also provide the opportunity to identify directly the genetic basis for psychiatric disorders. The contributions to this symposium describe exciting applications of molecular biology to neuropsychopharmacology and psychiatry.

Bloom's paper shows how recombinant DNA technology is being applied to identify messenger ribonucleic (RNA) molecules that are specific to brain, some of which code for precursers of neuropeptide transmitters. Beginning with a library of DNAs complementary to brain messenger RNAs, clones representing brain-specific messenger RNAs were isolated. This was achieved by first showing that these clones hybridized with messenger RNA from brain but not other tissues. In this way it was estimated that there are about 30,000 messenger RNAs unique to brain, and several have been studied in great detail. The major focus of Bloom's contribution is on the discovery of brain messenger RNAs that code for specific neuropeptides; and the subsequent use of other techniques to localize them and evaluate their function.

Herbert and colleagues describe the application of another general strategy to study a critical element in nervous system function. They have concentrated on factors that regulate expression of the genes that direct the synthesis of specific neuropeptides. They are also concerned with regulation of the processing of the protein precursors of these peptides by various cellular mechanisms. The focus of their contribution is on gene transfer techniques which have revolutionized the study of these regulatory processes. They describe how genes coding for protein precursors of neuropeptides can be introduced into a variety of cells. The techniques they use permit either stable integration of the transferred genes into the nuclear chromatin or their temporary expression in the cytoplasm of recipient cells. The transferred genes and their products are ideal subjects for studies of regulation of gene expression and of processing of gene products. This approach promises to markedly increase our understanding of regulation of brain protein and peptide metabolism.

What is particularly exciting about the introduction of recombinant DNA techniques into our specialized fields of interest is that it should greatly accelerate our detailed understanding of brain function and psychiatric disorders. Traditional psychiatric research has moved fairly slowly because each experiment is difficult to do and because the assays involved frequently take long periods of time. In contrast, the technologies described here promise rapid advances in knowledge, even in areas as complex as those of concern to this audience.

Identifying Neuropeptides by Gene Cloning

Floyd E. Bloom, M.D.[1]

A variety of specific molecules have provided insight into the limited knowledge of cellular operations in the brain. Neurotransmitter molecules, and the distinct molecular systems by which they are synthesized, stored, released, and recognized by their target cells, perhaps come most easily to mind. However, the catalog of neurotransmitters is far from completely compiled, and many important genetic and non-genetic disorders of the nervous system may only be amenable to diagnosis, treatment, and ultimate prevention when new transmitters are added to the list as probes of the pathology. Expanding the list of transmitter-related molecules thus can be taken to be as important to clinical problems of the brain as they will be to enlarging our understanding of the fundamental processes by which the brain performs its complex tasks. Our approach has been to attack the molecular specificity of the mature rat brain with a direct examination of the complexity of the genetic messages being expressed there. Every protein product being expressed in brain, as in all cells, depends for its synthesis on the transcription of a specific piece of genetic information into a messenger RNA that guides synthesis of the gene product. Using the powerful tools of recombinant DNA technology, my colleagues and I have embarked on a long-term study aimed at characterizing the messenger RNA molecules that are specific to brain. To do so, we have prepared an initial library of brain mRNA by recombinant cloning. Clones showing evidence of successful insertion of genetic information have been screened with RNA hybridization, so-called Northern blotting, and inserts representing brain specific mRNAs have been isolated. Those cloned brain mRNAs were then sequenced and the amino acid sequences of the products for which they code were deduced. Selected zones of these deduced peptides were then synthesized and used to develop peptide selective antisera. The antisera in turn were used to screen brain sections and protein extracts in order to document that novel molecules deduced from the structure of the mRNA being expressed selectively in brain were actually made and expressed in brain. Our results suggest that, on average, the mammalian brain derives its complexity through only 30,000 or so messenger RNAs specific to the brain, in that they are not detectible in other major organ systems. Among the more interesting of these highly specific, chemically determined marker molecules, we have found both neuron-specific and glia-specific examples. Our most intensively studied system has satisfied some, but not yet all, of the cellular, subcellular, and biochemical criteria of a neurotransmitter peptide pro-hormone. Thus, a genetic analysis of brain complexity and functional specificity is a potent and efficient strategy for molecular discovery.

Introduction

The topic of neuropeptide identification represents one of the most active aspects of cellular and molecular neuroscience with relevance to American College of Neuropsychopharmacology interests. In this short overview, I cover the major thrusts of such efforts. Molecular discovery in the neurosciences has, until recently, largely focused on neurotransmitters and hypothalamic hypophysiotrophic hormones. Historically we can view the topic of transmitter discovery as having had a "classical" period and a "modern" period. The "classical" period began with the discoveries of Dale, Loewi, Elliott, and their contemporaries when chemical signals were few, cellular arrays were confusing, and chemical isolation methods were primitive. Currently, we are in transition to an era

---

[1] Division of Preclinical Neuroscience and Endocrinology, Scripps Clinic and Research Foundation, La Jolla, CA 92037.

in which powerful molecular biological methods maintain a continued pace of discovery even after all the "easy" transmitter discoveries were already made.

Strategies of Transmitter Discovery

As we look back upon the growing list of consensus transmitters (*see* Bloom, 1984a,b) those discovered in the classical period can attribute their discovery to one of two strategies, depending on whether the factor was discovered before or after the biological actions for which it is now recognized.

In the "Factor First—Function Later" strategy are substances that bear mainly chemical names: acetylcholine, gamma amino butyrate, dopamine, glutamate, aspartate, glycine, or taurine. They earned chemical names because it was their chemical structure for which they were exclusively identified as biological products, without functional inferences. No peptides, until recently, were among this set.

In the "Assay First—Factor Later" strategy, the development of a bioassay for an unknown regulatory factor became the starting point for a purification-isolation process. This was the classical approach of Starling and the early gastrointestinal regulatory peptides, for insulin and glucagon, as well as "sympathin" of Cannon and colleagues. All of the largely peptidic messengers resulting from this approach carry functional names rather than chemical names: gastrin, cholecystokinin, prostaglandin, Substance P, angiotensin, oxytocin, vasopressin, as well as more conventional small molecules like the biogenic amines, adrenalin, histamine, and serotonin.

This methodology reached its zenith under the skilled prodding of Guillemin, Schally, McCann, and others who pushed their colleagues to detect the hypophysiotrophic factors conceived by Geoffery Harris in the mid-1940's and early 1950's (Guillemin, 1978; Krieger, 1983), requiring the development of sensitive new methods for peptide isolation, purification, and sequence analysis, as well as very large amounts of freshly dissected cattle brains. From this effort came the "Assay-First," functional names for thyrotropin releasing hormone, somatostatin, gonadotropin-releasing hormone, and prolactin, and including the last two of the originally postulated hypophysiotrophic factors predicted, corticotropin-releasing factor (Vale et al., 1981) and growth hormone-releasing factor (Guillemin et al., 1982) have been solved. This neo-classical approach is still being widely applied, as evidenced by the endorphins saga (*see* Snyder, 1984) and new families of gut and brain peptides.

Two Modern Strategies of Transmitter Discovery

Two series of developments over the past half decade have made their impressive effects on the emerging list of transmitters recognized. Both derive from the recognition of common chemical principles, but use different ways to exploit the general feature. Mutt and colleagues (Tatemoto & Mutt, 1980, 1981) looked at the frequent occurrence of C-terminally amidated peptides that functioned as messengers. Using chemical methods that detect C-terminally amidated peptide fragments, they were able to identify other important molecules with this common structure. Using this approach, they found new peptide members of the Glucagon-VIP family and the pancreatic polypeptide family, using the biochemical test as the primary assay for their isolation and classical structural determination.

The second new approach is based on the central dogma of molecular biology—all peptides are synthesized under the direction of a specific messenger RNA (mRNA) encoded by the gene for that peptide. With the emergence of recombinant DNA technologies, restriction endonucleases, and nucleotide sequencing, a new opportunity for molecular discovery became available. Nakanishi et al. (1979) were the first to use molecular biological methods to determine the sequence of the pituitary mRNA that encodes the expression of the common precursor of corticotropin and β-endorphin. Starting with the mRNA purified from 40 bovine pituitaries, they were able to analyze a cDNA library and identify this specific mRNA, determine its nucleotide sequence, and deduce the amino acid sequence of the gene product. In addition to revealing the continuous encoding of corticotropin and β-lipotropin, this mRNA sequence deduction also revealed a third biologically relevant peptide, termed gamma-melanocyte stimulating hormone (MSH) based solely from the mRNA sequence on the basis of its structural analogy to alpha and beta MSH.

Subsequently, the recombinant DNA approach has been employed to obtain the prohormone structural sequences, and some of the genomic sequences for almost every one of the previously identified neuropeptides: all of the major branches of the endorphin family (Gubler et al., 1982; Kakidani et al., 1982; Nakanishi et al., 1979; Noda et al., 1982); somatostatin (Goodman et al., 1982; Montminy et al., 1984); VIP (Itoh et al., 1983); neuropeptide tyrosine (Minth et al., 1984); oxytocin and vasopressin (Schmale & Richter, 1984; Ivell & Richter, 1984); gastrin (McDonald et al., 1983); corticotropin releasing factor (Furutani et al., 1983); growth hormone releasing factor (Gubler et al., 1983; Mayo et al., 1983); Substance P (Nawa et al., 1983); cholecystokinin (Deschenes et al., 1984; Gubler et al., 1984); luteinizing hormone/releasing hormone (Seeburg & Adelman, 1984): and the amphibian skin pro-thyrotrophin releasing hormone (Richter et al., 1984). Most recently, a neuropeptide with the properties of an endogenous benzodiazepine antagonist (Alho et al., 1985) and the previously uncertain prolactin-inhibitory factor peptide (Nikolics et al., 1985; Phillips et al., 1985) have been identified by similar methodology and their neuronal locations determined immediately.

Potentially new, previously unsuspected coexpressed peptides were suggested strictly from mRNA sequences to predict a new form of VIP (Itoh et al., 1983) and Substance P (Nawa et al., 1983). Moreover, pursuit of the pro-hormone for calcitonin led Rosenfeld and Evans and their collaborators to the recognition that rearrangements of parts of the mRNA domains of the pro-calcitonin could give rise to a "calcitonin-gene related peptide" (Rosenfeld et al., 1983) which in fact was found in special segments of the rat CNS and had unsuspected biological activity. In fact, the recombinant approach has yielded so many new molecules, all roughly equivalent candidates for consideration as neurotransmitters, that the next major phases of the investigation, localization and assessment of function, have lagged far behind.

Another Possible General Strategy for Transmitter Discovery

The appearance of the report suggesting that "pro-opiocortin" was actually "pro-opiomelanocortin" gave rise to the idea that better analysis of brain mRNAs could reveal unexpected multiple, biologically important, cleavage products. Believing that such an approach might not only yield neurotransmitters but might also yield information important to the complete characterization of the properties of neurons and their cell assemblies, my colleagues and I began an effort to employ recombinant DNA methods as a broad open-ended approach to characterizing important but unpredicted agonists and response systems of the brain. The continuous stream of results (Bloom et al., 1985; Milner & Sutcliffe, 1983; Milner et al., 1984; Malfroy et al., 1985; Sutcliffe et al., 1983a,b, 1984) suggest that all of our opportunistic wishes may be realizable.

Molecular Biologic Approaches to Identification

We have used molecular cloning methods to purify randomly chosen copies (cDNAs) of rat brain messengers RNAs (mRNAs). Poly(A)$^+$ RNA was purified from the brains of adult rats, copied into double stranded cDNA, and inserted into the plasmid pBR322 for cloning in *E. coli.* Clones bearing cDNA inserts that were at least 500 base pairs in length were nick translated and evaluated for their patterns of hybridization to mRNAs isolated from brain, liver, and kidney. Those clones that hybridize to brain mRNAs, but not to mRNAs extracted from other organs, we define as being brain-specific.

This categorization has been extremely productive since such basic quantitative characterizations had not previously been available. For example, Milner and Sutcliffe (1983) determined the approximate sizes of the mRNAs in brain, their relative abundances, and the total complexity of the brain mRNA population. Since the average length of brain-expressed mRNAs could thus be specified (approximately 4,000–5,000 nucleotides), and since the overall length of mammalian mRNA complexity has also been estimated (at 1.4 × 10^8 nucleotides in length), it is possible to calculate that approximately 30,000 mRNAs are expressed in the brain. The brain-specific mRNAs tend to be larger and more rare than the mRNAs found in other major organ systems, suggesting that genetic messages in brain may encode for more complex translation products. By using the method of "Northern Blot Analysis," one can separate the mRNAs transcribed in a given organ, like brain, liver, or kidney, and use the radioactive cDNA probes of brain-derived mRNAs to determine their presence or absence in other organs. Using such methods, mRNAs expressed in brain, but not detectable in liver or kidney, are operationally defined as "brain-specific" (Milner & Sutcliffe, 1983) and constitute over half of those expressed in brain.

Mapping the Brain With Molecular Biologically Defined Markers

Attempts to define the specific properties of the nervous system have generally begun with comparative analysis of its chemical or functional differences with cells of other organ systems. Likewise, attempts to clarify the uniquely complex structural organization of the brain were first approached through empirically derived cell staining methods supplemented later by more powerful and specific circuit tracing methodologies. During the past decade, anatomic studies have been powerfully extended by immunocytochemical probes specific for products known or inferred to be produced by neurons or glia. However, most neurotransmitter substances and their related synthetic or catabolic enzymes and receptors are not exclusive to the nervous system, being detected also in endocrine and exocrine tissues. Thus, relatively few brain-specific or neuron-specific molecules have been detected as yet.

An alternative approach to the specific, but unknown, properties of neurons, both generally and individually, is the direct analysis of the gene products expressed in brain, as noted above. Our examination of one apparently "brain-specific" protein product, as defined by our criteria, seems especially relevant to complete our documentation of the powers of neuropeptide localization. The clone 1B236 corresponds to a brain-specific mRNA of approximately 2,500 nucleotides, from which we have sequenced and deduced the amino acid order of a protein some 318 amino acids in length which was never previously identified. In RNA or "Northern" blotting analyses, 1B236 mRNA is found to be unequally distributed in the adult rat brain, with an abundance roughly following a caudal-to-rostral gradient in macroregional dissections (Sutcliffe et al., 1983a,b). Antisera raised against three fragments of the deduced amino acid sequence (Peptides 5,6,7 or P5, P6, P7; Figure 1), provided preliminary evidence of cellular heterogeneity of this presumptive gene product in pontine, cerebellar, cortical, and limbic structures (Sutcliffe et al., 1983).

An extensive, but virtually identical, pattern of immunoreactive fibers was visualized throughout the normal rat CNS with antisera raised against P5, P6, or P7. The immunoreactivity was especially dense in olfactory bulb and several other specific nuclei and defined regions (*see* Bloom et al., 1985). Virtually identical patterns of immunoreactivity were demonstrated by antisera against either of three synthetic peptides corresponding to non-overlapping regions of the carboxy-terminal of the presumptive polypeptide. These superimposable maps provide strong support for the interpretation that this protein corresponding to an mRNA cloned and selected as brain-specific (Sutcliffe et al., 1983a,b) is expressed in brain, and that this gene product is shared by a number of neuronal systems.

Given this array of features, as well as the evidence from mRNA hybridization studies already reported that attribute the 1B236 mRNA to neuronal and not glial sources (Sutcliffe et al., 1983a,b), we conclude that 1B236 protein is expressed by a selective set of central neurons. The peptides P5, P6, and P7 were initially selected as immunogens because these sequences were flanked in the primary 1B236 sequence by basic dipeptides that we considered to be possible proteolytic cleavage sites. Ongoing studies aimed at defining the molecular forms of the 1B236 peptide (Malfroy et al., 1985) indicate that small

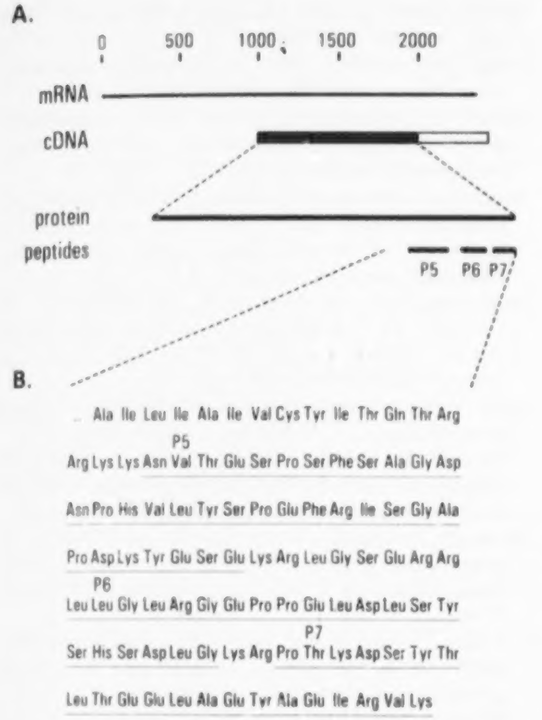

A.
0
500
1000
1500
2000
mRNA
cDNA
protein
peptides
P5
P6
P7
B.
... Ala Ile Leu Ile Ala Ile Val Cys Tyr Ile Thr Gln Thr Arg
P5
Arg Lys Lys Asn Val Thr Glu Ser Pro Ser Phe Ser Ala Gly Asp
Asn Pro His Val Leu Tyr Ser Pro Glu Phe Arg Ile Ser Gly Ala
Pro Asp Lys Tyr Glu Ser Glu Lys Arg Leu Gly Ser Glu Arg Arg
P6
Leu Leu Gly Leu Arg Gly Glu Pro Pro Glu Leu Asp Leu Ser Tyr
P7
Ser His Ser Asp Leu Gly Lys Arg Pro Thr Lys Asp Ser Tyr Thr
Leu Thr Glu Glu Leu Ala Glu Tyr Ala Glu Ile Arg Val Lys

FIGURE 1. Structure of the 1B236 protein. (A) The 1B236 mRNA, the p1B236 cDNA clone, and the 1B236 protein are schematically represented (2). The mRNA is ≈2,500 nucleotides in length: the cDNA clone p1B236 corresponds to the 3′ 1,500 nucleotides. The open reading frame in the cDNA sequence is shown by the filled bar; the 3′ noncoding region is shown by the open bar. Also indicated are the positions of peptides P5, P6, and P7. (B) The carboxyl-terminal sequence of the 1B236 protein is shown with peptides P5, P6, and P7 underlines. Notice the pairs of basic amino acids flanking the underlined peptides (*see* Malfroy et al., 1985).

peptides, similar in size to those selected for use as immunogens, and sharing immunoreactivity with them, may be formed by posttranslational processing. Such evidence will be critical to validate the hypothesis (Sutcliffe et al., 1983a,b) that the 1B236 protein is the precursor for a series of possible smaller messenger peptides. Until such issues can be firmly established, the observed ability of P5 and P6 to influence spontaneous or elicited activity of hippocampal or neocortical neurons (S.J. Henriksen, personal communication) and spontaneous locomotor behavior (G. Koob, personal communication) lack any direct transmitter-like connotation. However, the generally superimposable cellular maps, the vesicular location, the predominance of P6 immunoreactivity in those neurons which do become visualizable after colchicine pretreatment, and the loss of terminal like staining for all three peptides when cell body immunoreactivity is enhanced are consistent with the view that there is a large precursor form of the protein, which is processed during its transit through the perikaryal cytoplasm en route to nerve terminals.

Interpretations

Every new neuronal marker, including those that are likely to act as intercellular signals or signal transducers, has relevance for the College because it not only helps us sort out the structural and functional puzzles of the normal human brain, but it also provides specific markers to be used in diagnostic tests. The advent of molecular biological methods, especially that aspect of molecular biology that has been dubbed "cloning" has greatly accelerated the pace and breadth of molecular hunting expeditions. The avenues which my colleagues and I have embarked upon have already yielded more than a half dozen profoundly insightful molecular markers that are, in preliminary evidence, easily detected in human brains. The evidence seems clear therefore that knowledge such as this will remain of importance for generations to come.

References

Alho, H., Costa, E., Ferrero, P., Fujimoto, M., et al. Diazepam-binding inhibitor: a neuropeptide located in selected neuronal populations of rat brain. *Science*, 229:179–182, 1985.

Bloom, F.E. The functional significance of neurotransmitter diversity. *Am. J. Physiol.*, 246:C184–C194, 1984a.

Bloom, F.E. Chemical integrative processes in the central nervous system. In: *Handbook of Chemical Neuroanatomy*, 1984b, pp. 51–58.

Bloom, F.E., Battenberg, E.L.F., Milner, R.J., and Sutcliffe, J.G. Immunocytochemical mapping of 1B236, a brain specific neuronal polypeptide deduced from the sequence of a cloned mRNA. *J. Neurosci.*, 5:1781–1802, 1985.

Deschenes, R.J., Lorenz, L.J., Haun, R.S., et al. Cloning and sequence analysis of a cDNA encoding rat preprocholecystokinin. *Proc. Natl. Acad. Sci. (USA)*, 81:726–730, 1984.

Furutani, Y., Morimoto, Y., Shibahara, S., et al. Cloning and sequence analysis of cDNA for ovine corticotropin-releasing factor precursor. *Nature*, 301:537–540, 1983.

Goodman, R.H., Jacobs, J.W., Dee, P.C., and Habener, J.F. Somatostatin-28 encoded in a cloned cDNA obtained from a rat medullary thyroid carcinoma. *J. Biol. Chem.*, 257:1156–1159, 1982.

Gubler, U., Chua, A.O., Hoffman, B.J., et al. Cloned cDNA to cholecystokinin mRNA predicts an identical preprocholecystokinin in pig brain and gut. *Proc. Natl. Acad. Sci. (USA)*, 81:4307–4310, 1984.

Gubler, U., Monahan, J.J., Lomedico, P.T., et al. Cloning and sequence analysis of cDNA for the precursor of human growth hormone-releasing factor somatocrinin. *Proc. Natl. Acad. Sci. (USA)*, 80:4311–4314, 1983.

Gubler, U., Seeburg, P., Hoffman, B.J., et al. Molecular cloning establishes proenkephalin as precursor of enkephalin-containing peptides. *Nature*, 295:206–208, 1982.

Guillemin, R. Peptides in the brain: The new endocrinology of the neuron. *Science*, 202:390–402, 1978.

Guillemin, R., Brazeau, P., Bohlen, P., et al. Growth hormone-releasing factor from a human pancreatic tumor that caused acromegaly. *Science*, 218:585–587, 1982.

Itoh, N., Obata, K., Yanaihara, N., and Okamoto, H. Human preprovasoactive intestinal polypeptide contains a novel PHI-27-like peptide PHM-27. *Nature*, 304:547–549, 1983.

Ivell, R., and Richter, D. Structure and comparison of the oxytocin and vasopressin genes from rat. *Proc. Natl. Acad. Sci. (USA)*, 81:2006–2010, 1984.

Kakidani, H., Furutani, Y., Takahashi, H., et al. Cloning and sequence analysis of cDNA for porcine beta-neo-endorphin/dynorphin precursor. *Nature*, 298:245–249, 1982.

Krieger, D.T. Brain peptides: What, where, and why? *Science*, 222:975–985, 1983.

Malfroy, B., Bakhit, C., Bloom, F.E., et al. Brain-specific polypeptide 1B236 exists in multiple molecular forms. *Proc. Natl. Acad. Sci. (USA)*, 82:2009–2013, 1985.

Mayo, K.E., Vale, W., Rivier, J., et al. Expression-cloning and sequence of a cDNA encoding human growth hormone-releasing factor. *Nature*, 306:86–88, 1983.

McDonald, T.J., Jornvall, H., Tatemoto, K., and Mutt, V. Identification and characterization of variant forms of the gastrin-releasing peptide (GRP). *FEBS Lett.*, 156:349–356, 1983.

Milner, R.J., and Sutcliffe, J.G. Gene expression in rat brain. *Nucleic Acids Res.* 11:5497–5520, 1983.

Milner, R.J., Bloom, F.E., Lai, C., et al. Brain-specific genes have identifier sequences in their introns. *Proc. Natl. Acad. Sci. (USA)*, 81:713–717, 1984.

Minth, C.D., Bloom, S.R., Polak, J.M., and Dixon, J.E. Cloning characterization and DNA sequence of a human cDNA encoding neuropeptide tyrosine. *Proc. Natl. Acad. Sci. (USA)*, 81:4577–4581, 1984.

Montminy, M.R., Goodman, R.H., Horovitch, S.J., and Habener, J.F. Primary structure of the gene encoding rat preprosomatostatin. *Proc. Natl. Acad. Sci. (USA)*, 81:3337–3340, 1984.

Mutt, V. Further investigations of intestinal hormonal polypeptides. *Clin. Endocrinol.*, 5:175S–183S, 1976.

Nakanishi, S., Inoue, A., Kita, T., et al. Nucleotide sequence of cloned cDNA for bovine corticotropin-β-lipoprotein precursor. *Nature*, 278:423–427, 1979.

Nawa, H., Hirose, T., Takashima, H., et al. Nucleotide sequences of cloned cDNAs for two types of bovine brain Substance P precursor. *Nature*, 306:32–36, 1983.

Nikolics, K., Mason, A.J., Szonyi, E., et al. A prolactin-inhibition factor within the precursor for human gonadotropin-releasing hormone. *Nature*, 316:511–517, 1985.

Noda, M., Furutani, Y., Takahashi, H., et al. Cloning and sequence analysis of cDNA for bovine adrenal preproenkephalin. *Nature*, 295:202–206, 1982.

Phillips, H.S., Nikolics, K., Branton, D., and Seeburg, P.H. Immunocytochemical localization in rat brain of a prolactin release-inhibiting sequence of gonadotropin-releasing hormone prohormone. *Nature*, 316:542–545, 1985.

Richter, K., Kawashima, E., Egger, R., and Kreil, G. Biosynthesis of thyrotropin releasing hormone in the skin of Xenopus laevis: partial sequence of the precursor deduced from cloned cDNA. *The EMBO Journal*, 3:617–621, 1984.

Rosenfeld, M.G., Mermod, J.-J., Amara, S.G., et al. Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. *Nature*, 304:129–135, 1983.

Schmale, H., and Richter, D. Single base deletion in the vasopressin gene is the cause of diabetes insipidus in Brattleboro rats. *Nature*, 308:705–709, 1984.

Seeburg, P.H., and Adelman, J.P. Characterization of cDNA for precursor of human luteinizing hormone releasing hormone. *Nature*, 311:666–668, 1984.

Snyder, S.H. Drug and neurotransmitter receptors in the brain. *Science*, 224:130–138, 1984.

Sutcliffe, J.G., Milner, R.J., and Bloom, F.E. Cellular localization and function of the proteins encoded by brain-specific mRNAs. *Cold Spring Harbor Symp.* 48:477–484, 1983.

Sutcliffe, J.G., Milner, R.J., Shinnick, T.M., and Bloom, F.E. Identifying the protein products of brain-specific genes with antibodies to chemically synthesized peptides. *Cell*, 33:671–682, 1983.

Tatemoto, K., and Mutt, V. Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. *Nature*, 285:417–418, 1980.

Tatemoto, K., and Mutt, V. Isolation and characterization of the intestinal peptide porcine PHI (PHI-27) a new member of the glucagon-secretin family. *Proc. Natl. Acad. Sci. (USA)*, 78:6603–6607, 1981.

Vale, W., Spiess, J., Rivier, C., and Rivier, J. Characterization of a 41 residue ovine hypothalamic peptide that stimulates secretion of corticotropin and μ-endorphin. *Science*, 213:1394–1397, 1981.

Use of Gene Transfer Techniques to Study Neuropeptide Gene Regulation

Edward Herbert, Ph.D.,[1] Audrey F. Seasholtz, Ph.D.,[1] and Michael Comb, Ph.D.[2]

Introduction

Studies of vertebrate and invertebrate nervous systems over the past 20 years have suggested that simple forms of behavior and modifications of behavior attained through learning are expressed by changes in neurotransmitter levels at synapses and by changes in post-synaptic neurons that govern responses to neurotransmitters. In this model, an increase in neurotransmitter release may lead to learning by strengthening a synaptic connection of a complex neuronal circuit mediating that learning behavior. Persistence of the change in neurotransmitter release will create memory of the learning experience. Changes due to learning are imprinted on post-synaptic elements possibly through alterations of receptors and transmitted to other neurons or effector organs to produce a behavioral response.

What mechanisms underlie these changes at the synapse? Are specific genes turned on or off or activated to produce these changes in neurotransmitter levels or receptor levels? In the past 10 years, advances in molecular genetics and biochemistry have provided the tools necessary to answer these questions. These tools make it possible to clone genes that code for neuropeptides, neuropeptide receptors, and neuropeptide processing enzymes and to determine how their expression is regulated by intracellular and extracellular control factors.

Neuropeptides

A milestone in the field of neuroscience has been the discovery of a vast repertoire of neuropeptides that mediate specific behavior patterns in animals. Upon release at the synapse, neuropeptides like other kinds of neurotransmitters combine with receptors on post-synaptic neurons or target cells to initiate an intracellular cascade that leads to an electrical or chemical response. All of these processes (neuropeptide production and release, receptor function and intracellular cascades) must be defined at the molecular level to achieve an understanding of behavior. Molecular biology has provided us with methods and tools necessary to define these processes.

The impact of molecular biology on neuroscience is no more apparent than in the study of opioid peptides. Since the discovery of Met- and Leu-enkephalin in 1975 by Hughes et al., a large family of peptides exhibiting opioid activity have been isolated and subsequently shown by recombinant DNA techniques to be derived from three different precursor proteins (Figure 1). Proopiomelanocortin (POMC) gives rise to β-endorphin, ACTH, and melanocyte stimulating hormones (MSH) (Mains et al., 1977; Roberts and Herbert, 1977; Nakanishi et al., 1979). Proenkephalin (proenkephalin A) contains six Met-enkephalin sequences and one Leu-enkephalin sequence and gives rise to Met- and Leu-enkephalin as well as a variety of larger enkephalin containing peptides (Noda et al., 1982; Gubler et al., 1982; Comb et al., 1982; Legon et al., 1982). Prodynorphin (proenkephalin B) contains three Leu-enkephalin sequences and gives rise to α- and β-neoendorphin and dynorphin A and dynorphin B related peptides (Kakidani et al., 1982). Each opioid precursor undergoes proteolytic processing to generate biologically active peptides during its maturation and transport through the secretory pathway to storage vesicles (Douglass et al., 1984; Udenfriend and Kilpatrick, 1983). Recent evidence suggests that all three opioid precursors can be cleaved to different sets of biologically ac-

---

[1] Institute for Advanced Biomedical Research, The Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

[2] Department of Molecular Biology, Massachusetts General Hospital, Boston, MA 02114.

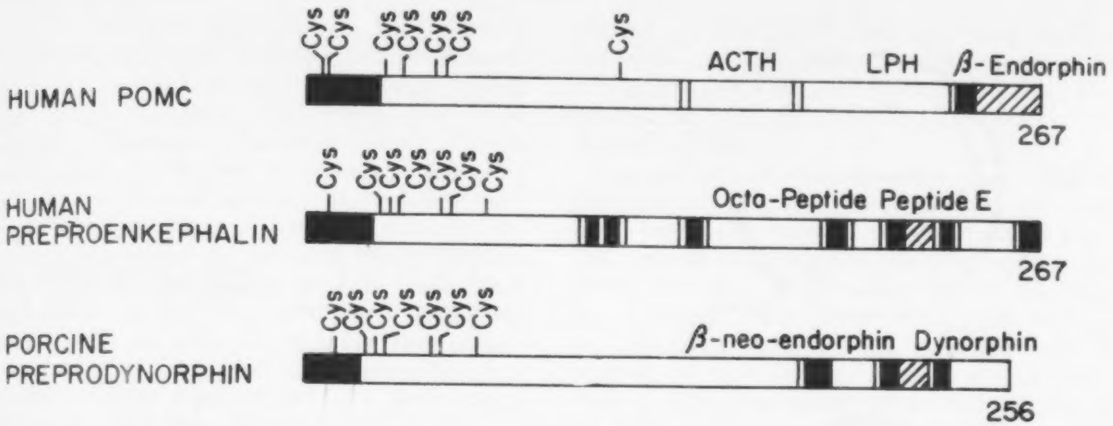


FIGURE 1. Structure of the three opioid peptide precursors; proopiomelanocortin (POMC), preproenkephalin and preprodynorphin. The black box at the left end of the precursors represents the signal sequence. The smaller black boxes are enkephalin sequences (Met- or Leu-enkephalin) and the double lines flanking the bioactive peptide domains represent pairs of basic amino acid residues.

tive peptides in the different tissues in which they are expressed (Douglass et al., 1984; Udenfriend and Kilpatrick, 1983; Seizinger et al., 1984). For example, POMC is cleaved in the anterior lobe of the pituitary to produce ACTH, β-LPH, and an N-terminal fragment while in the intermediate lobe of the pituitary this same molecule is processed to β-endorphin, α-melanocyte stimulating hormone (MSH), and a C-terminal fragment of ACTH which have different biological activities and target tissues (Herbert, 1981) (Figure 2). Similarly, proenkephalin is cleaved to free enkephalins in several brain regions while processing in the adrenal medulla yields a variety of large enkephalin containing peptides and very little free enkephalin (Udenfriend and Kilpatrick, 1983; Seizinger et al., 1984; Herbert, 1981; Liston et al., 1983).

Regulation of synthesis and release of peptides derived from opioid precursors is also tissue specific. Synthesis and release of POMC peptides, for example, are stimulated by corticotropin releasing factor (CRF) and vasopressin and inhibited by glucocorticoids (Vale et al., 1981; Rivier et al., 1982; Axelrod and Reisine, 1984) in the anterior lobe of the pituitary, whereas in the intermediate lobe, synthesis and secretion of POMC peptides are not affected by these agents but rather by input from dopaminergic neurons with cell bodies originating in the hypothalamus (Rosa et al., 1980).

The release and synthesis of proenkephalin are also differentially regulated in a variety of tissues. Chronic administration of haloperidol causes a twofold increase in Met-enkephalin immunoreactivity in rat striatum and globus pallidus, but not in hypothalamus, septum, or medulla oblongata where it is also expressed (Tang et al., 1983). In bovine adrenal medulla, neural input regulates the release of enkephalin-containing peptides (Lewis et al., 1981). In cultures of chromaffin cells from bovine adrenal medulla, the levels of enkephalin peptides and proenkephalin mRNA are dramatically increased by treatment with cAMP analogs (Quach et al., 1984) or activators of adenylate cyclase (Eiden et al., 1984). At present we know very little about the mechanisms involved in the action of these agents. Do these compounds cause an activation or repression of the opioid genes? What are the molecular mechanisms involved in these types of regulation of gene expression?

Gene Transfer Approaches to the Study of Neuropeptide Gene Expression

The availability of cloned genes and the development of new methods which permit their efficient transfer into eukaryotic cells have revolutionized the field of gene regulation and provided the means of examining the questions raised above. A variety of gene

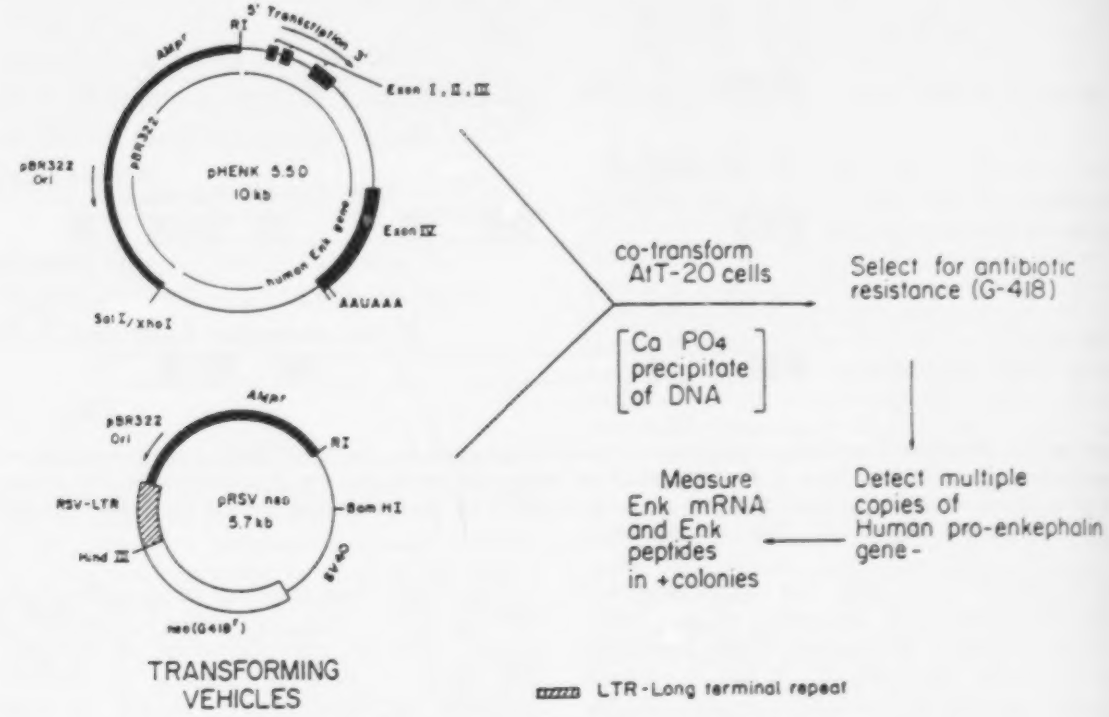

5' Transcription 3'
RI
AMPr
Exon I, II, III
pBR322 Ori
pBR322
pHENK 5.5D
10 kb
human Enk gene
Exon IV
AAUAAA
Sal I/xho I
co-transform AtT-20 cells
Ca PO4 precipitate of DNA
Select for antibiotic resistance (G-418)
Detect multiple copies of Human pro-enkephalin gene -
Measure Enk mRNA and Enk peptides in +colonies
AMPr
pBR322 Ori
RI
RSV-LTR
pRSV neo
5.7 kb
Bam HI
Hind III
SV40
neo(G418r)
TRANSFORMING VEHICLES
▨ LTR-Long terminal repeat

FIGURE 2. Technique for transfer of human proenkephalin gene into AtT-20 cells.

transfer techniques are now available which allow us to study the regulation of expression at a variety of levels. Transcriptional regulation appears to be controlled by a variety of DNA sequences in the structural gene (*cis*-acting elements) and *trans*-acting regulatory elements (factors that interact with *cis*-elements). The DNA sequences involved in *cis*-acting transcriptional regulation are quite diverse in function and structure, and act in the general stimulation of transcription (promoters and enhancers), tissue-specific gene expression, or the induction (or repression) of transcription by the action of specific agents. The *trans*-acting regulatory elements are often specific protein factors which interact with the *cis*-acting DNA sequences. Methylation patterns may also play a role in controlling the transcriptional activity of a gene. Gene transfer techniques can also be used to examine the sequences in the gene or cDNA which provide signals for post-translational modification, processing, and secretion. Therefore, by constructing specifically mutated genes and analyzing their activity in a variety of expression systems, it is now possible to determine the role of specific DNA sequences in different aspects of gene expression.

Gene transfer experiments with cloned genes can be divided into two major categories: a) stable transfections, and b) transient assay systems. To study stably transfected cell lines, one isolates a clone of eucaryotic cells that has integrated the foreign gene into its chromosomal DNA. The major advantage of this system is the ability to isolate stable cell lines which can be grown indefinitely in culture and used to study a variety of regulatory phenomena. The gene of interest can be introduced into the eucaryotic cells by several different methods: a) chemical methods such as the calcium phosphate precipitation method or the DEAE-dextran method; b) physical methods such as microinjection or electroporation; c) viral-mediated DNA transfer; and d) fusion of DNA-containing membranous vesicles such as liposomes, envelopes of Sendai virus particles, or protoplasts to cells.

The calcium phosphate precipitation method is the most widely used procedure, but is somewhat limited at the present time in the range of target cells which give high transfer efficiency. Microinjection and fusion techniques can be used to introduce the gene of interest into almost any mammalian cell, and microinjection of fertilized mouse embryos has allowed the performance of regulation studies in transgenic animals. Both RNA and DNA viruses have also been used very successfully as gene transfer vectors. However, all of the long term assay systems (regardless of the method used for gene transfer) suffer one limitation: an inability to control or evaluate the region of the genome into which the introduced gene is integrated. Thus, different clones carrying the same gene may show significant variability in RNA and protein production depending upon differences in location of the foreign gene in the host.

The second gene transfer approach involves the use of transient expression systems. In these systems, the foreign gene or cDNA is introduced into eucaryotic cells and its expression is assayed within a few hours to days prior to integration into the genome. The advantages of these assays are simplicity and rapidity. Furthermore, because the transferred molecules remain episomal (extrachromosomal), the problems associated with random chromosomal integration can be avoided. The major disadvantages are the relatively low levels of expression and the inability to conduct experiments over more than a few days. A variety of transient systems are presently available. In the first system the control region of the gene of interest is fused to the coding sequence of a gene which is readily assayed by enzymatic means such as *E. coli* chloramphenicol acetyltransferase or herpes thymidine kinase. With this type of system one can assay the transcriptional activity of the foreign gene by a simple and rapid enzymatic assay. A second transient assay utilizes the *Xenopus* oocyte. *Xenopus* oocytes will efficiently transcribe and translate an injected gene and can therefore be used to study transcriptional regulation and post-translational processing. The third transient assay system involves the use of vaccinia virus as a gene transfer vector. Vaccinia is a cytoplasmic virus with a broad host range and is therefore best-suited for examining the role of specific DNA sequences in controlling the processing and secretion of a protein in different cell lines.

We are currently using these gene transfer techniques to study the regulation and expression of the human proenkephalin gene and several other opioid genes. A mouse anterior pituitary corticotrophic cell line has been stably transfected with the human proenkephalin gene and the characteristics of several of the isolated clones will be discussed. The expression of proenkephalin in two transient systems will also be discussed: a) proenkephalin fusion genes, and b) vaccinia virus. By studying the expression and regulation of the wild-type human proenkephalin gene and a variety of site-specific mutants in both the stably transfected cell lines and a variety of transient expression systems, we hope to gain a better understanding of the DNA sequences involved in the expression and control of this gene.

Stably Transfected Cell Lines

The human proenkephalin gene has been introduced and expressed in AtT-20 cells in order to study the transcriptional regulation of this gene and to elucidate the mechanisms underlying processing of proenkephalin (Comb et al., 1985). The AtT-20 cell line was selected as the host system for these studies because the cells do not express proenkephalin, but possess well developed secretory vesicles and store and release large amounts of ACTH and β-LPH. They also respond to physiological regulators and process POMC in a manner similar to that of anterior pituitary cells. Hence these cells provide a well characterized secretory pathway in which to examine the processing and chemical modifications of neuropeptide precursors.

A recombinant plasmid containing the human proenkephalin gene ligated to pBR322 was introduced into AtT-20 cells by cotransformation with pRSVneo, a plasmid containing the *neo* gene which confers resistance to the aminoglycoside drug G418 and therefore acts as a dominant selectable marker as shown in Figure 2. Stable transformants which had one or more copies of the human proenkephalin gene integrated into the mouse chromosomal DNA expressed a 1.45 kb mRNA identical in size to authentic human proenkephalin mRNA.

Analysis of protein extracts from AtT-20 transformants using a radioimmunoassay specific for Met-enkephalin demonstrated that these cells synthesize proenkephalin protein and cleave it to form free Met-enkephalin. This result suggests that the processing enzymes present in AtT-20 cells can also recognize and efficiently process the cleavage sites flanking the Met-enkephalin sequences in the proenkephalin precursor. The secretion of Met-enkephalin from these cells was also examined. Treatment of cells with corticotropin releasing factor (CRF) resulted in a twofold stimulation of secretion of both ACTH and Met-enkephalin immunoreactivity. Therefore, these stably transformed cell lines will be very useful for studying the molecular mechanisms involved in processing and secretion of the proenkephalin protein along with the transcriptional regulation of the gene.

Transient Expression Systems

Fusion Genes: In these studies the putative regulatory region of a gene is linked to an enzymatic reporter function which is readily assayed in eucaryotic cells. The amount of enzyme activity reflects the amount of protein produced under the control of the linked regulatory region and thus provides a direct indication of the level of gene expression. We have selected the *E. coli* chloramphenicol acetyltransferase (CAT) reporter function developed by Gorman et al. (1982) because a) CAT activity is easily and sensitively assayed; and b) there is no interfering endogenous activity since CAT activity is not present in mammalian or avian cells. By fusing the 5′ end of the human proenkephalin gene to the CAT gene, we can analyze the efficiency of the proenkephalin gene promoter, map transcriptional control elements, and test for elements of the gene required for cell-specific expression following transfection into mammalian cells.

The fusion gene contains the first 406 base pairs (bp) of the human proenkephalin gene (193 bp of 5′ flanking region and 213 bp of human proenkephalin DNA including exon I, intron A, and exon II) fused to the CAT gene. The 3′ untranslated sequences, poly A addition sites and 3′ flanking sequences of the human proenkephalin gene were also placed 3′ to the CAT gene. In this fusion gene plasmid (called ENKAT-12), CAT expression is driven by the linked human proenkephalin promoter and utilizes both 5′ and 3′ human proenkephalin control signals (such as the transcription termination signal; Figure 3). This fusion plasmid was transfected into eukaryotic cells for transient expression by the calcium phosphate precipitation method. The cells were harvested at 36 to 48 hours post-transfection, and cell extracts were then assayed for CAT activity using ^{14}C-chloramphenicol and acetyl CoA. The production of chloramphenicol acetate was assayed by thin layer chromatography.

The transient expression of ENKAT-12 was examined in a variety of cell lines: rat adrenal PC-12 cells, mouse pituitary AtT-20 cells, human HeLa cells, mouse L cells, and monkey CV-1 cells. Relatively high levels of CAT expression were demonstrated 36 to 48 hours after transfection in all the tested cell lines, with values ranging from 20 to 80 percent of the level of expression directed by RSVcat, a plasmid containing the strong rous sarcoma virus promoter in front of the CAT gene. Thus, the 5′ 406 bp of the human proenkephalin gene contains an efficient promoter region capable of directing high levels of CAT expression.

The ENKAT-12 plasmid was also used in these transient assays to identify potential regulators of the human proenkephalin gene. Several groups have reported that proenkephalin mRNA levels are regulated by cAMP analogs (Quach et al., 1984) or activators of adenylate cyclase (Eiden et al., 1984). cAMP is thought to act as a second messenger system in transcriptional regulation of eucaryotic genes. Activation of adenylate cyclase by a variety of different mechanisms causes increased levels of intracellular cAMP. Increased cAMP concentrations cause increased cAMP dependent protein kinase activity, and changes in protein phosphorylation may be responsible for modulation of gene transcription. Thus, activators of adenylate cyclase, analogs of cAMP (8BrcAMP), or

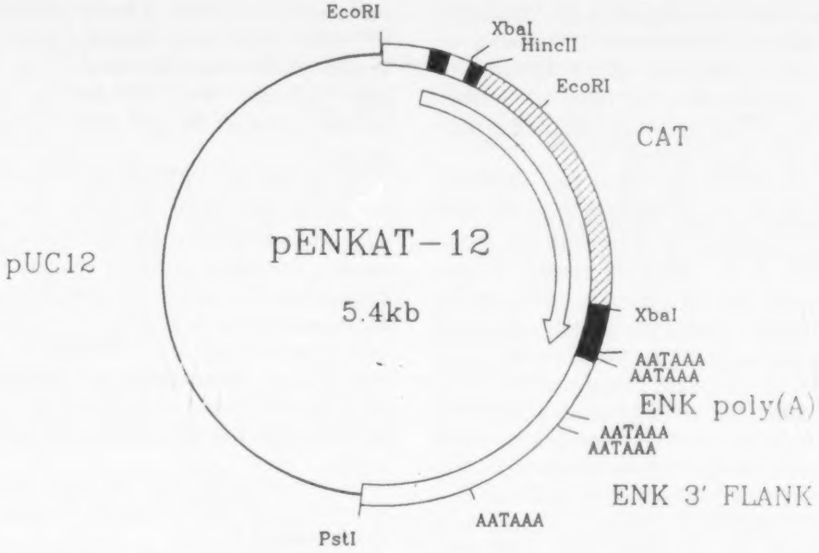


FIGURE 3. Structure of the human proenkephalin/CAT fusion gene.

phosphodiesterase inhibitors (IBMX) which prevent breakdown of intracellular cAMP may all affect gene transcription by a similar second messenger system.

When cAMP regulators were added to the media 18 hours after ENKAT-12 transfections, an increase in CAT activity was observed. 8BrcAMP (0.9 mM) alone caused a five-fold increase in CAT activity while 8Br-cAMP and IBMX (0.5 mM) together caused an 18-fold increase in CAT expression. These data suggest a clear role for cyclic AMP as a second messenger involved in mediating proenkephalin gene expression. Cholera toxin and forskolin, other stimulators of adenylate cyclase, also produced increases in ENKAT-12 directed CAT expression.

To localize the DNA sequences in the proenkephalin gene which were responsible for the cAMP transcriptional regulation, several plasmids were constructed which contained deletions or insertions in the 5′ flanking region of the human proenkephalin gene. Plasmid ENKAT B lacks the DNA sequence from −60 to −155 base pairs upstream of the human enkephalin cap site. Transfections with this plasmid gave a several-fold reduction in basal CAT activity and no induction with cAMP analogs. Reinsertion of the −60 to −155 sequence into the plasmid but in the opposite orientation restored both the basal and regulated expression. Thus, this region of the 5′ flanking sequence of the gene contains sequences required for both basal and regulated expression, and these sequences can work in an orientation independent fashion as enhancer elements in other genes.

It was also exciting to find that this region was capable of conferring cAMP regulation on a different promoter. The DNA sequence from −60 to −155 bp upstream of the human proenkephalin cap site was fused to a POMC-CAT fusion gene containing only 84 bp upstream from the POMC cap site. The POMC-CAT fusion gene expresses low basal CAT activity and shows very slight (two-fold) increases in CAT activity in response to cAMP. However, fusion of the DNA sequence from the human proenkephalin gene 5′ to the 84 bp of upstream sequences in the POMC-CAT construct showed increases of basal expression and conferred a larger (greater than 20-fold) induction by cAMP. This finding suggests that this region of the human proenkephalin 5′ flanking sequence is sufficient to confer cAMP inducibility on an intact promoter.

In order to map the exact location of the DNA sequences responsible for cAMP regulation, a series of 5′ deletion mutants have been constructed using Bal 31 exonuclease. We hope to be able to localize the regions responsible for basal activity and cAMP regulation using these deletions so that these sequences can be examined more fully with site-specific mutagenesis and used as probes to search for trans-acting proteins which may be involved in these processes.

Vaccinia Virus: Vaccinia virus has recently been introduced as a eucaryotic cloning and expression vector. There are several good reasons for this: a) broad host range of vaccinia virus which allows genetic information to be shuttled into a variety of species and cell types; and b) vaccinia is a cytoplasmic virus and therefore replicates, transcribes, and processes the vaccinia viral genes in the cytoplasm of the infected cells. Therefore, if the cDNA for a gene of interest is inserted downstream of a vaccinia promoter, it will be rapidly transcribed (within a few minutes) and expressed at high levels in the host cell cytoplasm. This system is very useful then for examining the expression of neuropeptides, such as proenkephalin, in a variety of different cell lines to address questions regarding the post-translational maturation of these proteins and the enzymes which normally catalyze the processing events.

To achieve this goal, a recombinant vaccinia virus was constructed which contains and expresses the human proenkephalin cDNA (G. Thomas, unpublished studies). Four different cell lines were infected with this recombinant vaccinia virus. Two of the cell lines, AtT-20 and GH_4C_1 (rat pituitary), contain a full complement of secretory organelles. The other two cell lines, BSC-40 (African green monkey kidney cells) and Ltk^- (mouse fibroblast), do not contain stored granules typical of secretory cells. Twenty-four hours after infection, cell extracts and culture media were collected for separation on a TSK-125 high performance liquid chromatography sizing column followed by radioimmunoassay for Met-enkephalin. BSC-40 cells infected with the recombinant virus revealed two prominent peaks of Met-enkephalin immunoreactivity (IR). The faster migrating peak eluted at the expected size for human proenkephalin (28,000 daltons). The slower migrating peak eluted with an apparent molecular weight of 16,000 daltons. Similar results were obtained with the GH_4C_1 and Ltk^- cells. The media of the BSC-40 cells were also analyzed. These results demonstrated that only the larger peak of Met-enkephalin IR was secreted from the cells and this protein was shown to be authentic proenkephalin by purification and sequence analysis.

In contrast, AtT-20 cells infected with the recombinant virus showed five major peaks of Met-enkephalin IR. The slowest migrating peak coeluted with authentic Met-enkephalin. Therefore, the AtT-20 cells are processing the proenkephalin protein to Met-enkephalin and will therefore be useful for examining the enzymes necessary for this process and for elucidating the proenkephalin processing pathway in these cells.

Conclusions

Gene transfer methods have given us the opportunity to examine the molecular mechanisms involved in the regulation of expression at almost every level: transcription, translation, processing, and secretion. It is our hope that by using a variety of gene transfer approaches to study regulation, we will be able to examine each level of regulation in detail. By then integrating the information which we have attained from each system, we hope to be able to gain a more complete understanding of the cellular mechanisms involved in the control of neuropeptide expression by hormones and neurotransmitters from the point at which these regulators interact with cell surface receptors to the activation of the intracellular cascade that leads to turning neuropeptide genes on and off.

References

Axelrod, J., and Reisine, T.D. Stress hormones: Their interaction and regulation. *Science*, 224:452–459, 1984.

Comb, M., Seeburg, P.H., Adelman, J., et al. Primary structure of the human Met- and Leu-enkephalin precursor and its mRNA. *Nature*, 295:663–666, 1982.

Comb, M., Liston, D., Martin, M., et al. Expression of the human proenkephalin gene in mouse pituitary cells: accurate and efficient mRNA production and proteolytic processing. *EMBO J.*, 4:3115–3122, 1985.

Douglass, J., Civelli, O., and Herbert, E. Polyprotein gene expression: Generation of diversity of neuroendocrine peptides. *Ann. Rev. Biochem.*, 53:665–715, 1984.

Eiden, L.E., Giraud, P., Affolter, H.-U., et al. Alternative modes of enkephalin biosynthesis regulation by reserpine and cyclic AMP in cultured chromaffin cells. *Proc. Natl. Acad. Sci. USA*, 81:3949–3953, 1984.

Gorman, C.M., Moffat, L.F., and Howard, B.M. Recombinant genomes which express chloramphenicol acetyltransferase in mammalian cells. *Mol. and Cell. Biol.*, 2:1044–1051, 1982.

Gubler, U., Seeburg, P., Hoffman, et al. Molecular cloning establishes proenkephalin as precursor of enkephalin-containing peptides. *Nature*, 295:206–208, 1982.

Herbert, E. Discovery of pro-opiomelanocortin: A cellular polyprotein. *Trend in Biochem. Sci.*, 6:184–188, 1981.

Hughes, J., Smith, T.W., Kosterlitz, H.W., et al. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature*, 258:577–579, 1975.

Kakidani, H., Furutani, Y., Takahashi, H., et al. Cloning and sequence analysis of cDNA for porcine β-neoendorphin/dynorphin precursor. *Nature*, 298:245–249, 1982.

Legon, S., Glover, D.M., Hugers, J., et al. The structure and expression of the proenkephalin gene. *Nucleic Acids Res.*, 10:7905–7917, 1982.

Lewis, R.V., Stern, A.S., Kilpatrick, D.L., et al. Marked increases in large enkephalin-containing polypeptides in the rat adrenal gland following denervation. *J. of Neurosci.*, 1:80–82, 1981.

Liston, D.R., Vanderhaeghen, J.J., and Rossier, R. Presence in brain of synenkephalin, a proenkephalin-immunoreactive protein which does not contain enkephalin. *Nature*, 302:62–65, 1983.

Mains, R.E., Eipper, B.A., Ling, N. Common precursor to corticotropins and endorphins. *Proc. Natl. Acad. Sci. USA*, 74:3014–3018, 1977.

Nakanishi, S., Inove, A., Kita, T., et al. Nucleotide sequence of cloned cDNA for bovine corticotropin-lipotropin precursor. *Nature*, 278:423–427, 1979.

Noda, M., Furutani, Y., Takahashi, H., et al. Cloning and sequence analysis of cDNA for bovine adrenal preproenkephalin. *Nature*, 295:202–206, 1982.

Quach, T.T., Tang, F., Kageyama, H., et al. Enkephalin biosynthesis in adrenal medulla: Modulation of proenkephalin mRNA content of cultured chromaffin cells by 8-Br-cyclic AMP. *Mol. Pharmacol.*, 26:255–260, 1984.

Rivier, C., Brownstein, M., Soiess, J., et al. *In vivo* corticotropin-releasing factor-induced secretion of adrenocorticotropin, β-endorphin, and corticosterone. *Endocrinology*, 110:272–278, 1982.

Roberts, J.L. and Herbert, E. Characterization of a common precursor to corticotropin and β-lipotropin: Cell-free synthesis of the precursor and identification of corticotropin peptides in the molecule. *Proc. Natl. Acad. Sci. USA*, 74:4826–4830, 1977.

Rosa, P.A., Policastro, P., and Herbert, E. A cellular basis for the differences in regulation of synthesis and secretion of ACTH/endorphin peptides in anterior and intermediate lobes of the pituitary. *J. Exp. Biol.*, 89:215–237, 1980.

Seizinger, B.R., Grimm, C., Hollt, V., and Herz, A. Evidence for a selective processing of proenkephalin B into different opioid peptide forms in particular regions of rat brain and pituitary. *J. of Neurochem.*, 42:447–457, 1984.

Tang, F., Costa, E., and Schwartz, J.P. Increase of proenkephalin mRNA and enkephalin content of rat striatum after daily injection of haloperidol for 2–3 weeks. *Proc. Natl. Acad. Sci. USA*, 80:3841–3844, 1983.

Udenfriend, S., and Kilpatrick, D. Biochemistry of the enkephalin and enkephalin-containing peptides. *Arch. Biochem. Biophys.*, 221:309–323, 1983.

Vale, W., Speiss, J., Rivier, C., Rivier, J. Characterization of 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β-endorphin. *Science*, 213:1394–1397, 1981.

Neuropsychopharmacology of Alcohol and Drug Abuse

Co-Chairs:

Jack H. Mendelson, M.D.
Nancy K. Mello, Ph.D.

McLean Hospital
Belmont, MA 02178

Interactions of Alcohol and Drugs of Abuse

Monique C. Braude, Ph.D.[1]

The focus of this symposium is the discussion of a number of critical issues concerning pharmacological intervention in alcohol and drug abuse disorders. Kreek and Stimmel (1984) published an excellent overview of this topic. This paper will cover more specifically what we know at present regarding interactions of alcohol with abused substances, i.e., compounds used either therapeutically like benzodiazepines and opiates, or on the street like amphetamines, cannabinoids, and cocaine.

Interactions between alcohol and other drugs fall into three basic categories: 1) additive/synergistic: the separate effects of each drug adds to the effect of the other when taken together, 2) potentiation when the resulting effect is greater than that of each component, and 3) antagonism.

A direct interaction is the result of the pharmacologic effects of the drugs. Indirect effects include pharmacokinetic interactions (in which a drug alters the absorption, distribution, metabolism, or excretion of another) and tolerance phenomena in which a drug alters the response of the target tissue to itself or another drug. Tolerance to alcohol has been reported after repeated use. Cross tolerance between alcohol and other drugs occurs when the physiologic changes induced by alcohol, for instance, carry over to another drug such as a barbiturate and the observed effect of the second drug is diminished. Interactions between alcohol and other drugs can usually be understood in terms of one or more of these phenomena.

Why are we interested in drug interactions? The important consequences of psychotropic drug interactions for an individual and society include the following:

1) Unexpected degree of impairment in performing daily tasks associated with a serious potential for injury (driving a car, operating machinery).

2) Accidental death from overdose.

3) Increase in behavioral toxicity (cognitive functions, memory impairment, etc.).

The concomitant oral ingestion of alcohol and other drugs could theoretically affect the absorption of these drugs but information is mostly lacking in this area and the existing evidence does not point to clinically significant effects. Alcohol in the body is primarily metabolized by the liver alcohol dehydrogenase to yield acetaldehyde. Research in the last 10 years also indicates that acute and chronic administration of alcohol can inhibit the biotransformation of many drugs that are normally degraded by hepatic microsomal mixed function oxidases. The most prominent result of this alcohol-induced inhibition of microsomal enzymes *in vivo* appears to be a prolongation of the plasma life of drugs such as pentobarbital, meprobamate, amphetamines, and others—but not phencyclidine (PCP). The amount of alcohol use as well as the direction of its use over a long or short period are also important factors in drug interactions.

---

[1] National Institute on Drug Abuse, 5600 Fishers Lane, Room 10A-31, Rockville, MD 20857.

Whereas acute alcohol intoxication usually inhibits the biotranformation of drugs, the long-term ingestion of alcohol can lead to hepatic microsomal enzyme induction and produce enhancement of the formation of intermediate metabolites that may be toxic to the liver thus increasing the hepatotoxic effect of alcohol. Such appears to be the case with cocaine. Finally, alcohol can influence the elimination of other drugs indirectly by causing hepatic dysfunction and/or nutritional deficiencies.

An excellent review by Muhoberac et al. (1984) on the mechanism(s) of ethanol-drug interaction focuses on the structure/function relationship of drugs at the microsomal levels. It complements two comprehensive reviews by Sellers (1978) and Linnoila (1979) that emphasize the pharmacokinetic aspects of drug interactions with alcohol.

Interactions of Alcohol With Central Nervous System (CNS) Depressants and Benzodiazepines

Interactive effects between alcohol and CNS depressants such as barbiturates, benzodiazepines, and methaqualone are frequent. In terms of CNS depression, use of these drugs with alcohol is usually additive. With drugs which are metabolized by the hepatic microsomal enzyme system, such as phenobarbital and pentobarbital, synergism has been reported leading to increased toxicity and death in humans.

Benzodiazepines have now significantly replaced barbiturates as anxiolytics and sedative hypnotics.

Benzodiazepines and Ethanol

The most extensively studied drug interactions have been those of benzodiazepines, and ethanol. Two recent reviews (Sellers, 1982; Chan, 1984) evaluate the effects and consequences of these interactions.

As noted in the review by Sellers, ethanol and benzodiazepines interact both at the pharmacokinetic and pharmacodynamic levels in a predictable manner qualitatively or quantitatively by enhancing each other's effects. However, benzodiazepines do not seem to potentiate the effects of alcohol as much as other sedatives do.

Kinetically, acute doses of alcohol impair the disposition of benzodiazepines that are metabolized by demethylation or hydroxylation. For instance, it increases the blood levels of orally administered diazepam but not of oxazepam which undergoes glucuronide conjugation. Chronic ethanol ingestion, on the other hand, increases the clearance of benzodiazepines that are demethylated or hydroxylated.

In general, alcohol and benzodiazepines when studied alone produce sedation, impair motor coordination, reaction time, memory acquisition, retention, and recall in a dose-related manner. Many studies indicate that the acute combination of both drugs produces the same impairment at a lower dose than given separately or reveals an impairment not apparent with the control dose of the drug alone. In this enhancing effect, alcohol appears to be the dominant partner. Although alcohol/benzodiazepine interactions are considered by Sellers less important than those involving alcohol and other psychotropic drugs such as cannabinoids, neuroleptics, stimulants, and antidepressants, Chan points out that this combination is associated with drug-induced deaths, drug overdoses, traffic accidents, and fatalities.

Interestingly, a major clinical use of benzodiazepines has been in the short- and long-term treatment of alcoholics as benzodiazepines were found very effective in alleviating alcohol-withdrawal symptoms. This is now controversial as some studies have pointed out that alcoholics may be more at risk of developing benzodiazepine or alcohol/benzodiazepine dependence than the general population. There is therefore a dire need for large scale controlled studies concerning the efficacy of benzodiazepines in the long-term treatment of alcoholics.

Alcohol and Cannabinoids

Marijuana and alcohol are ubiquitous. The combined use of ethanol and marijuana in variable amounts, frequencies, and settings has become a well-established fact (Mello, 1978). Animal studies performed by Siemens (1980) in rats showed that simultaneous administration of tetrahydrocannabinol (THC) and ethanol resulted in an increased rate and magnitude of ethanol tolerance and physical dependence. Complete ethanol tolerance was established within 12 to 16 days in animals receiving both drugs, whereas only minimal ethanol tolerance or cross tolerance was detected in ethanol- or THC-treated rats, respectively, at this time.

A few studies in humans have indicated that the acute administration of THC, the primary psychoactive component of marijuana, in combination with alcohol results in enhanced impairment of physical and mental performance, more marked subjective effects such as pupil size, and a greater increase in pulse rate and conjunctival congestion compared to ingestion of either drug alone (Manno, 1971; Bird, 1980). However, the magnitude of the enhancement of the drug effects was not very great.

In more recent studies, Belgrave and Chesher (1979a) from Australia using a battery of cognitive, perceptual, and motor function tests also found that both THC and ethanol produce significant decrements in the general performance factor but there was no evidence of any interaction between THC and ethanol and the effects of a combination of both compounds were no more than additive. The same was true when this group looked at the effect of cannabidiol (CBD) with alcohol using the same battery of tests (Belgrave, 1979b). CBD did not produce any demonstrable effects either alone or in combination with alcohol. However as CBD is one of the major components of some marijuana plants, there is still the possibility that there may be a THC-CBD-ethanol interaction. Consroe (1979) reported that the combination of alcohol with CBD in humans resulted in significantly lower blood-alcohol levels compared to alcohol given alone. However, he found very few differences between the pharmacological effects of alcohol given alone or given with CBD. Hollister (1986) who has reviewed this field many times concluded that there is no more than an additive effect between the cannabinoids and alcohol (both acting as CNS depressants) and that further studies in this area may not be necessary.

Alcohol and Opiates

Concomitant alcohol and narcotic abuse is very common. More than half of the "overdose" cases with heroin or methadone are in fact cases in which concomitant abuse of alcohol has played a prominent role. Most of the work on interactions of alcohol and opiates, especially exogenous opiates, comes from the laboratory of Mary Jeanne Kreek at the Rockefeller Institute and was reviewed by her in 1984.

Several studies have shown that alcohol may have a biphasic effect on the disposition of another opioid. During chronic use of large quantities of alcohol and at times when high blood levels of alcohol are present, alcohol may inhibit the metabolism of other drugs such as methadone. But when alcohol is no longer present in the body, drug metabolism may be accelerated due to the fact that, in the chronic alcoholic, alcohol has produced an enhancement of the hepatic microsomal P–450 enzyme dependent system. The presence of chronic alcoholic-induced liver disease may result in significant alterations in methadone disposition and prevent achievement of the steady state during methadone treatment. An interesting possible interaction between the opiate antagonist, naloxone, and ethanol gave promise for using an opiate antagonist to alleviate the ethanol-induced performance impairment. However, recent studies by Mendelson (1986) using the antagonist Naltrexone to assess the efficacy of this compound in attenuating acute alcohol intoxication in humans failed to find any significant differences between reported subjective levels of intoxication and detection of alcohol effects or blood alcohol levels following Naltrexone compared to placebo administration.

Combined Abuse of Alcohol and Stimulants: Amphetamines and Cocaine

Surprisingly few studies have dealt with the interaction of alcohol and amphetamines in humans in spite of the widespread use of both. Most of the studies that have investigated the effects of combined alcohol and amphetamine use have utilized either animal or volunteer subjects rather than members of the subculture directly involved in such abuse. Although synergism between alcohol and amphetamines was demonstrated in some preclinical studies, a large majority have reported antagonism between the two. As a result of the clinical evaluation of several patients for treatment of alcohol abuse, Kipperman and Fine (1974) made an interesting finding, i.e., that the clinical histories of these patients indicated the existence of two types of abuse patterns, one primarily concerned with the effects of amphetamine and the other with the effects of alcohol; the latter type of patients using amphetamine only to help them maintain a wakeful state.

A naturally occurring alkaloid, cocaine is a powerful and rapid CNS stimulant of short duration, which has recently become a prominent and favored drug of abuse. Cocaine is rapidly hydrolyzed in the body by esterases. It may also undergo hepatic microsomal oxidation to N-dealkylated metabolites. Smith, Freeman, and Harbison (1981) have shown that pretreatment with alcohol for 5 days at first reduces the immediate mortality rate produced by a large dose of cocaine, probably through a stimulation of the monooxygenase system which speeds up the degradation of cocaine. But this process can also produce greater amounts of intermediate metabolites that are toxic to the liver and delayed mortality (1 to 7 days after cocaine ingestion) is increased. The hepatic cytochrome P–450 content was doubled in ethanol-treated animals. These observations suggest that the early toxicity of cocaine is due to the parent drug and that ethanol pretreatment provides protection by enhancing the elimination of cocaine through induction of the cytochrome P–450 system. However, the more rapid degradation of cocaine produces greater concentration of norcocaine, an N-demethylated metabolite that is more toxic than cocaine.

Interactions of Alcohol and Other Abused Substances at the Perinatal Level

Another aspect of the combined use of alcohol and abused substances that requires further attention is the effect of combined perinatal exposure to these drugs on the fetus and offspring.

It was not until recently that it was shown by Abel (1985) that alcohol produced an enhancement of marijuana-induced fetotoxicity in rodents. The combination of marijuana and alcohol caused a 100 percent fetomortality that differed significantly from vehicle treatment. These studies suggest a potential danger to pregnancy resulting from the combined use of two commonly used drugs which is far greater than that associated with the use of either drug alone. This is especially significant in view of a recent study by Lex, Griffin, Mello, and Mendelson (1986) on concordant alcohol and marijuana use in women. This study shows strong correlations between alcohol and marijuana use, with the female heavy marijuana smokers reported drinking significantly more alcohol than female light marijuana smokers.

Epidemiology studies on the patterns of prevalence of combined use of alcohol and abuse substances by pregnant women are definitely called for.

Conclusion

In summary, most of the abused compounds interact with alcohol in a predictable manner. What is important to remember is that the pharmacokinetic and pharmacodynamic interactions of a given drug with alcohol is in part dependent on the length of the individual exposure to alcohol. The end response may be enhanced in the acutely intoxicated individual who does not have a history of alcohol abuse. Conversely, it may be diminished in the otherwise physically healthy but alcohol-dependent individual.

In general, appreciation of alcohol-drug interactions should provide a useful basis for the management of alcoholic patients and the prevention of accidental overdoses.

References

Abel, E. Alcohol enhancement of marijuana induced fetotoxicity. *Teratology*, 31:35–40, 1985.

Belgrave, B.E., Bird, K.D., et al. The effect of Delta-9-tetrahydrocannabinol, alone and in combination with ethanol on human performance. *Psychopharmacology*, 62:53–60, 1979a.

Belgrave, B.E., Bird, K.D., et al. The effect of cannabidiol alone and in combination with ethanol on human performance. *Psychopharmacology*, 64:243–246, 1979b.

Bird, K.D., Boleyn, T., et al. Intercannabinoid and cannabinoid-ethanol interactions and their effects on human performance. *Psychopharmacology*, 71:181–188, 1980.

Chan, A.W.K. Effects of combined alcohol and benzodiazepines. A review, *Drug and Alcoh. Depend.*, 13:315–341, 1984.

Consroe, P., Carlini, E., et al. Interaction of cannabidiol and alcohol in humans. *Psychopharmacology*, 66:45–50, 1979.

Hollister, L.E. Interactions of cannabis with other drugs in man. *National Institute on Drug Abuse Monograph Series*. Interactions of drugs of abuse, 1986 (in press).

Kipperman, A., and Fine, E.W. The combined abuse of alcohol and amphetamines. *Am. J. Psychiatry*, 131(11):1277–1280, 1974 (November).

Kreek, M.J., and Stimmel, B. Dual addiction—Pharmacological issues in the treatment of concomitant alcoholism and drug abuse. *Adv. Alcol. & Subst. Abuse*, 3(4):1–107, 1984.

Lex, B.W., Griffin, M.L., et al. Concordant alcohol and marijuana use in women (in press).

Linnoila, M., Mattila, J.B., and Kitchell, B.S. Drug interactions with Alcohol. *Drugs*, 18:299–311, 1979.

Manno, J.E., Kiplinger, G.F., et al. The influence of alcohol and marijuana on motor and mental performance. *Clin. Pharmacol. Ther.*, 12:201–211, 1971.

Mello, N.K., Mendelson, J.H., et al. Human polydrug use: Marijuana and alcohol. *J. Pharmacol. Exp. Therap.*, 207(3):922–935, 1978.

Mendelson, J.H., and Mello, N.K. Opioid antagonists for the treatment of alcohol abuse and dependence. *Ann. Meetg. Coll. Neuropsychopharmacol. Abstracts*, 35, 1986.

Muhoberac, B.B., Roberts, R.K., Hoyumpa, A.M., and Schenker, S. Mechanism(s) of ethanol-drug interaction. *Alcoholism: Clin. and Exp. Research*, 8(6):583–593, 1984.

Sellers, E.M., and Holloway, M.R. Drug kinetics and alcohol ingestion. *Clin. Pharmacokin.*, 3:440–452, 1978.

Sellers, E.M., and Busto, V. Benzodiazepines and ethanol: Assessment of the effects and consequences of psychotropic drug interactions. *J. Clin. Psychopharmacology*, 2(4):249–262, 1982.

Siemens, A.J. Effects of cannabis in combination with ethanol and other drugs. *Nat. Inst. Drug Abuse Res. Monogr. Ser.*, 31:167–198, 1980.

Smith, A.E., Freeman, R.W., Harbison, R.D. Ethanol enhancement of cocaine induced hepatoxicity. *Biochem. Pharmacol.*, 30(5):453–458, 1981.

Weller, R.A., and Preskorn, S.H. Psychotropic drugs and alcohol: pharmacokinetic and pharmacodynamic interactions. *Psychosomatics*, 25(4):301–309, 1984.

Neuropharmacological Approaches to the Obsessive-Compulsive Syndrome

Co-Chairs:

Joseph Lipinski, Jr., M.D.
The Mailman Research Center
Belmont, MA 02178

Kerrin White, M.D.
McLean Hospital
Belmont, MA 02178

Epidemiologic and Clinical Findings of Significance to the Design of Neuropharmacologic Studies of Obsessive-Compulsive Disorder

Steven A. Rasmussen, M.D., and Ming T. Tsuang, M.D., Ph.D.[1]

Over the past decade, neuropharmacologists have devoted increasing effort to understanding the neurobiologic basis of anxiety. Until recently, clinical researchers have focused their attention almost exclusively on panic disorder. Obsessive-compulsive disorder (OCD) has been relatively neglected, due to the general perception that it is a rare illness with a poor prognosis. This belief has been challenged by recent epidemiologic and treatment outcome studies that have set the stage for a resurgence of interest in OCD over the next decade. Recent data from the Epidemiologic Catchment Area (ECA) survey suggest that the disorder is 50 times more common than was previously believed (Myers et al., 1984; Robins et al., 1984). The average patient with OCD can currently look forward to a 70-percent chance of significant clinical improvement due to advances in behavioral and pharmacologic treatments developed over the past 15 years (Insel & Murphy, 1981; Marks, 1981). Newer pharmacologic treatment strategies for the treatment resistant patient have also begun to show increasing promise (Rasmussen, 1984).

When we initiated this project, we were surprised to discover that there had been no large scale phenomenologic or epidemiologic study of OCD in the last 20 years (Rasmussen and Tsuang, 1984). This paper describes our experience in establishing an obsessive disorders clinic over the past 2½ years. Preliminary results of a clinical descriptive study of a subgroup of these patients are described. Problems facing researchers interested in studying the neurobiology of the disorder are reviewed, and future clinical and epidemiologic studies that should proceed in concert with neuropharmacologic and treatment outcome studies are suggested.

---

[1] From the Department of Psychiatry and Human Behavior, Brown University and Butler Hospital, Providence, RI; the Harvard program in Psychiatric Epidemiology, Department of Psychiatry and Epidemiology, Harvard University, Boston; and the Psychiatry Service and Center for Mental Health and Behavioral Sciences, Brockton-West Roxbury VA Medical Center, Brockton, MA.

Supported in part by NIMH grants MH-38096 and MH-38079 and by Butler Hospital.

Jerome A. Fleming, M.S., provided assistance in the analysis of the data and preparation of this manuscript.

Reprint requests: Dr. Rasmussen, Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906.

Given its intrinsic clinical and phenomenologic interest, why has research in OCD been so limited up until now? Undoubtedly, the single most important factor has been the mistaken belief that OCD is a rare illness. This belief was based on a series of followup studies initiated in the 1950's and 1960's. These studies were consistent in finding that the incidence of OCD in psychiatric inpatient and outpatient settings was only 1 to 2 percent (Rasmussen and Tsuang, 1984). In our own review of over 10,000 psychiatric charts in the Rhode Island, Southeastern Massachusetts area, only 0.6 percent of inpatients and 1.8 percent of outpatients were found to have OCD. Most investigators felt that these figures significantly underestimated the disorders prevalence in the general population. In 1953, Rudin estimated the disorders prevalence in the general population at 0.5 percent. In 1984 preliminary results from the ECA were published. Among the most striking findings were the high lifetime, 2.5 percent (Robins et al., 1984), and 6-month point prevalence rates (1.6) of OCD (Myers et al., 1984).

If these figures are valid, it would make OCD the fourth most common psychiatric disorder, twice as prevalent as schizophrenia or panic disorder in the general population, and 50 times more common than Rudin's 1953 estimate. Critics of the ECA study have noted that the structured interview schedule questions for OCD may not have used a strict enough criterion for measuring significant impairment in social and occupational functioning. There is also debate about whether the severity of illness was reliably measured. Both of these would result in the inclusion of subjects who did not have clinically significant illness, leading to an overestimate of the true prevalence. There is a need for a study that compares a large OCD population from a typical clinical sample with an ECA OCD cohort using identical structured instruments. Future funding for biologic research and treatment outcome studies will be dependent on proving that the true prevalence and clinical significance of the illness are greater than has generally been held up until now.

Over the past 2½ years we have identified over 150 patients who meet criteria for DSM-III-R OCD in the Rhode Island, Southeastern Massachusetts area. Our success in recruiting this size sample in a 2½-year period supports our belief that the disorder is not rare. Our sample is representative of a clinical population that would typically present to a primary or secondary care setting. To this end, none of the patients were recruited by advertisement or articles in the media and all had presented to a physician or mental health professional for their obsessive compulsive (OC) symptoms. Unlike previous OC samples at the Maudsley Hospital or NIMH, 45 percent of this group had never been hospitalized.

We began to recruit the sample by reviewing the charts of all neighboring hospitals and mental health centers between 1965 and the present for an admission or discharge diagnosis of OCD. We found that most patients who were contacted, even up to 10 to 15 years after hospitalization, continued to suffer from significant symptoms, and were more than willing to participate in the research. In addition, talks were given at all the hospitals and mental health centers in the area, as well as at the local branch of the APA. Many patients came from direct physician referrals. Treatment resistant patients were offered pharmacologic or behavioral treatments that were not available elsewhere in the community.

We began to study the heterogeneity of OCD and its coexistence with other psychiatric disorders in a subgroup of 44 patients who meet DSM-III-R criteria for OCD by administering a semistructured interview to each of the probands (Rasmussen and Tsuang, unpublished). The interview covered demographics, obsessive and compulsive symptoms, course of illness, a checklist of symptoms for depression, psychosis, other anxiety disorders and personality disorders, and family history. We attempted to answer the following questions: (1) is OCD a heterogeneous diagnosis and, if so, can it be divided into homogeneous subgroups; (2) what are the difficulties one can encounter in the differential diagnosis of OCD; and (3) what are the disorders that are likely to coexist with

TABLE 1. Description of the Obsessive-Compulsive Sample ($n = 100$).

Sex	(%)	Race	(%)
Male	38.0	White	93.0
Female	62.0	Black	7.0
Mean Age at Admission	(%)	Religion	(%)
Male	25.2	Protestant	17.0
Female	30.9	Catholic	61.0
Marital Status	(%)	Jewish	4.0
Single	40.0	Other	18.0
Ever Married	55.0		
Ever Divorced	5.0		

OCD? Demographic characteristics of the sample are given in Table 1.

Can OCD be subdivided by symptoms or course of illness? The most common obsession, found in 24 (55%) of the patients, was fear of contamination. This obsession took many forms, among the most common being the fear of unseen dirt, germs, poisons, or toxins. Included in this group were several patients who developed morbid fears of potentially carcinogenic chemicals such as insecticides or asbestos. Twenty-five (57%) of the patients had cleaning rituals. Of those patients with contamination obsessions 83 percent also had cleaning rituals. Thirty-five (80%) of the patients had checking rituals, and nine (21%) had counting rituals. The next most common obsessive thought, present in 22 (50%) of the patients, were aggressive obsessions, typified by fears of harming or cheating others on purpose or inadvertently. A young mother who was obsessed with the fear that she would strangle her 6-month-old baby, a nurse who felt she would give a patient the wrong medication on purpose, and a mother who felt compelled to buy whatever she touched while shopping because she thought she had damaged it are a few illustrative examples. Eighty-four percent of the patients with aggressive obsessions also had checking rituals.

Thirty-two percent of the patients complained of sexual obsessions. These were most commonly fears of acting on sexual impulses that went against their value system, or fears of sexual perversions. As with the patients with aggressive obsessions, these patients were often unable to make a clear distinction between having an unacceptable thought and acting on it. Fifteen (68%) patients with aggressive obsessions also had fears about their sexual impulses. As a group the patients with sexual obsessions were usually preoccupied with guilt, at times of near delusional proportions. The patients with sexual obsessions followed in our clinic tended to have internal conflicts between their sexual and aggressive impulses and their value systems. They tended to have difficulty in expressing their anger and sexuality and were almost always neurotic as opposed to psychotic.

Sixteen (36%) of the patients had obsessive thoughts that involved what we have termed the need for symmetry or exactness. Examples would be the man who felt he had to walk through an office door exactly in the middle and sit at an 90° angle to the therapist, a woman who had to lean objects at just the right angle before she could complete an action, and a man with Tourette's syndrome (TS) who, if he had a certain number of tics on one side of his body that were involuntary, had to "even them up" with the same number of voluntary movements mimicking the tics on the other side. Patients could usually not express the reason behind these obsessions, other than a fear that something bad would happen if they did not "even things up." Many patients with this symptom also had developed checking and counting rituals. Most were perfectionistic and had had compulsive personalities from an early age. This obsession was significantly more common in men than women ($\chi^2 = 8.05, f = 1, p < .05$).

Fifteen (34%) of the patients had somatic obsessions. Their lives were dominated by incessant, compulsive checking rituals carried out to reassure them that they did not have a serious illness. Illustrative examples are the surgeon who was obsessed by the thought he had a hernia and who was compelled to examine himself continually to the point of creating an inguinal ulceration, and the woman who was compelled to examine her breasts up to 100 times a day to check that she had not developed cancer. Almost all of these patients had other associated obsessions or compulsions. Of the 15 patients with somatic obsessions, 73 percent had checking rituals. Six (14%) of the patients had obsessions classified as "other."

The most common compulsions were checking, cleaning, and counting rituals. Eighteen (41%) of the patients exhibited more than one ritual, and 26 (59%) exhibited multiple obsessions. Only two (4.5%) of the patients had obsessions with no compulsions, and only one (2%) had rituals without obsessions. Patients did not always carry the same symptoms throughout the course of their illness. Thus, patients, whose clinical picture was dominated by aggressive and sexual obsessions associated with checking rituals during an exacerbation of illness at one time could develop fears of contamination and handwashing rituals during another episode.

Each patient's course of illness was determined as falling in one of three categories: episodic, continuous, or deteriorative. Four patients had the onset of their illness within the year of admission. Therefore, these patients were classified as having acute-onset OCD. The remainder of the group had a mean ± difference between age of onset and age at interview of 15.5 ± 10.12 years. Only one (2%) of the patients had an episodic course, 37 (84%) were classified as having a continuous course, and six (14%) were classified as having a chronic deteriorative course. Many of the patients with a deteriorative course had given up resisting their obsessive or compulsive symptoms and had a tendency to manifest severe anxiety that did not habituate with flooding or desensitization techniques. Eleven (25%) of the patients could identify an environmental precipitant that appeared to trigger their illness and 31 (70%) could not. Data on precipitants were not available for two (5%) of the patients. Increases in responsibility such as the birth of a child, promotion to a new job, or significant losses such as the death of a family member or loss of a job were the most common precipitants noted. Almost all of the patients reported an increase in obsessive compulsive symptoms coincident with stressful life events.

While the most obvious way of subdividing the disorder is by type of obsessions, compulsion, or by course of illness, there are other possibilities that should be examined more closely with a larger sample in the future. Some of these include: (1) whether the OC symptoms are brought on by an internal or external cue, i.e., the fear of an internal drive versus an external object or situation; (2) whether the patient has insight into his illness and manifests high resistance towards the obsessions and compulsions versus poor insight and low resistance; and (3) those with impulsive vs. compulsive personality traits.

The development of valid and reliable exclusion criteria presents another dilemma for those interested in studying OCD, due to the extensive overlap of OCD with schizophrenia, major depression, and other anxiety disorders. Coexisting psychotic and affective symptoms may interact with obsessions and compulsions, thereby influencing the results of treatment outcome and neurobiologic studies. For example, it has been reported that OC patients resistant to standard behavioral treatment almost always have significant coexisting affective or psychotic symptoms (Foa, 1979). The differential diagnosis of OCD includes major depressive disorder, schizophrenia, panic disorder, phobia, (TS), hypochondriasis, and post-traumatic stress syndrome.

It can be extremely difficult to distinguish the OCD proband with prominent obsessions (e.g., somatic) from the patient with a primary major depression with ruminations. While guilt, obsessions, ambivalence, and anhedonia are clinical features of both OCD and major depression, true compulsions are rarely seen in the latter. Patients with a major depression also tend to have a later age of onset and are more likely to have an episodic course with normal intercurrent functioning. Patients with major depression as well as patients with OCD have a high frequency of dexamethasone nonsuppression. Both groups have abnormal REM latencies (Insel et al., 1985) and a negative response to yohimbine challenge (Rasmussen et al., unpublished). While both disorders respond to clomipramine (CMI), major depression also can be treated successfully with ECT, other tricyclics, and MAO inhibitors.

Two recent papers have described a subgroup of OCD patients who present with psychotic features (Solyom et al., 1985; Insel et al., unpublished). Separating patients suffering from severe OC symptoms who have little insight into their obsessive thoughts and no resistance from delusional schizophrenics with compulsions can also be difficult at times. About 10 percent of schizophrenics have true compulsions. Both illnesses have a chronic deteriorative course and a similar age of onset. Hallucinations and a formal thought disorder occur rarely in OCD. As a rule, schizophrenics show a more favorable treatment response to neuroleptics than obsessive compulsives with psychotic features.

Similarities between OCD and panic disorder with agoraphobia include the fact that both syndromes are characterized by high levels of generalized and anticipatory anxiety as well as a chronic waxing and waning course. They have a similar age of onset and sex distribution. Both disorders have a high incidence of coexisting depression, and both illnesses respond well to behavioral treatment. Patients with both disorders have episodes of panic anxiety. However, these episodes are triggered by thoughts or compulsions in OCD patients and can usually be distinguished from spontaneous attacks. While panic level anxiety tends to result in avoidance in probands with panic disorder, it causes an increased frequency of compulsions in OCD.

Several authors have commented on the significant incidence of obsessions and compulsions in patients with TS and their first degree family members (Nee et al., 1980; Pauls et al., 1984). Distinguishing a complex tic from a compulsion can be difficult. TS patients tend to suffer from aggressive and sexual obsessions. They also frequently exhibit the need for symmetry. In spite of some similarities between the illnesses, important distinctions exist. Phenomenologically, if you ask TS patients what it feels like to withhold a tic, they will describe a feeling of increasing tension that rapidly builds to a crescendo. They tend to describe that tension in physiologic terms (e.g., it's like I have to sneeze and I can't). In contrast, OCD probands, if asked what it feels like to stop a compulsion, will report that the feeling of increasing tension is inextricably linked to anxiety. In addition, TS has a male predominance and an earlier age of onset. TS is usually neuroleptic responsive while OCD is not. In contrast, CMI has been of little therapeutic benefit in TS but remains the best pharmacologic treatment for OCD.

Inclusion or exclusion of some or all of these patients who present diagnostic dilemmas will have an important effect on the outcome of neurobiologic and treatment efficacy studies. Although the inclusion of these patients may result in increased variance, excluding them may limit our knowledge of how these disorders interrelate.

The frequency of coexisting Axis I psychotic disorders in the sample we have interviewed is given in Table 2. One third of the

TABLE 2. Coexisting Psychiatric Symptoms and Diagnoses.

Depressive Symptoms (*n* = 44)	(%)	Psychotic Symptoms (*n* = 44)	(%)
Depressed mood	81.0	Delusional	5.0
Inadequacy	63.0	Hallucinations	4.0
Hopelessness	52.0	Thought Disorder	0
Secondary DSM-III Diagnoses			
Axis I	(%)	Axis II	(%)
Major depressive disorder	30.0	Compulsive	54.6
Simple phobia	6.8	Histrionic	9.1
Tourette's syndrome	4.5	Schizoid	6.8
Panic disorder	4.5	Dependent	4.5
Pervasive developmental	2.3	None	34.0
Alcohol abuse	2.3		
Mixed substance abuse	2.3		
None	47.0		

Lifetime History of Associated DSM-III Anxiety Disorder

Diagnosis	Simple Phobia	Social Phobia	Separation Anxiety	Panic Disorder	Agoraphobia	Tourette's Syndrome
%	27.3	18.2	17.6	13.8	8.9	6.8

patients had a major depressive disorder on admission. The next most common secondary diagnoses were simple phobia, TS, panic disorder, and substance abuse. Other Axis II diagnoses included histrionic, schizoid, and dependent personalities. Lifetime diagnosis of coexisting anxiety disorders suggests that OCD patients have an increased vulnerability to almost all of the other anxiety disorders. The incidence of lifetime major depression was 55 percent, a figure close to that seen for lifetime major depression in panic disorder.

One can also look at the coexistence question by asking how many patients with other primary psychiatric diagnoses have significant OC symptoms. Breier et al.'s (unpublished) interview study has shown that about 15 percent of patients with panic disorder have significant obsessions or compulsions. Chart review studies of the Iowa 500 (Rasmussen and Tsuang, unpublished), Chestnut Lodge Followup study (Fenton and McGlashan, unpublished), and records from the Maudsley Hospital (Rosen, 1958) have all shown that about 10 percent of schizophrenics have obsessions or compulsions. Several authors have found that a high percentage of TS patients have coexisting OCD (Nee et al., 1980; Pauls et al., 1984). Gittleson (1966) studied OC symptom patients who were psychotically depressed, while Videbach (1975) reported on depressed patients with compulsive personality traits. The incidence of obsessions and compulsions in a clinical sample of major depression is unknown. A controlled interview study that is designed to determine the frequency of obsessions and compulsions in representative clinical samples of patients with the above diagnoses has yet to be done.

The high frequency of coexistence between OCD and other psychiatric disorders is substantiated by findings from the ECA study (Boyd et al., 1984). The odds ratio for the coexistence of OCD with other DSM-III/Diagnostic Interview Schedule psychiatric disorders in subjects who were selected to represent the general population were as follows: panic disorder 20.6, schizophrenia 12.3, agoraphobia 10.9, major depression 10.8, and simple phobia 9.7.

In summary, several problems have limited neurobiologists' interest in OCD. The belief that OCD is a rare illness has recently been brought into question by data from the ECA study that suggests that OCD is the fourth most common psychiatric disorder. The heterogeneity of the illness, difficulties in establishing valid and reliable exclusion criteria, and OCD's coexistence with other psychiatric disorders all can directly or indirectly influence the results of biologic and treatment outcome studies. Several other problems face the neuropharmacologist who wishes to study OCD. First, psychosocial factors probably play an important role in OCD's pathogenesis. Our preliminary observations support previous data suggesting that the strictness of parental and religious upbringings may play an important role. This makes it more difficult to separate the biologic and genetic factors that may be involved in pathogenesis for OCD in comparison to an illness like panic disorder. Second, the presence and severity of OC symptoms are often dependent on environmental context. For example, it is not unusual for an OCD patient to be 2 hours late to a challenge procedure because he got stuck checking when leaving his house in the morning for his appointment. However, upon reaching the hospital where the test is to take place, he may report that he is asymptomatic and is not having any difficulties with obsessions and compulsions whatsoever. The dependence on environmental context can also be very useful, as behavioral challenges with phobic objects can be utilized to reliably elicit anxiety and compulsive behavior. Third, the degree of state anxiety or depression may have an important influence on the expression of OC symptoms. The importance of collecting ratings of anxiety and depression along with OC ratings in pharmacologic studies is clear. A fourth problem is the lack of a valid and reliable OC rating scale that adequately measures change over time. Finally, there is no short acting pharmacologic agent such as yohimbine or lactate for panic disorder that will reliably reproduce or diminish OC symptoms.

Future studies of the neuropharmacology of OCD need to be completed in tandem with clinical and epidemiologic studies that are designed to overcome or minimize some of the difficulties enumerated above. A more careful characterization of the heterogeneity of the illness and its coexistence with other psychiatric disorders in a large OCD sample is needed. It would be equally important to determine the incidence and significance of OC symptoms in panic disorder, schizophrenia, major depression, and TS. A comparison between a large clinical population and a cohort of OCD subjects identified in the ECA study using identical structured instruments is necessary to determine the true prevalence rate of the disorder in the general population. A careful controlled family study is needed to help determine the relative contribution of genetic and psychosocial factors to the pathogenesis of the illness. Finally, a prospective followup study of the children of adult patients in this sample would help to provide information about the natural history, high risk factors, and pathogenesis of OCD.

References

American Psychiatric Association, Taskforce on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders, Revised* (DSM-III-R). (In development) Washington, D.C.: American Psychiatric Association Press, 1985.

Boyd, J.H., Burke, J.D., Gruenberg, E., et al. Exclusion criteria of DSM-III. *Arch. Gen. Psychiatry,* 41:983–989, 1984.

Breier, A., Charney, D.S., and Heninger, G. "Coexisting psychiatric diagnosis in panic disorder" (unpublished, 1986).

Fenton, W., and McGlashan, T. "Obsessive compulsive symptoms in schizophrenia "(unpublished, 1985).

Foa, E.B. Failure in treating obsessive compulsives. *Behav. Res. Ther.*, 17:169–176, 1979.

Gittleson, N. The fate of obsessions in depressive psychosis. *Br. J. Psychiatry*, 112:705–708, 1966.

Insel, T., and Murphy, D.L. The Psychopharmacological treatment of obsessive compulsive disorder, A review. *J. Clin. Psychopharmacol.*, 1:304–311, 1981.

Insel, T.R., Mueller, E.A., Alterman, I., et al. Obsessive compulsive disorder and serotonin: Is there a connection? *Biol. Psychiatry*, 20:1174–1178, 1985.

Insel, T.R. "Obsessive compulsive psychosis" (unpublished, 1985).

Marks, I.M. Review of behavioral psychotherapy. I: Obsessive compulsive disorders. *Am. J. Psychiatry*, 138:584–592, 1981.

Myers, J.K., Weissman, M.M., Tischler, G.L., et al. Six month prevalence of psychiatric disorders in three sites. *Arch. Gen. Psychiatry*, 41:959–967, 1984.

Nee, L.E., Caine, E.O., Polinsky, R.J., et al. Gilles de la Tourette syndrome: Clinical and family study of 50 cases. *Ann. Neurol.*, 7:41–49, 1982.

Pauls, D.L., Cohen, D.T., Heimbuch, R., et al. Familial pattern and transmission of Gilles de la Tourette syndrome and multiple tics. *Arch. Gen. Psychiatry*, 38:1091–1093, 1983.

Rasmussen, S.A. Lithium and tryptophan augmentation of clomipramine resistant obsessive compulsive disorder. *Am. J. Psychiatry*, 141:1283–1285, 1984.

Rasmussen, S.A., and Tsuang, M.T. Epidemiology of obsessive compulsive disorder: A review. *J. Clin. Psychiatry*, 45:450–457, 1984.

Rasmussen, S.A., and Tsuang, M.T. Clinical characteristics and family history in DSM-III obsessive compulsive disorder. *Am. J. Psychiatry* (in press).

Rasmussen, S.A., and Tsuang, M.T. "Anxiety disorders in the Iowa-500 and non 500" (unpublished, 1986).

Rasmussen, S.A., Goodman, W., Charney, D.S., and Heninger, G.R. "^{2}Adrenoceptor receptor activity in obsessive compulsive disorder "(unpublished, 1986).

Robins, L.N., Helzer, J.E., Weissman, M.M., et al. Lifetime prevalance of specific psychiatric disorders in three sites. *Arch. Gen. Psychiatry*, 41:958–967, 1984.

Rosen, I. The clinical significance of obsessions in schizophrenia. *J. Mental Sci.*, 103:773–786, 1957.

Solyom, L., Dinicola, V.F., Soakman, D., et al. Is there an obsessive psychosis? *Can. J. Psychiatry*, 30:372–380, 1985.

Videbach, T. The psychopathology of anacestic endogenous depression. *Acta Psychiatrica Scand.*, 52:366–373, 1975.

A Possible Genetic Relationship Exists Between Tourette's Syndrome and Obsessive-Compulsive Disorder

David L. Pauls, Ph.D.,[1] James F. Leckman, M.D.,[1] Kenneth E. Towbin, M.D.,[1] Gwendolyn E.P. Zahner, Ph.D.,[1] and Donald J. Cohen, M.D.[1]

The diagnostic convention of DSM-III excludes the diagnosis of obsessive-compulsive disorder (OCD) in the presence of Tourette's syndrome (TS). However, prominent obsessive-compulsive symptoms (OCS) have been reported in TS patients from as early as 1885, when Tourette published his first descriptions (Tourette, 1885). Other reports (Meige & Feindel, 1907; Kelman, 1965; Fernando, 1967; Morphew et al., 1969; Nee et al., 1980; Jagger et al., 1982; Montgomery et al., 1982; Stefl, 1984) have suggested that the prevalence of OCS among TS sufferers has increased, with several large surveys reporting ranges from 55 to 74 percent (Jagger et al., 1982; Montgomery et al., 1982; Stefl, 1984). This represents a significant increase when compared to a reported population prevalence of 0.05 percent to 2.0 percent for OCD (Rudin, 1953; Robins et al., 1984). In OCD, 50 percent of patients will have the onset prior to age 25 and incidence peaks between ages 10 to 14 (Black, 1974). This is in contrast to OCS in TS which appears to increase in incidence as duration of illness increases (Montgomery et al., 1982). The present study is an attempt to look more closely at the relationship between OCS and TS by examining first-degree relatives of TS patients for the presence of OCS as well as tics. The proposed hypothesis is that TS and OCS are etiologically related and that OCS may be an alternative expression of the same etiology responsible for the expression of TS itself.

Methods

This study is part of an ongoing family study of TS. The methods of the family study have been described in an earlier publication (Pauls et al., 1984). Briefly, subjects were randomly ascertained from the Connecticut TS Association membership. After obtaining informed consent, the diagnosis of TS was verified by a semi-structured interview instrument which also screens for all major psychiatric disorders including OCD. An instrument devised by Carey was also administered by direct interview to further screen for OCS in all cases. For probands under age 16, parents were interviewed about their children. After obtaining permission, all first-degree relatives were contacted and, if they consented to participate, interviewed with the same instruments. Ninety-five percent of first-degree relatives were interviewed directly. Family history reports were obtained from each interviewed family member about each other family member. Best estimate diagnoses (Leckman et al., 1982) were made on each family member from all available data obtained. Diagnostic estimates were dichotomized according to the level of certainty. For the purposes of data analysis, "definite" and "probable" TS, Chronic Multiple Tics (CMT), and OCD diagnoses were combined in one group, while "possible" and "no" diagnoses were considered as unaffected.

In this study, OCD diagnoses were based on inclusionary DSM-III criteria; that is, the presence of obsessions or compulsions were sufficient to be awarded the diagnosis, so long as concomitant major depression, schizophrenia, or other major neuropsychiatric disorder was not also present. The exclusionary criterion in the presence of TS was dropped. Respondents described a range of obsessional and compulsive symptoms all having the basic features of being recognized as senseless, psychological in origin, or originating from the respondent, and were involuntary, insuppressible, clearly disruptive, unpleasant, and gave rise to some, though variable, degree of resistance.

---

[1] Yale Child Study Center, Yale University School of Medicine, 230 South Frontage Road, P.O. Box 3333, New Haven, CT 06510-8009.

Results

The subjects of the current report are 27 probands and their 103 first-degree relatives. Of the probands, 14 of 27 (51.8%) met criteria for both TS and OCD. The TS with OCD probands (TS + OCD)were clinically and demographically indistinguishable from the probands without OCD (TS−OCD) except that the TS + OCD probands had a mean age higher than the TS−OCD probands, 25.0 years vs. 16.5 years respectively. In addition, TS + OCD probands were on average lower in socioeconomic status (SES) according to the Hollingshead Scale ($p < 0.07$). On other demographic features (sex, marital status, religion, and education) the subgroups were essentially identical. On clinical features the two subgroups were also similar. There were no differences in tic frequency, tic disruption, age of onset, age of maximal severity, and, importantly, medication history.

By sub-dividing the 103 first-degree relatives according to proband diagnoses, comparisons could be made between those who were relatives of TS + OCD and TS - OCD probands. Figure 1 compares the frequency of the mutually exclusive categories of TS, Chronic Multiple Tics (CMT), and OCD among the relatives of TS + OCD and TS - OCD probands. In this study: 1) the rate of "definite" and "probable" OCD among these relatives (OCD + [TS + OCD] + [CMT + - OCD]=22/103, 22.3%) is elevated beyond what is expected for the general population, pected for the general population, whether the proband had OCD or not, and 2) the diagnosis of OCD is as prevalent among relatives of TS−OCD probands (12/45, 26.7%) as among those who were related to probands with TS + OCD (11/58, 19.0%). The interpretation of these data suggests that the risk of developing OCD in these relatives was increased and independent of whether the proband had OCD. The high frequency of "OCD only" among relatives also suggests that some OCD may be etiologically related to TS.

Discussion

The high frequency of OCD diagnoses in first-degree relatives of probands with TS−OCD and the development of OCD without tics in first-degree relatives of TS−OCD probands point to an etiologic relationship between TS and OCD. However, several weaknesses could call such an interpretation into question. Foremost among these is the difficulty in making accurate diagnoses of OCD. As several authors (Rachman et al., 1980; Rachman et al., 1978;

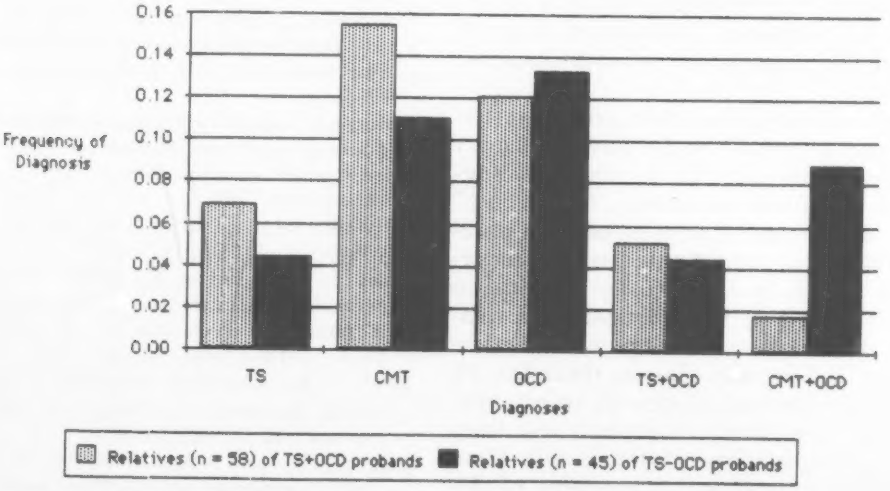


FIGURE 1. Frequency of diagnoses among first-degree relatives ($N = 103$).

Philpott, 1975; Insel, 1982) have pointed out in discussions of the epidemiologic and treatment literature on OCD, the response to a semi-structured questionnaire is not identical to a clinical diagnosis of OCD, and it is likely that occasional obsessions are normal phenomena (Rachman et al., 1980). Most of the disagreements appear to stem from disputes which are either over diagnostic criteria or over the validity of the methods used to ascertain symptoms. In this project the risk of over-estimating prevalence was lessened by the "best estimate" methodology, including in the diagnostic process interview data from family members about each subject and a specific self-rated instrument developed by Carey (unpublished), designed to provide detailed information about possible OCS. Descriptions provided by family members about each subject are of substantial assistance in making diagnostic decisions, especially when subjects are equivocal. When family members reveal that behaviors are carried to extremes infringing on day-to-day functioning, then OCD diagnoses become more credible. Even so, it must be acknowledged that a consensus on methods for accurately diagnosing OCD has not been reached.

What is particularly striking, nevertheless, is that even if these criticisms are taken into account, the rates of OCD found in this study are significantly increased when compared to those from the Epidemiologic Catchment Area Study, in which similar methodology was employed. The frequency of OCD in relatives of TS probands is increased 9 to 13 times over the population estimate obtained from the ECA.

Where previously it has been proposed that OCS are late symptoms in the natural history of TS, the findings of this family study suggest that, in some instances, "OCD only" could be an alternative expression of a putative TS gene. It is remarkable that the recurrence risk for OCD was virtually identical to that for TS itself in these first-degree relatives and that subjects developed OCD without TS or CMT at rates close to those for TS only. Work is currently underway to examine whether the hypothesis raised by these findings strengthen evidence for a simple Mendelian dominant mode of transmission of this complex behavioral disorder, as proposed by several other investigators (Kidd et al., 1982; Comings et al., 1984; Devor, 1984). These findings also suggest that there may be a TS-related form of OCD. Further efforts are, therefore, needed to characterize such features as the symptoms, course, and treatment response of the OCS observed in TS families. The study of the "OCD-only" relatives is of particular interest in this regard.

If these findings are replicated, there are several important implications for OCD research. The most important is the need to reevaluate the assumptions about etiologic homogeneity. If OCD is heterogeneous, methodologic changes in OCD studies will be necessary. Consideration of co-morbid conditions during diagnosis and allocation of subjects and the routine implementation of strategies to make accurate psychiatric diagnoses in relatives are imperative in any future studies. Findings from previous investigations about heredity, phenomenology, and treatment response may need to be re-evaluated in the light of a possible discrete etiologic subgroup.

References

Black, A. The natural history of obsessional neurosis. In: Beech, H.R. (ed.), *Obsessional States*. London: Metheun and Co., 1974, pp. 19–55.

Carey, G. "The obsessive compulsive checklist "(unpublished).

Comings, D.E., Comings, B.G., Devor, E.J., Cloninger, C.R. Detection of a major gene for Gilles de la Tourette syndrome. *Amer. J. Hum. Genet.*, 36:704–709, 1984.

Devor, E.J. Complex segregation analysis of Gilles de la Tourette syndrome: Further evidence for a major locus mode of transmission. *Amer. J. Hum. Genet.*, 36:704–709, 1984.

Fernando, S.J.M. Gilles de la Tourette's syndrome. *Br. J. Psychiatry*, 113:607–617, 1967.

Gilles de la Tourette, G. Etude sur une affection nerveuse caractérisée par de l'incoordination motrice accompagnée d'écholalie et de coprolalie. *Arch. Neurol.*, 9:19–42 and 158–200, 1885.

Insel, T.R. Obsessive compulsive disorder—Five clinical questions and a suggested approach. *Comp. Psychiatry*, 23:241–251, 1982.

Jagger, J., Prusoff, B.A., Cohen, D.J., Kidd, K.K., et al. The epidemiology of Tourette's syndrome: A pilot study. *Schizo. Bull.*, 8:267–278, 1982.

Kelman, D.H. Gilles de la Tourette's disease in children: A review of the literature. *J. Child Psychol. Psychiatry*, 6:219–226, 1965.

Leckman, J.F., Sholomskas, D., Thompson, W.D., Belanger, A., et al. Best estimate of lifetime psychiatric diagnoses: Methodological study. *Arch. Gen. Psychiatry*, 39:879–883, 1982.

Meige, H., and Feindel, E. In: Wilson, S.A.K. (translator and ed.), *Tics and Their Treatment*. New York: William Wood and Co., 1907.

Montgomery, M.A., Clayton, P.J., and Friedhoff, A.J. Psychiatric illness in Tourette syndrome patients and first degree relatives. In: Chase, T.N., and Friedhoff, A.J. (eds.), *Gilles de la Tourette Syndrome*. New York: Raven Press, 1982, pp. 335–339.

Morphew, J.A., and Sim, M. Gilles de la Tourette's Syndrome: A clinical and psychopathological study. *Br. J. Med. Psychol.*, 42:293–301, 1969.

Nee, L.E., Caine, E., Polinsky, R.J., Eldridge, R. et al. Gilles de la Tourette syndrome: Clinical and family study of 50 cases. *Ann. Neurol.*, 7:41–49, 1980.

Nee, L.E., Polinsky, R.J., and Ebert, M.H. Tourette syndrome: Clinical and family studies. In: Chase, T.N., and Friedhoff, A.J. (eds.), *Gilles de la Tourette Syndrome*. New York: Raven Press, 1982, pp. 291–295.

Pauls, D.L., Cohen, D.J., Heimbuch, R., Detlor, J., et al. Familial pattern and transmission of Gilles de la Tourette syndrome and multiple tics. *Arch. Gen. Psychiatry*, 38:1091–1093, 1981.

Pauls, D.L., Hurst, C.R., Kidd, K.K., Kruger, S.D., et al. Evidence against a genetic relationship between Tourette syndrome and Attention Deficit Disorder. *Arch. Gen. Psychiatry* (in press).

Pauls, D.L., Kruger, S.D., Leckman, J.F., Cohen, D.J., et al. The risk of Tourette's syndrome and chronic multiple tics among relatives of Tourette's syndrome patients obtained by direct interview. *J. Amer. Acad. Child Psychiatry*, 23:134–137, 1984.

Rachman, S., and DeSilva, P. Abnormal and normal obsessions. *Behav. Res. Ther.*, 16:233–248, 1978.

Rachman, S., and Hodgeson, R. *Obsession and Compulsions*. Englewood Cliffs, NJ : Prentice-Hall, 1980.

Robins, L.N., Helzer, J.E., Weissman, M.M., Orvaschel, H., et al. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch. Gen. Psychiatry*, 41:949–958, 1984.

Rudin, E. Ein betrage zur frage der Zwangskranheit, insobesondere ihrere hereditarn Beziehungen. *Arch. Psychiat. Nervenk.*, 191:14–54, 1953.

Stefl, M.E. Mental health needs associated with Tourette syndrome. *Amer. J. Public Health*, 74:1310–1313, 1984.

Yaryura-Tobias, J.A., Neziroglu, F., Howard, S., Fuller, B. Clinical aspects of Gilles de la Tourette syndrome. *Orthomolec. Psychiatry*, 10:263–268, 1981.

Problems and Promises of Post-Mortem Brain Tissue Analysis

Co-Chairs:

Steven Zalcman, M.D.

Neurosciences Reasearch Branch
National Institute of Mental Health
Rockville, MD 20857

Charles B. Nemeroff, M.D.

Dept. of Psychiatry and Pharmacology
Duke University Medical Center
Durham, NC 27710

Role of the Serotonergic System in the Postmortem Analysis of Suicide

Michael Stanley, Ph.D.,[1*] J. John Mann, M.D.,[2] and Lee S. Cohen, M.D.[3]

Suicide is a major cause of death in the United States (National Center for Health Statistics, 1979). Major efforts are underway to examine the personality, psychosocial, and biochemical correlates of this potentially preventable form of death; antemortem and postmortem studies are two of the biochemical parameters currently under investigation to examine their role in suicide. Experimental evidence derived from several research groups has suggested an association between suicidal behavior and the serotonergic system.

The following review will examine early and currently available postmortem data on the serotonergic system. This will include work on serotonin (5HT). Examination of receptors studies in this system will include 3H imipramine and $5HT_2$ binding sites, 5-hydroxyindoleacetic acid (5HIAA), and the degradative enzyme monoamine oxidase (MAO) as they pertain to postmortem suicidal research.

The advantages of human postmortem neurochemical studies must be balanced against those disadvantages which are inherent in these investigations. In postmortem research there are numerous confounding variables that may contribute to inconsistencies within a study or across studies. In this review we will assess the impact of the variables age, postmortem interval, and regional brain dissection on several of the neurochemical measures described above.

MAO

5HT is a substrate for MAO-A, an enzyme system that has been investigated in postmortem research. Three studies have examined postmortem MAO activity in suicide victims.

One study reported no differences in MAO activity compared with controls (Grote et al., 1974). A second study found reduced MAO activity in patients where the suicide was associated with alcoholism but not in depressives

---

[1] Departments of Psychiatry and Pharmacology, Columbia University and New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032.
[2] Department of Psychiatry, Cornell University, New York, NY
[3] Department of Psychiatry, Columbia University, New York, NY.

[*] Correspondence to Michael Stanley.

without a history of alcoholism (Gottfries et al., 1975). These studies, however, both include a significant proportion of patients who had died by carbon monoxide poisoning or drug overdose, which may have altered this enzyme's activity. They also employed a single substrate concentration, a method that is less informative and less sensitive than enzyme kinetic studies.

Our group assayed MAO-A and B in the frontal cortex of suicide victims and controls (Mann & Stanley, 1984) using labeled 5HT and phenylethylamine (PEA) as substrates for MAO-A and B respectively. Suicide methods in this study were generally by violent means with the exception of one overdose. There were no significant differences between the suicide and control groups with respect to factors such as age, sex, and postmortem interval. The results of our kinetic study show no significant difference between the groups for either substrate (5HT or PEA) with respect to maximal velocity *(V_{max})* or affinity *(K_m)*. There was a significant positive correlation between age and MAO-B V_{max} for both groups. There was no correlation between postmortem interval and MAO enzyme kinetics.

Our series of suicide victims was distinguished from those of other studies of brain MAO in suicide largely because we excluded those who died by overdose, thereby avoiding the potential problem of drug effects contaminating the results. Our data suggest that the reported lower brain MAO activity in alcoholic suicides, if confirmed, may be related primarily to alcoholism rather than suicidal behavior.

Serotonergic System

Initial postmortem suicide studies typically measured 5HT and 5HIAA in brain stem areas where serotonin cell bodies are concentrated in the raphe nuclei. Of note is that, in those studies where information was available, approximately 50 percent of the suicide victims carried a diagnosis of a major depressive episode, the remaining cases carried diagnoses of alcohol abuse, adjustment disorder with depressed mood, schizophrenia, or a personality disorder (Shaw et al., 1967; Cochran et al., 1976; Beskow et al., 1976; Korpi et al., 1983), again suggesting that the altered 5HT and 5HIAA levels were primarily associated with suicidal behavior rather than depression per se.

A total of 11 studies have investigated levels of 5HT, 5HIAA, or both in suicide victims. Significant reductions in levels of 5HT, 5HIAA, or both in suicide victims have been reported in eight of the aforementioned studies. Four of the 11 mentioned studies report no significant change in levels of 5HT or 5HIAA in suicide victims (Table 1).

In all the foregoing studies, however, factors such as method of suicide, i.e., drug overdose, carbon monoxide poisoning, extensive postmortem delay, and lack of appropriate age-matched control groups may affect the interpretation of these studies. These variables may also account in part for the lack of uniformity of findings among these postmortem studies.

(3H) Imipramine Binding

Imipramine binding has been shown in animal experiments to be associated with presynaptic serotonergic nerve terminals (Brunello et al., 1982). These binding sites have been characterized on platelets and various regions of the brain. Some of the additional experimental evidence linking imipramine binding with 5HT is that 1) radioautography studies of 3H imipramine binding sites

TABLE 1. Postmortem Neurotransmittor and Metabolite Studies in Completed Studies.

Study	Neurochemical Findings
Shaw et al., 1967	↓Brainstem 5HT
Bourne et al., 1968	↓Brainstem 5HIAA
Pare et al., 1968	↓Brainstem 5HT; No change in brainstem 5HIAA
Lloyd et al., 1974	↓Brainstem 5HT; No change in brainstem 5HIAA
Gilan et al., 1985	↓Hypothalamus 5HT ↓Nucleus Acumbens 5HIAA
Korpi et al., 1983	↓Hypothalamus 5HT
Beskow et al., 1976	↓Brain 5HIAA
Owens et al., 1983	No change in 5HIAA levels in frontal cortex
Crow et al., 1984	No change in brain 5HIAA levels in frontal cortex
Cochrane et al., 1976	No change in brain 5HT
Stanley et al., 1983	No change in 5HIAA or 5HT levels in frontal cortex

show distribution-similar serotonergic terminals (Rainbow et al., 1982), 2) chemical and electrolytic lesions of the raphe nucleus cause a significant reduction in serotonin level and in the number of imipramine binding sites (Brunello et al., 1982), 3) the use of an irreversible ligand results in reduced 3H imipramine binding and serotonin uptake, (Rehavi et al., 1981), 4) the potency of antidepressant drugs to inhibit serotonin uptake is significantly correlated with their potency to inhibit 3H imipramine binding (Paul et al., 1981), 5) serotonin is the only neurotransmitter known to inhibit 3H imipramine binding (Paul et al., 1981; Langer et al., 1980), and 6) there is a similar pharmacologic profile between brain and platelet 3H imipramine binding sites (Rehavi et al., 1980).

Initial studies of imipramine binding in the platelets of patients with a major depressive episode have indicated decreases in the number of binding sites (Langer et al., 1983). The combined association of imipramine binding with 5HT function as well as the significant reduction in binding density in depressives suggests a possible alteration in imipramine binding in suicide victims.

To test this hypothesis our group examined imipramine binding in the brains of suicide victims and controls (Stanley et al., 1982). In this study there were no significant differences between the two groups with respect to age, sex, or postmortem interval. Additionally, the mode of suicide studied in the suicides and controls was of a sudden and violent nature, e.g., gunshot wound, jumping from height, and hanging.

Our findings indicate a significant reduction in the number of imipramine binding sites (B_{max}) (Figure 1) with no difference in binding affinity (K_d) in suicide victims as compared with matched controls.

These results are consistent with the accumulating evidence suggesting the involvement of 5HT in suicide. Specifically, reduced imipramine binding (associated with presynaptic terminals) may be indicative of reduced 5HT release and would be in agreement with those reports of reduced postmortem levels of 5HT and 5HIAA in suicides cited above.

Additional work in imipramine binding has shown significant decreases in this parameter in completed suicides (Paul et al., 1984; Crow et al., 1984) and in depressed patients who died from natural causes (Perry et al., 1983). One study, however, indicated increased imipramine binding in completed suicides (Meyerson et al., 1982).

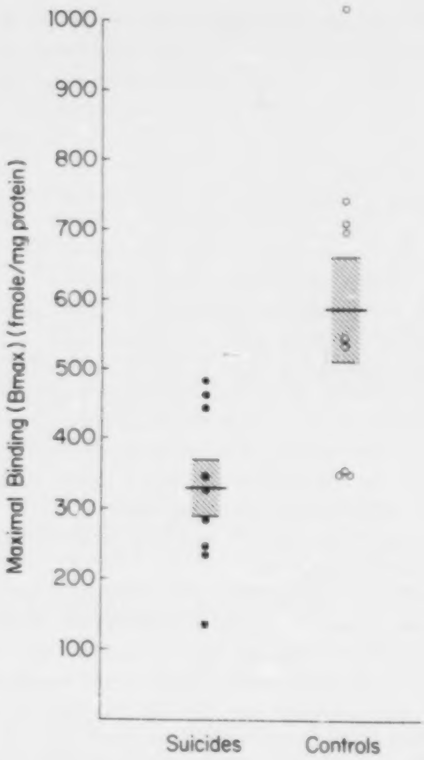


FIGURE 1. Suicide victims show a significant reduction in imipramine binding sites as compared with controls with no difference in binding affinity.

In addition to examining presynaptic neurotransmitters and receptor sites our group has studied postsynaptic 5HT binding sites using ^{3}H spiroperidol (specifically 5HT$_2$ receptor) (Stanley, Mann, & Gershon, 1983).

In our study we found a significant increase in the number of 5HT$_2$ binding sites with no change in affinity (Figure 2) in patients who committed sudden, violent suicide, i.e., gunshot wound, hanging, trauma from falling and stabbing, as compared to controls when matched for age, sex, and postmortem interval. This is consistent with an upregulation of this site in response to previously mentioned decreases in levels of 5HT, 5HIAA, and imipramine binding sites.

The finding of raised numbers of $5HT_2$ (postsynaptic) binding sites in the frontal cortex of suicide victims further supports the involvement of 5HT in suicidal behavior. Further work (Owens et al., 1983) in nonmedicated suicide victims compared to controls reported a trend towards an increase in $5HT_2$ binding with no difference in $5HT_1$ receptors; one study showed no change in $5HT_1$ or $5HT_2$ receptors (Crow et al., 1984).

These combined findings of decreased imipramine binding and increased $5HT_2$ binding are consistent with a decrease in the utilization of 5HT in suicide victims (Table 2).

In view of the above data we may postulate that the serotonergic system is altered as evidenced by changes in 5HT and 5HIAA levels, imipramine binding sites, and 5HT receptor binding sites in suicide victims as compared with controls.

However, as previously indicated in postmortem tissue analysis, a number of intervening variables such as age, postmortem interval, and regional brain dissections may have a significant impact on the above measures of serotonergic functioning in suicide victims. The following is a review of the role of these factors.

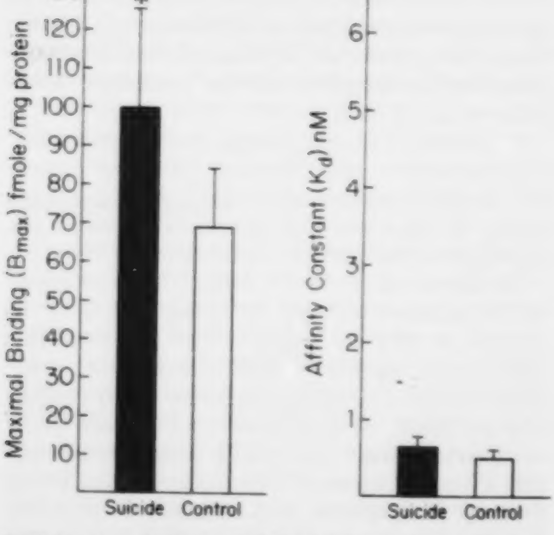


FIGURE 2. Number of $5HT_2$ binding sites increases significantly with no change in affinity.

TABLE 2. Postmortem Serotonergic Receptor Studies of Suicide Victims.

Study	Neurochemical Findings
Stanley et al., 1982	↓^{3}H-imipramine binding in cortex
Paul et al., 1984	↓^{3}H-imipramine binding in brain
Perry et al., 1983	↓^{3}H-imipramine binding in cortex*
Crow et al., 1984	↓^{3}H-imipramine binding in cortex
Meyerson et al., 1982	↑^{3}H-imipramine binding in cortex
Stanley and Mann, 1983	↑5-HT_2 binding in cortex
Owens et al., 1983	↑5-HT_2 binding in cortex**
Crow et al., 1984	No change $5HT_2$ binding in cortex

*Depressed dying of natural causes
**Increased, but not significantly

Age

Our group examined the relationship between age and 5HT, 5HIAA, homovanillic acid (HVA) in the cortex, and caudate and found no effect (Stanley, McIntyre, & Gershon, 1983). An additional study (Severson et al., 1985) examining 5HT and 5HIAA levels in human postmortem samples also noted that age did not appear to influence 5HT or 5HIAA levels or 5HIAA to 5HT ratio. Our group also (Stanley, unpublished) examined the effect of age on imipramine binding in human brain finding a positive correlation between age and the density of imipramine binding sites. This is confirmed by another study showing a positive correlation between advancing age and the density of specific binding sites for imipramine in postmortem samples of human hypothalamus, frontal and parietal cortex (Severson et al., 1985). This is in direct contrast to another study (Langer et al., 1980) indicating that platelet imipramine binding decreases as a function of aging.

The latter finding is of interest since imipramine binding in brain and platelet were thought to be identical. Examination of imipramine binding in cats (Arbilla et al., 1981) that received chronic administration of the tricyclic antidepressant imipramine shows reduction in this binding site in brain and platelets. It is problematic though to argue that drug-induced changes, i.e., down regulation, reflect what is seen in the nondrug state. Our data for imipramine binding in the untreated rat platelet and brain (Stanley, unpublished data) do not indicate a significant correlation between imipramine binding in these two sites. Needless to say, findings such as these raise numerous questions regarding the validity of peripheral measures in general to serve as indices of central systems.

Postmortem Interval

In postmortem research, postmortem interval (PMI) or delay (i.e., that time between death and the time the brain tissue is removed and frozen) may contribute to discrepancies in research results. In our human postmortem studies we have assessed the influences of PMI on 5HT and 5HIAA levels (Stanley, McIntyre, & Gershon, 1983). We found a significant positive correlation between frontal cortex 5HT levels and PMI. No significant findings were noted between 5HIAA or HVA levels and PMI. Additional work by our group in rat brain (McIntyre & Stanley, 1984) indicate a similar influence of PMI on 5HT level, with no change seen in 5HIAA levels. Another study (Severson et al., 1985), however, found a negative correlation between 5HT levels and PMI. One possible explanation for this discrepancy may be the difference in the length of PMI between the two studies. In our study PMI was approximately 15 hours (range: 6 to 45 hours) while in the aforementioned study finding a negative correlation PMI averaged approximately 36 hours (range: 27 to 54.7 hours). It may well be that while 5HT levels appear to rise initially with a shorter PMI they subsequently fall with a more extensive delay.

Previous research has shown that amines such as dopamine (DA) and 5HT are more sensitive to PMI than are their acidic metabolites. Our group looked at the influence of PMI on DA, 3,4-dihydroxyphenylacetic acid (DOPAC), and HVA levels (Wilk & Stanley, 1978; McIntyre & Stanley, 1984). Essentially DA, not DOPAC or HVA levels, is positively correlated with postmortem delay.

Regional Changes

In addition to the above data indicating the influence of age and PMI on measures of serotonergic function, regional or nonspecific brain dissection may also affect results. In an attempt to investigate possible regional differences of 5HT and 5HIAA concentrations within the cortex we dissected homogenous samples corresponding to frontal, temporal, and occipital cortex. In this experiment, the frontal cortex showed significantly higher concentrations of 5HT and 5HIAA compared to temporal or occipital samples. In a second experiment three progressive 1 mm slices of the frontal cortex were examined in a rostral to caudal fashion for regional concentration differences of 5HT and 5HIAA levels (McIntyre & Stanley, 1984). Additional variation was noted within the frontal cortex with a rostral to caudal increase in 5HIAA levels; 5HT levels were consistent. Therefore, differences are found not only among the general areas of cortex, i.e., frontal, temporal, and occipital, but differences are found within each area.

Summary

The above data indicate a strong correlation between various measures in the serotonergic system and suicidal behavior in postmortem studies. This is made evident by the data presented on 5HT and 5HIAA levels, imipramine binding studies, and $5HT_2$ receptor binding studies. From research of this nature it becomes evident that variables such as age, postmortem interval, and regional brain area dissection may have a role in the inconsistencies of data in postmortem evaluations.

References

Arbilla, S., Briley, F., and Cathala, S.Z. Parallel changes in [^{3}H]imipramine binding sites in cat brain and platelets following chronic treatment with imipramine. *Br. J. Pharmacol.*, 72:154, 1981.

Beigon, A., and Rainbow, T.C. Distribution of imipramine binding sites in the rat brain studied by quantitative autoradiography. *Neuro. Sci. Lett.*, 37(3):209–214, 1983.

Beskow, J., Gottfries, C.G., Roos, B.E., and Winbland, B. Determination of monoamine and monoamine metabolites in the human brain: Postmortem studies in a group of suicides and in a control group. *Acta Psyciatr. Scand.*, 53:7–20, 1976.

Bourne, H.R., Bunney, W.E., Jr., Colburn, R.W., et al., Noradrenaline, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid in the hindbrains of suicidal patients. *Lancet*, 805–808, October 12, 1968.

Brunello, N., Chuang, D.M., and Costa, E. Different synaptic location of mianserin and imipramine binding sites. *Science*, 215:1112–1115, 1982.

Cochran, E., Robins, E., and Grote, S. Regional serotonin levels in brain: A comparison of depressive suicides and alcoholic suicides with controls. *Biological Psychiatry*, 11(3):283–294, 1976.

Crow, T.J., Cross, A.J., Cooper, S.J., et al. Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression and suicides. *Neuropharmacology*, 23 (12B):1561–1569, 1984.

Crow, T., personal communication.

Gillin, J.C., Nelson, J., Kleinman, J. et al. Studies of the cholinergic system in suicide and depression. New York Academy of Sciences Conference on Psychobiology of Suicidal Behavior, Sept. 18–20, 1985.

Gottfries, C.G., Oreland, L., Wilberg, A., Winbland, G. Lowered monoamine oxidase activity in brains from alcoholic suicides. *J. Neurochem.*, 25:667–673, 1975.

Grote, S.S., Moses, S.G., Robins, E., et al. A study of selected catecholamine metabolizing enzymes: A comparison of depressive suicides and alcoholic suicides with controls. *J. Neurochem.*, 23:791–802, 1974.

Korpi, E.R., Kleinman, J.E., Goodman, S.J., et al. Serotonin and 5-Hydroxyindoleacetic acid concentration in different brain regions of suicide victims: Comparison in chronic schizophrenic patients with suicide as cause of death. Presented at the Meeting of the International Society for Neurochemistry, Vancouver, Canada, July 14, 1983.

Langer, S.F., Briley, M.S., Raisman, R., et al. ^{3}H-imipramine binding in human platelets. Influence of age and sex. *Naunyn Schmiedebergs Arch. Pharmacol.*, 313:189–194, 1980.

Langer, S.F., and Raisman, R. Binding of [^{3}H] imipramine and [^{3}H] desipramine as biochemical tools for studies in depression. *Neuropharmacology*, 22:407–413, 1983.

Lloyd, K.G., Fraley, I.J., Deck, J.H.N., and Hornykiewicz, O. Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brainstem of suicide victims and control patients. *Advances in Biochemical Psychopharmacology* Vol. II. New York: Raven Press, 1974, pp. 387–397.

Mann, J.J., and Stanley, M. Postmortem monoamine oxidase enzyme kinetics in the frontal cortex of suicide victims and controls. *Acta Psychiat. Scand.*, 69:135–139, 1984.

McIntyre, I.M., and Stanley, M. Postmortem and regional changes of serotonin, 5 hydroxyindoleacetic acid and tryptophan in brain. *J. Neurochem.*, 42(6):1588–1592, 1984.

Meyerson, L.R., Wennogle, L.P., Abel, M.S., et al. Human brain receptor alterations in suicide victims. *Pharmacol. Biochem. Behav.*, 17:159–163, 1982.

National Center for Health Statistics. *Facts of Life and Death*. DHEW Pub. No. (PHS)79-1222. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1979.

Owens, F., Cross, A.J., Crow, T.J., et al. Brain 5-HT$_2$ receptors and suicide. *Lancet*, ii:1256, 1983.

Pare, C.M.B., Yeung, D.P.H., Price, K., and Stacey, R.S. 5-hydroxytryptamine, noradrenaline, and dopamine in brainstem, hypothalamus, and caudate nucleus of controls and of patients committing suicide by coal-gas poisoning. *Lancet*, 133–135, July 19, 1969.

Paul, S.M., Rehavi, M., and Rice, K.C. Does high affinity [^{3}H] imipramine binding label serotonin reuptake sites in brain and platelet? *Life Sci.*, 28:2753–2760, 1981.

Paul, S.M., Rehavi, M., Skolnick, P., and Goodwin, F.K. High affinity binding of antidepressants to a biogenic amine transport site in human brain and platelet; studies in depression. Post, R.M., and Bellinger, J.C. (eds.), *Neurobiology of Mood Disorders*. Baltimore: Williams and Wilkins, 1984, pp. 845–853.

Peroutka, S.J., and Snyder, S.H. Regulation of serotonin (5HT$_2$) receptors labeled with [^{3}H] spiroperidol by chronic treatment with antidepressant amitriptyline. *Pharmacol. Exp. Ther.*, 215:582–587, 1980.

Perry, E.K., Marshall, E.F., Blessed, G., et al. Decreased imipramine binding in the brains of patients with depressive illness. *Br. J. Psychiatry*, 1412:188–192, 1983.

Rainbow, T.C., Biegon, A., and McEwen, D.S. Autoradiographic localization of imipramine binding in rat brains. *Eur. J. Pharmacol.*, 77:363–364, 1982.

Rehavi, M., Ittah, Y., Price, K.L., et al. 2-Nitroimipramine: A selective irreversible inhibitor of [^{3}H] serotonin uptake and [^{3}H] imipramine binding in platelets. *Biochem. Biophys. Res. Comm.*, 99:954, 1981.

Severson, J.A., Marwsson, J.O., and Osterburg, H.H. Elevated density of [^{3}H] imipramine binding in aged human brain. *J. Neurochem.*, 45(5), 1382–1389, 1985.

Shaw, D.M., Camps, F.E., and Eccleston, E.G. 5-hydroxytryptamine in the hind-brain of depressive suicides. *Br.J. Psychiatry*, 113:1407–1411, 1967.

Stanley, M., Virgilio, J., Gershon, S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science*, 216:1337–1339, 1982.

Stanley, M., and Mann, J.J. Increased serotonin—2 Binding sites in frontal cortex of suicide victims. *Lancet*, I(349):214–216, 1983.

Stanley, M., Mann, J.J., and Gershon, S. Alterations in pre- and postsynaptic serotonergic neurons in suicide victims. *Psychopharm. Bull.*, 19:684–687, 1983.

Stanley, M., McIntyre, I., and Gershon, S. Postmortem serotonin metabolism in suicide victims, presented at 1983 ACNP, Puerto Rico.

Stanley, M. (unpublished data)

Wilk, S., and Stanley, M. Dopamine metabolites in human brain. *Psychopharmacology*, 57:77, 1978.

Aminergic Receptor Binding Correlates of Suicide: Methodological Issues

J. John Mann, M.D.,[1,2] P. Anne McBride, M.D.,[1] and Michael Stanley, Ph.D.[3]

Animal studies of monoamine receptor binding in the central nervous system (CNS) have generated important hypotheses regarding the mechanism of therapeutic action of somatic antidepressant treatments (Sulser et al., 1978) and antipsychotic agents (Creese et al., 1976). Our laboratory and others have demonstrated the feasibility of assaying monoamine receptors in human postmortem brain tissue (Maggi et al., 1979: Stanley & Mann, 1983). Such studies have yielded important findings in schizophrenia (Snyder et al., 1974), Parkinson's disease, and suicide (Stanley & Mann, 1983). Most of these studies controlled to varying degrees for factors such as age, gender, antemortem drug effects, postmortem delay, and method of death. However, little information exists regarding the relative importance of these variables. This paper will address the impact of these factors upon monoamine receptor binding in postmortem human brain tissue and their specific relevance for findings in suicide research.

Methods

Samples were collected from 35 control subjects and 20 suicide victims with a postmortem delay to autopsy of less than 24 hours. All brains underwent macroscopic and microscopic examination to exclude neuropathology. Clinical history, autopsy findings, and toxicology were used to exclude alcoholism and drug abuse. All samples were stored at −70°C until assay. Details of tissue handling have been described elsewhere (Mann et al., 1986).

Beta-adrenergic receptors were assayed using 45 pM (^{125}I) iodopindolol and 10 μM (−)-propranolol to define specific binding. Serotonin-1 (5-HT$_1$) receptors were assayed using the ligand ^{3}H-serotonin (4 nM) and 10 μM serotonin to define specific binding. Serotonin-2 (5-HT$_2$) receptors were assayed with 0.2 nM H-spiroperidol and 1 μM ketanserin. Dopamine-2 (D2) receptors were assayed with 0.2 nM ^{3}H-spiroperidol and 1 μM (+)-butaclamol. These methods have been previously described (Mann et al., 1986). All ligands were purchased from New England Nuclear, Massachusetts. Complete saturation binding isotherms for 5-HT$_1$ and 5-HT$_2$ receptors were carried out on a limited number of samples. Binding was quantified in terms of protein content (Lowry et al., 1951) and calculated using a Scatchard transformation.

Results

1. *Effects of Postmortem Delay.* The only significant effect of postmortem delay on the monoamine receptor binding indices measured was a decline in cortical β-adrenergic binding that correlated with the time delay before refrigeration at 4°C. This effect was accounted for by samples with a >4 hour delay to storage at 4°C. For other receptors no significant correlations were found between binding and overall time to autopsy (5-HT$_1$, $r = -0.2$; 5-HT$_2$, $r = -0.2$; D$_2$, $r = -0.12$).

2. *Effects of Age.* A significant age-related decline was observed in 5-HT$_2$ binding in frontal cortex ($r = -0.42$, $p < 0.01$, $n = 34$). This was due to fewer binding sites (B_{max}) and occurred in the absence of a change in K_D. In contrast no statistically significant age-related changes were observed in 5-HT$_1$, β-adrenergic, or D$_2$ binding. However it should be noted that the age range of the samples assayed for β-adrenergic and D$_2$ binding included too few samples from younger sub-

---

[1] Laboratory of Psychopharmacology, Department of Psychiatry, Cornell University Medical College, 1300 York Avenue, New York, NY 10021.

[2] Address all correspondence to Dr. Mann.

[3] Department of Psychiatry, Columbia College of Physicians and Surgeons, New York, NY 10032.

jects (mean ages 61.7 and 64.9 years, respectively) and therefore an age effect could not be excluded with certainty. In fact, when separated on the basis of median split for age, older subjects had 40 percent less β-adrenergic binding than younger subjects (3.1 ± 0.9 versus 4.9 ± 1.1 fmol/mg, respectively).

3. *Effect of Gender*. Gender did not appear to affect any of the monoamine receptor binding indices. Furthermore, although the number of samples from premenopausal women was small, no suggestion was found for an effect due to menopause.

4. *Method of Death: The Effects of Violence and Hypoxia*. In the control subjects no effect of violent versus nonviolent cause of death was found upon either 5-HT$_2$ or β-adrenergic binding (99.9 ± 18.4 versus 103.7 ± 16.3; 10.1 ± 2.7 versus 8.9 ± 2.5, fmol/mg, respectively). Similar data were not available for the suicide victims since the protocol required the exclusion of subjects dying from drug overdose and therefore the bulk of the remainder used violent means for suicide.

The effects of hypoxia were assessed by comparing suicide victims who died by asphyxiation to those who died by other methods. No significant differences were found in 5-HT$_1$, 5-HT$_2$, and β-adrenergic binding. D$_2$ binding was not determined in suicide victims.

Discussion

The apparent selective susceptibility of β-adrenergic binding to delays of >4 hours prior to refrigeration at 4°C indicates the importance of distinguishing between overall time to autopsy and time to storage at 4°C. Autopsies on suicide victims are usually carried out by medical examiners or their equivalent, and there is usually a longer delay to refrigeration at 4°C than with hospital cases where the autopsy is carried out inhouse. Since we and others have demonstrated changes in β-adrenergic binding in suicide victims, it is clearly of importance to use appropriately matched controls, preferably collected from the same source.

We found a 50 percent decline in the number of 5-HT$_2$ binding sites in frontal cortex between the ages of 15 and 70 years. A similar age-related decline in β-adrenergic sites could not be excluded on the basis of our preliminary data. The same receptor sites were found to be upregulated in suicide victims relative to matched controls. Clearly matching for age is essential in studying these systems in suicide victims.

Paradoxically, there is an age-related decline in most measures of noradrenergic indices including norepinephrine cell bodies in the locus coreleus, norepinephrine, MHPG, tyrosine hydroxylase, and dopa decarboxylase. A compensatory upregulation of postsynaptic β-adrenergic receptors may be hypothesized on the basis of this evidence of a decline in presynaptic noradrenergic activity. However, our findings indicate that this does not occur. Animal studies are even clearer and indicate an age-related decline in β-adrenergic binding. Therefore, apart from an age effect upon presynaptic noradrenergic function, there appears to be an additional effect upon the postsynaptic receptors.

In the serotonergic system the consequences of aging appear to differ significantly from what is observed in the noradrenergic system. Levels of 5-HT, 5-HIAA, and in animal studies tryptophan hydroxylase do not alter significantly with aging. In the absence of an alteration in presynaptic serotonergic indices, the finding of a loss in postsynaptic 5-HT$_2$ binding sites suggests a direct aging effect on the as yet unidentified cortical neuron on which the 5-HT$_2$ receptor is located.

As mentioned previously in contrast to 5-HT$_2$ receptors we found no age effect on 5-HT$_1$ receptors. However, considerable evidence exists to indicate that 5-HT$_1$ and 5-HT$_2$ receptor populations are independently regulated and have a different regional distribution in the brain. Therefore, the relative sparing of the 5-HT$_1$ receptors in normal aging may be another example of this independent regulation. Also consistent with this dissociation is our finding that, although 5-HT$_2$ receptors are upregulated in suicide victims, 5-HT$_1$ binding indices are unaltered.

Several laboratories have reported an age-related decline in nigrostriatal dopaminergic neurons and a fall in dopamine levels (Carlsson et al., 1980). Such an apparent reduction in dopaminergic function does not result in a detectable increase in D$_2$ binding, and it is possible that aging may impair this homeostatic adjustment. Animal studies actually report an age-related loss of D_2 binding sites. The direction of change is therefore indicative of a postsynaptic aging effect on these receptors.

Gender is an important factor in determining the prevalence of affective disorders (2 to 3 times greater in females) and suicide (2 to 3 times more common in men). In normal controls with no known psychiatric history no gender differences were seen in monoamine receptor binding. This finding is consistent with the absence of gender differences in levels of norepinephrine, 5-HT, 5-HIAA, and dopamine (Gottfries, 1980). Thus, gender does not appear to affect monoaminergic measures. However, it should be noted that most studies assayed tissue from the frontal lobe where there are relatively few estrogen receptors and therefore important gender-related differences in monoamine may have been missed.

Other factors such as violence or suddenness of death or a hypoxic death did not appear to affect binding indices. While this study tended to exclude samples from subjects with confounding antemortem drug use, it should be noted that psychotropic drugs can affect binding. Antidepressant drugs have been shown in animal studies to reduce the B_{max} of 5-HT_2 and/or β-adrenergic binding sites after chronic administration. Antipsychotics are competitive inhibitors of D_2 and 5-HT_2 sites and would therefore alter K_D. Since these classes of compounds are frequently used in depression and schizophrenia and their effects on β-adrenergic and 5-HT_2 binding are in the opposite direction to that found in suicide victims and perhaps depression, it is critical to exclude subjects where antemortem use of these drugs can be established.

An important area for future work involves the study of regional differences using techniques such as quantitative autoradiography and immunocytochemistry. Regional studies will yield information about the distribution of effects and will assist in the distinguishing presynaptic system effects from localized regional effects. Confident interpretations of the significance of disease-related findings can only be made against a background of such normative data.

Acknowledgments

This work was supported by PHS grant MH 40210 and a Hirschl Trust Research Scientist Award to Dr. Mann. Ms. Joanie Chin provided skilled technical assistance and Ms. Isadora Johnson and Ms. Mary Ruth Goodley expertly typed the manuscript.

References

Carlsson, A., Adolfsson, R., Aquilonius, S.M., et al. Biogenic amines in human brain in normal aging, senile dementia and alcoholism. In: Goldstein, M., et al. (eds.), *Ergot Compounds and Brain Function: Neuroendocrine and Neuropsychiatric Aspects*. New York: Raven Press, 1980, pp. 295–304.

Creese, I., Burt, D.R., and Snyder, S.H. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*, 192:481–483, 1976.

Gottfries, C.G. Amine metabolism in normal aging and in dementia disorders. In: Roberts, R.J. (ed.), *Biochemistry of Dementia*. London: John Wiley and Sons Ltd., 1980, pp. 213–241.

Lowry, O., Rosebrough, S., Farr, A., and Randall, J. Protein measurement with the folin phenol reagent. *J. Biol. Chem.*, 193:265–268, 1951.

Maggi, A., Schmidt, M.J., Ghett, B., and Enna, S.J. Effect of aging on neurotransmitter receptor binding in rat and human brain. *Life Sci.*, 24:367–374, 1979.

Mann, J.J., Petito, C., McBride, P.A., et al. Amine receptor binding and monoamine oxidase activity in postmortem human brain tissue: Effect of age, gender and postmortem delay. In: Burrows, G.D., et al. (eds.) *Affective Disorders: Pharmacological Studies*. London: John Wiley and Sons Ltd., 1986, pp. 37–39.

Snyder, S.H., Banerjee, S.P., Yamamura, H.I., and Greenberg, D. Drugs, neurotransmitters and schizophrenia. *Science*, 1984:1243–1253, 1974.

Stanley, M., and Mann, J.J. Serotonin-2 binding sites are increased in the frontal cortex of suicide victims. *Lancet*, i:214–216, 1983.

Sulser, F., Vetulani, J., and Mobley, P.L. Mode of action of antidepressant drugs. *Biochem. Pharmacol.*, 27:257–271, 1978.

Appetite and Satiety Regulation: Pharmacological Strategies

Chair:

Regina Casper, M.D.

Illinois State Psychiatric Institute
Chicago, IL 60612

Neuropeptides as Stimulators of Feeding

John E. Morley, M.D.,[1] James E. Mitchell, M.D.,[2] and Allen S. Levine, Ph.D.[3]

The complexities of the ingestive process make it extremely unlikely that any *single* neurotransmitter will be found to regulate this behavior. Over recent years it has become clear that a variety of neurotransmitters can modulate ingestion (Morley & Levine, 1985). For simplicity, the regulation of feeding can be divided into a peripheral satiety system and a central feeding system. This model suggests that the majority of hormones and neurotransmitters released during the passage of food through the gastrointestinal tract are responsible for relaying inhibitory messages to the central nervous system (CNS). Two exceptions to the rule that peripherally released hormones produce satiety are the well-recognized hunger provoking effects of insulin administration and the fact that motilin increases food intake in starved rats (Garthwaite, 1985).

Within the CNS, it appear that the regulation of feeding involves the interaction of a variety of neurotransmitters. Based on neuropharmacological data it has been suggested that these neurotransmitters are arranged in a cascade system similar to the well-recognized cascade systems responsible for the regulation of blood clotting and complement fixation (Morley, 1980). Growing evidence also suggests that there are, in fact, a number of systems arranged in parallel allowing the food selection process to take place.

Within the CNS a number of these neurotransmitters appear to be primarily stimulators of feeding (Table 1). The classical CNS stimulator of feeding is the monoamine, norepinephrine, which appears to exert its effect predominantly within the paraventricular nucleus (Leibowitz, 1980). Dopamine can also stimulate feeding at low concentrations; while at higher concentrations, the development of dopamine-induced stereotypy inhibits feeding (Morley et al., 1982). The amino acid neurotransmitter, gamma amino butyric acid, and its analog, muscimol, will stimulate feeding when applied to the medial hypothalamus while inhibiting feeding in the area of the lateral hypothalamus (Morley et al., 1981). Recently, Kyrkouli et al. (1985) have shown that the 29 amino acid peptide, galanin, which co-exists with norepinephrine in the paraventricular nucleus, will stimulate feeding. Growth hormone-releasing hormone has been shown to stimulate feeding at low concentrations while inhibiting it at

---

[1] Geriatric Research, Education and Clinical Center Sepulveda VA Medical Center, Sepulveda, CA and Department of Medicine, University of California, Los Angeles, CA 91343.

[2] Department of Psychiatry, University of Minnesota, Minneapolis, MN 55417.

[3] Minneapolis VA Medical Center, Minneapolis, MN 55417.

TABLE 1. Neurotransmitters That Stimulate Feeding Within the Central Nervous System

A. MONOAMINES
    Norepinephrine
    Dopamine
B. AMINO ACIDS
    Gamma amino butyric acid
C. NEUROPEPTIDES
    Opioid peptides
        - Beta-endorphin
        - Dynorphin
        - Alpha-neo-endorphin
    Pancreatic polypeptide family
        - Neuropeptide Y
        - Peptide Y
    Galanin
    Growth Hormone Releasing Hormone

higher concentrations (Vaccarino et al., 1985). Two other families of peptides, the opioid peptides and the pancreatic polypeptide family, have also been demonstrated to be potent stimulators of feeding, and the remainder of this brief review will address the effects of these neurotransmitters.

Opioid Peptides and Feeding

The ability of opioid peptides to stimulate feeding and for the opioid antagonist, naloxone, to inhibit feeding has been comprehensively reviewed recently (Morley et al., 1983). There is now increasing evidence that the kappa opioid receptor is primarily responsible for the ability of opioids to stimulate feeding. In particular, the endogenous kappa ligand, dynorphin, appears to be a potent stimulator of feeding (Morley & Levine, 1981). Although the primary opioid system involved in the stimulation of feeding is the kappa opioid system, there is also evidence for a second non-mu, opioid feeding system (Morley et al., 1985c). It appears that opioids can regulate feeding within at least three separate areas within the CNS, viz. the paraventricular nucleus, the amygdala, and the globus pallidus (Gosnell et al., 1984, 1986; Stanley et al., 1984).

A number of studies have now demonstrated that naloxone will decrease the amount of food eaten over a single meal (Atkinson, 1982; Cohen et al., 1985; Morley & Levine, 1982; Trenchard & Silverstone, 1983). Of particular interest is the fact that naloxone decreased food intake without altering the perception of satiety (Trenchard & Silverstone, 1983). Similarly, we found that while butorphanol tartrate, a mixed opiate agonist/antagonist which preferentially binds to the kappa receptor, could increase food intake in normal subjects over 6 hours, it failed to alter the perception of hunger (Morley et al., 1985a). Using the longer acting analog of naltrexone, nalmafene, we found that food intake could be suppressed for up to 24 hours (Billington et al., 1985). In these studies we found that opioid antagonism predominantly decreased fat intake, which is in keeping with previous studies in rodents (Marks-Kaufmann & Kanarek, 1981). It needs to be pointed out, however, that fat-containing foods tend to be the most palatable; and, thus, the effect of opioid antagonism may be more specifically directed towards palatability rather than fat *per se*.

Unfortunately, it appears that tolerance to the effects of opiate antagonism on food intake develops rapidly. We gave naltrexone (300 mg/day or placebo) for 8 weeks in a double-blind, controlled trial to obese males. We could demonstrate no advantage of naltrexone over placebo as far as weight loss was concerned. In addition, naltrexone produced mild hepatotoxicity in some of the subjects.

The animal literature has suggested that opioids may play a particularly important role in the induction of stress (Morley & Levine, 1980) and 2-deoxy-glucose induced feeding in humans is inhibited by naloxone (Thompson et al., 1983). We, therefore, examined the effect of naloxone on binge-eating episodes in bulimic patients. Our preliminary data show that naloxone infusion attenuates the amount of food consumed during binge-eating episodes. Cholecystokinin was ineffective at altering binge-eating behavior. These results support the hypothesis that the endogenous opioid system is involved in the maintenance of binge-eating behavior in patients with bulimia.

Anorexia occurs commonly in the elderly. Although it is often precipitated by bereavement and, in some cases, is accompanied by depression, in many patients there appears to be no physical or psychological cause for the onset of anorexia. These patients often appear unaware of the dramatic effects of the associated weight loss and repeatedly deny that they wish to die. In some instances, the patients chew food and then spit it out. This syndrome of senile marasmus bears certain similarities to anorexia nervosa. Recent animal studies have shown that opiates are relatively ineffective at stimulating feeding in older rats and mice (Gosnell et al., 1983; Kavaliers & Hirst, 1985). Naloxone also fails to decrease feeding in older rodents. These animal studies suggest that an attenuated opioid feeding system may play a role in the pathogenesis of the anorexia associated with the development of senile marasmus.

We have previously suggested that the original function of opioid peptides was to stimulate food seeking with the analgesic functions of opioids developing as a genetic mutation when the food seeking animal was forced to forage for food, thus coming into contact with danger and pain (Morley & Levine, 1982). Many of the other functions of opioids fit with this general construct. Thus, opioids also enhance immune function, decrease gastric acid secretion, elevate blood glucose, and decrease sexual function and luteinizing hormone secretion (Morley, 1980). Further, when opioid function is reduced by feeding or the administration of naloxone, memory is enhanced, thus allowing the animal to fix in its memory the details of its successful foraging expedition!

Pancreatic Polypeptides and Feeding

The pancreatic polypeptide family consists of pancreatic polypeptide, neuropeptide Y, and peptide YY. The latter two peptides were isolated by Tatemoto and his colleagues (1982) and are characterized by having tyrosine at both ends of the molecule and hence the designation YY and Y (Y being the biochemical nomenclature for tyrosine). Neuropeptide Y (NPY) is widely distributed throughout the central and peripheral nervous systems, whereas peptide YY occurs mainly in peripheral tissues. High concentrations of NPY are found within the paraventricular nucleus, suggesting that it may play a role in feeding.

Clark et al. (1984) demonstrated that both human pancreatic polypeptide and, to a greater extent, NPY increased feeding after injections into the third ventricle of ovariectomized rats. Stanley and Leibowitz (1984) reported a similar potent increase in feeding in intact male rats after direct injection into the paraventricular nucleus. Studies in our laboratory confirmed the potent orexigenic effect of NPY in intact male rats (Levine & Morley, 1984). Not only does NPY increase feeding during the daytime when rats don't normally eat, but it also increases nocturnal feeding and feeding in animals after 24-hour starvation. NPY is inactive after peripheral administration. NPY also causes a major increase in water ingestion and this increase in water ingestion is still present, although diminished, in the absence of food. NPY is a highly specific enhancer of the ingestion of carbohydrate-rich foods, being much more potent than norepinephrine in this regard.

As NPY was shown to coexist with norepinephrine within the CNS, a number of studies have attempted to examine the relationship between norepinephrine and NPY on ingestive behaviors. Neither our group (Levine et al., 1984) nor Stanley and Leibowitz (1985) could block the effects of NPY on feeding with the alpha antagonist, phentolamine. In addition, we could demonstrate no synergistic or additive effects of NPY and norepinephrine on feeding. Table 2 compares the effects of NPY and norepinephrine on feeding based on studies in our laboratory. Perusal of these results clearly suggests that NPY and norepinephrine produce their effects on feeding through different mechanisms.

We compared the potency of NPY to PYY and rat pancreatic polypeptide (Morley et al., 1985). We could find no effect of rat pancreatic polypeptide on food or water intake in male rats. PYY, on the other hand, proved to be significantly more potent than NPY. This is in keeping with the potencies of NPY and PYY in the brain receptor assay and in the biological responses in the rat vas deferens as reported by Chang et al. (1985). Of interest is that in the chicken avian pancreatic polypeptide is a far more potent stimulator of feeding than is NPY (Steinman and Morley, unpublished observations).

Chronic administration of PYY every 6 hours for 48 hours leads to a marked increase

TABLE 2. Comparison of the Effects of Neuropeptide Y (NPY) and Norepinephrine on Feeding

	NPY	Norepinephrine
Food Intake	Increase by 7-10 g after ICV injection	Increase by 2-4 g after ICV injection
Water Intake	Increased	No change or decreased
Nutrient Selection	Carbohydrate	Carbohydrate and fat
Blocked by Phentolamine	No	Yes
Site of Action	Anterior VMH and PVN	PVN
Blocked by Vagotomy	No	Yes
Blocked by Adrenalectomy	No	Yes

in food intake (Morley et al., 1985b). There is no tolerance to the orexigenic effect of PYY. Of particular interest in this study was the profound distension of the gastrointestinal tract observed at the end of the 48 hours. The food intakes and stomach distension of the PYY-injected animals attest to the fact that central factors can override the physiological satiety signals from the periphery. Stanley et al. (1985) have demonstrated that rats given repeated NPY injections for 10 days doubled their daily food intake and increased body weight compared to vehicle-injected animals.

These studies suggest that NPY is among the most potent endogenously occurring orexigenic agents yet to be described. The magnitude of food intake seen following NPY is greater than that observed after central administration of any other neurotransmitter. The fact that NPY also produces a selective increase in carbohydrate suggests to us that consideration should be given to the possibility that NPY plays a role in the pathophysiology of bulimia. Should this prove to be the case, we suggest that the term "bulimin" might be used as a suitable descriptive trivial name for NPY.

References

Atkinson, R.L. Naloxone decreases food intake in obese humans. *J. Clin. Endocrinol. Metab.*, 55:196–198, 1982.

Billington, C.J., Shafer, R.B., and Morley, J.E. Effects of opioid blockade with nalmafene in older impotent men. *Endocrinology*, 116:237A, 1985.

Chang, R.S.L, Lotte, V.J., Chen, T-B., et al. Neuropeptide Y binding sites in rat brain labeled with ^{125}I-Bolton-Hunter NPY. *Life Sci.*, 37:2111–2122, 1985.

Clark, J.J., Kalra, P.S., Crowley, W.R., and Kalra, S.P. Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology*, 115:427–429, 1984.

Cohen, M.R., Cohen, R.M., and Pickar, D. Naloxone reduces food intake in humans. *Psychosomat. Med.*, 47:132–138, 1985.

Garthwaite, T.L. Motilin stimulates feeding in fasted rats. *Peptides*, 6:41–45, 1985.

Gosnell, B.A., Levine, A.S., and Morley, J.E. The effects of aging on opioid modulation of feeding in rats. *Life Sci.*, 32:2793–2799, 1983.

Gosnell, B.A., Morley, J.E., and Levine, A.S. Lesions of the globus pallidus and striatum attenuate ketocyclazocine-induced feeding. *Physiol. Behav.*, 33:349–355, 1984.

Gosnell, B.A., Morley, J.E., and Levine, A.S. Opioid-induced feeding: Localization of sensitive brain sites. *Brain Res.*, 369:177–184, 1986.

Kavaliers, M., and Hirst, M. The influence of opiate agonists on day-night feeding rhythms in young and old mice. *Brain Res.*, 326:160–167, 1985.

Kyrouli, S.E., Stanley, B.G., and Leibowitz, S.F. Galanin: Stimulation of feeding induced by medical hypothalamic injection of this novel peptide. Abstracts of Mechanisms of Appetite and Obesity, San Antonio, TX, 1985.

Leibowitz, S.F. Neurochemical systems of the hypothalamus: Control of feeding and drinking behavior and water electrolyte excretion. In: Morgane, P.J., and Panksepp, J. (eds.), *Handbook of the Hypothalamus.* New York: Raven Press, 1980, pp. 299–437.

Levine, A.S., and Morley, J.E. Neuropeptide Y: A potent inducer of consummatory behavior in rats. *Peptides*, 5:1025–1030, 1984.

Marks-Kaufmann, R., and Kanarek, R.B. Modification of nutrient selection induced by naloxone in rats. *Psychopharmacology*, (Berlin) 74:321–324, 1981.

Morley, J.E. The neuroendocrine control of appetite: The role of the endogenous opiates, cholecystokinin, TRH, gamma-amino butyric acid and the diazepam receptor. *Life Sci.*, 27:355–368, 1980.

Morley, J.E. The endocrinology of the opiates and the opioid peptides. *Metabolism*, 30:195–209, 1981.

Morley, J.E., and Levine, A.S. Stress-induced eating is mediated through endogenous opiates. *Science*, 209:1259–1261, 1980.

Morley, J.E., and Levine, A.S. Dynorphin-(1–13) induces spontaneous feeding in rats. *Life Sci.*, 29:1901–1903, 1981.

Morley, J.E., and Levine, A.S. The role of the endogenous opiates as regulators of appetite. *Am. J. Clin. Nutr.*, 35:757–761, 1982.

Morley, J.E., and Levine, A.S. Pharmacology of eating behavior. *Ann. Rev. Pharmacol. Toxicol.*, 25:127–146, 1985.

Morley, J.E., Levine, A.S., and Kneip, J. Muscimol induced feeding: A model to study the hypothalamic regulation of appetite. *Life Sci.*, 29:1213–1218, 1981.

Morley, J.E., Parker, S., and Levine, A.S. Effect of butorphanol tartrate on food and water consumption in humans. *Am. J. Clin. Nutr.*, 42:1175–1178, 1985.

Morley, J.E., Levine, A.S., Grace, M., and Kneip, J. Dynorphin-(1–13), dopamine and feeding in rats. *Pharmacol. Biochem. Behav.*, 16:701–705, 1982.

Morley, J.E., Levine, A.S., Yim, G.K.W., and Lowy, T. Opioid modulation of appetite. *Neurosci. Biobehav. Rev.*, 7:281–305, 1983.

Morley, J.E., Levine, A.S., Grace, M., and Kneip, J. Peptide YY (PYY) - a potent orexigenic agent. *Brain Res.*, 341:200–203, 1985b.

Morley, J.E., Levine, A.S., Kneip J., et al. The kappa opioid receptor and food intake. *Europ. J. Pharmacol.*, 112:17–25, 1985.

Stanley, B.G., and Leibowitz, S.F. Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. *Life Sci.*, 35:2635–2642, 1984.

Stanley, B.G., Lanthier, D., and Leibowitz, S.F. Feeding elicited by the opiate peptide D-ala-2-met-enkephalinamide: Sites of action in the brain. *Soc. Neurosci. Abstr.*, 10:1103, 1984.

Stanley, B.G., and Leibowitz, S.F. Neuropeptide Y injected in the paraventricular hypothalamus: A powerful stimulant of feeding behavior. *Proc. Natl. Acad. Sci. USA*, 82:3940–3943, 1985.

Stanley, B.G., Jhanwar-Unival, M., and Leibowitz, S.F. Hypothalamic neuropeptide Y: Endogenous immunoreactivity and exogenous administration in relation to appetite and obesity and food deprivation. Abstracts of Mechanisms of Appetite and Obesity, San Antonio, TX, 1985.

Tatemoto, K., Carlquist, D.M., and Mutt, V. Neuropeptide Y - A novel brain peptide with structural similarities to peptide YY and pancreatic polypeptide. *Nature*, 296:659–660, 1982.

Thompson, D.A., Welle, S.L., and Lilavivict, U. Opiate receptor blockage in men reduced 2-deoxy-D-glucose-induced food intake but not hunger, thirst and hypothermia. *Life Sci.*, 31:847–852, 1983.

Trenchard, E., and Silverstone, T. Naloxone reduces the food intake of normal human volunteers. *Appetite*, 4:43–50, 1983.

Vaccarino, F.J., Bloom, F.E., Rivier, J., et al. Stimulation of food intake in rats by centrally administered hypothalamic growth hormone-releasing factor. *Nature*, 314:147–148, 1985.

Psychotoxic Manifestations in Amphetamine Abuse

Co-Chairs:

Tomoji Yanagita, M.D., Ph,D.
Central Institute for Experimental Animals
Kawasaki 213 Japan

Everett H. Ellinwood, Jr., M.D.
Duke University Medical Center
Durham, NC 27710

Acute Exacerbation of Methamphetamine Psychosis and Lasting Dopaminergic Supersensitivity—A Clinical Survey

Mitsumoto Sato, M.D.[1]

Introduction

Methamphetamine (MAP) psychosis has characteristic psychotic features very similar to those of paranoid schizophrenia. In Japan, the number of persons arrested for offenses against the Amphetamine Control Law has increased steadily for more than a decade (Figure 1). Although it is almost impossible to calculate the exact number of MAP abusers, it is presumed that there are 10 to 15 abusers for each person arrested. Accordingly, the total number of abusers in 1984 was estimated to be between 200,000 and 300,000. Thus, the incidence of both MAP abuse and MAP psychosis has dramatically increased in Japan in the last decade, forming a second peak following the first peak of MAP abuse seen shortly after World War II. This clinical survey was made first to re-evaluate the clinical course of MAP psychosis after abstinence and the relapse of the paranoid psychotic state after MAP re-use. It appears important to distinguish between at least two kinds of psychiatric abnormalities: the abnormality related to the acute but transient psychotomimetic action of MAP, and the abnormality resulting from chronic MAP abuse that persists for a long time after abstinence from MAP. Secondly, the prophylactic effect of neuroleptics on the relapse of the paranoid psychotic state was examined in patients with MAP psychosis.

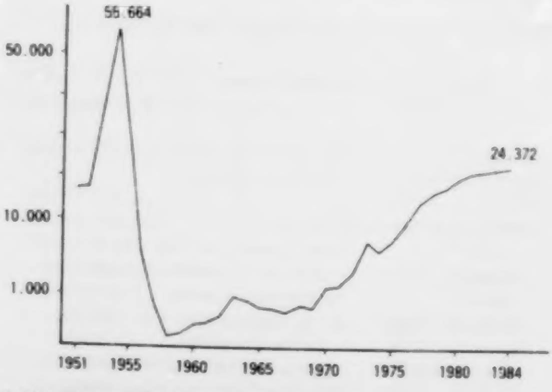


FIGURE 1. Number of persons arrested.

---

[1] Department of Neuropsychiatry, Okayama University Medical School, Okayama 700 Japan

Methods

Two hundred forty-six patients with MAP-use disorders who were admitted to 21 mental hospitals were included in this study. A questionnaire method was applied to 164 patients by team members as a special project of the Japanese Ministry of Welfare (1983–1984). In addition, individual clinical charts of 82 inpatients with MAP psychosis were also examined. The background data of all of the patients are summarized in Table 1.

Most patients used MAP for several years and had a social or occupational impairment due to the pathological pattern of MAP use or the acute pharmacological action of MAP. The drug was self-administered intravenously, and the mean amount of MAP for one injection was estimated by the police to be 30 mg. High-quality MAP in a fine crystal powder form was used. Smuggled MAP produced illicitly in other Asian countries is supplied by Japanese organized crime.

Results

The Mental Symptoms When Admitted to the Mental Hospitals

The symptoms observed in more than half of the 246 patients were: psychomotor excitement, auditory hallucination, delusion of persecution, suspiciousness, anxiety, irritation, emotional lability, and sharpened sensation. Visual hallucination, illusion, delusion of reference, and delusional perception were observed in 25 to 49 percent of the patients. This result is consistent with previous reports by Connell (1958) that the clinical picture of MAP psychosis is primarily a paranoid psychosis with delusion of persecution and hallucination under clear consciousness.

TABLE 1. Background Data of 246 Patients.

Sex	male vs. female = 7.5 : 1
Age when admitted	30's > 20's > under 19 > more than 40
Poly-user	66% (alcohol>glue>hypnotic>other)
Re-admitted case	139 of 246 patients
Methamphetamine (MAP) abuse	
Period	5 to 10 years
Pattern	Inability to reduce or stop use
Route	Intravenous injection
Amount of MAP	30–90 mg/injection, 1 to more than 10 injections/day
Form of MAP	High-quality fine crystal powder
Supply	Smuggled MAP produced illicitly

MAP = methamphetamine

Duration of the Psychotic State After Admission

By treatment with antipsychotics and abstinence from MAP, the active paranoid psychotic state disappeared within 10 days in 64 percent, while it continued for more than 11 days in 36 percent, and for more than 1 month in 18 percent (more than 6 months in 10 percent) of the 82 inpatients. Since the urine MAP test turns negative within 3 to 5 days after abstinence, it is clear that the paranoid psychotic state with hallucination may continue for a long time after excretion of MAP.

Period of MAP Abuse Necessary to Produce an Initial and a Secondary Psychotic Episode (Relapse)

A significantly shorter period of MAP abuse was sufficient to reproduce the psychotic state than to produce the initial episode (Figure 2). Sixty of 101 patients had a relapse after reusing MAP for less than 1 week, while no patient had an initial psychotic episode within 1 week of MAP use. These findings indicate a lasting susceptibility to relapse of the psychotic state after the initial episode.

There was a marked individual variation in the MAP abuse period up to the first admission with the initial psychotic episode. This result is consistent with previous reports (Tatetsu et al., 1956), suggesting a possible role of disposition, such as a pathoplastic factor, in MAP psychosis. In addition, no relation was found statistically between the duration of MAP abuse before the initial episode and that before the relapse. Occurrence of the initial psychotic episode itself, rather than the period of MAP abuse for the initial episode, may indicate the emergence of biological susceptibility to relapse of the psychotic state.

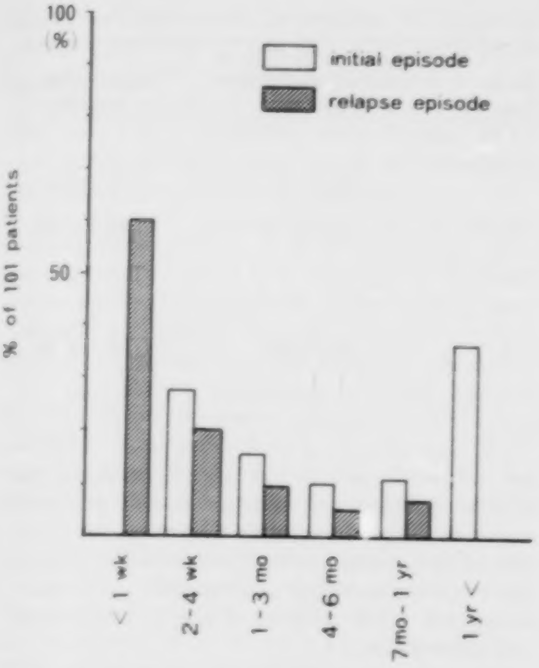


FIGURE 2. Duration of MAP abuse.

Pattern of Acute Exacerbation by MAP Reuse

Twenty-one patients were selected according to four criteria: 1) a history of MAP use of more than 1 month, 2) an experience of MAP-induced psychotic state similar to acute schizophrenia, 3) the reactivation of any psychotic state with re-exposure to MAP with an abstinence interval of more than 1 month, and 4) the availability of reliable information about the status of MAP use given by a third person.

The clinical pictures during the initial psychotic episode and relapses were compared (Table 2). Bizarre delusions included delusions of being controlled, thought insertion, or thought broadcasting. The incidence of each psychotic item in relapses of the psychotic episode did not differ significantly from that in the initial psychotic episode. This result indicates that relapse of the psychotic state is almost identical to the initial psychotic episode.

Patterns of the Relapse. With a long abstinence interval, acute exacerbation of the psychotic state was observed after a single injection in 10 cases and after a few injections in 6 cases (Table 3). A single injection of a smaller amount of MAP than the initial injection was enough to cause recurrence of the psychotic state in 4 patients.

Prophylactic Effects of Antipsychotics on Relapse of MAP Psychosis

There were 8 patients who used MAP again without the knowledge of the doctor, while they were receiving neuroleptics in the outpatient clinic. All of them had an initial psychotic episode in the past, and 3 of them had one or more relapses after using MAP again (Table 4). Two to 3 mg/day of haloperidol prevented the recurrence of any paranoid psychotic state when the patients injected themselves with 30 to 90 mg of MAP once a day or 10 times within a few days. One patient who took 1.5 mg/day of haloperidol and injected himself with 30 to 90 mg several times a day developed a marked suspicious tendency and illusional experience, but he did not develop a paranoid psychotic state resembling the initial psychotic episode. One hundred mg of levomepromazine and trifluperazine also prevented recurrence of the psychotic state, but 30 mg/day of thioridazine was insufficient to prevent the relapse completely.

Discussion

The present study indicates two types of clinical course in MAP psychosis after abstinence. Type A is a psychotic state which begins to improve along with a disappearance of

TABLE 2. Clinical Manifestations of the Acute Phase of 21 MAP Patients.

Symptoms	Episode	
	Initial	Relapse
Bizarre delusion	23.8%	37.5%
Delusions with jealous or persecutory content	100.0	100.0
Hallucinations		
Auditory	76.2	93.8
Visual	38.1	43.8
Incoherence, loosening of association	19.0	18.8

MAP = methamphetamine.

TABLE 3. Patterns of MAP Reuse ($N = 16$).

	No. of Patients	Duration of MAP Abuse Until the Initial Episode (years)	Abstinence Period (months)
A. Relapse with a single re-injection			
With a small amount of MAP (½–⅕)	4	3.0 (0.1–5)	3.5 (1–9)
With the usual amount of MAP (30–90 mg)	5	9.1 (0.3–14)	22.0 (4–60)
With a large amount of MAP (2 times)	1	7	12
B. Relapse with a few injections			
With the usual amount of MAP	5	8.9 (4–16)	12.2 (3–28)
With a large amount of MAP	1	15	12

the acute central action of MAP. This type suggests a paranoid psychotic state which is dependent on the MAP-induced hypercatecholaminergic state, probably hyperdopaminergic state. In Type B, the psychotic state continued for more than 11 days in 36 percent and for more than 1 month in 18 percent of the patients, even though MAP is metabolized and excreted rapidly. This suggests a paranoid psychotic state in which the clinical course is independent of a MAP-induced hyperdopaminergic state. Thus, chronic MAP use results in a lasting change in both brain dopaminergic and non-dopaminergic systems that relate to the paranoid psychotic state. The data from this study do not allow us to discuss a difference in the clinical picture of the paranoid psychotic states in Types A and B. However, the content of delusions and hallucination in Type A was realistic and characterized by great suspiciousness, while that in Type B was bizarre and unrealistic.

Since no urine MAP test was performed in most cases, it is hard to exclude the possibility completely that the patients continued to use MAP after admission, although it seems almost impossible. Another possibility is that MAP brought about a worsening of a preexisting schizophrenic state from which the patient was unable to recover. Although there were some reports indicating exacerba-

TABLE 4. Reuse of MAP During Medication With Neuroleptics ($N = 8$).

	Neuroleptics (mg/day)	Case No.	Initial Psychosis	Abstinence Period (mo.)	No. of MAP Injections	Relapse
A.	Haloperidol					
	3	1	a,b	1	10/few days	–
	3	2	a,b	4	1/day	–
	3	7	a,b	6	1/day	–
	3	8	a,b	¼	1/day	–
	2	6	a,b,c	¼	1/day	–
	1.5	4	a,b,c	1	>1/day	±
B.	Phenothiazine					
	Levomepromazine					
	100	6	a,b,c	¼	1/day	–
	75	7	a,b	½	4/day	+
	25	7	a,b	¼	1/day	–
	Trifluperazine					
	100	3	a	4	1/day	–
	Thioridazine					
	30	6	a,b,c	6	1/day	+
	20	5	a	1	6–15/few days	+

[a] Auditory hallucination; [b] paranoid delusion; and [c] delusions of being controlled, thought insertion, or thought broadcasting.

tion of schizophrenic symptoms by amphetamines (Janowski & Davis, 1976), such exacerbations were transient and cannot explain the clinical course of Type B patients. Type B may indicate a possibility that chronic MAP can result in the same kind of biological changes as those of schizophrenia.

The present study showed that a significantly shorter period of MAP use, even a single injection with a lesser amount of MAP than before, reproduced a psychotic state identical to that in the initial episode after years of abstinence. This result indicates a very long-lasting augmentation and qualitative alteration of the response to MAP presumably established during the chronic MAP abuse. In addition, this study showed that acute exacerbation by reuse of MAP was prevented by a small dose of haloperidol. Since haloperidol has an antipsychotic action by blockade of dopamine$_2$ receptor sites, a lasting dopaminergic hyperreactivity may play an important role in the long-term susceptibility to relapse of the paranoid psychotic state.

The clinical course of MAP psychosis with susceptibility to relapse (Sato et al., 1983) can be reproduced in animal experiments (Figure 3). As in the psychotic state of MAP psychosis in humans, the chronic intermittent administration of MAP produces progressive and enduring changes in animal behavior, a phenomenon known as behavioral sensitization.

In both cases, behavioral abnormalities are easily reproduced when the drug is administered again after a long time of abstinence. Since this behavioral sensitization has been regarded as an animal model of MAP psychosis, there have been many attempts to identify a lasting change in the brain of amphetamine-treated animals. Up to date, several working hypotheses have been proposed from the animal studies to explain the mechanisms for acute exacerbation of the psychotic state. With regard to an excessive brain dopaminergic response to MAP and/or psychological stress, a lasting subsensitivity of presynaptic autoreceptors in the striatum (Antelman & Chiodo, 1981) and nucleus accumbens (Kashihara et al., in press), lasting increase in postsynaptic DA receptors in the nucleus accumbens (Akiyama et al, 1982), lasting enhancement in frontal cortex DA utilization (Robinson et al., 1985), and many other findings have been reported. As to a change outside of the brain DA system, a lasting decrease in TRH receptor sites in the striatum has been reported (Kajita et al., 1985). However, it should be stressed that dopaminergic hyperreactivity may be crucial for relapse of the paranoid psychotic state by MAP reuse and/or stress, rather than maintainance of the induced psychotic state.

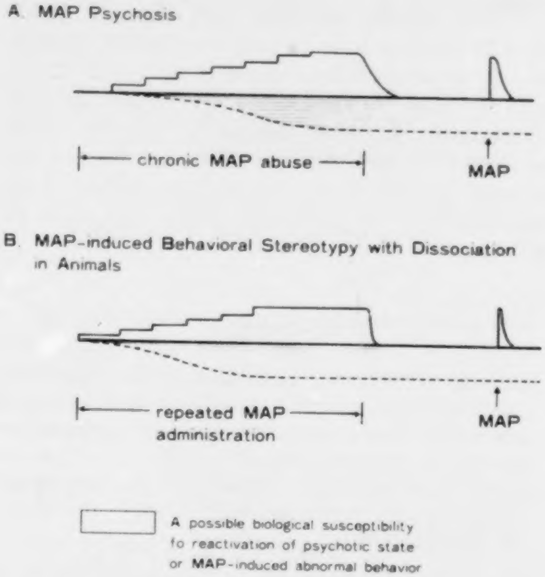

A. MAP Psychosis
chronic MAP abuse
MAP
B. MAP-induced Behavioral Stereotypy with Dissociation in Animals
repeated MAP administration
MAP
A possible biological susceptibility to reactivation of psychotic state or MAP-induced abnormal behavior

FIGURE 3. Chronological pattern of MAP psychosis and its experimental reproduction.

Summary

The present clinical survey of MAP psychosis in Japan showed the following: 1) chronic MAP abuse produced a paranoid psychotic state similar to that of schizophrenia, 2) the paranoid psychotic state continued for more than 1 month in 18 percent, while it disappeared within a week in 64 percent of 82 patients, 3) the psychotic state of the relapse was identical to that of the initial episode, 4) relapse of the psychotic state resulted from a lesser amount of MAP reuse even after a long abstinence, and 5) a small amount of haloperidol prevented the relapse by MAP reuse.

These results indicate that chronic MAP may result in a long-lasting qualitative change in the acute psychotomimetic action of MAP and increase susceptibility to relapse and, in some cases, prolong psychotic features. The well-known DA hypothesis of schizophrenia relates especially to triggering, rather than maintaining, the paranoid delusional state of schizophrenia as well as MAP psychosis.

References

Akiyama, K., Sato, M., and Otsuki, S. Increased ^{3}H-spiperone binding sites in mesolimbic area related to methamphetamine-induced behavioral hypersensitivity. *Biol. Psychiatry*, 17:223–231, 1982.

Antelman, S.M., and Chiodo, L.A. Dopamine autoreceptor subsensitivity. *Biol. Psychiatry*, 16:717–727, 1981.

Connell, P.H. *Amphetamine Psychosis*. Oxford University Press, New York, 1958, pp. 75–76.

Janowski, D.S., and Davis, J.B. Methylphenidate, dextroamphetamine, levamphetamine effects on schizophrenic symptoms. *Arch. Gen. Psychiatry*, 28:185–191, 1976.

Kajita, S., Fujiwara, Y., Sato, M., et al. Changes in brain TRH systems in rats treated by chronic methamphetamine [in Japanese]. *Bull. Jpn. Neurochem. Soc.*, 24:454–458, 1985.

Robinson, T.E., Becker, J.B., Moore, C.J., et al. Enduring enhancement in frontal cortex dopamine utilization in animal model of amphetamine psychosis. *Brain Res.*, 343:374–377, 1985.

Sato, M., Chen, C-C., Akiyama, K., et al. Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biol. Psychiatry*, 18:429–440, 1983.

Tatetsu, S., Goto, A., and Fujiwara, T. *The methamphetamine-psychosis* [in Japanese]. Igaku Shoin Ltd, Tokyo, 1956, pp. 214–219.

Reverse Tolerance to the Ambulation-Increasing Effect of Methamphetamine in Mice as an Animal Model of Amphetamine-Psychosis

Sakutaro Tadokoro, M.D., Ph.D.,[1] and
Hisashi Kuribara, Ph.D.[1]

Amphetamine Abuse in Japan

Before World War II, serious drug-abuse problems had been seen rarely in Japan. However, immediately after the end of the war in 1945, the country experienced an amphetamine abuse epidemic. In 1955, it was estimated that approximately 2 million people abused amphetamines (mainly methamphetamine) and that 200,000 people showed mental disorders, namely amphetamine-psychosis (Tatetsu et al., 1956; Snyder, 1974). This first prevalence period was almost completely suppressed in 1958 by legal regulation, and only a few abusers were observed until 1970.

However, beginning 15 years ago (1970), methamphetamine abuse has made a comeback in Japan, and the number of abusers arrested has progressively increased (the second prevalence period). According to an official report of the Japanese Ministry of Welfare and Public Health in 1985, more than 20,000 methamphetamine abusers have been arrested annually since 1980. These data suggest that approximately 400,000 to 500,000 people may abuse methamphetamine in Japan. Simultaneously, various types of criminal cases, including indiscriminant homicide, have been linked to methamphetamine abuse.

Figure 1 shows the trend in the number of methamphetamine abusers arrested annually since the regulation law went into effect in 1951. The first and second prevalence periods of abuse are clearly demonstrated.

Problems of Amphetamine Abuse

The problems of amphetamine abuse divide mainly into two categories. The first is based on the circulation network of the drugs, mainly methamphetamine. In general, the drug is illegally produced and imported through Korean, Taiwanese, and other Southeast Asian routes, and the black-marketing is controlled mainly by gangster groups (Yakuza or Boryoku). Furthermore, all abusers know that even the possession of the drug is completely illegal; therefore, it is extremely difficult to remove the drug from the black market, and dissuade the abusers from self-administration.

The second category is based on its pharmacologic properties. The problems of amphetamine abuse are not based on drug-taking behavior itself, but rather on the psychotoxic effect of the drug, which induces paranoid-hallucinatory schizophrenia-like symptoms (amphetamine-psychosis) (Tatetsu et al., 1956; Snyder, 1974). It has been considered that amphetamine-psychosis is frequently induced by repeated abuse of amphetamines, i.e., showing a reverse tolerance (sensitization or supersensitivity). In contrast, a tolerance to the euphorogenic effect, which is the main reinforcing effect of amphetamine abuse, is easily induced (Yanagita, 1980). This results in an increase in dosage, frequency, and number of abuses, and simultaneously accelerates the development of amphetamine-psychosis. It has been suggested that schizophrenia-like symptoms appear in about half of the people who have abused daily (30 to 100 mg of amphetamines) for 2 to 3 months (Tatetsu et al., 1956). Moreover, the reverse tolerance to the psychotoxic effect, once produced, persists for a long period, and frequently causes an acute exacerbation of the schizophrenia-like symptoms (Sato et al., 1983).

---

[1] Division for Behavior Analysis, Behavior Research Institute, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi 371 Japan.

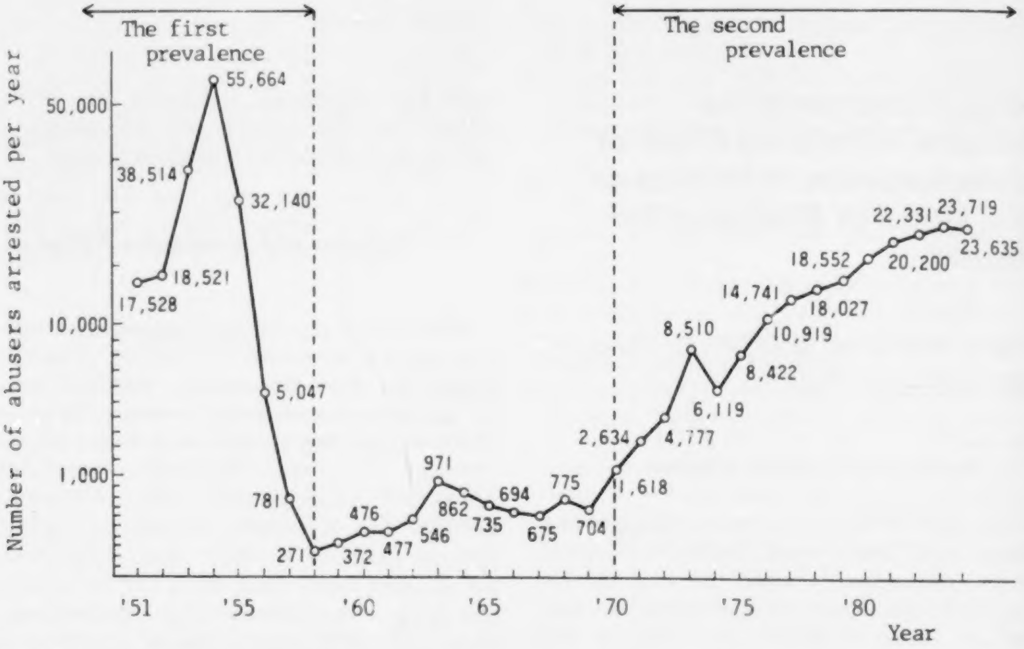


FIGURE 1. Trend of amphetamine abusers arrested annually in Japan since 1951.

In these clinical respects, it is important to study the behavioral effects of amphetamines not only after single but also after repeated administration, in particular concerning reverse tolerance phenomena.

Reverse Tolerance to Amphetamines in Animals

When amphetamines are administered to mice and/or rats, they show a hyperactivity (marked increase in compulsive ambulation or locomotion), and stereotypy such as sniffing, licking, gnawing, backward locomotion, pivotting, etc., depending on the doses administered. Since such behavioral effects of amphetamines have been considered to be intimately related with psychotoxic effects of these drugs in humans, reverse tolerance phenomena to the behavioral effects have been extensively investigated in animals (cf. Kilbey and Sannerud, 1985). In particular, study of the stereotypy-producing effect of comparatively higher doses of amphetamines has been carried out. Although it is difficult to estimate the doses abused in human cases, the usual amount of methamphetamine abused in Japan is considered to be less than 1 mg/kg according to the official report of the Japanese Ministry of Welfare and Public Health. Therefore, the authors have mainly studied the reverse tolerance phenomena to the ambulation-increasing effect of relatively smaller doses of amphetamines in mice. This is because the ambulatory activity and stereotypy shift depending on the doses (Tadokoro, 1985). Furthermore, the ambulatory activity can be measured quantitatively, automatically, and continuously.

Figure 2 shows temporal changes in the ambulatory activity counts after administration of 1 to 16 mg/kg s.c. of methamphetamine in drug-naive mice (Hirabayashi and Alam, 1981). The ambulatory activity of mice was individually measured by a tilting-type ambulometer (Model AM-10; O'Hara & Co. Ltd., Tokyo) which had been assembled originally in the authors' laboratory (Hirabayashi et al., 1978).

Low doses of methamphetamine (1 to 4 mg/kg) increase the ambulatory activity in a dose-dependent manner, whereas no marked stereotypy is observed at these doses. The

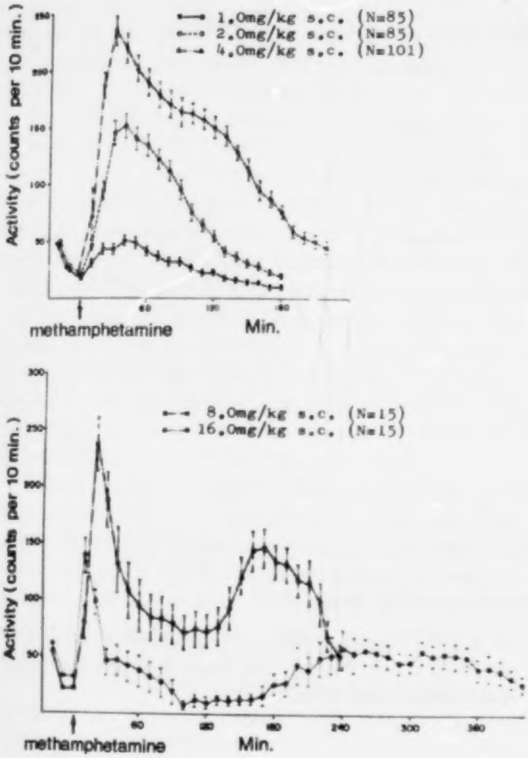


FIGURE 2. Temporal changes in the mean ambulatory activity counts after administration of methamphetamine (1, 2, 4, 8, and 16 mg/kg s.c.) in drug naive mice.

ambulation-increasing effect of methamphetamine attains a peak at 40 to 60 min and persists for 2 to 4 hr after the administration as shown in the upper panel of Figure 2. The behavioral effect of methamphetamine is somewhat stronger than that of *d*-amphetamine. When 8 and 16 mg/kg of methamphetamine are administered, the mice frequently show stereotypy, and the rate of occurrence and the grade of the stereotypy increase in a dose-dependent manner. Since the stereotypy strongly modifies the ambulatory activity, the temporal change in the activity shows irregular patterns at high dosage as demonstrated in the lower panel of Figure 2. Therefore, doses of less than 4 mg/kg have to be used to study reverse tolerance phenomena to the ambulation-increasing effect of methamphetamine in mice.

Figure 3 shows dose-response relations after repeated administration (10 times) of methamphetamine (1, 2 and 4 mg/kg s.c.) at intervals of 1, 3 to 4, and 7 days (Kuribara and Hirabayashi, 1985). The mean overall ambulatory activity counts during a 3 hr observation period in the 1st, 3rd, 5th, 7th, and 10th administration are presented. The ambulatory activity counts progressively increase according to the repetition of the drug administration, showing a development of reverse tolerance to methamphetamine.

Since such reverse tolerance to methamphetamine in animals is similar to enhancement of psychotoxicity of the drug in humans, it is expected that it will be possible to find the basic mechanism of the reverse tolerance to the psychotoxic effect as well as its clinical therapy from the animal studies. The following sections present characteristics of the reverse tolerance to the ambulation-increasing effect of methamphetamine in mice obtained in the authors' laboratory.

1) Doses and Administration Intervals

As demonstrated in Figure 3, there is an optimum dose necessary to observe a clear reverse tolerance to the ambulation-increasing effect of methamphetamine. Two mg/kg s.c. is considered to be optimum in mice.

Administration intervals strongly affect development of the reverse tolerance. For example, repeated administration of *d*-amphetamine at short intervals (e.g., 3-hr intervals) rarely produces a clear reverse tolerance to the ambulation-increasing effect, but rather a tolerance to the effect (characterized by a decline in the duration of the drug effect) is sometimes observed during repeated administration (Tadokoro, 1978). This type of tolerance may be due to an increase in a urinary excretion of the drug resulting from acidification of the urinary pH level which is induced by anorexia (Schuster, 1978). However, a reverse tolerance to *d*-amphetamine is produced in these mice when the drug is readministered 24 hr (or later) after the repeated administration (Tadokoro, 1978).

When the optimum dose of methamphetamine is repeatedly administered at intervals of longer than 1 day, reverse tolerance is induced. However, as demonstrated in Figure 3, the ambulatory activity count attains a ceiling level within several administrations when

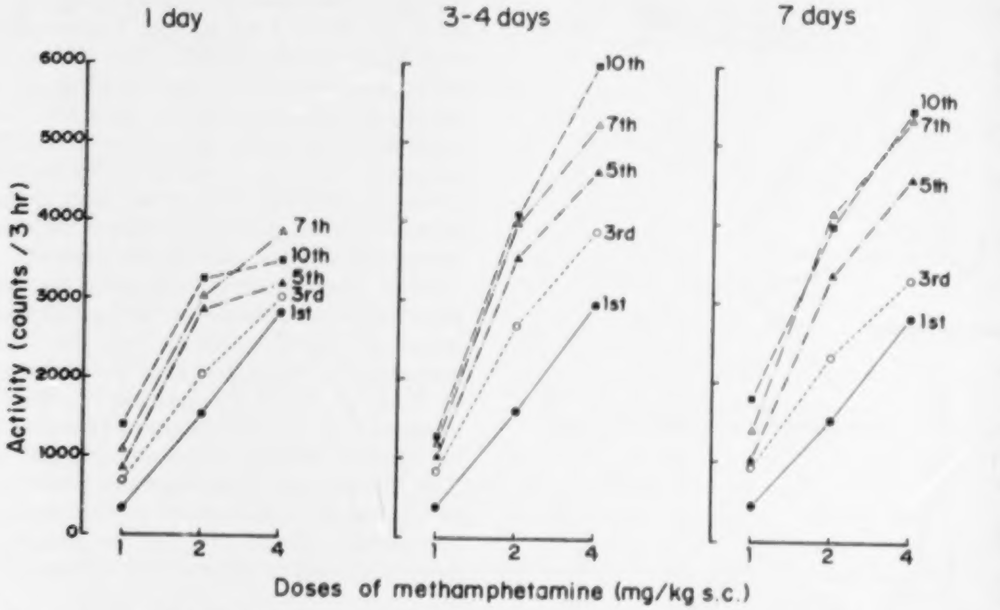


FIGURE 3. Changes in the dose-response curves for the ambulation-increasing effect of methamphetamine (1, 2, and 4 mg/kg s.c.) administered 10 times to mice at intervals of 1, 3 to 4, and 7 days. The mean overall ambulatory activity counts of 30 to 40 mice in the 1st, 3rd, 5th, and 10th administration are plotted.

the repetition is carried out at intervals of 1 day. In contrast, the counts progressively increase throughout the repetition of 10 administrations when the drug administration is done at intervals of 3 to 4 and 7 days. Of course, the activity counts finally attained are higher in the cases of 3 to 4 and 7 days repetition than in the daily repetition.

2) Irreversibility

The reverse tolerance to the ambulation-increasing effect of methamphetamine once produced is maintained for more than 2 months (Hirabayashi and Alam, 1981). The result may be related to the clinical observation that the schizophrenia-like symptoms are easily exacerbated by a readministration of methamphetamine even after withdrawal from drug abuse for several years (Sato et al., 1983).

On the other hand, the development of the reverse tolerance to the ambulation-increasing effect of *d*-amphetamine or methamphetamine is inhibited by a combined administration of antipsychotic drugs such as chlorpromazine or haloperidol in a dose-dependent manner (Tadokoro, 1978; Kuribara and Hirabayashi, 1985). However, the reverse tolerance once produced is not affected by antipsychotic drugs when they are administered repeatedly thereafter (Kuribara et al., 1986).

3) Environmental Effects

The development of reverse tolerance to the ambulation-increasing effect of methamphetamine is strongly affected by environmental situations to which the mice have been exposed during the acute drug exposure. Mice pretreated with repeated administration of methamphetamine in a glass jar (less than 9 cm in diameter), in which the ambulatory movement but not vertical movement is perfectly obstructed, for 3 hr after each drug administration, do not show the reverse tolerance to the ambulation-increasing effect (Hirabayashi and Alam, 1981). In order to produce a clear reverse tolerance, mice have to be exposed to an experimental situation that allows free movement, a diameter of more than 16 cm, which corresponds to 3 times the body length of the mouse (Kuribara and Hirabayashi, 1985).

Furthermore, when a flickering light is presented to the mice during the presence of acute drug effect as a conditioned stimulus, the reverse tolerance tends to be accelerated as compared with that observed in the mice without the flickering light (Hayashi et al., 1980). In addition, the mice that exhibited the reverse tolerance to *d*-amphetamine frequently show an increase in the ambulatory activity when physiological saline is administered, even though the increase persists only for a short time (less than 10 min) (Hayashi et al., 1980).

These results suggest that conditioning of the drug effect is involved in the development of reverse tolerance to the ambulation-increasing effect of amphetamines as emphasized by Kilbey and Sannerud (1985). It is highly probable that such a conditioning mechanism is also involved in the development of amphetamine-psychosis as well as an acute exacerbation and/or the flashback phenomenon in humans.

4) Circadian Variation

There is circadian variation in the sensitivity of mice to the ambulation-increasing effect of methamphetamine; the highest and lowest sensitivities are observed during the late dark and late light periods, respectively (Kuribara and Tadokoro, 1982). The reverse tolerance to methamphetamine is induced almost independently of time of day of repeated administration, and the circadian variation in the drug sensitivity is still maintained (Kuribara and Tadokoro, 1984a).

5) Strain Differences

Sensitivity to the ambulation-increasing effect of methamphetamine differs among strains of mice. The dd, ICR, DBA/2, and C3H/He strains show a comparatively higher sensitivity, and they exhibit a clear reverse tolerance after repeated administration of the drug. Although the BALB/c and C57BL/6 strains show a lower sensitivity to methamphetamine, they also exhibit the reverse tolerance (Kuribara and Hirabayashi, 1985). Recent investigation in the authors' laboratory indicates marked differences in the catecholamine receptor binding sites in the brain (e.g., striatum and cortex) among these strains (Hayashi et al., unpublished data).

The strain differences might be important in relation to individual differences in drug sensitivity in humans. However, the present results also suggest that amphetamine-psychosis is induced in all abusers.

6) Cross Reverse Tolerance

Other drugs such as cocaine, methylphenidate, ephedrine, apomorphine, L-dopa, bromocriptine, morphine, etc., increase ambulatory activity in mice. Repeated administration of these drugs produces a reverse tolerance to the ambulation-increasing effect when optimum doses are administered (Kuribara and Hirabayashi, 1985). The mice that exhibited reverse tolerance to these drugs sometimes show an increase in sensitivity to amphetamines, and vice versa, showing a cross reverse tolerance (Kuribara and Hirabayashi, 1985).

In addition, although repeated treatment with scopolamine and toluene induces tolerance to their ambulation-increasing effect, the mice exposed to these drugs demonstrate an increase in the sensitivity to methamphetamine (Kuribara and Tadokoro, 1984b, 1984c).

These results suggest the possibility that amphetamine abusers use such drugs as substitutes for amphetamines, and vice versa, and that amphetamine-psychosis may be induced and/or exacerbated by these drugs.

7) Neurochemical Changes

It has been reported that repeated administration of high doses of amphetamines decreases monoamine and their metabolite contents and causes changes in presynaptic dopamine autoreceptor binding sites in the brain for a long period even after withdrawal (cf. Kilbey and Sannerud, 1985). However, the neurochemical changes are considered to be insufficient to explain the process of reverse tolerance to the ambulation-increasing effect at low amphetamine dosage. Study of the correlation between amphetamine-induced neurochemical changes and reverse tolerance in the same experimental situation on the same animals could clarify these observations.

Conclusion

In this paper. the authors demonstrated the reverse tolerance phenomenon to ambulation-increasing effect of amphetamines in mice using behavioral pharmacologic models. The main characteristics are: 1) an enhancement of the behavioral effect, 2) long persistence, and 3) easy reproducibility by readministration. It is considered that these characteristics are quite similar to the development of amphetamines-induced psychotoxicity during repeated abuse of the drugs in humans. Since the ambulatory activity of mice can be measured quantitatively and continuously with an automatic apparatus, reverse tolerance to the ambulation-increasing effect of amphetamines in mice is a useful tool to study amphetamine-psychosis.

References

Hayashi, T., Ohashi, K., and Tadokoro, S. Conditioned drug effects to *d*-amphetamine- and morphine-induced motor acceleration in mice: Experimental approach for placebo effects. *Jpn. J. Pharmacol.*, 30:93–100, 1980.

Hirabayashi, M., Iizuka, M., and Tadokoro, S. Simple and easy method for measurement of ambulatory activity in mice. *Folia Pharmacol. Japon.*, 74:629–639, 1978 (abstract English, text Japanese).

Hirabayashi, M., and Alam, M.R. Enhancing effect of methamphetamine on ambulatory activity produced by repeated administration in mice. *Pharmacol. Biochem. Behav.*, 15:925–932, 1981.

Kilbey, M.M., and Sannerud, C.A. Models of tolerance: Do they predict sensitization to the effects of psychomotor stimulants? In: Seiden, L.S., and Balster, R.L. (eds.), *Behavioral Pharmacology: The Current Status.* New York: Alan R. Liss, Inc., 1985, pp. 295–321.

Kuribara, H., and Tadokoro, S. Circadian variation in methamphetamine- and apomorphine-induced increase in ambulatory activity in mice. *Pharmacol. Biochem. Behav.*, 17:1251–1256, 1982.

Kuribara, H., and Tadokoro, S. Circadian variation in susceptibility to methamphetamine after repeated administration in mice. *Pharmacol. Biochem. Behav.*, 20:247–250, 1984a.

Kuribara, H., and Tadokoro, S. Effects of scopolamine on reverse tolerance to ambulation-increasing effect of methamphetamine in mice. *Jpn. J. Pharmacol.*, 36(Suppl.):160p, 1984b.

Kuribara, H., and Tadokoro, S. Changes in sensitivity to ambulation-increasing effect of methamphetamine after exposure to toluene vapor in mice. *Jpn. J. Alcohol and Drug Dependence*, 19:193–204, 1984c.

Kuribara, H., and Hirabayashi, M. Reverse tolerance to psychotropic drugs. *Jpn. J. Neuropsychopharmacol.*, 7:421–439, 1985. (In Japanese)

Kuribara, H., Asami, T., and Tadokoro, S. Effects of haloperidol and pilocarpine, and of an experimental situation on reverse tolerance to the ambulation-increasing effect of methamphetamine in mice. *Jpn. J. Psychopharmacol.*, 6:127–128, 1986. (In Japanese)

Sato, M., Chen, C.-C., Akiyama, K., and Otsuki, S. Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biol. Psychiatry*, 18:429–440, 1983.

Schuster, C.R. Theoretical basis of behavioral tolerance: Implication of the phenomenon for problems of drug abuse. In: Krasnergor, N.A. (ed.), *NIDA Research Monograph 18.* Washington, D.C.: U.S. Government Printing Office, 1978, pp. 4–17.

Snyder, S.H. *Madness and the Brain.* New York: McGraw-Hill Book Co., 1974.

Tadokoro, S. Environments and drug effects. In: Shimoda, S. (ed.), *Environment and Adaptation, Responses of Organisms to Stress.* Tokyo: Hirokawa Pub. Co., 1978, pp. 19–27. (In Japanese)

Tadokoro, S. Stereotyped behaviors in mice and rats. *Jpn. J. Psychopharmacol.*, 5:63–64, 1985. (In Japanese)

Tatetsu, S., Goto, A., and Fujiwara, T. *The Methamphetamine-Psychosis.* Tokyo: Igaku Shoin Ltd., 1956. (In Japanese)

Yanagita, T. Drug dependence and behavior. In: Yamamura, Y. (ed.), *Behavior: Physiological and Medical Basis.* Tokyo: Nakayama Book Co., 1980, pp. 937–943. (In Japanese)

Psychotic Manifestations in Amphetamine Abuse—Experimental Study on the Mechanism of Psychotic Recurrence

Kiyoshi Ando, Ph.D.,[1] Naoyuki Hironaka, M.A.,[1] and Tomoji Yanagita, M.D., Ph.D.[1]

Amphetamine psychosis is usually developed with repeated administration of amphetamines at high doses. Following termination of the amphetamine administration, recurrence of the psychotic symptoms may be observed after a single dose of amphetamine, after taking some other drug such as alcohol, or seemingly triggered by some other undetermined event.

The mechanisms involved in such recurrence, flashback, or supersensitivity to amphetamine in humans are not well understood. On the other hand, there exists considerable evidence that repeated administration of amphetamine to rats and mice also produces increased sensitivity to amphetamine (Hayashi, Ohashi, & Tadokoro, 1980; Segal & Mandell, 1974). It was also reported that increased sensitivity to amphetamines as observed in rat motor activity, may be attributable to respondent, or Pavlovian conditioning of the activity to the environmental stimuli associated with the amphetamine-injection procedure (Beninger & Hahn, 1983; Pickens & Crowder, 1967; Tilson & Rech, 1973). However, no studies so far seem to have addressed the question of conditioning of amphetamine effects by non-amphetamine drugs using a respondent conditioning paradigm in laboratory animals.

The purpose of our study was to examine whether the behavioral effects of amphetamines were conditioned by other drugs in laboratory animals and whether the data obtained by the animals give the basis for understanding the mechanisms of psychotic manifestations in amphetamine abuse.

Method

Experiment 1. Conditioning of the effects of *d*-amphetamine on spontaneous motor activity by other drugs in mice.

Spontaneous motor activity of male ICR mice was measured by an activity count system (Automex, Columbus Instruments, Ohio). Upon receiving the mice, they were randomly divided into three groups of eight mice per group according to the drugs paired with *d*-amphetamine at 2 mg/kg, administered subcutaneously (s.c.), in the conditioning sessions. Before the conditioning sessions were started, the spontaneous motor activity of the mice of each group was observed for 1 h before and for 2 h after administration of saline 10 ml/kg, s.c. Three or four days after the saline administration test, the drug to be paired with *d*-amphetamine at 2 mg/kg, s.c., was tested by the subcutaneous route in the same manner as in the saline administration test. The drugs to be paired with *d*-amphetamine at 2 mg/kg, s.c., were pentobarbital 8 mg/kg for pentobarbital group, caffeine 6 mg/kg for caffeine group, and *d*-amphetamine 0.25 mg/kg (to be distinguished from the main dose at 2 mg/kg) for *d*-amphetamine group each administered subcutaneously. After the above tests, conditioning sessions were started. In conditioning sessions, activity counts were measured in the same manner as before; however, depending on the group, either pentobarbital, caffeine, or the *d*-amphetamine at above described doses was administered by the subcutaneous route. Five min after the administration of one of the paired drugs, *d*-amphetamine 2 mg/kg, s.c., was administered, and immediately after this administration, the activity counts were measured for 2 h. This kind of conditioning session was given two times per week, with contiguous sessions separated by 3 to 4 days. After nine conditioning sessions, test sessions were given in the same manner except that either saline at 10 ml/kg, s.c., pentobarbital at 8 mg/kg, caffeine 6 mg/kg, or *d*-amphetamine at 0.25 mg/kg was administered regardless of group, and 5 min after the administration, saline 10 ml/kg, s.c., was administered instead of *d*-amphetamine 2 mg/kg, s.c. Each test session was repeatedly given between conditioning sessions with at least one conditioning session before each test session. Relative activity counts were obtained as the percent ratio of activity counts during 1 h after administrations against the values for 1 h before administrations.

---

[1] Preclinical Research Laboratories, Central Institute for Experimental Animals, 1433, Nogawa, Miyamaeku, Kawasaki 213 Japan.

Experiment 2. Conditioning of the effects of methamphetamine on schedule controlled behavior by imipramine and external stimuli in rats.

Male Sprague-Dawley rats were used. Daily food was limited to 18 g per rat and water was freely available in home cages and during experimental sessions in operant chambers.

Responding was established under a differential reinforcement of low rate (DRL) 20-sec schedule where each lever press response that was followed by no less than 20 sec of nonresponding timed at least 20 sec was reinforced with a food pellet (50 mg). After establishment of responding under this schedule, rats were divided in two groups, an experimental and a control group. In the experimental group ($N = 5$), conditioning sessions and baseline sessions were given. In the conditioning sessions, imipramine 2 mg/kg, s.c., was administered after observation of responding under this schedule for 1 h. Methamphetamine 0.5 mg/kg, s.c., was administered 5 min after the imipramine administration, and then responding under the DRL schedule was observed for 1 h. During the 1-h sessions, synchronized presentations of interrupted buzzer sounds and lights (0.5 sec on and 1 sec off) were made in the operant chamber. The buzzer sounds and lights (external stimuli) were given during 1-min periods separated by 1-min time-out intervals of the presentation of the external stimuli. Such conditioning sessions were given twice a week for several weeks. In baseline sessions which were given three times a week on nonconditioning session days during the same period, responding under the DRL schedule was maintained and observed for 2 h without any administration or presentation of the external stimuli. After nine conditioning sessions, conditioning sessions and baseline sessions were given in the same manner, but test sessions were given on one of the conditioning session days of each week. Test sessions were conducted in the same manner as the conditioning sessions except that methamphetamine was not administered and one of the components, i.e., imipramine administration or the external stimuli, was removed or changed. In the control group ($N = 6$), the baseline sessions and control sessions were given in the same manner as in the experimental group. The control sessions were the same as the conditioning sessions except that saline 1 ml/kg, s.c., was administered instead of methamphetamine 0.5 mg/kg, s.c. The test sessions in the control group were given in the same manner as in the experimental group.

The data were number of responses during post-administration 30 min or comparable period in the baseline sessions.

Results

Experiment 1. Conditioning of the effects of *d*-amphetamine on spontaneous motor activity by other drugs in mice.

Figure 1 shows the change in mean percent activity counts before, during, and after conditioning sessions in the caffeine group.

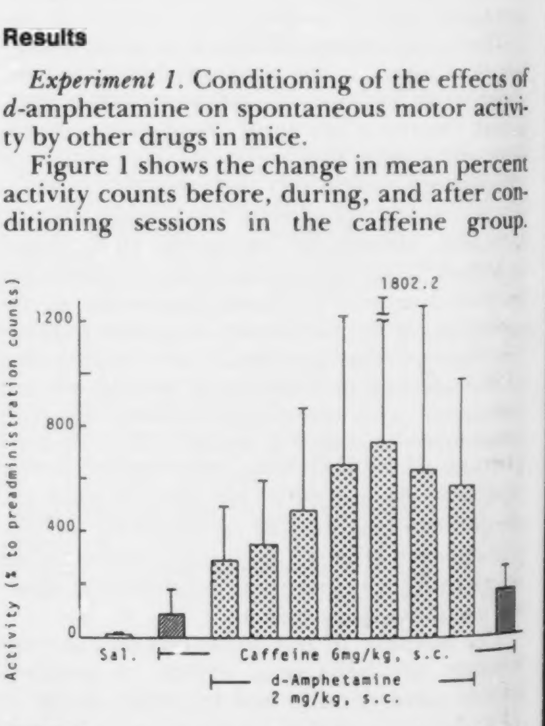


FIGURE 1. Mean percent activity counts with standard deviation for 1 h after administrations before, during, and after conditioning sessions in caffeine group mice ($N = 8$).

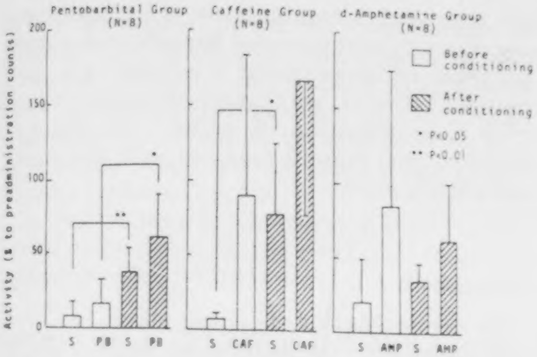


FIGURE 2. Mean percent activity counts with standard deviation in mice 1 h after administrations in tests before and after conditioning sessions in each group. S: Saline 10 ml/kg, s.c. PB: Pentobarbital 8 mg/kg, s.c. CAF: Caffeine 6 mg/kg, s.c. AMP: *d*-Amphetamine 0.25 mg/kg, s.c.

Before conditioning, the counts with saline were relatively low and the counts with caffeine 6 mg/kg, s.c., were higher than with saline. The counts increased with caffeine 6 mg/kg, s.c., and *d*-amphetamine 2 mg/kg, s.c., during conditioning. In a test with caffeine 6 mg/kg, s.c., without *d*-amphetamine after conditioning, the counts were higher than those with caffeine before conditioning. In the other two groups, the changes in counts were basically similar to those of the caffeine group; that is, the counts were highest in conditioning sessions and lowest in sessions with saline before conditioning.

Figure 2 shows the mean percent activity counts before and after conditioning sessions for each group. In the pentobarbital group, the activity counts with saline and with pentobarbital at 8 mg/kg in the tests after conditioning were significantly higher than those before the conditioning. In the caffeine group, caffeine 6 mg/kg, s.c., alone increased activity counts before conditioning. After conditioning, the counts with saline and with caffeine were higher than before conditioning. The increase with caffeine after conditioning was not significantly different from the counts with caffeine before conditioning, because of high variability in the counts with caffeine. In the *d*-amphetamine group, *d*-amphetamine at 0.25 mg/kg, s.c., alone increased activity counts but the counts with *d*-amphetamine at that dose after conditioning were not higher than before conditioning.

In other tests given after conditioning, each group received not only the designated paired drug but also the paired drugs used in the other groups. As shown in Table 1, the activity counts were highest with caffeine at 6 mg/kg, s.c., in the caffeine group as well as in the other groups after conditioning. Thus, the counts were not highest with the designated paired drug in the pentobarbital and *d*-amphetamine groups.

Experiment 2. Conditioning of the effects of methamphetamine on schedule controlled behavior by imipramine and external stimuli in rats.

Figure 3 shows the changes in the number of responses for 30 min after administrations in the experimental group. Imipramine 2 mg/kg, s.c., did not significantly increase the numbers of responses with the external stimuli in comparison with the numbers in the baseline sessions before conditioning. The number of responses increased with the addition of methamphetamine 0.5 mg/kg, s.c. After nine conditioning sessions, the number of responses in a test session with imipramine 2 mg/kg, s.c., and with the external stimuli but without methamphetamine were significantly higher than the number in the baseline ses-

TABLE 1. Mean Percent Activity Counts of Mice With Standard Deviation in Tests With Cross Drugs Given After Conditioning Sessions.

Group	Test Drug			
	SAL 10 ml/kg	CAF 6 mg/kg	PB 8 mg/kg	AMP 0.25 mg/kg
CAF	77.5 + 47.5	166.3 + 89.4	64.2 + 60.8	104.2 + 79.5
PB	37.3 + 16.6	125.2 + 67.7**	61.0 + 29.7*	75.3 + 37.3
AMP	34.5 + 21.4	137.0 + 61.7**	56.3 + 18.5*	61.7 + 37.6

SAL: Saline, CAF: Caffeine, PB: Pentobarbital, AMP: *d*-Amphetamine
*: $p < 0.05$ vs. saline, **: $p < 0.01$ vs. saline.

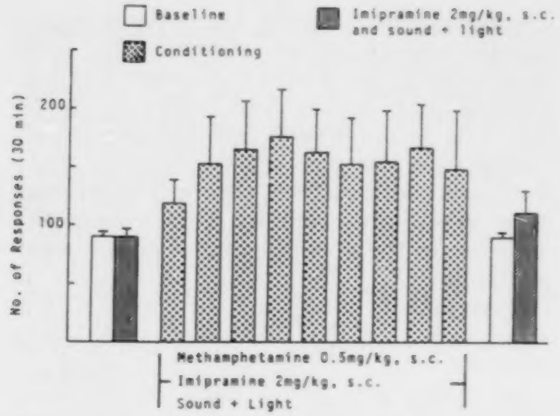


FIGURE 3. Mean number of responses with standard deviation for 30 min before, during, and after conditioning sessions in the experimental group. The mean number of responses in the baseline sessions given between each pair of conditioning sessions is not shown in this figure.

sion immediately prior to the test session and the number in a session with imipramine and the external stimuli before conditioning. In the control group, no changes in the numbers of responses compared with the baseline sessions were observed, and the numbers in the control sessions and baseline session were stable throughout the experiment.

The results of the tests given after conditioning are shown in Table 2. The number of responses were compared between the control and experimental groups and were statistically tested in various tests. The mean number of responses in the experimental group was higher than that in the control group in the tests with a combination of imipramine 2 mg/kg, s.c., and external stimuli, with a combination of imipramine 2 mg/kg, i.p., and external stimuli, with imipramine alone, and with a combination of saline 1 ml/kg, s.c., and external stimuli, but not with the external stimuli alone.

Discussion

In the context of the respondent conditioning paradigm, the effects of amphetamines may be considered as unconditioned stimuli with the other stimuli associated with amphetamine administration serving as conditioned stimuli, if it can be shown that the stimuli alone without amphetamine produce effects similar to those of amphetamines. In experiment 1, repeated administration of *d*-amphetamine with a paired drug produced increased activity like that reported in the case of repeated administration of amphetamine alone (Hayashi et al., 1980; Segal & Mandell, 1974). Since activity counts in three groups with saline after conditioning increased to a greater extent than before conditioning, it may be considered that the injection procedure and/or environmental stimuli served as conditioned stimuli in increasing the activity counts. Both pentobarbital and caffeine alone increased activity counts after conditioning in the respective drug groups. This fact may indicate that the pharmacological effects of these drugs have cueing effects in increasing activity counts, although the possibility of cross sensitization between *d*-

TABLE 2. Mean Number of Responses of Rats With Standard Deviation Under Differential Reinforcement of Low Rate Schedule.

Session	Combination of Pairing	Number of Responses during 30-min Period	
		Control Group ($N = 6$)	Experimental Group ($N = 5$)
Baseline	No Injection and No External Stimuli	90.0 + 7.5	89.6 + 3.9
Pairing	IMP 2 mg/kg, s.c., Saline 1 ml/kg, s.c., External Stimuli	83.3 + 4.9	—
	IMP 2 mg/kg, s.c., MA 0.5 mg/kg, s.c., External Stimuli	—	147.6 + 50.0
Test	IMP 2 mg/kg, s.c., External Stimuli	87.3 + 7.4	103.2 + 2.7*
	IMP 2 mg/kg, i.p., External Stimuli	80.7 + 4.7	94.2 + 8.5**
	IMP 2 mg/kg, s.c.	80.5 + 8.3	93.4 + 7.7*
	Saline 1 ml/kg, s.c., External Stimuli	86.0 + 3.3	96.2 + 1.9**
	External Stimuli	86.0 + 6.4	93.0 + 1.5

IMP: imipramine, MA: methamphetamine, External Stimuli: sound and light stimuli.
*: $p < 0.05$ vs. control group, **: $p < 0.01$ vs. control group.

amphetamine and the paired drugs cannot be excluded. According to the results of the cross tests, caffeine increased activity counts after conditioning regardless of the group. This increase seems to generalize from one drug to the other, but the rule for the generalization remains unclear.

In experiment 2, the increase in the number of responses with the combination of imipramine plus external stimuli and without methamphetamine may indicate that the combination of the stimuli served as a conditioned stimulus, although cross sensitization may be a factor. Administration of either imipramine or saline played a more important role in increasing the number of responses than did the external stimuli, because the external stimuli alone failed to increase the number of responses.

In summary, a possible mechanism by which the behavioral effects of amphetamines may be conditioned by other drugs is worth considering. The findings in the present study suggest that the recurrence of amphetamine psychosis can be developed by a respondent conditioning mechanism being triggered by other drugs.

References

Beninger, R.J., and Hahn, B.L. Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. *Science*, 220:1304–1306, 1983.

Hayashi, T., Ohashi, K., and Tadokoro, S. Conditioned drug effects to *d*-amphetamine- and morphine-induced motor acceleration in mice: Experimental approach for placebo effect. *Japan. J. Pharmacol.*, 30:93–100, 1980.

Pickens, R., and Crowder, W.F. Effects of CS-US interval on conditioning of drug response, with assessment of conditioning. *Psychopharmacologia*, 11:88–94, 1967.

Segal, D.S., and Mandell, A.J. Long-term administration of *d*-amphetamine: Progressive augmentation of motor activity and stereotypy. *Pharmac. Biochem. and Behav.*, 2:249–255, 1974.

Tilson, H.A., and Rech, R.H. Conditioned drug effects and absence of tolerance to *d*-amphetamine induced motor activity. *Pharmac. Biochem. and Behav.*, 1:149–153, 1973.

Visual Perception Process in Amphetamine Psychosis and Schizophrenia[1]

Takuya Kojima, M.D.,[2,3] Eisuke Matsushima, M.D.,[3] Hisayuki Iwama, M.D.,[3] Harunobu Ando, M.D.,[3] Hirobumi Moriya, M.D.,[3] Katsumi Ando, M.D.,[3] Ryo Takahashi, M.D.,[3] and Yasuo Shimazono, M.D.[4]

In daily practice, the facial expression and eye movements of patients are observed to understand the mental state. In order to observe the eye movements of psychotic patients while viewing a picture we have utilized an eye mark recorder. In the previous study (Moriya et al., 1979; Ando et al., 1979) it was reported that chronic schizophrenics and their relatives had less frequent eye movements and a more limited area of inspection than normal controls. The result suggested that eye movements could be considered as a marker for susceptibility for schizophrenia.

Amphetamine psychosis and schizophrenia are very similar symptomatically. The flashback phenomenon of amphetamine psychosis may give us valuable information concerning relapse of schizophrenia. Therefore, we compared the eye movements of amphetamine psychosis with schizophrenia and examined the difference in visual perception process between both psychoses.

Subject and Method

Twenty-eight methamphetamine psychotics, 30 chronic schizophrenics, and 30 normal controls were examined. The two patient groups were on neuroleptic medication. All amphetamine psychotics showed delusion at the time of admission to the hospitals. The amphetamine psychotics were diagnosed by DSM-III criteria and a urine test positive for amphetamine. The chronic schizophrenics were inpatients of mental hospitals and were diagnosed by DSM-III criteria. Most of them were residual and disorganized type.

The subject was asked to sit in a chair 1.5 m in front of a screen and an eye-mark recorder was placed on his/her head. Three geometric figures were projected on the screen (the first and the other two partially different figures are shown in Figure 1). The width of the figure is 0.9 m on the screen and the angle of sight is 20 degrees. The eye movements and fixation points during perception of the figure were examined.

The test procedure is as follows:

1) Each subject was shown an "S"-shaped figure for 15 sec.

2) The subject was then asked to draw the picture immediately after viewing it.

3) Two other figures partially different from the original were then shown in turn for 15 sec. The subject was requested to look at the figures, comparing them with the original in order to answer the question, "Are there any differences between this figure and the first one?" After they finished answering, another question, "Are there any other differences?" was asked. These questions were asked for each figure.

4) The subject was then shown the original and told to look carefully at it in order to draw it again.

5) Finally, the subject was asked to draw the picture.

The eye-mark recorder consists of a helmet which is equipped with very small video cameras attached to the left and right sides of the helmet and another camera attached to the top of the helmet. The side cameras record

---

[1] This study was supported by a fund from the Ministry of Health and Welfare, Japan, and by Grant No. 85-9 from National Center for Nervous, Mental and Muscular Disorders (NCNMMD) of the Ministry of Health and Welfare, Japan.

[2] Psychiatry, UCI Medical Center, 101 City Drive South Rt. 88, Orange, CA 92668.

[3] Dept. of Neuropsychiatry, Tokyo Medical and Dental University, 5-45, Yushima 1-Chome, Bunkyo-ku, Tokyo 113 Japan.

[4] National Musashi Research Institute for Mental and Nervous Diseases, 4-1-1 Ogawa Higashi-Machi, Kodaira, Tokyo 187 Japan.

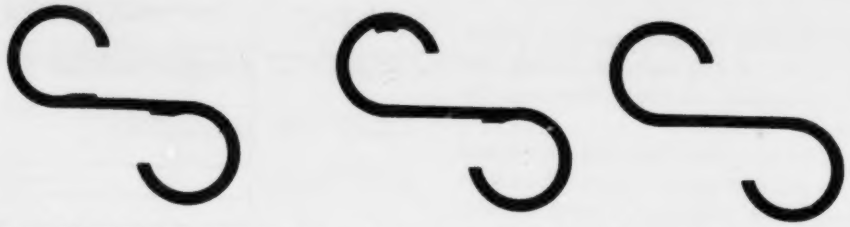


FIGURE 1. The original (left hand figure) and two other partially different figures were projected on the screen in turn.

the lights reflected on the eye balls. The camera on the top of the helmet records the figure on the screen. These three recordings are mixed into one and recorded on a videotape-recording system. This technique enables one to see the eye-fixation points and eye movements simultaneously on the figure. The recorded data are analyzed with a computerized analyzing system and slow motion replay of the video recorder.

Results

Figure 2 demonstrates the sequence of eye movements and fixations of an amphetamine psychotic patient, a schizophrenic patient, and a normal control during the first 5-sec viewing of the "S"-shaped figure. The number on the figure shows the order of eye fixations. The eyes moved less frequently and the moving range of the fixations was much more limited in the schizophrenic patient and amphetamine psychotic patient than in the normal control. The moving range of the fixations was also more limited in the schizophrenic patient than in the amphetamine psychotic patient.

Elementary Components of Eye Movements

The elementary components of eye movements consist of: number of eye fixations, eye-tracking length, and eye-fixation time. Eye-tracking length is the distance between two eye fixations. Eye-fixation time is the

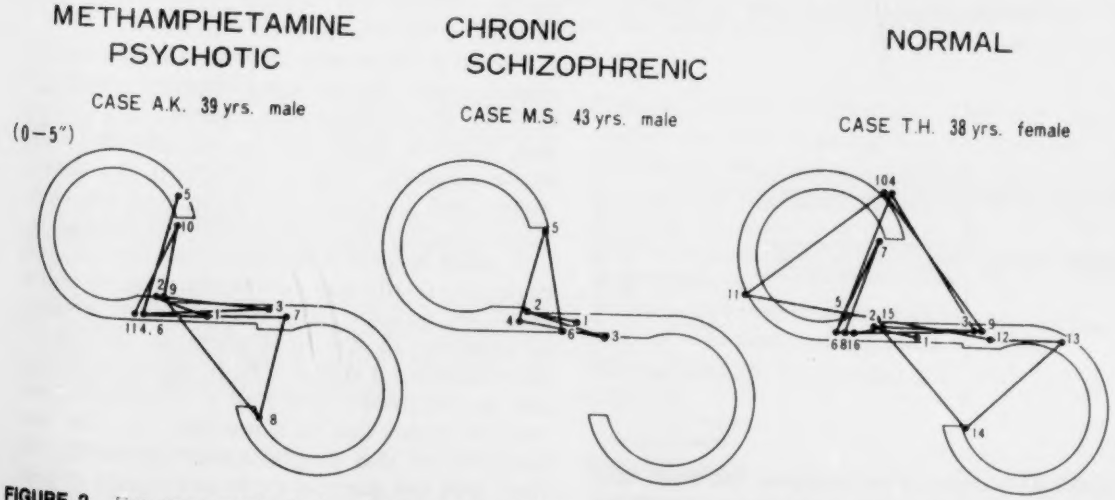


FIGURE 2. Eye movements during first 5 sec of viewing. The number on the figure shows the order of eye fixation. The eyes moved less frequently and the moving range of the fixations was much more limited in the schizophrenic and amphetamine psychotic patients than in the normal control. The moving range of the fixations was also more limited in the schizophrenic patient than in the amphetamine psychotic patient.

time that eyes remain focused on one point. These components of eye movements of the subjects were analyzed during viewing the original figure for 15 sec.

The number of eye fixations was measured (Figure 3). The mean number of eye fixations of the amphetamine psychotics and schizophrenics was less than that of normal controls ($p < .01$). There was no significant difference between amphetamine psychotics and schizophrenics.

The mean eye-fixation time of the amphetamine psychotics and schizophrenics was greater than that of normal controls ($p < .01$). There was no significant difference between amphetamine psychotics and schizophrenics.

Figure 4 shows the total eye-tracking length. The total eye-tracking length represents the combined eye-tracking length for 15 sec. The schizophrenics had shorter eye-tracking length than amphetamine psychotics ($p < .01$). The amphetamine psychotics also had shorter eye-tracking length than normal subjects ($p < .05$). Each group was significantly different from the other two groups.

From the results of components of eye movements, it was found that there was no difference in number of eye fixations and eye-fixation time between amphetamine psychotics and schizophrenics, but remarkable differences in eye-tracking length between them.

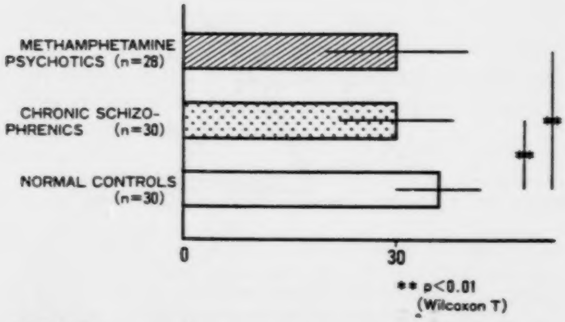


FIGURE 3. Number of eye fixations. The mean number of eye fixations of the amphetamine psychotics and schizophrenics were less than those of normal controls respectively ($p < .01$). There was no significant difference between amphetamine psychotics and schizophrenics.

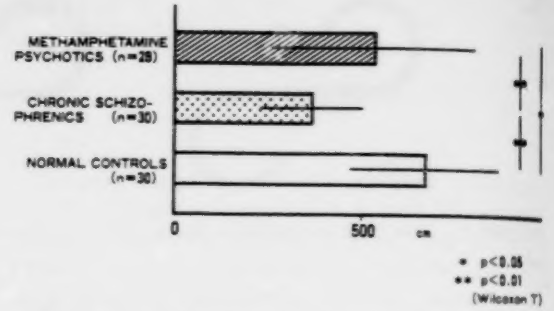


FIGURE 4. Total eye-tracking length. The schizophrenics had shorter eye-tracking length than amphetamine psychotics ($p < .01$). The amphetamine psychotics also had shorter eye-tracking length than normal controls ($p < .05$). Each group was significantly different from the other two groups.

Eye Movements Following Verbal Stimuli (Responsive Search Score)

The subjects were asked to answer the question "Are there any differences between this figure and the original one?" After they finished answering, we asked them "Are there any other differences?" In this situation we can observe the active attitude of the subjects to try to ascertain more information accompanied with the question. The eye movements during this search were scored and called the responsive search score.

Figure 5 shows how to score the responsive search score for an amphetamine psychotic patient, a schizophrenic patient, and a normal control. Each figure was divided into seven sections. The incidence of eye movements and fixations on these sections were scored during the response to the final question; each subject was shown two figures. For example, in the top figure the amphetamine psychotic patient fixed his eyes on 6 sections in response to the final question and therefore received a score of 6. In the bottom figure he received a score of 5. His total score was 11 points out of a possible 14. The eye fixations of this amphetamine psychotic patient and the normal control covered almost all of the sections and the total score was 11 and 12 points, respectively. The schizophrenic patient's eye movements were more restricted with a total score of 5 points.

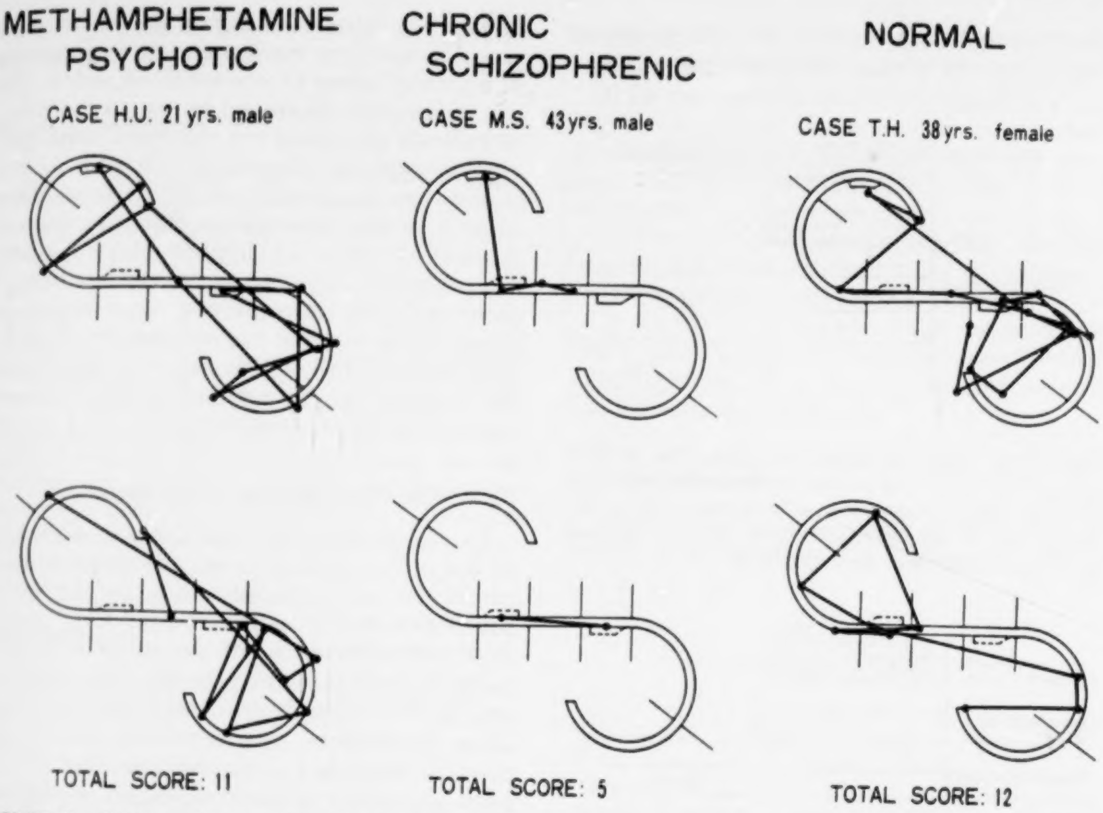


FIGURE 5. Scoring of the responsive-search score. Each figure was divided into 7 sections. The incidence of eye movements and fixations on these sections was scored during the response to the final question. The scores for the two figures, illustrated at the top and bottom, were totaled. The eye fixations of the amphetamine psychotic patient and normal control covered almost all of the sections; total score was 11 and 12 points, respectively. The schizophrenic patient's eye movements were more restricted with a total score of 5 points.

Figure 6 shows the results of the responsive search score. The amphetamine psychotics and normal controls had higher responsive search scores than schizophrenics ($p < .01$). There was no significant difference between amphetamine psychotics and normal controls.

In the analysis of eye movements following the question, it was found that amphetamine psychotics showed much better response to the question than schizophrenics.

Reproduced Picture

The "S"-shaped figure was drawn by subjects and it was evaluated by our criteria (Kojima et al., 1985). Figure 7 shows the evaluation score of the reproduced picture of the first and second drawing. The top figure shows the first drawing and the bottom figure shows the second drawing. In the first and second drawings, amphetamine psychotics had evaluation scores as low as schizophrenics and they in turn had lower scores than normals.

The amphetamine psychotics drew the picture of the original figure as incorrectly as schizophrenics in comparison with normal controls.

Drug Influence

The influence of neuroleptic drugs must be considered. We examined the correlation with "linear regression" between all measures of the eye movements and dosage of chlorpromazine in schizophrenics. There was no significant correlation between them.

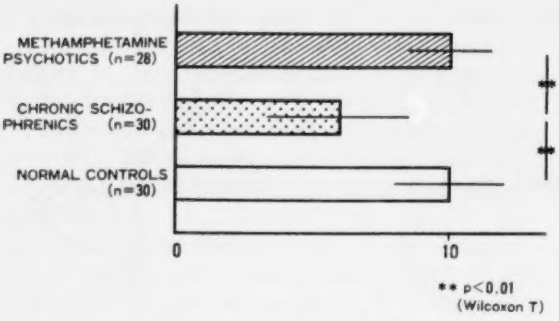


FIGURE 6. Responsive-search score. The amphetamine psychotics and normal controls had higher responsive-search scores than schizophrenics ($p < .01$). There was no significant difference between amphetamine psychotics and normal controls.

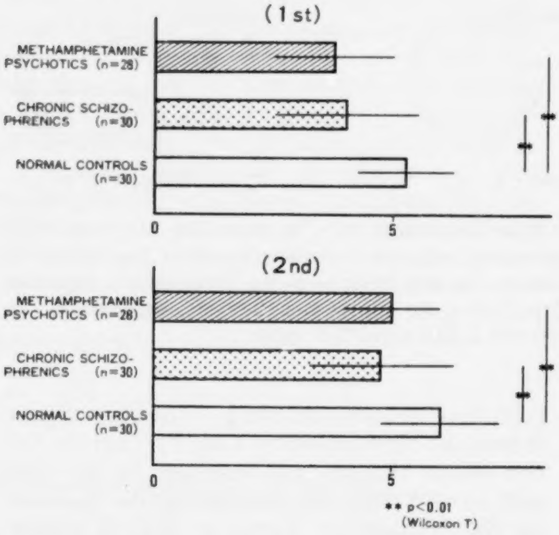


FIGURE 7. Reproduced picture scores. The top figure shows the first drawing and the bottom figure shows the second drawing. In the first and second drawings, amphetamine psychotics had an evaluation score as low as schizophrenics and they in turn scored lower than normals.

Comments

Many researchers have reported the dysfunction of pursuit eye movements in schizophrenia beginning with P. Holzman in 1973. Since 1972 (Moriya et al.) we have been studying saccadic eye movement during viewing of a picture using an eye-mark recorder. The eye movement measured by us is considered to indicate the visual behavior and visual perception and/or cognition. Therefore, our studies are remarkably different from those of pursuit eye movements. But it is interesting that the results (1979) in which not only schizophrenics but also their relatives showed abnormal eye movements, are similar to those of pursuit eye movements by P. Holzman et al. (1974). In this paper we focused on the comparison between the amphetamine psychotics and schizophrenics.

Elementary Components of Eye Movement

In comparison of elementary components of eye movements between the amphetamine psychotics and schizophrenics, amphetamine psychotics had a longer eye-tracking length than schizophrenics but the other two components were similar to those of schizophrenics. At first it had been considered that these three components might reflect equally the positive attitude to the environment of patients. But the eye-tracking length of amphetamine psychotics seemed to be dissociated from the other two components. The eye-tracking length of schizophrenics was negatively correlated with negative symptoms such as blunted affect. This may suggest that amphetamine psychotics have less negative symptoms than schizophrenics but more than normal controls.

Eye Movements Following Verbal Stimuli

The amphetamine psychotics and normal controls searched the figure quickly as if they had tried to confirm it again after the question, "Are there any other differences?" But schizophrenics hardly searched the figure. This visual behavior was scored as the responsive-search score. The responsive-search score of amphetamine psychotics was as high as that of normals and was higher than that of schizophrenics. The results of responsive-search score are consistent with clinical findings (reported by Prof. Tatetsu) that amphetamine psychotics showed much better response to persons other than schizophrenics in spite of their having delusions and/or hallucinations.

Reproduced Picture

The amphetamine psychotics and schizophrenics drew the original figure less correctly than normal controls. The previous study (Moriya, 1979; Shimazono et al., 1983) indicated that the chronic schizophrenics and their relatives drew it less correctly than normals. Kojima et al. (1985) reported that amphetamine psychotics and schizophrenics did not look at the important areas of the figure long enough to recognize it. The results of the reproduction quality and the eye movements suggest that amphetamine psychotics have poor information aquisition and disturbance of the visual-perception process.

Drug Influence

There was no significant correlation between all measures of the eye movement and dosage of chlorpromazine in schizophrenics. In many cases limited eye movements were found in the parents of schizophrenics (Moriya, 1979). These data suggest that the abnormal eye movement of schizophrenics is not due to the influence of medication.

Finally, it was concluded that the amphetamine psychotics in general had very similar eye movements, although with several different components of eye movements, compared to schizophrenics. These results suggest that the amphetamine psychotics may have a little different disturbance of visual perception and/or cognition than schizophrenics.

Summary

1) The eye movements of 28 methamphetamine psychotics, 30 chronic schizophrenics, and 30 normal controls were examined using an eye mark recorder.

2) In the analysis of the elementary components of eye movements, there was a remarkable difference in eye-tracking length between the amphetamine psychotics and schizophrenics but no difference in other components between them.

3) In the analysis of eye movement following verbal stimuli the amphetamine psychotics showed much better response to the question than the schizophrenics (high responsive-search score).

4) The amphetamine psychotics drew the original figure as incorrectly as schizophrenics in comparison with normal controls.

5) These data suggest that the amphetamine psychotics may have a little different disturbance of visual perception and/or cognition than schizophrenics.

Acknowledgments

The authors wish to thank Prof. S. Potkin and Prof. W. Bunney, Jr. for helpful advice.

References

Ando, K., Moriya, H., Toyota, T., et al. Visual perception process in chronic schizophrenia and endogenous depression. In: Obiols, J., Ballus, C., Gonzalez Monclus, E., and Pujol, J. (eds.), *Biological Psychiatry Today.* Amsterdam/New York/Oxford: Elsevier/North-Holland Biomedical Press, 1979, pp. 1472–1477.

Holzman, P.S., Proctor, L.R., Levy, D.L., et al. Eye-tracking dysfunctions in schizophrenic patients and their relatives. *Arch. Gen. Psychiat.*, 31(2):143–151, 1974.

Holzman, P.S., Proctor L.R., and Hughes, D.W. Eye-tracking patterns in schizophrenia. *Science*, 181(13):179–181, 1973.

Kojima, T., Matsushima, E., Iwama, H., et al. Studies on schizophrenia and methamphetamine psychosis using an eye mark recorder. *Advances in Neurological Sciences*, 29(6):939–949, 1985.

Moriya, H. A study of eye movement in patients with chronic schizophrenia and in their relatives, using an eye mark recorder. *Psychiatria et Neurologia Japonica*, 81(8):523–558, 1979.

Moriya, H., Ando, K., Kojima, T., et al. Eye movements during perception of pictures in chronic schizophrenia. *Folia Psychiat. Neurol. Jpn.*, 26(3):189–199, 1972.

Shimazono, Y., Ando, K., Moriya, H., et al. Schizophrenia, movements of the eye. In: Ohashi, H., Nakayama, K., Saito, M., and Saletu, B. (eds.), *WPA Regional Symposium Kyoto.* Tokyo: The Japanese Society of Psychiatry and Neurology, 1983, pp. 128–134.

Tatetsu, S., Goto, A., and Fujiwara, T. *The Methamphetamine Psychosis.* Tokyo: Igaku Shoin Ltd., 1956.

Membrane Lipids: From Signal Transduction to Neuropsychiatric Disease

Co-Chairs:

John Rotrosen, M.D.
New York VA Medical Center
New York, NY 10010

Steven M. Paul, Ph.D.
National Institute of Mental Health
Bethesda, MD 20896

Changes in Receptor Stimulated Phosphoinositide Hydrolysis in Brain During Ethanol Administration, Aging, and Other Pathological Conditions*

Fulton T. Crews, Ph.D.,[1] Rueben A. Gonzales, Ph.D.,[1] Reinhard Palovcik, Ph.D.,[2] M. Ian Phillips, Ph.D.,[2] Cynthia Theiss, M.P.E.,[1] and Mohan Raizada, Ph.D.[2]

Recent studies in a variety of cell types have indicated that receptor activated hydrolysis of phosphoinositides is an early event in the transduction of hormone and neurotransmitter signals (Berridge, 1984). Phosphoinositides are a group of minor membrane phospholipids, e.g., phosphatidylinositol, phosphatidylinositol 4-phosphate, and phosphatidylinositol 4,5-bisphosphate (PIP_2). Hormones and transmitters bind to their individual receptors and activate a specific phospholipase C which hydrolyzes the phosphoinositides into two separate second messengers, diacylglycerol and inositol 1,4,5-trisphosphate (Berridge, 1984). Diacylglycerol is a lipid which induces an allosteric activation of a phosphatidylserine, calcium dependent protein kinase frequently referred to as C kinase (Nishizuka, 1984). C kinase has very high activity in nervous tissue. Whereas diacylglycerol is formed from the hydrolysis of any of the phosphoinositides, inositol 1,4,5-trisphosphate is formed only from phospholipase C hydrolysis of phosphatidylinositol 4,5-bisphosphate. Inositol 1,4,5-trisphosphate releases calcium from the endoplasmic reticulum of a number of cell types (Streb et al., 1983). Intracellular calcium can activate calcium dependent protein kinases as well as activating calcium dependent ion channels. In some cell types there is a synergism between the calcium and diacylglycerol signals, whereas in other cell types separate functions appear to be involved.

The number of receptors linked to phosphoinositide hydrolysis in brain is not presently known. Two receptors which clear-

---

* Supported by NIAAA Grants AA-06069 and AA-05208.

[1] Department of Pharmacology and Therapeutics, University of Florida Medical School, Box J-267 JHMHC, Gainesville, FL 32610.

[2] Department of Physiology, University of FL Medical School, Box J-274 JHMHC, Gainesville, FL 32610.

Please address correspondence to Dr. Fulton Crews at the above address.

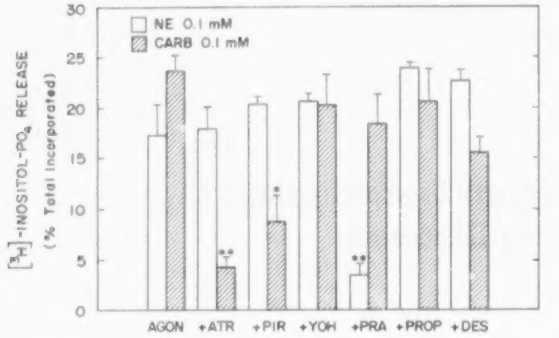


FIGURE 1. Effects of antagonists on cholinergic and adrenergic stimulated inositide hydrolysis in rat cortical slices. Slices were prepared, labelled with [^{3}H]inositol, stimulated with norepinephrine or carbachol, and the released [^{3}H]inositol phosphates were analyzed as described in Gonzales and Crews (1985a). Nonstimulated values have been subtracted from the stimulated to obtain net release. $^{**}p < 0.01$ and $^{*}p < 0.05$ by analysis of variance and Newman-Keuls test.

ly cause a marked stimulation of phosphoinositide hydrolysis in brain are the muscarinic-cholinergic and the α_1-adrenergic receptor (Figure 1). Stimulation of inositide hydrolysis by norepinephrine is blocked by α_1-adrenergic antagonists. Among brain regions the hippocampus has the largest response to norepinephrine, although the striatum, cerebral cortex, and hypothalamus also have large responses (Gonzales and Crews, 1985a). Similarly, acetylcholine and carbachol, a prototypical cholinergic agonist, stimulate phosphoinositide hydrolysis in the cerebral cortex, hippocampus, striatum, and to a lesser extent in most other brain regions except the cerebellum where there was only a small response (Gonzales and Crews, 1984). Cholinergic stimulation of inositide hydrolysis in the cerebral cortex is inhibited by atropine, the muscarinic antagonist, as well as pirenzepine, the selective M1 muscarinic antagonist (Figure 1). Studies of a variety of cholinergic agonists indicate that certain drugs, such as oxotremorine, which were previously thought to be good cholinergic agonists, are actually weak partial agonists for the stimulation of phosphoinositide turnover (Figure 2). Furthermore, oxotremorine has been shown to inhibit stimulation of inositide hydrolysis by full cholinergic agonists. This suggests that in vivo studies with oxotremorine may actually be looking at cholinergic antagonist actions and not agonist responses. Since the predominant cholinergic receptors in the cerebral cortex are muscarinic it is likely that much of cortical cholinergic neurotransmission is mediated by M1 muscarinic receptors coupled to phosphoinositide hydrolysis.

To fully understand cholinergic and adrenergic neurotransmission the mechanism by which muscarinic-cholinergic and α_1-adrenergic receptors couple to phospholipase C must be understood. Receptor purification studies have suggested that the neurotransmitter recognition site, i.e., the receptor, is not itself a phospholipase. Furthermore, cholinergic and adrenergic agonists are less than additive in certain brain regions suggesting that the two receptors share the same phospholipase C and phosphoinositide pool (Gonzales and Crews, 1985a). Most phospholipases are found in lysosomes, are not specific for any particular lipid, and are activated by calcium. Phosphoinositide specific phospholipase C is likely to be in the plasma membrane in close

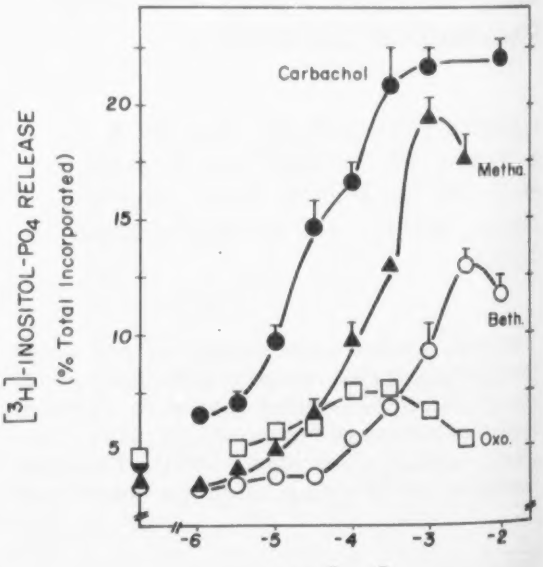


FIGURE 2. Concentration-effect curves for cholinergic agonists on inositide hydrolysis in rat cortical slices. Results were obtained as described in Figure 1 for carbachol, methacholine (metha), bethanechol (beth), and oxotremorine (oxo).

proximity to receptors and the inositol phospholipids. The β-adrenergic receptor has been shown to stimulate the enzyme adenylate cyclase through an interaction with a specific guanine nucleotide binding protein (Lefkowitz et al., 1983). Recent studies have suggested that receptors coupled to inositide hydrolysis may also require a guanine nucleotide binding protein, which is different from that involved with adenylate cyclase and cyclic-AMP formation, for the activation of phospholipase C (Cockroft and Gomperts, 1985; Litosch et al., 1985). Incubation of cerebral cortical membranes with the guanine nucleotide Gpp(NH)p and/or calcium stimulates the hydrolysis of phosphoinositides (Figure 3), and PIP_2 may be a substrate for Gpp(NH)p activated phospolipase C (Gonzales and Crews, 1985b). Since both guanine nucleotides and calcium can activate phosphoinositide hydrolysis in cerebral cortical membranes, it is possible that the phosphoinositide cascade in brain can be activated by receptors as well as through increases in cellular calcium. In any case, these studies suggest that when muscarinic-cholinergic or α_1-adrenergic receptors are occupied by an agonist they interact with a guanine nucleotide binding protein in the plasma membrane to activate phosphoinositide specific phospholipase C and thereby release the two second messengers, diacylglycerol and inositol 1,4,5-trisphosphate.

Additional evidence supporting the role of phosphoinositide hydrolysis in neurotransmission has been obtained using primary cell cultures and electrophysiological studies of neuronal responses to cholinergic drugs. A comparison of primary cultures composed of almost exclusively neurons or glia indicate that cholinergic and adrenergic receptor stimulated phosphoinositide hydrolysis is far more robust in neurons than glia (Gonzales et al., 1985). Electrophysiological studies of the hippocampal pyramidal cell response to carbachol have found that the concentration response curve and time course for excitation of pyramidal cells is almost identical to that found for phosphoinositide hydrolysis. Furthermore, carbachol is a full agonist and oxotremorine a weak partial agonist at stimulation of pyramidal cell firing similar to that found for phosphoinositide hydrolysis (Figure 4). Muscarinic receptors have been shown to decrease potassium conductances in hippocampal pyramidal cells (Cole and Nicoll, 1983). Taken together, these data suggest

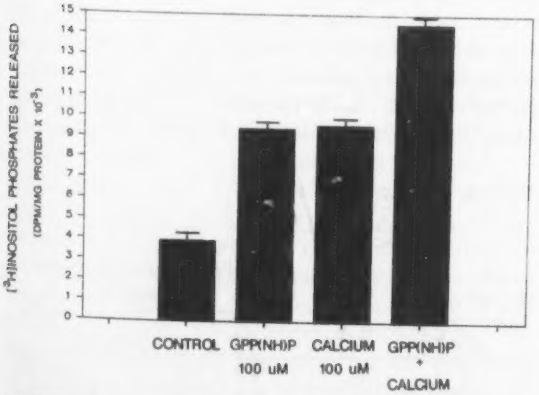


FIGURE 3. Guanine nucleotide and calcium activated inositide hydrolysis in rat cortical membranes. Membranes were prepared from prelabelled cortical slices as described in Gonzales and Crews (1985b). Gpp(NH)p and calcium were added to the membrane preparation and [^{3}H]inositol phosphates released were analyzed by anion exchange chromatography.

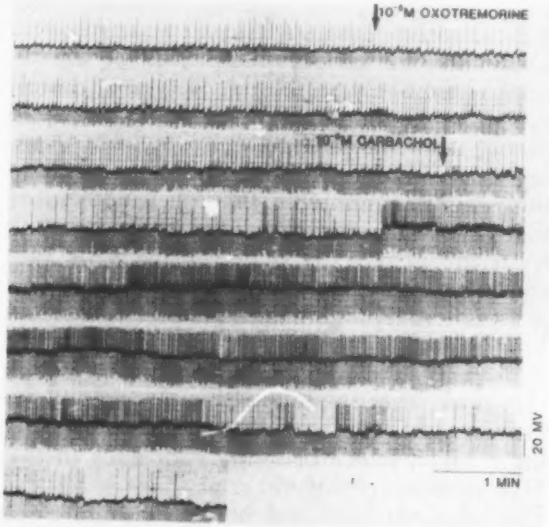


FIGURE 4. Effect of cholinergic agonists on electrophysiology of hippocampal pyramidal cells. This intracellular recording of a CA1 hippocampal pyramidal neuron response shows a slight increase in firing rate to 10 μM oxotremorine and a much larger increase in firing rate and depolarization to 10 μM carbachol.

that activation of muscarinic receptors initiates a cascade in neurons which involves phosphoinositide hydrolysis to form second messengers. The second messengers may then lead to activation of protein kinases and phosphorylation of membrane potassium channels which may alter neuronal membrane conductance.

The discovery that cholinergic-muscarinic and α_1-adrenergic mediated neurotransmission involves phosphoinositide hydrolysis suggests that changes in this response may underlie phenomena such as receptor plasticity, disease states, and drug effects. Experiments with primary neuronal cultures have shown that continuous stimulation of neurons with norepinephrine causes an 80-percent decrease in the α_1-adrenergic response within 2 hours without changing the number of α_1 receptors (Figure 5). Stimulation for longer times leads to the loss of α_1-adrenergic receptor binding sites with a maximum loss reached after approximately 24 hours of stimulation with norepinephrine (Gonzales et al., unpublished). A similar uncoupling of muscarinic-cholinergic receptors has been reported in astrocytoma cells (Masters et al., 1985). These findings indicate that there are rapid changes in the responsiveness of these two receptors. Drugs which increase synaptic concentrations of norepinephrine or acetylcholine are likely to induce this type of desensitization in the brain. Recent studies comparing neuronal primary cultures from spontaneously hypertensive rats (SHR) with their normotensive controls (WKY) have shown that the α_1-adrenergic receptors in neurons from the genetically hypertensive SHR rats are poorly coupled to phosphoinositide hydrolysis. Norepinephrine stimulated inositide hydrolysis is significantly greater in WKY neurons than in SHR neurons (Table 1). Furthermore, there are more α_1-receptor binding sites in SHR than WKY neurons indicating a much lower coupling efficiency in the SHR neurons (Feldstein et al., 1986). Muscarinic-receptor sites and phosphoinositide responses are identical in SHR and WKY neurons. Thus α_1-adrenergic and muscarinic-cholinergic receptors rapidly change their coupling efficiency and alterations in coupling of α_1-adrenergic receptors may be related to the pathology of hypertension.

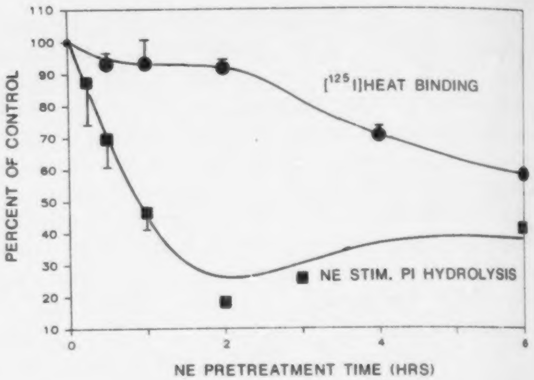


FIGURE 5. Norepinephrine induced loss of α_1-stimulated inositide hydrolysis and α_1-binding sites in neuronal primary cultures. Neuronal cultures were prepared from neonatal WKY rat brains and exposed to 10 μM norepinephrine for various times. Inositide hydrolysis in prelabelled cultures was measured after washing out the norepinephrine and adding either buffer or 10 μM norepinephrine back to the cultures in the presence of 10 mM LiCl. Alpha$_1$-binding sites were assessed by measuring the level of [^{125}I]HEAT binding in the presence and absence of 1 mM naphazoline.

Ethanol is one of the most widely used drugs. It does not have a specific receptor, but appears to alter neurotransmission by modifying membrane viscosity. Since α_1 and muscarinic receptor mediated neurotransmission involves membrane lipid hydrolysis, it is not surprising that ethanol can disrupt adrenergic and cholinergic neurotransmission. In the cerebral cortex the effects of various concentrations of ethanol on membrane viscosity parallel the inhibition of norepinephrine stimulated inositide hydrolysis (Figure 6).

TABLE 1

Norepinephrine Concentration (μM)	N	WKY	SH
		[^{3}H]inositol phosphates released (MEAN + SEM) (% total ^{3}H incorporated)	
0	4	18.2 ± 0.8	19.0 ± 0.9
0.1	2	21.9 ± 1.1	20.6 ± 2.0
0.3	2	25.5 ± 0.9	21.4 ± 3.2
1	4	30.9 ± 1.1	25.2 ± 1.1**
3	4	35.0 ± 1.2	28.5 ± 1.3**
10	4	34.5 ± 1.2	29.2 ± 1.1**
100	3	35.3 ± 1.5	27.3 ± 1.2**

Norepinephrine stimulated inositide hydrolysis in neurons from whole brains of WKY and SH rats. Inositide hydrolysis was determined as described in Figure 5.
**$p < 0.01$ by analysis of variance and Newman-Keuls test.

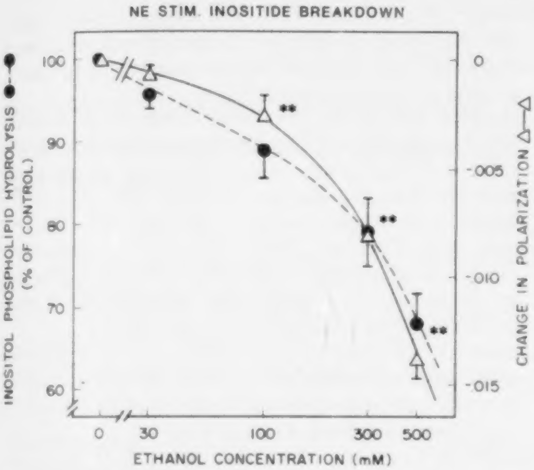


FIGURE 6. Effects of ethanol on rat cortical synaptosomal membrane organization and norepinephrine stimulated inositide hydrolysis. Norepinephrine (100 μM) stimulated inositide hydrolysis was measured as described in Figure 1. Membrane order was estimated by measuring the fluorescence polarization of diphenylhexatriene in purified synaptosomes.

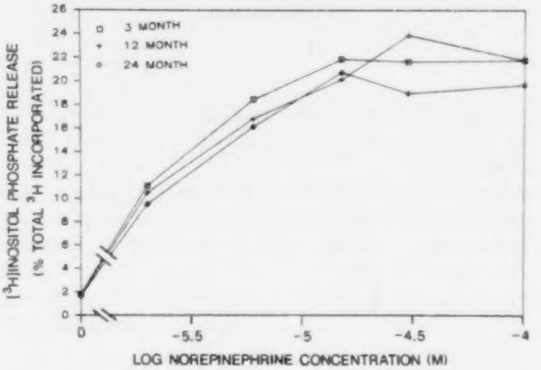


FIGURE 7. Alpha$_1$-stimulated inositide hydrolysis in cortical slices from 3-, 12-, and 24-month old Fisher 344 rats. Inositide hydrolysis was measured as described in Figure 1. No significant differences were found between any of the age groups (analysis of variance).

This change in responsiveness does not appear to be due to a loss of receptor sites, but due to an uncoupling of the α_1 response. Cerebral cortical muscarinic receptor-stimulated inositide hydrolysis is not very sensitive to ethanol (Gonzales et al., unpublished).

Studies of cholinergic neurotransmission have indicated that there is a decrease in the release of acetylcholine in the cerebral cortical synaptosomes (Meyer et al., 1984) and a decrease in the hippocampal electrophysiological response to acetylcholine in senescent rats (Lippa et al., 1981). However, no difference in either α_1-adrenergic (Figure 7) or muscarinic-cholinergic (Figure 8) stimulated phosphoinositide hydrolysis in cortical slices was found between 3-, 12-, and 24-month old Fisher 344 rats. Thus, adrenergic and cholinergic stimulation of phosphoinositide hydrolysis does not appear to be altered in the cerebral cortex during aging. Further studies are required to determine if changes in responsiveness occur at other sites in the phosphoinositide cascade or in other brain regions during aging.

In summary, α_1-adrenergic and muscarinic-cholinergic receptor mediated neurotransmission is thought to be mediated by the hydrolysis of phosphoinositides and the formation of the second messengers diacylglycerol and inositol 1,4,5-trisphosphate. Responsiveness in this cascade changes rapidly during agonist stimulation and/or in the presence of drugs such as ethanol. A decrease in α_1-receptor responsiveness may be related to genetic hypertension. Future studies on these receptor mechanisms are required to fully understand their roles in neurotransmission, drug responses, and central nervous system pathology.

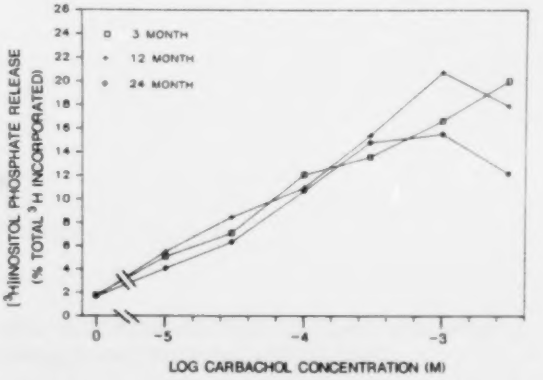


FIGURE 8. Muscarinic cholinergic-stimulated inositide hydrolysis in cortical slices from 3-, 12-, and 24-month old Fisher 344 rats. Results obtained were as in Figure 7.

References

Berridge, M.J. Inositol trisphosphate and diacylglycerol as second messengers. *Biochem. J.*, 220:345–360, 1984.

Cockcroft, S., and Gomperts, B.D. Role of guanine nucleotide binding protein in the activation of polyphosphoinositide phosphodiesterase. *Nature*, 314:534–536, 1985.

Cole, A.E., and Nicoll, R.A. Acetylcholine mediates a slow synaptic potential in hippocampal pyramidal cells. *Science*, 221:1299–1301, 1983.

Feldstein, J.B., Gonzales, R.A., Baker, S.P., et al. Decreased alpha$_1$-adrenergic receptor mediated inositide hydrolysis in neurons from hypertensive brain. (Submitted, *Am. J. Physiol.*, 1986.)

Gonzales, R.A., and Crews, F.T. Cholinergic and adrenergic-stimulated inositide hydrolysis in brain: Interaction, regional distribution, and coupling mechanisms. *J. Neurochem.*, 46:1076–1084, 1985a.

Gonzales, R.A., and Crews, F.T. Guanine nucleotides stimulate production of inositol trisphosphate in rat cortical membranes. *Biochem. J.*, 232:799–804, 1985b.

Gonzales, R.A., Feldstein, J.B., Crews, F.T., and Raizada, M.K. Receptor-mediated inositide hydrolysis is a neuronal response: Comparison of primary neuronal and glial cultures. *Brain Res.*, 345:350–355, 1985.

Gonzales, R.A., Crews, F.T., and Raizada, M.K. "Agonist regulation of alpha$_1$-stimulated phosphoinositide hydrolysis and alpha$_1$ receptor number in cultured neurons." (unpublished, 1986)

Lefkowitz, R.J., Stadel, J.M., and Caron, M.G. Adenylate cyclase-coupled beta-adrenergic receptors: Structure and mechanisms of activation and desensitization. In: *Ann. Rev. Biochem.* Vol. 52. Palo Alto, California: Annual Reviews, Inc., 1983, pp. 159–186.

Lippa, A.S., Critchett, D.J., Ehlert, F., Yamamura, H.I., et al. Age-related alterations in neurotransmitter receptors: An electrophysiological and biochemical analysis. *Neurobiol. Aging*, 2:3–8, 1981.

Litosch, I., Wallis, C., and Fain, J.N. 5-Hydroxytryptamine stimulates inositol phosphate production in a cell-free system from blowfly salivary glands. *J. Biol. Chem.*, 260:5464–5471, 1985.

Masters, S.B., Quinn, M.T., and Brown, J.H. Agonist-induced desensitization of muscarinic receptor-mediated calcium efflux without concomitant desensitization of phosphoinositide hydrolysis. *Mol. Pharmacol.*, 27:325–332, 1985.

Meyer, E.M., St. Onge, E., and Crews, F.T. Effects of aging on rat cortical presynaptic processes. *Neurobiol. Aging*, 5:1–3, 1984.

Nishizuka, Y. Turnover of inositol phospholipids and signal transduction. *Science*, 225:1365–1370, 1984.

Streb, H., Irvine, R.F., Berridge, M.J., and Schulz, I. Release of Ca^{2+} from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. *Nature*, 306:67–69, 1983.

"Autocannibalism" of Membrane Choline-Phospholipids: Physiology and Pathology

Jan K. Blusztajn, Ph.D.,[1] Pamela G. Holbrook, M.S.,[1] Michael Lakher, M.S.,[1] Mordechai Liscovitch, Ph.D.,[1] Jean-Claude Maire, Ph.D.,[2] Charlotte Mauron, B.S.,[1] U. Ingrid Richardson, Ph.D.,[1] Mariateresa Tacconi, Ph.D.,[3] and Richard J. Wurtman, M.D.[1]

Cholinergic neurons derive their choline from the circulation [choline crosses the blood-brain barrier via a facilitated diffusion mechanism (Pardridge et al., 1979)] or from its synthesis in situ (Blusztajn and Wurtman, 1981). Within cholinergic neurons choline can undergo two transformations: it may be acetylated by choline acetyltransferase (CAT) to form the neurotransmitter acetylcholine (ACh), or it may be incorporated into choline phospholipids (Ch-PL) [phosphatidylcholine (PtdCho), sphingomyelin, or plasmalogens] via the CDP-choline (Kennedy and Weiss, 1956) or base-exchange (Porcellati et al., 1971; Abdel-Latif and Smith, 1972) pathways. The authors hypothesize that a dynamic equilibrium exists between choline's reversible fluxes into and out of ACh and Ch-PL, and that these fluxes are well regulated in order to maintain both adequate ACh synthesis and the functional integrity of membranes (Ch-PL are the major lipid components of all biological membranes). However, under some circumstances, the choline obtained from Ch-PL degradation may be used for ACh synthesis; for example when the neuron is persistently firing frequently, or when the supply of free choline is inadequate for ACh synthesis (because the neuron makes too little choline or is unable to take up enough of it from the brain's extracellular fluid). The rate at which Ch-PL are hydrolyzed to yield free choline may transcend the neuron's ability to resynthesize these molecules, resulting in the net "autocannibalism" of its membranes. The choline obtained by "autocannibalism" could derive from the general metabolic "pool" of choline phospholipids, or perhaps from a pool specifically mobilized for that purpose. Membrane phospholipids like PtdCho are compartmented in three ways: by their subcellular localization (for example, synaptic vesicles vs. plasma membranes); by their fatty acid composition; and by their mode of synthesis [methylation of phosphatidylethanolamine (PtdEtn) vs. incorporation of pre-existing choline via the CDP-choline or base-exchange pathways] (*see* below). Excessive destruction of membrane PtdCho might lead to changes in membrane composition (for example, in the ratios of PtdCho to other phospholipids, or to proteins) or to a loss in total membrane surface. Either alteration could affect the neuron's functional properties and even its viability. Such changes would be most likely to occur in nerve terminals (the neuronal structures that are specialized for neurotransmitter synthesis and release) initially damaging them, and only later affecting cell bodies.

This paper describes the relationships between choline, ACh, and Ch-PL in the nervous system, presenting evidence derived from experiments on brain slices, synaptosomes, and cultured cells. Based on these basic studies and clinical observations the authors discuss the possible role of the "autocannibalism" in the pathophysiology of Alzheimer's disease.

Effects of Neuronal Activity on Acetylcholine Release and Phospholipid Turnover

Since CAT has a low affinity for choline and is highly unsaturated with this substrate in vivo (White and Wu, 1973; cf. Blusztajn and Wurtman, 1983), ACh synthesis and re-

---

[1] Department of Applied Biological Sciences, M.I.T., Cambridge, MA 02139.
[2] Département de Pharmacologie, Centre Medical Universitaire, Geneva, Switzerland.
[3] Instituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

lease can be increased by treatments that elevate extracellular choline levels. The effect of the choline is enhanced in cholinergic neurons that are firing frequently (cf. Blusztajn and Wurtman, 1983). For example, the authors measured ACh release from rat striatal slices superfused with or without choline (Maire and Wurtman, 1985). In the absence of free choline, ACh was released spontaneously at a rate of 7.5 ± 1.3 pmol/mg protein/min (mean ± S.D.). Electrical field stimulation (15 Hz for 30 min) accelerated this release (25.6 ± 5.9 pmol/mg protein/min), and addition of choline (20 μM) to the superfusate significantly enhanced both the spontaneous (22.7 ± 5.7 pmol/mg protein/min) and the electrically evoked (37.4 ± 6.7 pmol/mg protein/min) release of the transmitter. Although the amount of ACh in the tissue did not depend on extracellular choline concentration (in this range of choline concentrations) tissue choline contents did increase when choline levels in the superfusate were raised.

The breakdown of membrane PtdCho in neurons can also be accelerated by frequent firing, especially when extracellular choline is unavailable. This was first shown by Parducz et al. (1976) who electrically stimulated the preganglionic trunk of the cat's superior cervical ganglion (in the presence of hemicholinium-3) and observed that the number of synaptic vesicles decreased to 18% that of controls, while ganglionic PtdCho levels fell to 69% of controls. (Other phospholipids were not affected.) These observations indicate that when adequate extracellular choline is not available (e.g., after inhibition of its uptake by hemicholinium-3), vesicular PtdCho is used to supply choline for ACh synthesis. The authors have observed similar phenomena in their striatal slices preparations: In the absence of exogenous choline, the combined efflux of *choline + ACh* into the superfusate was 75-pmol/mg protein/min; however, the decrease in *choline + ACh* within the tissue was only 16 pmol/mg protein/min (Maire and Wurtman, 1985). Thus, an endogenous pool of choline, present within a larger molecule, must have provided the free choline to sustain ACh synthesis and tissue choline and ACh levels. The only known compounds whose pool sizes would be sufficient for this purpose are the Ch-PL. Evidence that these compounds are indeed the source of the free choline is provided by the finding that the amount of phosphate in the phospholipids of the slices also decreased (by 23%) when the slices were stimulated (Mauron and Wurtman, in preparation), i.e., suggesting that neuronal activity accelerated the metabolic degradation of phospholipids. Addition of exogenous choline (20 μM) to the superfusate prevented the loss of phospholipid phosphate from stimulated slices. This suggests either that the apparent acceleration in phospholipid degradation reflected increased need for choline in order to maintain ACh release from cholinergic neurons (i.e., shifting the equilibrium between ACh, choline, and Ch-PL, towards ACh); or a general increase in phospholipid turnover, related to neuronal firing. In the former case the exogenous choline presumably was used to maintain high ACh synthesis, and thus prevented the shift in the equilibrium; in the latter, the choline presumably provided sufficient substrate to allow the rate of Ch-PL synthesis to catch up with their accelerated degradation. Preliminary data suggest that when slices are stimulated in the absence of exogenous choline, the rate of PtdCho synthesis by the de novo methylation pathway (*see* below) is increased (Lakher and Wurtman, unpublished). Perhaps this reflects a mechanism for sustaining membrane PtdCho levels (i.e., when PtdCho degradation is accelerated due to firing), or one to maintain the appropriate PtdEtn/PtdCho ratio within the membrane (PtdCho degradation would tend to increase this ratio; PeMT activation would decrease it by converting PtdEtn to PtdCho).

Relationships Between Acetylcholine and Choline Phospholipid Synthesis in a Cholinergic Cell Line, NG108-15

The authors have studied the relationships between Ch-PL and ACh levels in a purely cholinergic cell line, the neuroblastoma × glioma hybrid, NG108–15 (Hamprecht, 1977). The synthesis of ACh in these cells was found to vary with extracellular choline concentrations. When the cells were incubated for 1 hour in the presence of various [^{3}H-methyl]choline concentrations, the accumulation of [^{3}H-methyl]ACh exhibited saturable kinetics, with an apparent K_m of 193 ± 34 μM, and V_{max} of 268 ± 23 pmol/mg protein/hr. At the same time, incorporation of the labeled choline into phosphocholine (an intermediate in PtdCho synthesis) proceeded at a much higher rate (apparent V_{max} = 16.8 ± 1.2 nmol/mg protein/hr) and had a lower apparent K_m (14.9 ± 5.4 μM). Thus choline was more likely to be used in these cells for PtdCho than for ACh synthesis (because choline kinase was more likely than CAT to attack the choline). The authors hypothesized that a treatment that inhibited choline kinase activity in the cells might enhance their formation of ACh, and observed that addition of ethanolamine to the incubation medium (0.5 mM), which suppressed formation of phosphocholine and PtdCho (in a competitive fashion, apparent K_i = 180 μM) did indeed enhance the labeling of [^{3}H-methyl]ACh. These data demonstrate that the dynamic equilibrium between ACh, choline, and Ch-PL can be shifted towards ACh when choline's utilization for Ch-PL synthesis is slowed.

Choline Synthesis in Neurons

Choline is synthesized in brain neurons, de novo, by a multienzymatic pathway; the terminal steps in this pathway, catalyzed by phosphatidylethanolamine N-methyltransferase (PeMT), involve the stepwise methylation of PtdEtn to PtdCho, using S-adenosylmethionine (SAM) as methyl donor. This newly formed PtdCho is hydrolyzed to free choline by a number of phospholipases and other hydrolases. The authors found that free choline constituted 23 percent of the total PtdCho synthesized by synaptosomal PeMT (from [^{3}H-methyl]SAM) during a 30-min incubation period. Furthermore, the enrichment of the free choline pool with newly formed [^{3}H]choline was 50-fold greater than that of the PtdCho pool by newly formed [^{3}H]PtdCho (Blusztajn and Wurtman, 1981). Thus, the relatively small amount of PtdCho synthesized in nerve terminals de novo may have a considerably faster turnover than the bulk of synaptosomal PtdCho. (One might anticipate that PtdCho pool which preferentially provided free choline for acetylcholine synthesis would turn over more rapidly than "storage" PtdCho.) Perhaps this pool has a special fatty acid composition. The bulk of synaptosomal PtdCho contains mainly (77 percent) fatty acids with 0-2 double bonds. However the PtdCho newly synthesized by the methylation has a high proportion (up to 97 percent) of polyunsaturated fatty acids (4-6 double bonds) (Tacconi and Wurtman, 1985), reflecting the fatty acid composition of its precursor PtdEtn (Tacconi and Wurtman, 1985). Synaptosomal PtdCho newly synthesized from preexisting choline molecules either by cholinephosphotransferase-catalyzed reaction (phosphocholine moiety of a cofactor, cytidinediphosphocholine is esterified with a diacylglycerol) or by base-exchange enzyme [free choline is incorporated into PtdEtn or phosphatidylserine (PtdSer) with a concomitant release of free ethanolamine or serine, respectively] also contains higher proportion of polyunsaturated fatty acids (65 percent) (Holbrook et al., 1985) in comparison to the steady state (25 percent) (Breckenridge et al., 1972; Holbrook et al., 1985).

Although the authors showed that the brain synthesized choline molecules de novo both in vivo and in vitro, the question whether this process actually could occur within cholinergic neurons, remained unanswered due to the heterogeneity of brain tissue. The authors therefore used a culture of purely cholinergic cells (human neuroblastoma, LA-N2) in order to address this issue. When the LA-N2 cells were incubated with [^{14}C]ethanolamine for 24 hours, most of the radioactivity in cells was recovered in [^{14}C]PtdEtn; however, 3 to 7 percent of that was present in [^{14}C]PtdCho. Using a newly developed high performance chromatography method (Liscovitch et al., 1985); the authors established that 5 to 10 percent of this PtdCho was apparently hydrolyzed yielding [^{14}C]phosphocholine intracellularly or free [^{14}C]choline which was recovered from the cell growth media (Blusztajn et al., 1986). Thus cholinergic neurons can synthesize choline de novo via the PtdEtn methylation and subsequent PtdCho hydrolysis. Studies now in progress are designed to determine whether some of this choline can be utilized as a precursor of ACh.

"Autocannibalism" and Pathophysiology of Alzheimer's Disease

An overwhelming consensus now exists among investigators that a) certain ACh-releasing brain neurons, the septal neurons projecting to the hippocampus and basal forebrain neurons innervating the cerebral cortices, invariably degenerate in Alzheimer's disease (Bowen et al., 1982; Perry et al., 1978; Wilcock et al., 1982; Wurtman, 1985); b) other neurons (for example, serotonin-releasing neurons in the raphe nucleus; noradrenergic neurons of the locus coeruleus; cortical somatostatin-releasing neurons) are also often afflicted but to a lesser extent; and, c) many neuronal populations are largely unaffected in the disease. If one or more groups of neurons are invariably damaged in Alzheimer's disease, then examination of their biochemical peculiarities may yield insights as to the disease's etiology or to the pathogenetic process that ultimately causes the neurons to die. Moreover, if the deficient neurotransmitter can be implicated in the abnormal behaviors typical of the disease—like ACh in memory loss, or norepinephrine in the impaired ability to sustain attention, or serotonin in disturbances of mood or in aggressiveness—then drugs which substitute for the deficient transmitter or which increase its availability in synapses might be useful in treating the disease.

The authors propose that the selective vulnerability of cholinergic neurons is due to "autocannibalism." The hypothesis begs the question of the etiology of the Alzheimer's disease, focusing instead on why cholinergic neurons are more likely than others to be damaged by the etiologic factor: It applies equally well whether the etiologic factor is present only in diseased cells or is distributed throughout the brain. The factor itself that presumably causes a choline deficiency might be a decrease in choline's production (by de novo synthesis); a decrease in its uptake from the synaptic cleft and extracellular space; or an excessive utilization of choline to form a particular phospholipid. Choline uptake might be impaired if the delivery of oxygen or glucose to the nerve terminals is deficient, perhaps secondary to a diffusion block caused by the perivascular amyloidosis that is characteristic of Alzheimer's disease (Mandybur, 1975). Alternatively, the hypothetical choline deficiency might simply result from its overuse for ACh synthesis, as might happen if the firing frequency of vulnerable neurons is persistently enhanced, or if the presynaptic storage of ACh is impaired. Once cholinergic terminals begin to deteriorate and to release less of the transmitter, it seems likely that surviving, "healthy" terminals might start to release *more* ACh—because the firing frequencies of their neurons will increase or because release is no longer subject to presynaptic inhibition. Increased ACh synthesis might also be expected to increase the demand for its precursor, choline, within "healthy" terminals, a process which might ultimately lead to "autocannibalism" in these terminals as well.

Several pieces of clinical evidence are consistent with the "autocannibalism" hypothesis of the pathogenesis of Alzheimer's disease:

1. It is the terminals of cholinergic neurons, in the cerebral cortex, and not the perikarya, in the basal forebrain, which apparently degenerate first in Alzheimer's disease (Pearson et al., 1983; Perry et al., 1985). This is consistent with the fact that most of the neurons' ACh is formed in the pre-synaptic terminals.

2. Only long-axon cholinergic neurons are affected by the disease process: the short-axon interneurons in the striatum are spared. Perhaps the short-axon neurons can more easily resynthesize their membranes because Ch-PL are more readily available to them through axoplasmic transport (Abe et al., 1973; Droz et al., 1981). This transport would occur over a considerably shorter distance than that separating cholinergic perikarya in the nucleus basalis or septum from terminals in the frontoparietal cortex or hippocampus.

3. Patients with Down's syndrome invariably develop pathological signs (senile plaques and tangles) indistinguishable from those observed in the brains of people with Alzheimer's disease (*see* Epstein, 1983 for a review) as well as a decrease in cortical CAT activity (Yates et al., 1980). Brain PtdEtn and PtdSer purified from autopsy specimens of

fetuses affected with this genetic disorder exhibit abnormal fatty acid composition (Brooksbank et al., 1985), suggesting that abnormal phospholipid metabolism might also be found in the brains of people with Alzheimer's disease.

4. PtdCho and PtdEtn are metabolized by brain phospholipases A (PLA) and lysophospholipases to form glycerophosphocholine or glycerophosphoethanolamine, respectively. The amounts of glycerophosphocholine in brain autopsy specimens from patients that died with Alzheimer's disease reportedly are 3.6 fold higher than those present in samples from normal people (Barany et al., 1985). (The amounts of PtdCho and PtdEtn were found to be unchanged in that study.) The increase in glycerophosphocholine is suggestive of the increased rates of PtdCho degradation. It is possible that PtdCho degradation is catalyzed by PLA in Alzheimer's disease to a higher extent than by phospholipase D (PLD) (*see* below), hence an increase in glycerophosphocholine. Since PLA might be specific for a different pool of PtdCho (e.g., containing different fatty acids) than PLD, the net result might be a change in molecular species of PtdCho that might be pathogenic to membranes.

5. The activity of PLD (the enzyme that catalyzes the hydrolysis of PtdCho to free choline) and of CAT are decreased to a similar extent in autopsy specimens of cortexes of patients that died with Alzheimer's disease (Julian Kanfer, personal communication). It is tempting to speculate that PLD is specifically localized within cholinergic nerve terminals, and the decrease in its activity is a reflection of their degeneration; alternatively the decrease in PLD activity might reflect a general abnormality in phospholipid metabolism characteristic to Alzheimer's disease.

Since the discoveries of cholinergic deficits in Alzheimer's disease, several clinical studies have been performed that utilized various doses of choline or lecithin as possible therapeutic agents in the treatment of the disease (cf. Wurtman et al., 1984). The rationale for these clinical trials was that the choline (free or liberated from lecithin) would be used by the surviving cholinergic neurons as the precursor of ACh resulting in some restoration of the cholinergic tone in the brain. It is apparent that these procedures might also lead to increases of Ch-PL synthesis and therefore improve the functions of membranes that might be affected by "autocannibalism." Though these clinical trials have been mildly successful at best, it has to be stressed that people with symptoms of Alzheimer's disease probably suffer a cholinergic lesion so severe that it might be irreparable. The choline/lecithin supplementation regimens might be more useful in treating patients with smaller lesions, i.e., those who are at risk of getting the disease. Therefore it would be highly desirable to develop a diagnostic tool that would help identify such individuals so that they could be placed on lecithin treatments early in the course of their illness.

References

Abdel-Latif, A.A., and Smith, J.P. Incorporation *in vitro* of $[^{14}C]$choline into phosphatidylcholine of rat synaptosomes and the effect of calcium ions. *Biochem. Pharmacol.*, 21:436–439, 1972.

Abe, T., Haga, T., and Kurokawa, M. Rapid transport of PtdCho occurring simultaneously with protein transport in the frog sciatic nerve. *Biochem. J.*, 136:731–740, 1973

Barany, M., Chang, Y-C., Arus, C., et al. Increased glycerol-3-phosphorylcholine in post-mortem Alzheimer's brains. *Lancet*, 1:517, 1985.

Blusztajn, J.K., and Wurtman, R.J. Choline biosynthesis by a preparation enriched in synaptosomes from rat brain. *Nature*, 290:417–418, 1981.

Blusztajn, J.K., and Wurtman, R.J. Choline and cholinergic neurons. *Science*, 221:614–620, 1983.

Blusztajn, J.K., Richardson, U.I., Liscovitch, M., and Wurtman, R.J. Syntheses of acetylcholine and choline in human neuroblastoma cells, LA-N2. *Transactions of the American Society for Neurochemistry*, 17, 1986.

Bowen, D.M., Benton, J.S., Spillane, J.A., et al. Choline acetyltransferase activity and histopathology of frontal neocortex biopsies of demented patients. *J. Neurol. Sci.*, 57:191–202, 1982.

Breckenridge, W.C., Gombos, C., and Morgan, I.G. (1972) The lipid composition of adult rat brain synaptosomal plasma membranes. *Biochim. Biophys. Acta*, 266:695–707, 1972.

Brooksbank, B.W.L., Martinez, M., and Balazs, R. Altered composition of polyunsaturated fatty acyl groups in phosphoglycerides of Down's syndrome fetal brain. *J. Neurochem.*, 44:869–874, 1985.

Droz, B., Brunetti, M., Di Giambernardino, L., et. al. Axonal transport of phosphoglycerides to cholinergic synapses. In: Pepeu G. (ed.), *Cholinergic Mechanisms.* New York: Plenum Press, 1981, pp. 377–386.

Epstein, C. Down's syndrome and Alzheimer's disease: Implications and approaches. In: Katzman, R. (ed.), *Biological Aspects of Alzheimer's Disease.* Cold Spring Harbor Laboratory, 1983, pp. 169–182.

Hamprecht, B. Structural, physiological, biochemical, and pharmacological properties of neuroblastoma-glioma cell hybrids in cell culture. In: *International Review of Cytology,* Vol 49. New York: Academic Press, 1977, pp. 99–170.

Holbrook, P.G., Mauron, C., and Wurtman, R.J. Molecular species of phosphatidylcholine formed by base-exchange and phosphocholine transferase in nerve endings. Proceedings of the satellite meeting of the International Society for Neurochemistry in Mantova, Italy, 1985.

Kennedy, E.P., and Weiss, S.B. The function of cytidine coenzymes in the biosynthesis of phospholipids. *J. Biol. Chem.*, 222:193–214, 1956.

Liscovitch, M., Freese, A., Blusztajn, J.K., and Wurtman, R.J. High performance liquid chromatography of water-soluble choline metabolites. *Anal. Biochem.*, 151:182–187, 1985.

Maire, J.-C., and Wurtman, R.J. Source of choline for the release of choline and acetylcholine from brain slices. *J. Physiol.* (Paris), 80:189–195, 1985.

Mandybur, T.I. The incidence of cerebral amyloid angiopathy in Alzheimer's disease. *Neurology* (Minneap.), 25:120–126, 1975.

Pardridge, W.M., Cornford, E.M., Braun, L.D., and Oldendorf, W.H. Transport of choline and choline analogues through the blood-brain-barrier. In: *Nutrition and the Brain,* Vol 5. New York: Raven Press, 1979, pp. 25–34.

Parducz, A., Kiss, Z., and Joo, F. Changes of the phosphatidylcholine content and the number of synaptic vesicles in relation to neurohumoral transmission in sympathetic ganglia. *Experientia,* 32:1520–1521, 1976.

Pearson, R.C.A., Sofroniew, M.V., Cuello, A.C., et al. Persistence of cholinergic neurons in the basal nucleus in a brain with senile dementia of the Alzheimer's type demonstrated by immunohistochemical staining for choline acetyltransferase. *Brain Res.*, 289:375–379, 1983.

Perry, R.H., Candy, J.M., Perry, E.K., et al., Extensive loss of choline acetyltransferase activity is not reflected by neuronal loss in the nucleus of Meynert in Alzheimer's disease. *Neurosci. Lett.*, 33:311–315, 1985.

Perry, E.K., Tomlinson, B.E., Blessed, G., et al. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Brit. J. Med.*, 2:1458–1459, 1978.

Porcellati, G., Arienti, G., Pirotta, M., and Giorgini, D. Base-exchange reaction for the synthesis of phospholipids in nervous tissue: the incorporation of serine and ethanolamine into phospholipids of isolated brain microsomes. *J. Neurochem.*, 18:1395–1417, 1971.

Tacconi, M-T., and Wurtman, R.J. Phosphatidylcholine produced in rat synaptosomes by N-methylation is enriched in polyunsaturated fatty acids. *Proc. Natl. Acad. Sci. USA,* 82:4828–4831, 1985.

White, H.L., and Wu, J.C. Kinetics of choline acetyltransferase (EC 2.3.1.6) from human and other mammalian central and peripheral nervous tissue. *J. Neurochem.*, 20:297–307, 1973.

Wilcock, G.K., Esiri, M.M., Bowen, D.M., and Smith, C.C.T. Alzheimer's disease: correlation of cortical choline acetyltransferase activity with the severity of dementia and histological abnormalities. *J. Neurol. Sci.*, 57:407–417, 1982.

Wurtman, R.J., Corkin, S.H., and Growdon, J.H. (eds.), *Alzheimer's Disease: Advances in Basic Research and Therapies.* Cambridge, Massachusetts, CBSM, 1984.

Wurtman, R.J. Alzheimer's disease. *Scientific American,* 252:62–75, 1985.

Yates, C.M., Simpson, J., Maloney, A.J.F., et al. Alzheimer-like cholinergic deficiency in Down syndrome. *Lancet,* 2:39, 1980.

Panic Disorder: Clinical Characteristics, Epidemiology, and Treatment

Chair:

Myrna M. Weissman, Ph.D.

Yale University School of Medicine
New Haven, CT 06519

The Relationship Between Panic Disorder and Agoraphobia: An Epidemiologic Perspective

Myrna M. Weissman, Ph.D.,[1] Philip J. Leaf, Ph.D.,[1] Dan G. Blazer, M.D., Ph.D.,[2] Jeffrey H. Boyd, M.D., M.P.H.,[3] and Louis Florio, B.A.[1]

Introduction

This paper presents the most recent data on the epidemiology of panic disorder and agoraphobia based on findings from the Epidemiologic Catchment Area (ECA) Project, and examines the relationship between agoraphobia and panic disorder and symptoms in light of these epidemiologic data.

Studies of large population samples that include both treated and untreated persons, such as the ECA, are essential for obtaining a true estimate of the prevalance of a disorder and for understanding the complete clinical picture. Since, for many disorders, few ill persons seek medical treatment, those who do seek treatment may represent the more severely ill persons or persons with multiple disorders. The need for epidemiologic data is particularly true for the anxiety disorders where the presenting symptoms may be misconstrued as cardiac problems, as in panic disorder, and may never come to the attention of a psychiatrist, or where the presenting symptoms may include social withdrawal, as in agoraphobia, and may never lead the person to seek treatment.

Epidemiologic Studies Using RDC or DSM-III Criteria

Data on the epidemiology of panic disorder and agoraphobia based on Research Diagnostic Criteria (RDC) or DSM-III criteria are now available from four epidemiologic surveys: the 1975 New Haven Survey (Weissman et al., 1978); the 1979 National Survey of Psychotherapeutic Drug Use (Uhlenhuth et al., 1983); the Zurich Study (Angst & Dobler-Mikola, in press); and the ECA (Regier et al., 1984). The details of these findings have been presented elsewhere (Merikangas & Weissman, 1985; Weissman, 1985; Weissman et al., 1985). This report will focus on recent data from the NIMH ECA study.

---

[1] Department of Psychiatry, Depression Research Unit, Yale University School of Medicine, 350 Congress Avenue, New Haven, CT, 06519.

[2] Duke University Medical Center, Box 3173, Durham, NC 27710.

[3] Center for Epidemiologic Studies, Division of Clinical Research, National Institute of Mental Health, 5600 Fishers Lane, Rockville, MD 20857.

The Epidemiologic Catchment Area Survey (ECA)

The ECA study, based on interviews with community samples of over 15,000 adults age 18 years and older, using the Diagnostic Interview Schedule (DIS), was independently conducted at five sites: New Haven, Connecticut (Yale University); Baltimore, Maryland (Johns Hopkins University); St. Louis, Missouri (Washington University); Piedmont area, North Carolina (Duke University); and Los Angeles, California (UCLA). Thus far, data have been published or presented for the first wave of interviews at Yale, Johns Hopkins, and Washington University (Boyd, 1985; Boyd et al., 1985; Myers et al., 1984; Robins et al., 1984; VonKorff et al., 1985). However, preliminary data are now available from all five sites. More comprehensive presentations of these data will be made in future reports. The full details of the design and methods of this survey are described elsewhere (Eaton & Kessler, 1985; Regier et al., 1984).

Results

Six-Month Prevalence Rates of Panic Disorder and Agoraphobia

There is reasonable consistency of findings in the 6-month prevalence rates/100 of panic disorder across the five ECA sites, where the range of rates is 0.6 to 1.0/100 (Table 1). At all sites (not shown here) the rates are higher in women than men.

There is greater variability between sites in the 6-month prevalence rates of agoraphobia (2.7 to 5.8/100). The rates are highest in Baltimore and Piedmont. At all sites (not shown here) the rates are higher in women than men.

TABLE 1. Six-Month Prevalence Rates/100 Panic Disorder and Agoraphobia: ECA.

	Panic Disorder	Agoraphobia
New Haven, CT	0.6	2.8
Baltimore, MD	1.0	5.8
St. Louis, MO	0.9	2.7
Piedmont, NC	0.7	5.4
Los Angeles, CA	0.9	3.2

Relationship Between Agoraphobia and Panic Disorder

There is good evidence from epidemiologic and clinical studies that more than one anxiety disorder tends to occur in individuals over their lifetime. In the 1975 New Haven survey, over 80 percent of persons with GAD had had at least one of the other anxiety disorders in their lifetime; 30 percent of persons with phobias had had panic disorder at some time in their life. There was also an overlap of the anxiety disorders with major depression: Over 7 percent of persons with GAD, 2 percent with panic disorder, and 4 percent with phobia had major depression at some time in their life (Weissman, 1985).

Similarly, on the basis of data from three ECA sites, Boyd et al. (1984) found that the odds of having a second anxiety disorder or a major depressive episode, given the presence of an anxiety disorder, were significantly and substantially increased. Angst and Dobler-Mikola (in press) also found a high overlap between the anxiety disorders. Longitudinal studies are necessary for understanding the relationship among the anxiety disorders and between anxiety and affective disorders.

Of particular interest has been the relationship between panic disorder and symptoms and agoraphobia. According to Klein's observations, agoraphobia is a conditioned reaction to the sudden onset of unexplained panic attacks—a view that has been adopted widely by many clinicians and researchers who rarely find patients who have agoraphobia without panic disorder or symptoms.

Agoraphobia With Panic Disorder or Symptoms—ECA

The lifetime rates of agoraphobia with and without panic disorder or symptoms were examined in the five-site ECA data (Table 2). The lifetime rates of agoraphobia with panic disorder or symptoms ranged from 1.7 to 2.6/100, and without panic disorder or symptoms ranged from 1.4 to 6.6/100 in the five sites. Thus a substantial portion of subjects in all five sites met the criteria of agoraphobia without panic disorder or symptoms ever.

TABLE 2. Lifetime Rates/100 Agoraphobia: ECA.

	With Panic Disorder or Symptoms	Without Panic Disorder or Symptoms
New Haven, CT	2.2	1.4
Baltimore, MD	2.6	6.6
St. Louis, MO	1.9	2.3
Piedmont, NC	2.0	5.8
Los Angeles, CA	1.7	3.1

In a closer examination, we found that at all five sites there were subjects with agoraphobia and some symptoms of panic who did not have the three attacks in 3 weeks as required to meet the diagnostic criteria for panic disorder.

Figure 1 shows the percent of subjects with agoraphobia plus panic disorder or symptoms, other psychiatric disorders, or no other disorder over a lifetime in the five ECA sites. The excess risk of agoraphobia in Piedmont and Baltimore is largely accounted for by the subjects with pure agoraphobia. The pure agoraphobics comprise nearly 44 percent of the agoraphobics in Baltimore and 53 percent in Piedmont, but only 23 percent in New Haven, 34 percent in St. Louis, and 37 percent in Los Angeles. The subjects with agoraphobia and panic disorder comprise the smallest percent of agoraphobics at all five sites (range 6 percent to 13 percent). The range of persons with agoraphobia who also have other disorders is 16.5 percent to 28.1 percent across the five sites. There was more variability between sites of subjects with agoraphobia and panic symptoms (50.4 percent in New Haven, 22.5 percent Baltimore, 32.4 percent St. Louis, 16.8 percent Piedmont, 28.0 percent Los Angeles).

A range of other psychiatric disorders (not shown here) occurred in subjects with agoraphobia and no panic disorder or symptoms. The most common diagnoses were depression and alcohol or drug abuse.

Conclusion

1) The 6-month prevalence rate of panic disorder is approximately 1 percent, which is consistent across the five sites. The rates are higher in women than men at all sites.

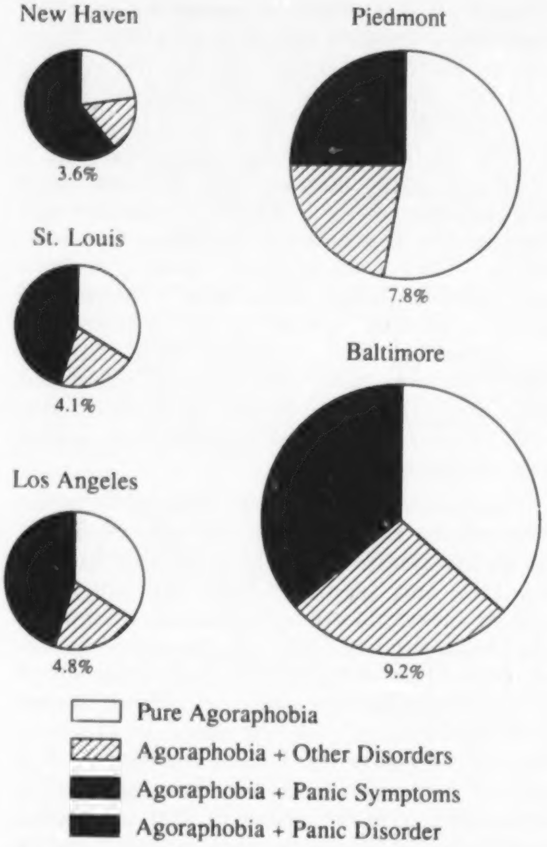


FIGURE 1. Percent of subjects with agoraphobia, with and without other disorders over a lifetime: ECA.

2) There is more variability between sites in the 6-month prevalence rates of agoraphobia. At all sites, the rates are higher in women than men; and the rates are higher than for panic disorder.

3) Agoraphobia is a heterogeneous disorder. The clinicians who want to revise the DSM-III to include agoraphobia as a variant of panic disorder from their perspective may be correct in that agoraphobia *usually* occurs with panic disorder or panic symptoms in clinical practice, especially in anxiety clinics.

Moreover, the patient with agoraphobia and panic symptoms is more likely to be motivated to come for the treatment of the distressing symptoms of panic, whereas the patient with only agoraphobia is more apt to stay home. Thus, from the clinician's perspective, agoraphobia is probably rarely seen without panic symptoms or disorder.

Boyd et al. (1985; in press) found that, when they divided agoraphobics into those who received and those who did not receive treatment by a mental health specialist in the last 6 months, at every ECA site a larger proportion of the treated agoraphobics have a history of panic attacks than did untreated agoraphobics. Only at Piedmont did this difference reach statistical significance, however. They concluded that treated agoraphobics more often have a history of panic attacks than do untreated agoraphobics. The epidemiologic studies, which include both treated and untreated cases, suggest that there may be several pathways to agoraphobia other than as an avoidance of panic.

The discrepancy between clinical observation and the ECA findings also may be inherent in the assessment of agoraphobia itself in the DIS and in the SADS. As noted by Spitzer (personal communication, December 18, 1985), the key DSM-III concept of agoraphobia—"fear of being in a place from which escape might be impossible or difficult in case of incapacitation"—is not asked in precisely that way in either the DIS or the SADS. The key concept in the DIS is "strong fear of something or some situation that is avoided even though there is no real danger," and in the SADS-L it is "usually the avoidance is recognizable as unreasonable. In some cases, however, subjects avoid situations because they anticipate overwhelming anxiety." These subtle differences in wording could account for some of the findings.

We are planning a follow-up study to clinically examine those subjects in the community who have agoraphobia without panic disorder or symptoms. It is possible that misdiagnosis has occurred. In addition to our clinical reappraisal, further study might include family studies as well as use of other available diagnostic assessments.

On the other hand, the ECA project raises questions as to the DSM-III criteria for agoraphobia. It may be that these criteria now designate as disordered a group of individuals meeting the criteria for agoraphobia but who experience no panic. Those agoraphobics seen in tertiary care settings may represent the most severely ill cases, or may be individuals entering treatment due to the panic attacks.

Acknowledgments

This research was supported in part by grant MH30929, the Yale Mental Health Clinical Research Center, National Institute of Mental Health; by the John D. and Catherine T. MacArthur Foundation Mental Health Research Network on Risk and Protective Factors in the Major Mental Disorders; and by the Epidemiologic Catchment Area (ECA) Program.

The Epidemiologic Catchment Area Program is a series of five epidemiologic research studies performed by independent research teams in collaboration with staff of the Division of Biometry and Epidemiology of the National Institute of Mental Health. The NIMH Principal Collaborators are Darrel A. Regier, Ben Z. Locke, and Jay Burke; the NIMH Project Officer is Carl A. Taube. The Principal Investigators and Co-Investigators from the five sites are: Yale University, U01 MH34224—Jerome K. Myers, Myrna M. Weissman, and Gary L. Tischler; Johns Hopkins University, U01 MH33870—Morton Kramer, Ernest Gruenberg, and Sam Shapiro; Washington University, St. Louis, U01 MH33883—Lee N. Robins and John Helzer; Duke University, U01 MH35386—Dan Blazer and Linda George; University of California, Los Angeles, U01 MH35865—Marvin Karno, Richard L. Hough, Javier I. Escobar, M. Audrey Burnam, and Dianne M. Timbers.

References

Angst, J., and Dobler-Mikola, A. The Zurich study: Anxiety and phobia in young adults. *Arch. Psychiatry Neurol. Sci.* (In press.)

Boyd, J.H. Are panic attacks the cause of agoraphobia? Proceedings of the Annual Meeting of the American Psychiatric Association, Dallas, Texas, May, 1985.

Boyd, J.H., Burke, J.D., Gruenberg, E., et al. Exclusion criteria of DSM-III. *Arch. Gen. Psychiatry*, 41:983-989, 1984.

Boyd, J.H., Regier, D.A., and Burke, J.D. The contribution of epidemiology to the advancement of nosology. Proceedings of the World Psychiatric Association, Section on Nomenclature and Classification, "International Classification in Psychiatry." Montreal, Canada, June 27, 1985.

Boyd, J.H., Regier, D.A., and Burke, J.D. The contribution of epidemiology to the advancement of nosology. In: Mezzich, J. and Von Cranach, M. (eds.), *International Classification in Psychiatry*. New York: Cambridge University Press, in press.

Eaton, W.W., and Kessler, L.G. *Epidemiologic Methods in Psychiatry: The NIMH Epidemiologic Catchment Area Program*. New York: Academic Press, 1985.

Merikangas, K.R., and Weissman, M.M. Epidemiology of anxiety disorders in adulthood. In: Michels, R., and Cavenar, J.O. (eds.), *Psychiatry*. Vol. 3. Philadelphia: J.B. Lippincott Company, 1985.

Myers, J.K., Weissman, M.M., Tischler, G.L., et al. Six-month prevalence of psychiatric disorders in three communities: 1980–1982. *Arch. Gen. Psychiatry*, 41:959–967, 1984.

Regier, D.A., Myers, J.K., Kramer, M., et al. The NIMH Epidemiologic Catchment Area Program: Historical context, major objectives, and study population characteristics. *Arch. Gen. Psychiatry*, 41:934–941, 1984.

Robins, L.N., Helzer, J.E., Weissman, M.M., et al. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch. Gen. Psychiatry*, 41:949–958, 1984.

Uhlenhuth, E.D., Balter, M.B., Mellinger, G.D., et al. Symptom checklist syndromes in the general population: Correlations with psychotherapeutic drug use. *Arch. Gen. Psychiatry*, 40:1167–1173, 1983.

VonKorff, M., Eaton, W., Keyl, P. The epidemiology of panic attacks and disorder: Results from three community surveys. *Amer. J. Epidemiol.*, 122:970–981, 1985.

Weissman, M.M., Myers, J.K., Harding, P.S. Psychiatric disorders in a U.S. urban community. *Am. J. Psychiatry*, 135:459–462, 1978.

Weissman, M.M., Leaf, P.J., Holzer, C.E., Merikangas, K.R. The epidemiology of anxiety disorders: A highlight of recent evidence. *Psychopharmacol. Bull.*, 21(3):538–541, 1985.

Weissman, M.M. The epidemiology of anxiety disorders: Rates, risks, and familial patterns. In: Tuma, A.H., and Maser, J.D. (eds.), *Anxiety and the Anxiety Disorders*. Hillsdale, N.J.: Lawrence Erlbaum Associates, Inc., 1985, 275–296.

Recent Developments in the Understanding and Pharmacotherapy of Panic Attacks

Michael R. Liebowitz, M.D., Abby J. Fyer, M.D., Jack Gorman, M.D., and Donald F. Klein, M.D.[1]

Because of the prevalence and morbidity of panic disorder and agoraphobia with panic attacks, development of effective pharmacological treatment over the past two decades has been one of the important developments in modern psychiatry. The ramifications for clinical practice, diagnostic classification, and elucidation of pathophysiology have been vast.

With regard to treatment, pharmacotherapy has rendered panic attacks relatively easy to treat and agoraphobia with panic attacks much more amenable to treatment.

With regard to diagnostic classification, imipramine responsivity of panic attacks but not of anticipatory anxiety, and the reverse for standard benzodiazepines, suggested panic differed qualitatively rather than quantitatively from generalized anxiety. This substantially contributed to the subdivision of the DSM-II category of anxiety neurosis into panic disorder and generalized anxiety disorder, with most anxiety disorder patients who come for psychiatric treatment falling into the former category. Pharmacotherapy also demonstrated the importance of panic attacks as a core feature in most cases of agoraphobia.

With regard to pathophysiology, effective drug treatments suggest that panic attacks are neurochemically mediated, although important questions remain about what specific neurotransmitter systems are involved and to what degree cognitive factors are operative.

Below we review new findings, continued uncertainties regarding drug treatment, and models of how drugs might actually operate in panic disorder.

New Findings

The efficacy of imipramine in blocking panic attacks is well established in double blind placebo controlled studies (Klein, 1964; Zitrin, 1983), as is the antipanic efficacy of phenelzine (Sheehan et al., 1980). More recently, the triazolobenzodiazepine alprazolam has been shown to block panic attacks (Sheehan, 1984). In agoraphobia with panic attacks alprazolam definitely blocks the panic attack, although in our pilot study of 20 patients resolution of anticipatory anxiety and phobic avoidance sometimes accompanied and sometimes followed full panic blockade (Liebowitz et al., 1986). Curiously, in one open treatment study the nonresponders differed from responders in having higher baseline Hamilton Anxiety scores (Liebowitz et al., 1986).

Although never demonstrated by a controlled study, in our clinic desmethylimipramine (DMI) seems as effective as imipramine in blocking panic attacks, although somewhat higher doses appear to be needed. In one sample, mean effective daily antipanic dose for DMI was 271 mg as opposed to an effective antipanic dose of imipramine of 178 mg.

Several investigators have reported antipanic efficacy with clomipramine (CMI) in open clinical trials (Gloger et al., 1981; Caetano, 1985). Interestingly, effective CMI doses in 22 patients in one trial ranged from 10 to 50 mg/day with a mean of 26.4 mg, and several patients had initial exacerbations on 25 mg/day (Caetano, 1985). The investigator recommended that one begin with a 5 mg dose. Also, major panic attacks tended to be suppressed within 7 to 14 days of treatment. A limitation of this study was concomitant use of benzodiazepines, which were not

---

[1] New York State Psychiatric Institute and the College of Physicians and Surgeons, Columbia University.

Address reprint requests to Michael R. Liebowitz, M.D., 722 West 168 Street, New York, NY 10032

Supported in part by MH 903-1163C, MHCR 903-C006 and Research Scientist Development Award MH-00416 (Dr. Gorman) from the National Institute of Mental Health.

specified as to dose or type. Gloger et al. (1981) used up to 100 mg/day of CMI in an open trial of 8 patients with panic disorder and 12 agoraphobics; 75 percent of each group were reported asymptomatic after 8 weeks of treatment. Forty percent of the sample showed initial worsening on 25 mg/day of CMI, and required smaller starting doses. Forty-five percent of the sample required CMI doses of less than 50 mg/day for effective symptom control.

Gorman et al. (unpublished data) administered fluoxetine, a specific serotonin reuptake blocker, to 16 patients with panic disorder or agoraphobia with panic attacks in an open clinical trial. Patients dropped out of the clinical trial prematurely because of overstimulation or became panic-free with approximately equal frequency. A substantial number of panic patients apparently cannot tolerate fluoxetine 10 mg/day at least as initial therapy, and 2.5 and 5 mg initial doses need to be tried.

The serotonin precursor 5 hydroxytryptophan (5 HTP), in conjunction with carbidopa, has also been found in an open pilot study to be effective in blocking panic attacks, although, again, a certain percentage of patients showed overstimulation but were successfully treated with lower doses (Kahn & Westenberg, 1985). Zimelidine, another selective serotonin reuptake blocker, also appeared to block panic attacks in an open clinical trial of 13 patients (Koczkas et al., 1981). In this study, seven patients definitely improved while six discontinued treatment after 6 weeks because of poor health. This study involved patients with agoraphobia, social phobia, or mixed phobia, so it is impossible to assess the antipanic effect, especially since panic attacks themselves were not a dependent measure. Another limitation was the allowed concomitant use of oxazepam. Dizziness and dry mouth increased in the nonresponders.

There are anecdotal data that trazadone, another drug with relatively greater impact on serotonin than norepinephrine, is effective in panic patients. One open clinical series suggested that clonazepam, a high potency benzodiazepine that does not have a triozolo structure, is also effective in blocking panic attacks (Fontaine & Chouinard, 1984). Interestingly, in addition to its effect on the benzodiazepine-GABA receptor complex, clonazepam has also been reported to increase both serotonin synthesis and function in man at normal clinical doses (Chouinard, 1985).

Finally, Sheehan has reported that phenelzine is somewhat more potent than imipramine or alprazolam in blocking panic attacks and reducing related anticipatory anxiety and phobic avoidance. There are no published studies of monoamine oxidase inhibitors (MAOI) other than phenelzine in panic patients. We have treated three panic patients with the MAO B inhibitor deprenyl up to 40 mg/day and one has shown an antipanic effect, which is inconclusive.

Uncertainties

The relapse rate after tapering drug treatment for panic patients is uncertain. In a report of several hundred mixed phobic patients treated openly with phenelzine, Kelly et al. (1970) found that 30 percent of the patients who were well for 1 year were able to come off medication and remain well, although the length of follow-up is not specified. Another 30 percent relapsed after attempting to reduce or stop the MAOI, while 34 percent were advised not to try drug withdrawal.

Zitrin and Klein (1983) found a relapse rate from 19 to 31 percent in agoraphobic patients treated for 6 months with imipramine and supportive or behavioral therapy who showed at least moderate improvement, and were then followed for 2 years. Relapse in this study was defined as a return of avoidance behavior. There were no significant differences in relapse between supportive or behavioral therapy. Sheehan (personal communication, 1985), however, reports relapse rates of over 70 percent after stopping imipramine, phenelzine, or alprazolam. Relapse in this series was defined as any return of unexpected anxiety episodes or avoidance such that the patient requested to restart medication on two separate occasions.

Criteria for relapse are not the same in the Zitrin-Klein and Sheehan studies. One variable is whether you are talking about one or two panic attacks when patients come off drug or a full relapse. This may be a crucial point in terms of withdrawing panic patients from alprazolam, which may be more problematic than discontinuing imipramine or phenelzine in terms of withdrawal symptoms and return of panic attacks. There is some suggestion, however, that even if patients have panic attacks coming off alprazolam, if they can continue for several weeks off the drug, this may disappear.

While there are substantial data showing the efficacy of behavioral treatment approaches such as exposure on agoraphobic symptoms of avoidance, the efficacy of behavior therapy for the actual panic attack has received little study. Beck (1985) has hypothesized that a panic attack represents a cognitive reaction of great alarm to a benign physical disturbance. He gives as an example somebody standing up, feeling lightheaded and then feeling very distressed that something terrible might be happening, or a skier with a history of a heart attack having rapid heart beat from exertion and reacting with great alarm when he thought he might be having another heart attack. These are not, however, representative of the kinds of patients seen in anxiety research programs. Here patients complain that their initial panic attacks consist of dramatic physical disturbances involving racing heart, shortness of breath, dizziness, etc. preceded by, accompanied by, or immediately followed by panicky feelings that they are about to die, lose control, or pass out.

Nevertheless, it is possible to conceptualize that panic attacks do consist of some kind of profound physical arousal to which patients then react with profound emotional disturbance because they think this physical arousal means something terrible is happening and they are in grave danger. The anxious thoughts may exacerbate the physical symptoms and vice versa in a positive feedback loop until panic sets in. This is a two-component hypothesis as opposed to a one-component hypothesis where the physical- and mental-emotional symptoms are part of a single, biologically based arousal process. In the two-component process the cognitive reaction is usually seen as an overreaction conditioned by some previous experience, although it could be a "hardwired" alarm reaction to sensations normally associated with real danger to the organism.

A two-component hypothesis provides a rationale for cognitive-behavioral therapy, which attempts to have patients learn to relabel their physical arousal, changing it from "something terrible must be happening" to "there goes my heart again" or "there goes my dizzy symptom again," etc. They would still have physical disturbances but no longer react with fear that escalates into terror, turning a panic attack into a symptom attack. The efficacy of this approach is only now, however, receiving systematic study, although anecdotal data suggest benefit in some panic patients. There are several open clinical reports that training in slow breathing can lower frequency and lessen intensity of panic attacks in subsets of panic patients (Bonn et al., 1984; Rapee, 1985; Clark et al., 1985), perhaps by preventing secondary emotional escalation and hyperventilation.

Models of How Drugs Work

There are several types of data that need to be taken into account.

1) Effective pharmacotherapy blocks lactate-induced as well as clinical panics. A reasonable formulation is that clinical panic attacks involve discharge of specific centrally mediated neurophysiological circuits, and that effective antipanic drugs raise the threshold for firing of these circuits. This is true while the drugs are being taken and, for many patients, for months to years after drug therapy is stopped. If drugs simply blocked nonspecific physical arousals that, in turn, provoked cognitive overreactions, then lactate-induced arousal should not be blocked unless antipanic drugs also blocked the physical effects of lactate, which they do not appear to do. Antipanic drugs could hypothetically also block cognitively mediated panic responses to any stimulus, but in practice do not do so.

2) Certain cognitive behavioral procedures, while not totally suppressing all vestiges of panic attacks, are anecdotally reported to alter their characteristics. Untreated, most panic patients report at least occasional episodes where they feel profound autonomic arousal plus the experience of being about to

die, lose control, or pass out. If cognitive-behaviorally treated patients can prevent themselves from reaching the extremes of panic while continuing to experience mild to moderate or even severe degrees of autonomic arousal (palpitations, lightheadedness, etc.), it would suggest that this physical arousal is the core of panic attacks, with the extreme of terror and/or hyperventilation as secondary, cognitively mediated reactions. Controlled studies are now needed to see what aspects of panic attacks can be treated by cognitive and behavior therapies. It has already been demonstrated that drug therapy can suppress the physical and emotional aspects of panic, but leave the patient initially with high anticipatory anxiety as he or she still feels helpless and vulnerable should an attack occur.

One would predict that if successful in ameliorating panic attacks, cognitive-behavioral therapy would produce more steep declines in anticipatory anxiety than in physical accompaniments of panic (the reverse of drug therapy) because the fear of what to do when an attack starts is directly addressed via new cognitive and/or breathing techniques. With drug therapy no coping tools are provided, so anticipatory anxiety can only extinguish with time, while the actual somatic manifestations of a panic attack are directly blocked.

3) Some patients manifest lactate sensitivity in the face of being clinically well (Fyer et al., 1985). We have 10 patients who panicked with lactate, were successfully treated with drug therapy, remained panic free after drug withdrawal, and were rechallenged with lactate 1 to 6 months off medication. Six of them panicked with lactate, but remained clinically well for at least 6 months after that. Here one has to assume that the threshhold for discharge of relevent CNS systems remains sufficiently high to prevent spontaneous triggering of panics, but not high enough to be refractory to lactate challenge. In normals, the threshold for firing of the relevant systems is sufficiently high to be refractory to spontaneous discharge and lactate activation, at least with 0.5 molar DL-lactate. Higher doses of lactate, however, have not been tested in normals.

If our conjectures about panic are correct, then we should include as (for now, separate) types of clinical and laboratory-induced panic certain patterns of distressing physical symptoms with abrupt onset that are not accompanied by profound emotional arousal. Supporting this view is our finding that patients with clinical panics who do not panic with lactate still look physiologically and clinically different during the infusion than normal controls, suggesting some added or pathological arousal from the lactate that does not go on to meet *current* criteria for a *panic attack* (Liebowitz et al., 1985). These lactate nonpanickers may be showing a somatic response to lactate that reflects their neurochemical vulnerability, but not of sufficient magnitude in that particular setting to set off significant emotional anxiety.

If specific patterns of somatic arousal are the biological core of panic, this could explain the difference between panic and generalized anxiety. Generalized anxiety may be an overreaction to nonspecific internal or external events, while panic is one or more centrally mediated specific pattern of somatic arousal with variable emotional responses.

The final issue is the neurochemical nature of panic vulnerability, be it somatic arousal with cognitive overreaction or a unitary physical-emotional arousal process. Adrenergic systems have received the most attention, initially suggested by Redmond's work (1979) with locus ceruleus stimulation and blockade in primates. As discussed earlier, however, drugs that enhance the effects of serotonin appear both active as antipanic agents and overly stimulatory if given in initially too high doses, a set of findings that has received little attention. Lingjaerde (1985) has recently reported that lactate facilitates serotonin uptake in platelets and suggests comparable effects in the CNS. Serotonergic stimulation and blockade studies are therefore indicated for panic patients, since serotonergic systems, acting independently or via effects on noradrenergic or other systems, may be involved in the pathophysiology of panic attacks.

References

Beck, A.T., and Emery, G. *Anxiety Disorders and Phobias: A Cognitive Perspective*. New York: Basic Books, 1985.

Bonn, J.A., Readhead, C.P.A., and Timmons, B.H. Enhanced adaptive behavioral response in agoraphobic patients pretreated with breathing retraining. *Lancet*, September, 665–669, 1984.

Caetano, D. Treatment for panic disorders with clomipramine (Anafranil): An open study of 22 cases. Ciba-Geigy reprint. *J. Brasileiro de Psiquiatria*, 34(2):123–132, 1985.

Chouinard, G. Antimanic effects of clomazepam. *Psychosomatics*, 26(125):7–12, 1985.

Clark, D.M., Salkovskis, P.M., and Chalkley, A.J. Respiratory control as a treatment for panic attacks. *J. Behav. & Exp. Psychiat.*, 16(1):23–30, 1985.

Fontaine, R., and Chouinard, G. Antipanic effect of clonazepam. *Am. J. Psychiat.*, 141:1, 1984.

Fyer, A.J., Liebowitz, M.R., Gorman, J.M., et al. Lactate vulnerability of remitted panic patients. *Psychiat. Res.*, 14:143–148, 1985

Gloger, S., Grunhaus, L., Birmacher, B., and Troudart, T. Treatment of spontaneous panic attacks with clomipramine. *Am. J. Psychiat.*, 138(9):1215–1217, 1981.

Kahn, R.S., and Westenberg, G.M. L-5-hydroxytryptophan in the treatment of anxiety disorders. *J. Affec. Dis.*, 8:197–200, 1985.

Kelly, D., Guirguis, W., Frommer, E., et al. Treatment of phobic states with antidepressants. *Br. J. Psychiat.*, 116:387–398, 1970.

Klein, D.F. Delineation of two drug-responsive anxiety syndromes. *Psychopharm.*, 5:397–408, 1964.

Koczkas, S., Holmberg, G., and Wedin, L. A pilot study of the effect of the 5-HT-uptake inhibitor, zimeldine, on phobic anxiety. *Acta Psychiatr. Scand.*, 63 (Suppl 290):329–341, 1981.

Liebowitz, M.R., Gorman, J.M., Fyer, A.J., et al. Lactate provocation of panic attacks: II. Biochemical and physiological findings. *Arch. Gen. Psychiat.*, 42:709–719, 1985.

Liebowitz, M.R., Fyer, A.J., Gorman, J.M., et al. Alprazolam in the treatment of panic disorder. *J. Clin. Psychopharm.*, 6(1):13–20, 1986.

Lingjaerde, O. Lactate-induced panic attacks: Possible involvement of serotonin reuptake stimulation. *Acta Psychiatr.*, 72:206–208, 1985.

Rapee, R. A case of panic disorder treated with breathing retraining. *J. Behav. Ther. & Exp. Psychiat.*, 16(1):63–65, 1985.

Redmond, D.E. New and old evidence for the involvement of a brain norepinephrine system in anxiety. In: Fann, W.E., Karacan, I., Pokorny, A.D., and Williams, R.L. (eds.), *Phenomenology and Treatment of Anxiety*. New York: Prentice-Hall Inc., 1979, 153–203.

Sheehan, D.V., Ballenger, J., and Jacobson, G. Treatment of endogenous anxiety with phobic hysterical and hypocondriacal symptoms. *Arch. Gen. Psychiat.*, 37:51–59, 1980.

Sheehan, D.V., Coleman, J.H., Greenblatt, D.J., et al. Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J. Clin. Psychopharm.*, 4(2):66–75, 1984.

Zitrin, C.M., Klein, D.F, Woerner, M.G., and Ross, D.C. Treatment of phobias: I. Comparison of imipramine and placebo. *Arch. Gen. Psychiat.*, 40:125–138, 1983.

Possible Respiratory Abnormalities in Panic Disorder

Jack M. Gorman, M.D.,[1] Michael R. Liebowitz, M.D.,[1] Abby J. Fyer, M.D.,[1] Minna R. Fyer, M.D.,[1] and Donald F. Klein, M.D.[1]

Some abnormality in respiratory physiology has been hinted at as the cause of panic attacks for decades. One school of thought sees hyperventilation as the cause of panic attacks. Retraining the subject to breathe abdominally instead of thoracically is held to be curative (Lum, 1981).

Because little scientific rigor has been attached to the investigation of these claims, they have understandably been met with considerable skepticism in the psychiatric community. The prevailing opinion has been that hyperventilation is one of the many manifestations of a panic attack, no different from tachycardia, trembling, or sweating (Missri & Alexander, 1978).

Recent work, however, has again placed hyperventilation into a key role in the pathogenesis of panic. While it still appears simplistic to insist that hyperventilation alone is the root cause of panic disorder, it is becoming increasingly clear that disordered ventilatory responses, and the consequent alterations in acid-base physiology, are indeed etiologically important.

Are Panic Disorder Patients Chronic Hyperventilators?

Several experiments have shown that patients with broadly defined anxiety disorder breathe faster and more deeply, with more frequent sighs, than normal controls at rest (Tucker, 1963; Huey & West, 1983). These have been taken to mean that patients with anxiety disorder are chronic hyperventilators.

There are several problems with such an interpretation. First, and most obvious, we now know that lumping patients with "anxiety disorder" into one general category only serves to blur physiological findings and obscure possible diagnostically related markers. Second, an increased minute ventilation could be the product of acute stress, merely reflecting (in anxious patients) a greater cognitive reaction to being part of an experiment. Finally, increased minute ventilation does not necessarily reflect hyperventilation. Hyperventilation refers to ventilation in excess of cellular metabolic demands. The anxious patients could be hypermetabolic compared to the normal controls.

True hyperventilation quickly—that is, within seconds—produces a reduction in the arterial concentration of carbon dioxide (CO_2), known as hypocapnia. This in turn causes respiratory alkalosis, defined as a pH exceeding 7.45. Hypocapnia is a potent stimulator to vasoconstriction. With sufficient hyperventilation the subject will feel faint, confused, nauseated, dizzy, and anxious. Heart rate increases and the subject feels dyspneic, even though the reverse is actually the problem.

With chronic hyperventilation, two additional physiological changes take place. First, the kidney attempts to compensate for alkalosis by excreting additional bicarbonate and retaining titratable acid (Stanbury & Thomson, 1952). Second, the constriction of cerebral vessels leads to cellular hypoxia which stimulates dilatation (Plum et al., 1968). The chronic hyperventilator will have nearly normal pH, low PCO_2, low bicarbonate, and normal vascular caliber. Both acute and chronic hyperventilation cause hypophosphatemia (Mostellar & Tuttle, 1964) by complex and incompletely understood mechanisms.

---

[1] The New York State Psychiatric Institute, 722 W. 168th Street, New York, NY 10032.

This work was supported in part by National Institute of Mental Health grants MH-37592 and MH-30906, and by a Research Scientist Development Award, MH-00416, to Dr. Gorman.

We were surprised to find, in the course of analyzing data from our sodium lactate infusion experiments of patients with panic disorder, evidence of chronic, rather than acute, hyperventilation (Liebowitz et al., 1985). That is, in the 30-minute period of baseline measurement before we started the infusion, the patients with panic disorder had lower PCO_2 and lower bicarbonate, but not higher pH, than normal controls. Had the patients merely been reacting to the stress of being in the laboratory or the anticipation of getting lactate, we would have expected acute hyperventilation and alkalosis. This was not found.

In a subsequent analysis with larger sample size (Gorman et al., in press) we again observed chronic hyperventilation in panic disorder. In addition, we now show that acute hyperventilation is superimposed on chronic hyperventilation, so that at the point of a lactate-induced attack the patient drops the PCO_2 even further. Finally, in a *post hoc* analysis, an inorganic phosphate level lower than 2.25 mg/dl just prior to starting lactate appeared to assure that the patient would go on to have lactate-induced panic.

These findings are precisely what the hyperventilation theorists would have predicted. Specifically, the chronic hyperventilator, when stressed, appears to hyperventilate even more and quickly throw him or herself into respiratory alkalosis. This, plus the cerebral arterial constriction, could account for the symptoms of a panic attack. In addition, hypophosphatemia itself can cause neurologic symptoms including anxiety and paresthesias (Kreisberg, 1977). The fact that panic disorder patients do not appear to be hyperventilating when seen outside the laboratory is not a problem for this theory; several studies have shown that once the chronic hyperventilatory pattern of blood gas changes has been established, only a few deep breaths every hour are sufficient to maintain it (Salzman et al., 1963).

Does Treatment Cure Hyperventilation?

Of course, there are abundant claims, mostly anecdotal, that behavioral treatment aimed at stopping hyperventilation also cures panic attacks. But if hyperventilation is truly involved in the etiology of panic, then any treatment that blocks the attack should also eliminate the biological evidence of chronic hyperventilation.

Here, we have some suggestive evidence. First, we restudied a group of 20 panic-disorder patients after they had been panic-free by virtue of anti-panic medication for at least 4 weeks (Gorman et al., 1985). What we observed was a normalization of venous pH, PCO_2, and bicarbonate. That is, the variance of these measures was greater in the patients before treatment than controls, but after treatment the patient variance equalled that of the controls. In other words, pH, PCO_2, and bicarbonate became normal after treatment, although in a few cases this meant pH rising to normal and PCO_2 declining to normal.

The variance may be accounted for by our recent observation that patients with panic disorder and mitral-valve prolapse have higher PCO_2 than patients with panic disorder without mitral-valve prolapse (unpublished data). This suggests that not all patients with panic disorder are chronic hyperventilators: perhaps patients with prolapse are a different subgroup with autonomic abnormalities other than respiratory.

Another way to look at the treatment issue with respect to hyperventilation is to see what symptoms patients complain of before and after panic blockade is achieved.

Patients who do not panic during lactate infusion still experience greater symptomatic discomfort than controls. This is measured by a 17-item checklist called the Acute Panic Inventory (API). We compared items on the API among three groups: controls receiving lactate infusion, patients receiving lactate infusion for the first time while still ill but not experiencing a lactate-induced panic attack (NP1), and patients receiving a second lactate infusion after panic blockade by anti-panic medication and again not experiencing a lactate-induced panic (NP2). The API was administered three times to each subject during each infusion.

A drug responsive API-item should have the following four characteristics by analysis of variance for repeated measures (ANOVAR):

1) The item should show a time effect within the infusion, with increasing severity.

2) The item slope over time should be greater for the NP1 group than the NP2 group.

3) The item slope over time should be greater for the NP1 group than controls.

4) The item should be equal between NP2 and controls, thereby showing normalization with drug.

We would be interested in whether there is a group by time interaction indicating that the slope of the increment in symptomatology for a given item in the NP1 group exceeds the slopes in both the control and NP2 groups. This would indicate that the NP1 group, that is the unmedicated patients, were responding to lactate infusion in a qualitatively unique way.

Only one group of items each met these criteria: feeling faint, difficulty breathing, feeling dizzy, feeling confused, derealization, difficulty concentrating, and twitching. These are all symptoms characteristic of hyperventilation. The other items are fear of dying, general fear, palpitations, urge to urinate, urge to defecate, depersonalization, sweating, difficulty speaking, and feeling nauseated.

Hence, we can conclude that it is precisely those items that reflect hyperventilation that are both highly reactive to lactate infusion and normalized by anti-panic medication.

Can Hyperventilation Acutely Provoke Panic?

Can enforced hyperventilation in a patient with panic disorder actually provoke panic? The standard laboratory provocation of panic is the lactate infusion. Other groups claim to provoke attacks with a variety of other agents, including yohimbine, isoproterenol, norepinephrine, and caffeine. But could something as simple as asking the patient to breathe hard be equally effective?

Here, the literature is misleading. There are many references to a "hyperventilation test" as if it were a clinically accepted procedure. No one had seemingly bothered to test its usefulness. Patients supposedly had attacks during room air hyperventilation (RAH). But were these attacks due to the actual induction of respiratory alkalosis or merely to the fatigue and discomfort of breathing fast? Also, how was the obvious demand on the subject to present some symptoms controlled for?

What was needed was a control for hyperventilation in which the subject must breathe fast without becoming hypocapnic or alkalotic. This can be accomplished by the inhalation of 5 percent CO_2 in room air. Five-percent CO_2 inhalation triples minute ventilation but, because carbon dioxide is constantly being added, no hypocapnia develops. We felt this would be a good control for RAH.

Our results were unexpected (Gorman et al., 1984). Seven of the first 12 patients with panic disorder had attacks during the 5-percent CO_2 inhalation phase. Only three had attacks during RAH. Controls were sensitive to neither CO_2 nor RAH.

We subsequently learned that Cohen had performed a similar experiment on patients with "neurocirculatory asthenia" almost 30 years ago and obtained the same result (Cohen & White, 1950). Another group has since replicated our findings (Woods et al., 1981).

One of the things that CO_2 does is to stimulate locus ceruleus discharge (Elam et al., 1981). One speculation was, therefore, that CO_2 was panicogenic because it induced an increase in central noradrenergic discharge.

It is also the case that lactate is quickly metabolized to bicarbonate and then to carbon dioxide. How quickly and to what degree lactate actually crosses the blood-brain barrier is controversial (Nemato et al., 1974). Bicarbonate does not cross readily at all (Pierce et al., 1971). Hence, lactate panic might actually be caused by an increase in central CO_2 concentration.

We have now extended our RAH-CO_2 protocol. The results are basically the same. To date, 12 of 31 patients with panic disorder have had acute panic attacks during a 20-minute inhalation of 5-percent CO_2. The CO_2 panickers have a faster rate of increase than nonpanicking patients or controls in almost every ventilatory measure: respiratory rate, tidal volume, minute ventilation, duty cycle, and inspiratory flow. They also have greater increases in diastolic blood pressure and plasma norepinephrine. However, no differences were found for plasma cortisol, systolic blood pressure, or plasma epinephrine. This is also the case for lactate-induced panic. Neither normal controls nor patients with other anxiety disorders (social phobia, obsessive compulsive disorder, and generalized anxiety disorder) were sensitive to 5-percent CO_2.

We have raised the "dose" of CO_2 in a few trials. Now, the rate of panic in patients with panic disorder increases to six of nine subjects, but three of three social phobics also panicked. Normal controls remain insensitive. At the 7-percent level, therefore, it is possible that sensitivity is enhanced but specificity sacrificed. This clearly needs further study.

Our rate of panic to RAH has increased somewhat to 7 of 30 subjects. Very few biologic changes characterize these RAH-induced attacks, however, and the change in API score is generally less than that seen for CO_2 panickers. In fact, two of the seven RAH panickers did not even become alkalotic because they stopped overbreathing too quickly. Hence, it remains possible that hyperventilation panic reflects a peculiar vulnerability to fatigue rather than the effects of alkalosis.

One other striking finding was that in the period following both CO_2 and RAH-induced panic attacks, the patient continues to hyperventilate. The normal response to the cessation of hyperventilation is virtual breath holding to allow CO_2 levels to rise to normal. But those patients who had panicked while hyperventilating continue to hyperventilate after being told to stop.

Van den Hout and Griez (1985) have done a number of experiments with CO_2 inhalation. They believe that "CO_2-induced" symptomatology does not occur until immediately after CO_2 is actually stopped. The method of CO_2 administration is simpler than ours: a double breath inhalation via face mask of a combination of 35-percent CO_2 and 65-percent oxygen (O_2). This procedure can be administered in a matter of minutes.

We have now used the Griez and van den Hout method in a few trials. Five of eight patients with panic disorder had attacks immediately following inhalation of 35-percent CO_2/65-percent O_2. Two additional patients felt in a "pre-panic" state. Only one of the eight had no increase in anxiety. By comparison, there were no attacks in five normal controls; only one complained of increased anxiety. The patients found the attacks very similar to their spontaneous attacks, although shorter in duration.

How do we account for the fact that patients with panic disorder appear to be chronic hyperventilators, yet panic when administered carbon dioxide? One possibility is that panic-disorder patients have a hypersensitivity to CO_2. This could conceivably involve the peripheral arterial chemoreceptors (carotid bodies and aortic bodies), intrapulmonary receptors, or the medullary chemoreceptors. Relatively low concentrations of CO_2 would trigger these centers to induce hyperventilation and other autonomic changes. Overwhelming the system with CO_2 produces such autonomic unrest that panic is provoked.

In order to avoid triggering these hypersensitive receptors, patients with panic disorder chronically hyperventilate, thereby maintaining CO_2 concentration as low as possible. Medications that block panic may work directly on the hypersensitive chemoreceptors to normalize their reactions. This would obviate the need for hyperventilation as an adaptive response. While hyperventilation is not the cause of panic according to this theory, abnormal respiratory physiology assumes a place of critical importance.

References

Cohen, M.E., and White, P.D. Life situations, emotions, and neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome). *Proc. Assoc. Res. Nerv. Men. Dis.*, 29:832–869, 1950.

Elam, M., Yao, T., Thoren, P., and Svensson, T.H. Hypercapnia and hypoxia: Chemoreceptor-mediated control of locus ceruleus neurons and splanchnic, sympathetic nerves. *Brain Res.*, 222:373–381, 1981.

Gorman, J.M., Askanazi, J., Liebowitz, M.R., et al. Response to hyperventilation in a group of patients with panic disorder. *Am. J. Psych.*, 141:857–861, 1984.

Gorman, J.M., Cohen, B.S., Liebowitz, M.R., et al. Blood gas changes and hypophosphatemia in lactate-induced panic. *Arch. Gen. Psych.* (In press.)

Gorman, J.M., Fyer, A.J., Ross, D.C., et al. Normalization of venous pH, pCO_2, and bicarbonate levels after blockade of panic attacks. *Psych. Res.*, 14:57–65, 1985.

Huey, S.R., and West, S.G. Hyperventilation: Its relation to symptom experience and to anxiety. *J. Abnl. Psychology*, 92(4):422–432, 1983.

Kreisberg, R.A. Phosphorus deficiency and hypophosphatemia. *Hosp. Proc.*, 12:121–128, 1977.

Liebowitz, M.R., Gorman, J.M., Fyer, A.J., et al. Lactate provocation of panic attacks: II. Biochemical and physiological findings. *Arch. Gen. Psych.*, 42:709–719, 1985.

Lum, L.C. Hyperventilation and anxiety states *J. R. Soc. Med.*, 74:1–4, 1981.

Missri, J.C., and Alexander, S. Hyperventilation syndrome: A brief review. *J.A.M.A.*, 240:2093–2096, 1978.

Mostellar, M.E., and Tuttle, E.P. Effects of alkalosis on plasma concentration and urinary excretion of inorganic phosphate in man. *J. Clin. Invest.*, 13:138–234, 1964.

Nemato, E.M., Hoff, J.J., and Severinghaus, J.W. Lactate uptake and metabolism by brain during hyperlactemia and hypoglycemia. *Stroke*, 5:548–553, 1974.

Pierce N.F., Fedson, D.S., Brigham, K.C., et al. Relation of ventilation during base deficit to acid base values in blood and spinal fluid. *J. App. Physiol.* 30:677–683, 1971.

Plum, F., Posner, J.B., and Smith, W.W. Effect of hyperbaric-hypoxic hyperventilation on blood, brain, and CSF lactate. *Am. J. Physiol.*, 215(5):1240–1244, 1968.

Salzman, H.A., Heyman, A., and Sicker, H.J. Correlation of clinical and physiologic manifestations of sustained hyperventilation. *New Engl. J. Med.*, 268:1431–1436, 1963.

Stanbury, S.W., and Thomson, A.E. The renal response to respiratory alkalosis. *Clin. Sci.*, 11:357–374, 1952.

Tucker, W.I. Hyperventilation in differential diagnosis. *Med. Clin. N. Amer.*, 47:491–497, 1963.

Van den Hout, M.A., and Griez, E. Peripheral panic symptoms occur during changes in alveolar carbon dioxide. *Comp. Psychiatry*, 26(4):381–387, 1985.

Woods, S.W., Charney, D.J., Lake, J., et al. CO_2 sensitivity in panic anxiety: Ventilatory and anxiogenic response to CO_2 in healthy subjects and panic anxiety patients before and after alprazolam treatment. *Arch. Gen. Psych.* (In press.)

Behavioral Conception and Treatment of Panic

David H. Barlow, Ph.D.[1]

Behavior therapy "cut its teeth" on phobias. Since Wolpe's (1958) pioneering book on the treatment of neurotic problems a variety of behavioral procedures have been tested and proven effective in the treatment of phobia. During the 1960's and 1970's scores of studies were performed isolating the effective ingredients of these treatments. The overriding conclusion that emerged from this systematic research during the 1970's was that one particular procedure was common to all successful behavioral treatments for phobia (Mavissakalian & Barlow, 1981). This procedure, which came to be called exposure, consisted of motivating the patient to expose him or herself to a series of increasingly more difficult situations that provided the context for the phobic reactions and arranging conditions to facilitate this exposure. At present there are many psychologically based theories as to why this treatment is successful, including but not limited to extinction, habituation, emotional processing, and increases in perceived self-efficacy (Barlow & Mavissakalian, 1981; Barlow, in press). While none of these theories is fully supported as yet, there is clear evidence that exposure-based treatments are effective with phobias in general and agoraphobia with panic in particular. Some of these data are represented in Table 1 which summarizes the results of 24 controlled outcome studies testing exposure-based treatments for agoraphobia as reviewed by Jannson and Ost (1982). The data summarized in this review indicate that 70 percent of patients improved substantially with exposure-based treatments. The dropout rate averages 12 percent, although it is consistently higher for the type of exposure program which is administered in a very intensive fashion, for example, over a 2-week period, and much lower for programs administered in a more gradual self-paced manner (e.g., Barlow, O'Brien, & Last, 1984).

At the same time this systematic research was ongoing, research from another perspective was isolating the phenomenon of panic. In 1959 when agoraphobics were still called schizophrenics by most clinicians because of their severe symptoms and marked social impairment, Donald Klein had a clinical hunch regarding the importance of panic. From this idea emerged a progression of descriptive and pharmacological research identifying panic as a central component in many of the anxiety disorders. This, in turn, led to revisions in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*) designating panic disorder as a separate diagnostic entity (American Psychiatic Association, 1980). Now the evidence is strong from both pharmacological and behavioral investigators that agoraphobias with panic and panic disorder do not differ in any substantial manner with the exception of the development of avoidance behavior as a complication in some, but not in all, people who initially suffer from unexpected panic attacks (Barlow, 1986).

If panic is indeed the central feature of agoraphobia, two questions arise. Why are exposure-based treatments as successful as they are, and what happens to panic attacks during exposure? Because of a somewhat different conceptualization of this disorder, behavior therapists very seldom measured panic in past studies, although clinical reports would indicate that panic attacks did indeed

TABLE 1. Outcome of Exposure Treatments for Agoraphobia Based on 24 Studies at Followup of at Least 5 Months (range 5 months to 5 years).

Global Clinical Ratings (%)			
Improved (Median)	Range	Dropouts (Median)	Range
70	58–83	12	0–35

Adapted from Jannson & Ost, 1982.

---

[1] Center for Stress and Anxiety Disorders, Department of Psychology, State University of New York at Albany, 1535 Western Avenue, Albany, NY 12203.

decrease during successful exposure-based treatments. Nevertheless, more recently, clinical researchers investigating exposure-based treatments have measured panic more systematically, and the results are somewhat surprising. For example, Chambless, Goldstein, Gallager et al. (in press) assessed panic and avoidance behavior in a series of 35 patients receiving exposure-based treatments who were medication free at all times. They chose patients from a larger series who were medication free in order to observe more systemically the effects of exposure on panic. While this was not a controlled experimental study, the results, which are presented in Table 2, indicate that almost two-thirds of these 35 patients were free of panic attacks for at least a 1-week period at the 6-month follow-up. In fact, the results with panic seem to be somewhat better than the results for avoidance behavior where only 29 percent of the patients were free of avoidance. However, avoidance behavior was measured by a very conservative questionnaire which probably overestimates phobic avoidance. In any case, it seems that exposure-based treatments are consistently effective in reducing panic attack when this is measured, and that this is a very important result in exposure-based treatments. For example, Barlow et al. (1984), in a study examining the effectiveness of adding the spouse to exposure-based treatments, discovered that among those who responded to the treatment, significant reductions occurred in a composite measure of panic combining frequency, duration, and intensity of attacks. But for those who were judged to be nonresponders on a broadly based criteria, this measure of panic actually showed increases. One-third of the responders in this study reported no panic attacks whatsoever after treatment. These results are presented in Table 3. These results have now been replicated in several other studies examining exposure-based treatments (Michelson, Mavissakalian, & Marchione, 1985; Ghosh & Marks, in press).

Why do exposure-based treatments result in improvements in panic? To explain this one has to combine one old idea and one relatively new idea into a behavioral conceptualization of panic. This conceptualization leads to new behavioral treatments directed specifically at panic attacks which are in an early stage of development.

TABLE 2. Outcome of Behavioral Treatment of Agoraphobia on Avoidance and Panic for 35 Medication Free Patients at 6 Months.

Panic Attacks		Avoidance While Alone (as compared to normals)	
Yes	No	Yes	No
36%	64%	71%	29%

Adapted from Chambless et al., in press.

Retrospective survey evidence strongly suggests that the first unexpected panic occurs in the context of some marked life stress (Roth, 1960; Doctor, 1982; Last, Barlow, & O'Brien, 1984). It now seems that the occurrence of panic attacks in the population is far more widespread then we expected. For example, Norton (1985) found that almost 35 percent of the population reported one or more panics in the past year as indicated in Table 4. Norton has now substantiated these data in a replication study and other data from around the world are beginning to appear supporting this finding (Klerman, 1985).

If this is true, then one fascinating question concerns the differences between nonclinical people having occasional unexpected panics vs. those who end up in clinics seeking help for this problem. This latter group seems to comprise less than 5 percent of the population (Myers, Weissman, Tischler, et al., 1984). One possibility is that the latter group learns to fear the possibility of having another panic attack, a condition which seems to be present in almost all patients with panic disorder presenting at a clinic (Barlow, Vermilyea, Blanchard, et al., 1985). That is, some learning takes place in that the recent

TABLE 3. Ratings of Frequency Duration and Intensity of Panic Attacks for Prior Three Days After Couples Treatment.

	Pre	Post	
Responders			
N = 18	3.22	2.27	
Non-Responders			
N = 10	3.30	4.13	$p<.05$
	N = 6 Report no panic		

Adapted from Barlow, O'Brien, & Last, 1984.

TABLE 4. Panic in the Normal Population (*N* = 186).

One or More Panics In Last Year	34.4%
Panic Frequency Last Year	
1–2	17.2%
3–4	11.3%
5+	6.0%
Panic Frequency Last 3 Weeks	
1	17.2%
2	4.8%
3+	2.1%

Adapted from Norton et al., 1986.

panicker acquires an extreme sensitivity to somatic events because of the marked fear that panic may reoccur. The occurrence of slight physiological sensations, even if for perfectly normal reasons, may then evoke marked fear in the patient. This fear activates the autonomic nervous system and increases the intensity of somatic sensations resulting in an increasing spiral of fear with panic at the top of the spiral. The marked fear concerning the possibility of having another panic attack seems particularly likely to develop when no ready explanation or cause is available to which to attribute the initial panic attack. Thus, patients develop a "phobia" of internal physical sensations that may represent the beginnings of another panic attack. This phobia increases anticipatory anxiety, as well as a variety of somatic events, which, paradoxically, insure that future panic attacks will occur in an ever-spiralling pattern. The behavioral conception of panic, then, involves a psychobiological process wherein persons susceptible to anxiety experience an initial panic attack while under stress and subsequently develop a fear of certain patterns of somatic sensations that might represent the beginnings of another panic through a process called interoceptive conditioning. The four steps involved in this process, whether in the laboratory or in the natural environment are presented below.

1. The elicitation of physiological sensations.

2. The strength of the subjects' previously learned association between physiological sensations and psychological feelings of acute anxiety.

3. The degree of current (baseline) anxiety.

4. The degree of anxiety elicited by the experimental setting.

This, in fact, is the old idea referred to above since this pathway to panic was first published in 1964 (Breggin, 1964) as what was considered the best explanation for a long series of panic provocation studies in the laboratory using epinephrine.

Furthermore, this conceptualization of panic is very different from the "nonspecific stress" hypothesis often mentioned as a cause of laboratory panic. Interoceptive conditioning suggests that patients become acutely sensitized to specific patterns of internal physiological responses rather than to generalized arousal, and this seems to be well-illustrated in a very early study where panic was experimentally provoked in the laboratory (Lindemann & Finesinger, 1938). In this study 20 patients were administered either adrenaline or mecholyl, a parasympathetic stimulant with a very different pattern of physiological activation in a counterbalanced fashion. This was an extremely well-done study for the time. For example, verbatim accounts of panic attacks are provided which should convince even the most skeptical critic that what was being studied in 1938 was the same phenomenon of panic with which we are dealing today. Six of the patients panicked during adrenaline but not during mecholyl. Five panicked during mecholyl but not during adrenaline. Five panicked both during mecholyl and adrenaline, while four panicked under neither condition. Although studies such as these will have to be replicated using more current methodology, the results indicate that patients seem to learn to fear specific patterns of physiological responses.

Based on this conceptualization, new behavioral methods for treating panic directly have been devised in our center and elsewhere. What these methods have in common is that the important cues for exposure in patients with panic are not external cues found in shopping malls or any location away from a safe place or person, but rather the interoceptive cues that they have come to fear. Treatment then revolves around reproducing the physiological sensations that are most feared by individual patients in order to produce extinction or emotional processing of fear cues. Types of procedures that should be effective in this regard are listed in Table 5 and preliminary evidence exists for the effectiveness of some of them (Barlow, Cohen, Waddell, et al., 1984; Waddell, Barlow, & O'Brien, 1984; Clark, Salkovskis, & Chalkley, 1985; Orwin, 1973; Beck & Emory, 1985). In our clinic, for example, we assess for patterns of fear by having patients engage in a variety of exercises designed to produce different patterns of physiological symptoms. To activate cardiovascular symptoms we use exercise. For respiratory symptoms we induce voluntary hyperventilation. For audiovestibular systems we induce dizziness. When feared patterns are identified, these become part of treatment. Clark et al. (1985) treated 18 patients identified as sensitive to the effects of hyperventilation. Eleven were agoraphobic while seven were panicking without avoidance behavior. Panics were essentially eliminated in all patients as represented in Figure 1 through repeated exposure to the effects of hyperventilation combined with other behavioral procedures. Barlow et al. (1984) treated patients with panic disorder in a small controlled pilot study and found significant reductions on panic compared to the control group. Paradoxically, some of the effectiveness of exposure with panic may result from repeated evocation of panic in a benign context with resulting extinction or cognitive reappraisal of the consequences of panic.

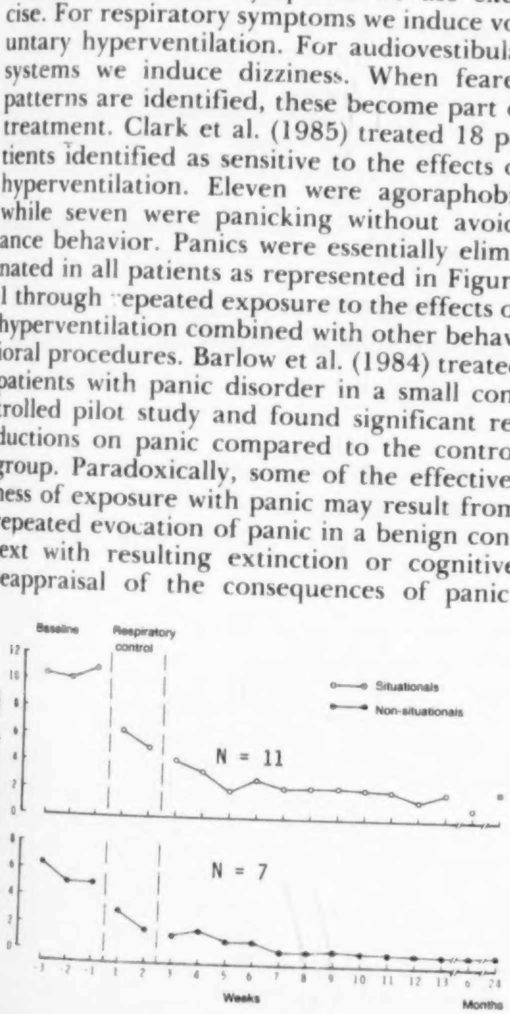


FIGURE 1. Effect of respiratory control on panic attacks. From Clark, D.M., Salkovskis, P.M., and Chalkley, A.J. Respiratory control as a treatment for panic attacks. *Journal of Behavior Therapy and Experimental Psychiatry*, 16:23–30, 1985. Permission granted to reproduce this figure.

TABLE 5. Psychological Treatment for Panic.

1)	Exercise
2)	Breathing Hyperventilation
3)	CO_2 Inhalation
4)	Imagined Physio Cues
5)	Cognitive Reattribution
6)	Relaxation

While current evidence is mostly at the level of open clinical trials, preliminary results seem promising and controlled experimentation will be forthcoming.

References

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders.* 3d ed. Washington, DC: The Association, 1980.

Barlow, D.H. In defense of panic disorder with agoraphobia and the behavioral treatment of panic: A comment on Kleiner. *The Behav. Therapist*, 9:99–100, 1986.

Barlow, D.H. (ed.), *The Anxiety Disorders.* New York: The Guilford Press. (In press.)

Barlow, D.H., Cohen, A.S., Waddell, M., et al. Panic and generalized anxiety disorders: Nature and treatment. *Behav. Ther.*, 15:431–449, 1984.

Barlow, D.H., O'Brien, G.T., and Last, C.G. Couples treatment of agoraphobia. *Behav. Ther.*, 15:41–58, 1984.

Barlow, D.H., Vermilyea, J., Blanchard, E.B., et al. The phenomenon of panic. *J. Abnormal Psych.*, 94:320–328, 1985.

Beck, A.T., and Emory, G. *Anxiety Disorders and Phobias: A Cognitive Perspective.* New York: Basic Books, 1985.

Breggin, P.R. The psychophysiology of anxiety with a review of the literature concerning adrenaline. *J. Nerv. Ment. Dis.*, 139:558–568, 1964.

Chambless, D.L., Goldstein, A.J., Gallager, R., et al. Integrating behavior therapy and psychotherapy in the treatment of agoraphobia. *Psychotherapy.* (In press.)

Clark, D.M., Salkovskis, P.M., and Chalkley, A.J. Respiratory control as a treatment for panic attacks. *J. Behav. Ther. & Exp. Psychiat.*, 16:23–30, 1985.

Doctor, R.M. Major results of a large-scale pretreatment survey of agoraphobics. In: DuPont, R.L. (ed.), *Phobia: A Comprehensive Summary of Modern Treatments.* New York: Brunner/Mazel, Inc., 1982, pp. 203–230.

Ghosh, A., and Marks, I.M. Self-treatment of agoraphobia by exposure. *Behav. Ther.* (In press.)

Jansson, L., and Ost, L.G. Behavioral treatment for agoraphobia. An evaluative review. *Clin. Psychol. Rev.*, 2:311–336, 1982.

Klerman, G.L. Personal communication (1985).

Last, C.G., Barlow, D.H., and O'Brien, G.T. Precipitants of agoraphobia: Role of stressful life events. *Psych. Reports*, 54:567–570, 1984.

Lindemann, E., and Finesinger, J.E. The effect of adrenaline and mecholyl in states of anxiety in psychoneurotic patients. *Am. J. Psychiat.*, 95:353–370, 1938.

Mavissakalian, M., and Barlow, D.H. (eds.). *Phobia: Psychological and Pharmacological Treatment*. New York: Guilford Press, 1981.

Michelson, L., Mavissakalian, M., and Marchione, K. Cognitive and behavioral treatments of agoraphobia: Clinical, behavioral, and psychophysiological outcomes. *J. Consult. Clin. Psychol.*, 53:913–925, 1986.

Myers, J.K., Weissman, M.M., Tischler, C.E., et al. Six-month prevalence of psychiatric disorders in three communities. *Arch. of Gen. Psychiat* 41:959–967, 1984.

Norton, G.R., Dorward, J., and Cox, B.J. Factors associated with panic attacks in non-clinical subjects. *Behav. Ther.*, 17:239–252, 1986.

Norton, G.R.; Harrison, B.; Hauch, J.; and Rhodes, L. Characteristics of people with infrequent panic attacks. *J. Abnorm. Psychol.*, 94:216–221, 1985.

Orwin, A. 'The running treatment': A preliminary communication on a new use for an old therapy (physical activity) in the agoraphobic syndrome. *Brit. J. Psychiat.*, 122:175–179, 1973.

Roth, M. The phobic anxiety-depersonalization syndrome and some general aetiological problems in psychiatry. *J. of Neuropsychiat.*, 306:293–306, 1960.

Waddell, M.T., Barlow, D.H., and O'Brien, G.T. A preliminary investigation of cognitive and relaxation treatment of panic disorder: Effects on intense anxiety vs. 'background' anxiety. *Behav. Res. Ther.*, 22:393–402, 1984.

Wolpe, J. (ed.), *Psychotherapy by Reciprocal Inhibition*. California Stanford University Press, 1958.

Etiology and Treatment: Basic and Clinical Neuroscience Investigations

Chair:

Dennis S. Charney, M.D.

Connecticut Mental Health Center
Yale University School of Medicine
New Haven, CT 06508

Nonbenzodiazepine Anxiolytics: Insights Into Possible Mechanisms of Action

Cam P. VanderMaelen, Ph.D.,[1,2] Duncan P. Taylor, Ph.D.,[1] Greta Gehlbach, M.S.,[1] and Michael S. Eison, Ph.D.[1]

A wide variety of drugs have been used over the years in the treatment of anxiety; these include the opiates, alcohol, barbiturates, meprobamate, dopaminergic agents, various sedatives, and the benzodiazepines (BZs). The BZs were introduced 26 years ago and constituted a major advance in the treatment of anxiety; they are widely prescribed and are extremely effective for this indication. The pharmacology of BZs is well known; besides being effective in the treatment of anxiety, these compounds are also muscle relaxants, anticonvulsants, and sedative-hypnotics. Unfortunately, they interact with alcohol and other CNS depressants, such as the barbiturates, to produce potentially lethal effects. Benzodiazepines are sometimes abused, the potential for the development of dependence exists, and withdrawal symptoms sometimes occur upon cessation of benzodiazepine treatment (Lader, 1984). Because of these undesirable and unwanted effects of BZs, the search has continued for agents which would be more selective in the treatment of anxiety. As a result, a number of compounds have been synthesized in recent years which have demonstrated a pharmacological profile that has been termed "anxioselective" (Taylor et al., 1980).

One approach in the search for anxioselective drugs has been to modify the basic BZ structure in hopes of retaining anti-anxiety properties while eliminating unwanted ancillary effects. This effort has produced several candidates including Ro 16–6028 and Ro 17–1812, which appear to function as partial agonists at the BZ receptor. Neither of these two BZs, however, has proven to be sufficiently advantageous to warrant further clinical development (Merz, 1984).

Another approach to developing more anxioselective drugs has been to abandon the BZ structure altogether. This has resulted in the synthesis of a number of nonBZ compounds with clinical or preclinical indications of anxiolytic activity. However, it is important to point out that while these compounds are "nonBZ" from a chemical standpoint, not all of them are "nonBZ" from a pharmacological, mechanistic, or clinical standpoint. Indeed, some of these nonBZ anxiolytic compounds bind to the BZ receptor or to allosteric sites elsewhere on the GABA-BZ-chloride (GABA-BZ-Cl^-) ionophore complex (Williams, 1983).

---

[1] Preclinical CNS Research, Pharmaceutical Research and Development Division, Bristol-Myers Company, Evansville, IN 47721.

[2] To whom correspondence should be addressed.

Thus, these nonBZ anxiolytics and putative anxiolytics may be categorized into two groups (Table 1). In Group 1 are included nonBZ compounds which bind to the GABA-BZ-Cl^- ionophore complex in some fashion. Group 2 compounds are those nonBZ compounds which do not bind to the GABA-BZ-Cl^- ionophore complex.

The Group 1 compounds can be further differentiated into subgroup. Subgroup A compounds are nonBZs which do, in fact, bind directly to the BZ receptor in much the same way that the BZs do. In subgroup B are nonBZs which bind to allosteric sites elsewhere on the GABA-BZ-Cl^- ionophore complex (Williams, 1983). In either case A or B, it is likely that the Group 1 compounds derive their associated anxiolytic activities by a mechanism similar or identical to that of the BZs: by potentiating GABAergic neurotransmission in the brain (Bowery, 1984). For example, zopiclone and suriclone are compounds in Group A which bind to BZ sites. They share most of the pharmacologic properties of the BZs in preclinical studies.

TABLE 1. New Nonbenzodiazepine Anxiolytics

Group 1: Agents which bind to the GABA-BZ-Cl^- ionophore complex.
    A. Agents which bind directly to benzodiazepine sites.
        1. Triazolopyridazines (CL 218,872)
        2. Cyclopyrrolones (zopiclone, suriclone, suproclone)
        3. Phenylquinolines (PK 8165, PK 9084)
        4. Pyrazoloquinolines (CGS 9895, CGS 9896)
        5. β-Carbolines
    B. Agents which bind elsewhere (to "allosteric" sites) on the complex.
        1. Barbiturates
        2. Pyrazolopyridines (tracazolate)
Group 2: Agents which do not bind to the GABA-BZ-Cl^- ionophore complex.
    1. Thiazolopyridines (ritanserin)
    2. Arylpiperazines (buspirone, gepirone, TVX Q 7821)

On the other hand, PK 8165, CGS 9896, and CL 218,872 display more anxioselective preclinical profiles and appear to achieve anticonflict activity in animals by acting selectively at subtypes of the BZ receptor (Petrack & Yokoyama, 1985). Subgroup B compounds include the pyrazolopyridines such as tracazolate, which do not bind directly to BZ receptors, but which appear to alter or influence the BZ receptor. Also included are the barbiturates, which act directly on the chloride channel. Tracazolate displays a more anxioselective profile in being relatively less potent at causing sedation, muscle relaxation, or anticonvulsant action compared to its anticonflict activity in animal studies (Petrack & Yokoyama, 1985).

Exactly why a potentiation of GABAergic neurotransmission in the brain results in antianxiety action is still not well understood, but the general notion is that certain areas or systems in the brain involved in anxiety disorders are differentially affected. Just what these areas and systems are remains the topic of considerable discussion, but some light may be shed on this question by examining the remaining nonBZ anxiolytics listed in Table 1.

The Group 2 compounds listed in Table 1 are not only nonBZ in their chemical structures, but in their biochemical and pharmacological properties as well. They do not bind to the BZ receptor nor to other parts of the GABA-BZ-Cl^- ionophore complex. Nevertheless, they display clinical or preclinical indications as antianxiety drugs, and all of them interact with the serotonin system.

Ritanserin is an interesting compound in that it is a serotonin type 2 (5-HT_2) antagonist. Preliminary clinical trials with this agent have suggested efficacy in the treatment of anxiety (Ceulemans et al., 1985). Buspirone and its analogs, gepirone, and TVX Q 7821, also act on the serotonergic system, but they appear to be agonists at the type 1A serotonin (5-HT_{1A}) receptor. These compounds have shown activity in some animal models predictive of anxiolytic activity in humans (Eison et al., 1983; Riblet et al., 1982; Traber et al., 1984). Buspirone is the only compound of this group which has been shown to be a clinically effective anxiolytic (Taylor et al., 1985). Buspirone, gepirone, and TVX Q 7821 bind to 5-HT_{1A} receptors and, based upon electrophysiological and/or biochemical studies, appear to function as agonists or, in some cases, as partial agonists at this receptor. While it may at first seem paradoxical that serotonin agonists and antagonists might both be useful for the same indication, it appears that both types of agents produce similar functional effects in the brain. This common effect, at least for acute administration of these compounds, is to decrease serotonergic neurotransmission in the brain. Ritanserin does this by blocking postsynaptic 5-HT_2 receptors, while buspirone, gepirone, and TVX Q 7821 decrease serotonergic neurotransmission by directly inhibiting the firing of serotonergic neurons in the brain (Gehlbach et al., 1985; Sprouse & Aghajanian, 1985; VanderMaelen & Wilderman, 1984).

The BZs also affect serotonergic neurotransmission in the brain. This notion goes back to the work of Stein and colleagues (Stein et al., 1975) and predates the concept that the BZs achieve their effects via the GABA system. The connection between anxiety, anxiolytic drug efficacy, and the serotonin system has been reviewed recently (Iversen, 1984). The serotonin system is quite well suited for modulating various brain functions (VanderMaelen, 1985). Serotonergic neurons located mainly within the raphe nuclei send axonal projections rostrally and caudally to innervate all levels of the neuroaxis, including limbic structures, the hippocampus, and the cerebral cortex. Stein et al. (1975) showed that methysergide, a serotonin antagonist, had an effect similar to the BZs in the Geller-Seifter conflict procedure. If the BZs were to attenuate the conflict-induced suppression of behavior by reducing serotonergic neurotransmission, one might predict that lesions of the raphe nuclei would have a similar effect. Stein and colleagues (1975) employed 5,6-dihydroxytryptamine as a neurotoxin in just such an experiment. The resulting degeneration of the serotonergic system did, in fact, mimic the effect of the BZs. Similar results were obtained by Tye et al. (1977) using a more specific neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT).

Since similar effects are obtained with the BZs as with serotonin antagonists or lesions of the serotonin system, does this mean that the BZs decrease serotonergic neurotransmission in the brain? Based upon electrophysiological and biochemical studies, the answer appears to be yes. These studies indicate that, at least in unanesthetized animals, there is a decrease in the firing of serotonergic neurons following administration of the BZs (Laurent et al., 1983; Soubrie et al., 1983; Trulson et al., 1982). When the serotonin system is lesioned by 5,7-DHT in rats, diazepam, as well as buspirone and gepirone, lose their anticonflict activities, suggesting that an intact serotonin system is needed in order to observe the anticonflict ("anxiolytic") effects of these drugs (Eison et al., 1986).

Additional studies have looked at the effects of buspirone and gepirone on the firing of serotonergic dorsal raphe neurons (Gehlbach and VanderMaelen, 1985; Gehlbach et al., in preparation; VanderMaelen and Wilderman, 1984a,b; VanderMaelen et al., unpublished). It was found that systemic administration of these drugs very potently inhibited the firing of serotonergic neurons. The ED_{50} for intravenously administered buspirone was 11 μg/kg, and for gepirone the ED_{50} was 25 μg/kg. Using the technique of microintophoresis it was found that these were direct effects of the parent compounds acting on these cells (VanderMaelen and Wilderman, 1984b; VanderMaelen et al., submitted). Figure 1 illustrates some of the electrophysiological results obtained with buspirone, the prototypical agent among the 5-HT_{1A} agonist anxiolytics.

Further studies of buspirone and gepirone were carried out in the isolated brain slice preparation. It was found that buspirone and gepirone, like serotonin, inhibit the firing of 5-HT neurons in the dorsal raphe nucleus (Gehlbach et al., in preparation). Previous work by Aghajanian and VanderMaelen (1982) had shown that another 5-HT_{1A} agonist, LSD, as well as serotonin itself hyperpolarized the membrane and inhibited firing. Aghajanian and Lakoski (1984) have demonstrated that this hyperpolarization is due to an increase in membrane conductance to po-

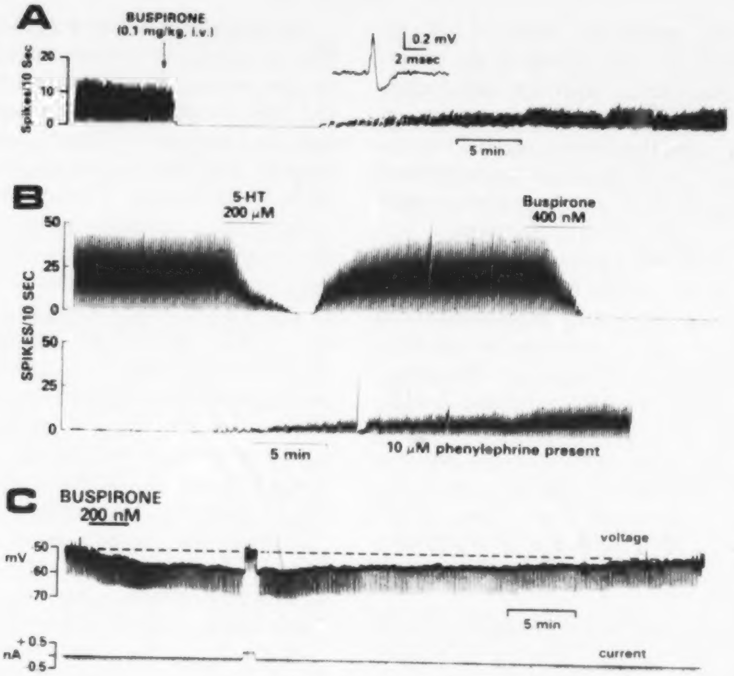


FIGURE 1. A. Inhibition by buspirone of a serotonergic dorsal raphe (DR) neuron recorded extracellularly from a chloral hydrate anesthetized rat. Inset shows oscilloscope tracing of action potential (from VanderMaelen et al., unpublished). B. Inhibition by serotonin and buspirone of a serotonergic DR neuron recorded *in vitro* in a rat brain slice preparation. The IC_{50} for buspirone was 18.9 nM (Gehlbach and VanderMaelen, 1985; Gehlbach et al., in preparation). C. Membrane hyperpolarization and decreased input resistance caused by buspirone, in a serotonergic DR neuron recorded intracellularly in a rat brain slice (VanderMaelen, in press). The step in the voltage and current traces indicates when the membrane was "manually voltage clamped" to the original resting potential to observe the magnitude of the input resistance change (measured by constant current hyperpolarizing pulses) independent of any anomalous rectification.

tassium ions. Intracellular recording experiments (VanderMaelen et al., in press) have shown that buspirone produces an effect similar to that of serotonin; that is, a hyperpolarization of the membrane and a decrease in input resistance, probably indicative of an increase in membrane conductance to potassium ions (Figure 1C). Sprouse and Aghajanian (1985) had looked at the effects of two other 5-HT_{1A} agonists, TVX Q 7821 and LY 165163, and reported similar results. These 5-HT_{1A} compounds all seem to be acting at the serotonin autoreceptor, producing inhibitory effects similar to those of serotonin.

The BZs decrease impulse discharge not only of serotonergic neurons but of noradrenergic and dopaminergic neurons as well (Laurent et al., 1983). Buspirone, on the other hand, decreases neurotransmission only in the serotonin system. In the norepinephrine system (locus coeruleus) and the dopaminergic system (substantia nigra), impulse flow is actually increased (McMillen et al., 1983; Sanghera et al., 1983). So the common effect of the BZs and buspirone is to decrease impulse flow in the serotonergic system.

Gray (1982) has proposed an elaborate theory in which the septohippocampal system plays an important role in anxiety. This system is modulated by monoaminergic systems, including the serotonergic neurons of the raphe nuclei. Yocca and Maayani (1985) studied buspirone and gepirone in the guinea pig hippocampus where serotonin stimulates the production of cyclic AMP. They found that buspirone and gepirone function as partial agonists at the 5-HT$_{1A}$ receptor in the hippocampus. It is significant that essentially the same conclusion has been drawn using electrophysiological techniques in the hippocampus. Andrade and Nicoll (1985) made intracellular recordings from hippocampal pyramidal cells in brain slices and found that buspirone, as well as gepirone, functioned as a partial agonist. Buspirone produced a smaller hyperpolarization of the membrane than serotonin, while in the presence of buspirone, the effect of serotonin was blocked.

This brings up what may be a very important point as far as the pharmacology of buspirone and gepirone are concerned: To what extent is the partial agonist activity of these compounds important, as opposed to the full agonist activity? Buspirone and gepirone may have full agonist activity in the dorsal raphe nucleus; there is no evidence that these compounds block serotonin there. On the other hand, in the hippocampus the main effect of these compounds may be their antagonism of serotonin rather than their agonist activity. It may be that some kind of balance between full agonist and partial agonist activities is required in order for a compound such as this to be effective in the clinic.

Evidence regarding the Group 2 nonBZ anxiolytics supports the notion that a decrease in serotonergic neurotransmission plays some role in anxiolytic mechanisms of action. This, of course, does not mean that all agents which have this action would be clinically effective anxiolytic drugs. LSD, 5-methoxy-N,N-dimethyl tryptamine, and lisuride are just three examples of compounds which inhibit the firing of central serotonergic neurons (VanderMaelen, 1985), but which are not clinically useful in the treatment of anxiety. Nonetheless, a direct and primary involvement of serotonergic systems, that is 5-HT neurons and 5-HT$_{1A}$ receptors, is strongly implicated in the antianxiety mechanism of action of buspirone since neurochemical, receptor binding, and autoradiographic anatomical studies indicate that buspirone binds to, localizes to, and most potently interacts with serotonergic brain systems (Taylor et al., 1985). In addition, a variety of indirect effects on other neurotransmitter systems also occurs, and contributes to the overall pharmacology of buspirone and related compounds (Eison & Eison, 1984; Taylor et al., 1985). These indirect effects may play a critical role in producing the correct combination of pharmacological actions resulting in clinical therapeutic efficacy.

References

Aghajanian, G.K., and Lakoski, J.M. Hyperpolarization of serotonergic neurons by serotonin and LSD: Studies in brain slices showing increased K$^+$ conductance. *Brain Res.*, 305:181–185, 1984.

Aghajanian, G.K., and VanderMaelen, C.P. Intracellular recordings from serotonergic dorsal raphe neurons: Pacemaker potentials and the effect of LSD. *Brain Res.*, 238:463–469, 1982.

Andrade, R., and Nicoll, R.A. The novel anxiolytic buspirone elicits a small hyperpolarization and reduces serotonin responses at putative 5-HT$_1$ receptors on hippocampal CA1 pyramidal cells. *Soc. Neurosci. Abstr.*, 11:597, 1985.

Bowery, N.G. (ed.) *Actions and Interactions of GABA and Benzodiazepines*. New York: Raven Press, 1984.

Ceulemans, D.L.S., Hoppenbrouwers, M.-L.J.A., Gelders, Y.G. and Reyntjens, A.J.M. The influence of ritanserin, a serotonin antagonist, in anxiety disorders: A double-bind placebo-controlled study versus lorazepam. *Pharmacopsychiatry*, 18:303–305, 1985.

Eison, A.S., Eison, M.S., Stanley, M., and Riblet, L.A. Serotonergic mechanisms in the behavioral effects of buspirone and gepirone. *Pharmacol. Biochem. Behav.*, 24:701–707, 1986.

Eison, M.S., and Eison, A.S. Buspirone as a midbrain modulator: Anxiolysis unrelated to traditional benzodiazepine mechanisms. *Drug Dev. Res*, 4:109–119, 1984.

Gehlbach, G., and VanderMaelen, C.P. The nonbenzodiazepine antidepressant-anxiolytic candidate, gepirone, inhibits serotonergic dorsal raphe neurons in the rat brain slice. *Soc. Neurosci. Abstr.*, 11:186, 1985.

Gehlbach, G., Wilderman, R.C., and VanderMaelen, C.P. Inhibition of serotonergic neurons *in vitro* by buspirone and gepirone, 5-HT$_{1A}$ agonists with anxiolytic activity. In preparation.

Gray, J.A. *The Neuropsychology of Anxiety*. New York: Oxford University Press, 1982.

Iversen, S.D. 5-HT and anxiety. *Neuropharmacol.*, 23 (12B):1553–1560, 1984.

Lader, M. Benzodiazepine dependence. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, 8:85–95, 1984.

Laurent, J.P., Mangold, M., Humbel, U., and Haefely, W. Reduction by two benzodiazepines and pentobarbitone of the multiunit activity in substantia nigra, hippocampus, nucleus locus coeruleus and nucleus raphé dorsalis of encéphale isolé rats. *Neuropharmacology*, 22:501–511, 1983.

McMillen, B.A., Matthews, R.T., Sanghera, M.K., Shepard, P.D., and German, D.C. Dopamine receptor antagonism by the novel antianxiety drug, buspirone. *J. Neurosci.*, 3:733–738, 1983.

Merz, W.A. Partial benzodiazepine agonists: Initial results in man. *Clin. Neuropharmacol.*, 7(Suppl. 1):672–673, 1984.

Petrack, B., and Yokoyama, N. Anti-anxiety agents and sedative-hypnotics. In: Bailey, D. (ed.), *Annual Reports in Medicinal Chemistry*, vol. 20. New York: Academic Press, 1985, pp. 1–9.

Riblet, L.A., Taylor, D.P., Eison, M.S., and Stanton, H.C. Pharmacology and neurochemistry of buspirone. *J. Clin. Psychiatry*, 43(12, sec. 2):11–16, 1982.

Sanghera, M.K., McMillen, B.A., and German, D.C. Buspirone, a non-benzodiazepine anxiolytic, increases locus coeruleus noradrenergic neuronal activity. *Eur. J. Pharmacol.*, 86:106–110, 1983.

Soubrie, P., Blas, C., Ferron, A., and Glowinski, J. Chlordiazepoxide reduces in vivo serotonin release in the basal ganglia of encéphale isolé but not anesthetized cats: Evidence for a dorsal raphe site of action. *J. Pharmacol. Exptl. Ther.*, 226:526–532, 1983.

Sprouse, J.A., and Aghajanian, G.K. Serotonergic dorsal raphe neurons: Electrophysiological responses in rats to 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtype ligands. *Soc. Neurosci. Abstr.*, 11:47, 1985.

Stein, L., Wise, C.D., and Belluzzi, J.D. Effects of benzodiazepines on central serotonergic mechanisms. In: Costa, E., and Greengard, P. (eds.), *Mechanism of Action of Benzodiazepines*. New York: Raven Press, 1975, pp. 29–44.

Taylor, D.P., Eison, M.S., Riblet, L.A., and VanderMaelen, C.P. Pharmacological and clinical effects of buspirone. *Pharmacol. Biochem. Behav.*, 23:687–694, 1985.

Taylor, D.P., Hyslop, D.K., and Riblet, L.A. Buspirone: A model for anxioselective drug action. *Soc. Neurosci. Abstr.*, 6:791, 1980.

Traber, J., Davies, M.A., Dompert, W.U., et al. Brain serotonin receptors as a target for the putative anxiolytic TVX Q 7821. *Brain Res. Bull.*, 12:741–744, 1984.

Trulson, M.E., Preussler, D.W., Howell, G.A., and Frederickson, C.J. Raphe unit activity in freely moving cats: Effects of benzodiazepines. *Neuropharmacology*, 21:1045–1050, 1982.

Tye, N.C., Everitt, B.J., and Iversen, S.D. 5-Hydroxytryptamine and punishment. *Nature*, 268:741–743, 1977.

VanderMaelen, C.P. Electrophysiological studies of buspirone's effects on serotonergic neurons. In: Tunnicliff, G., Eison, A.S., and Taylor, D.P. (eds.), *Buspirone: Mechanisms and Clinical Aspects*. Orlando, Florida: Academic Press (in press).

VanderMaelen, C.P., Matheson, G.K., Wilderman, R.C., and Patterson, L.A. "Inhibition of serotonergic dorsal raphe neurons by systemic and iontophoretic administration of buspirone, a nonbenzodiazepine anxiolytic drug" (unpublished).

VanderMaelen, C.P., and Wilderman, R.C. Buspirone, a non-benzodiazepine anxiolytic drug, causes inhibition of serotonergic dorsal raphe neurons in the rat brain slice. *Soc. Neurosci. Abstr.*, 10:259, 1984a.

VanderMaelen, C.P., and Wilderman, R.C. Iontophoretic and systemic administration of the non-benzodiazepine anxiolytic drug buspirone causes inhibition of serotonergic dorsal raphe neurons in rats. *Fed. Proc.*, 43:947, 1984b.

Williams, M. Anxioselective anxiolytics. *J. Med. Chem.*, 26:619–628, 1983.

Yocca, F.D., and Maayani, S. Actions of gepirone (BMY 13805) on functional 5-HT receptors. *The Pharmacologist*, 27:195, 1985.

Serotonin Receptor Subtypes: Biochemical, Physiological, Behavioral, and Clinical Implications

Co-Chairs:

George R. Heninger, M.D.
Yale University
New Haven, CT 06508

Herbert Y. Meltzer, M.D.
Case Western Reserve University School of Medicine
Cleveland, OH 44106

Analysis of 5-HT$_1$ Binding Site Subtypes and Potential Functional Correlates[1]

Stephen J. Peroutka, M.D, Ph.D.,[*][2] Richard E. Heuring,[2] Michael D. Mauk, Ph.D.,[2] and Jeffery D. Kocsis, Ph.D.[2]

Serotonin (5-hydroxytryptamine; 5-HT) has been implicated in a number of human diseases such as anxiety, depression, migraine, and epilepsy. However, a specific role for 5-HT has not been documented in any human disease. Receptor-site analysis is one approach which may elucidate the functional role of 5-HT in the central nervous system (CNS). Since the analysis of M and D receptors in 1957, it has become clear that multiple 5-HT receptors exist. In the past 3 years, a number of novel pharmacologic agents have been developed which have greatly facilitated the analysis of 5-HT receptor subtypes in the CNS. For example, 8-hydroxy-2-N,N-(di-propylamino)tetralin (8-OH-DPAT), RU 24969, ketanserin, and ritanserin have been shown to be potent and selective binding-site subtype agents.

At the present time, at least four distinct subtypes of 5-HT receptors have been identified in brain membranes (Hoyer et al., 1985b). The present report will focus on the current classification of 5-HT$_1$ binding-site subtypes. All 5-HT$_1$ binding-site subtypes can be labeled by ^{3}H-5-HT. Radioligand binding studies have clearly demonstrated that total 5-HT$_1$ binding as defined by ^{3}H-5-HT is heterogeneous in the rat frontal cortex (Pedigo et al., 1981). In studies performed in this laboratory (Peroutka, in press), computer analysis of drug competition curves with total ^{3}H-5-HT binding shows that 5-HT competition with ^{3}H-5-HT binding to total 5-HT$_1$ sites is consistent with a homogeneous receptor population. However, the interactions of *d*-LSD, (m-trifluoro-methylphenyl) piperazine HCl (TFMPP), methysergide, spiperone, and mianserin with total 5-HT$_1$ sites are more consistent with a two-site model of 5-HT$_1$ binding. In addition, computer-assisted curve fitting analysis of RU 24969 competition studies is most consistent with a three-site model of 5-HT_1 binding in rat frontal cortex. 8-OH-DPAT is approximately 10,000-fold selective for the 5-HT_{1A} site versus all other known 5-HT_1 binding site subtypes. As a result, 100 nM 8-OH-DPAT can be used to effectively block ^{3}H-5-HT binding to the 5-HT_{1A} site without markedly affecting the binding or ^{3}H-5-HT to non-5-HT_{1A} sites. Indeed, Scatchard analysis of ^{3}H-5-HT binding in the absence or presence of 100 nM 8-OH-DPAT demonstrates a significant decrease in the B_{max} without markedly affecting the K_D of ^{3}H-5-HT in the rat frontal cortex. Analysis of residual ^{3}H-5-HT binding reveals that the competition curve for RU 24969 is even more shallow than at total 5-HT_1 sites. Computer-assisted analysis reveals that the interactions of methysergide, TFMPP, mianserin, and RU 24969 are still consistent with at least a two-site model of non-5-HT_{1A} binding. No pharmacologic agent could be identified which has more than a 440-fold selectivity for subtypes of putative non-5-HT_{1A} binding.

---

[1] Stephen J. Peroutka was supported in part by the John A. and George L. Hartford Foundation, Alfred P. Sloan Foundation, and NS #12151-11.

[2] Departments of Neurology and Pharmacology, Stanford University School of Medicine, Stanford, CA 94305.

[*] To whom all correspondence should be addressed.

As a result, 5-HT_{1B} binding in this laboratory was defined as ^{3}H-5-HT binding in the presence of 100 nM 8-OH-DPAT plus 3,000 nM mianserin. 5-HT_{1C} binding in rat frontal cortex was defined as specific ^{3}H-5-HT binding in the presence of 100 nM 8-OH-DPAT plus 10 nM RU 24969. Under these conditions, pharmacological competition studies reveal that each putative 5-HT_1 binding-site subtype has a distinct pharmacological profile (Table 1). The 5-HT_{1B} site has extremely high affinity for RU 24969 (0.38 nM) and relatively high affinity for TFMPP. The 5-HT_{1C} site has relatively high affinity for 5-HT, mianserin, and methysergide.

However, a species study revealed interesting variations in the presence of 5-HT_1 binding site subtypes (Heuring et al., 1986). In both the rat and mouse, RU 24969 distinguishes two distinct subpopulations of non-5-HT_{1A} binding sites. In contrast, RU 24969 interactions with non-5-HT_{1A} binding in guinea pig, dog, human, cow, chicken, turtle, and frog brain membranes are consistent with a single population non-5-HT_{1A} binding-site subtype. These results suggest that certain 5-HT_1 binding-site subtypes are species specific. In particular, the 5-HT_{1B} site (as defined above) appears to be unique to rat and mouse brain membranes.

These data are consistent with the findings of multiple other laboratories. A number of radioligands have been shown to label the 5-HT_{1A} binding site: ^{3}H-8-OH-DPAT (Gozlan et al., 1983; Hall et al., 1985; Peroutka, 1985), ^{3}H-TVX Q 7821 (Dompert et al., 1985), ^{3}H-buspirone (Moon & Taylor, 1985), and ^{3}H-1-(2-(4-aminophenyl)ethyl)-4-(3-trifluoromethylphenyl) piperazine (PAPP) (Asarch et al., 1985). In addition, ^{3}H-WB 4101, previously considered a selective alpha$_1$-adrenergic radioligand, has been demonstrated to label the 5-HT_{1A} site (Norman

TABLE 1. Characteristics of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} Binding-Site Subtypes

	5-HT_{1A}	5-HT_{1B}	5-HT_{1C}
Radiolabeled by	^{3}H-5-HT ^{3}H-8-OH-DPAT ^{3}H-TVX Q 7821 ^{3}H-WB 4101 ^{3}H-Buspirone ^{3}H-PAPP	^{3}H-5-HT I^{125}CYP	^{3}H-5-HT ^{3}H-Mesulergine I^{125}LSD
High-Density Regions	Raphe nuclei Hippocampus	Dorsal Subiculum Globus Pallidus Substantia Nigra	Choroid Plexus
Potent Pharmacologic Agents	5-HT 8-OH-DPAT 5-MeDMT TVX Q 7821 Buspirone RU 24969	5-HT RU 24969	5-HT Mesulergine Mianserin Methysergide

et al., 1985). Regardless of the ^{3}H-ligand used to label the site, it displays high and selective affinity for 8-OH-DPAT, 5-methoxydimethyltryptamine (5-MeDMT), TVX Q 7821, and buspirone. The 5-HT$_{1A}$ site is densely present in the CA1 region and dentate gyrus of the hippocampus and in the raphe nuclei (Glaser et al., 1985; Pazos & Palacios, 1985). In addition, the fact that 5,7-dihydroxytryptamine-induced lesions of the raphe system cause a loss of ^{3}H-8-OH-DPAT binding in the striatum but not hippocampus has led Hamon and colleagues to hypothesize that ^{3}H-8-OH-DPAT may also label a presynaptic 5-HT autoreceptor (Gozlan et al., 1983).

The putative 5-HT$_{1B}$ site has been labeled in rat brain with I^{125} cyanopindolol (Hoyer et al., 1985a; Pazos et al., 1985). The I^{125} cyanopindolol (I^{125}CYP) site has high affinity for 5-HT and RU 24969 and relatively low affinity for *d*-LSD and 8-OH-DPAT. The highest densities of 5-HT$_{1B}$ sites in rat brain are found in the caudate nucleus, superior colliculus, lateral geniculate body, subiculum, and substantia nigra (Pazos & Palacios, 1985a).

The 5-HT$_{1C}$ site was first characterized in membranes from pig choroid plexus and cortex (Pazos et al., 1984). The site was labeled by both ^{3}H-5-HT and ^{3}H-mesulergine. Independently, Yagaloff and Hartig (1985) labeled the site with I^{125} LSD in the rat choroid plexus. The site has high affinity for 5-HT, methysergide, and mianserin and relatively low affinity for RU 24969. Another 5-HT$_1$ binding-site subtype having low affinity for RU 24969 has been identified in the bovine striatum (Peroutka, 1985). The relationship between putative 5-HT$_{1C}$ sites in rat, bovine, and pig brain is currently being investigated in this laboratory.

A number of functional correlates of the 5-HT$_1$ class of binding sites have been proposed (Peroutka, 1984) (Table 2). In particular, the extensive characterization of the 5-HT$_{1A}$ binding-site subtype has enabled an analysis of this putative receptor in many 5-HT-mediated effects. For example, the ability of 5-HT$_{1A}$ selective drugs to stimulate a 5-HT sensitive cyclase (Shenker et al., 1985) and the potent effects of guanosine triphosphate (GTP) on ^{3}H-8-OH-DPAT binding (Schlegel & Peroutka, in press) suggest a linkage of the 5-HT$_{1A}$ site to an adenylate cyclase. A role for the 5-HT$_{1A}$ site has been proposed for the mediation of certain components of the 5-HT behavioral syndrome (Smith & Peroutka, in press; Tricklebank et al., in press), canine basilar artery contractions (Peroutka, Huang, et al., in press; Taylor et al., in press), the potentiation of ejaculation and/or seminal emissions (Kwong et al., in press), hypothermia (Gudelsky et al., 1985; Middlemiss et al., 1985), and hypotensive effects of 5-HT (Doods et al., 1985).

The interactions of 5-HT$_{1A}$ selective agents have also been analyzed in an in vitro rat hippocampal slice preparation. Application of 8-OH-DPAT, buspirone, or TVX Q 7821 leads to a dose-dependent decrease in the amplitude of the population spike (Peroutka, Mauk, et al., in press). Ketanserin, a selective 5-HT$_2$ antagonist, has no independent effect on the amplitude of the population spike. In addition, ketanserin has no effect on the buspirone or TVX Q 7821-induced inhibition of the CA1 population spike. In addition, Beck et al. (1985) have shown that spiperone partially blocks 5-HT-induced changes in the CA1 population spike. Therefore, modulation of hippocampal CA1 neuronal activity may be a functional correlate of 5-HT$_{1A}$ receptor activation.

The 5-HT$_{1B}$ site has recently been analyzed in terms of the 5-HT "autoreceptor." A significant correlation has been found between the potencies of drugs at the 5-HT$_{1B}$ site as labeled by I^{125} cyanopindolol and the "autoreceptor" (Engel et al., 1986). Finally,

TABLE 2. Proposed Functional Correlates of 5-HT$_1$ Binding-Site Subtypes

5-HT$_{1A}$
Adenylate cyclase stimulation
Forepaw treading, tremor, head-weaving
Canine basilar artery contractions
Facilitation of ejaculation and/or seminal emissions
Hypothermia
Hypotensive effects
CA1 Hippocampal inhibition
5-HT$_{1B}$
"Autoreceptor"
5-HT$_{1C}$
Phosphoinositide turnover

preliminary studies suggest that phosphoinositide turnover may be mediated by the 5-HT_{1C} sites in rat choroid plexus (Sanders-Bush & Conn, 1986).

Clearly, significant progress in the analysis of 5-HT_1 binding-site subtypes has been made in the past few years. Future studies will be directed at obtaining more selective radioligands or relatively "pure" regions or species. Ideally, a radioligand should label a homogeneous population of receptors. Finally, although substantial progress is being made, the role of 5-HT in the CNS is still quite unclear. Functional correlates of 5-HT_1 binding-site subtypes may significantly add to the understanding of the role of 5-HT in the CNS.

Acknowledgment

We thank Faith Smith for manuscript preparation.

References

Asarch, K.B., Ransom, R.W., and Shih, J.C. [^{3}H]-1-(2-(4-Aminophenyl)ethyl)-4-(3-trifluoromethylphenyl) piperazine: A selective radioligand for 5-HT_{1A} receptors in rat brain. *Soc. Neurosci. Abs.*, 11:1257, 1985.

Beck, S.G., Clarke, W.P., and Goldfarb, J. Spiperone differentiates multiple 5-hydroxytryptamine responses in rat hippocampal slices in vitro. *Eur. J. Pharmacol.*, 116:195–197, 1985.

Dompert, W.U., Glaser, T., and Traber, J. ^{3}H-TVX Q 7821: Identification of 5-HT_1 binding sites as target for a novel putative anxiolytic. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 328:467–470, 1985.

Doods, H.N., Kalkman, H.O., De Jonge, A., et al. Differential selectivities of RU 24969 and 8-OH-DPAT for the purported 5-HT_{1A} and 5-HT_{1B} binding sites. Correlation between 5-HT_{1A} affinity and hypotensive activity. *Eur. J. Pharmacol.*, 112:363–370, 1985.

Engel, G., Gothert, M., Hoyer, D., et al. Identity of inhibitory presynaptic 5-hydroxytryptamine (5-HT) autoreceptors in the rat brain cortex with 5-HT_{1B} binding sites. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 332:1–7, 1986.

Glaser, T., Rath, M., Traber, J., et al. Autoradiographic identification and topographical analysis of high affinity serotonin receptor subtypes as a target for the novel putative anxiolytic TVX Q 7821. *Brain Res*, 358:129–136, 1985.

Gozlan, H., El Mestikawy, S., Pichat, L., et al. Identification of presynaptic serotonin autoreceptors using a new ligand: ^{3}H-PAT. *Nature*, 305:140–142, 1983.

Gudelsky, G.A., Koenig, J.I., and Meltzer, H.Y. Serotonin receptor subtypes and thermoregulation. *Abs. Am. Soc. Neuropsychopharmacol.*, 24:64, 1985.

Hall, M.D., El Mestikawy, S., Emerit, M.B., et al. [^{3}H]8-hydroxy-2-(Di-n-Propylamino)tetralin binding to pre- and postsynaptic 5-hydroxytryptamine sites in various regions of the rat brain. *J. Neurochem.*, 44:1685–1696, 1985.

Heuring, R.E., Schlegel, J.R., and Peroutka, S.J. Species variations in RU 24969 interactions with non-5-HT_{1A} binding sites. *Eur. J. Pharmacol.*, 122:279–282, 1986.

Hoyer, D., Engel, G., and Kalkman, H.O. Characterization of the 5-HT_{1B} recognition site in rat brain: Binding studies with (-)[^{125}I] iodocyanopindolol. *Eur. J. Pharmacol.*,118:1–12, 1985a.

Hoyer, D., Engel, G., and Kalkman, H.O. Molecular pharmacology of 5-HT_1 and 5-HT_2 recognition sites in rat and pig brain membranes: Radioligand binding studies with [^{3}H]5-HT, [^{3}H]8-OH-DPAT, (−)[^{125}I]iodocyanopindolol, [^{3}H]mesulergine, and [^{3}H]ketanserin. *Eur. J. Pharmacol.*,118:13–23, 1985b.

Kwong, L.L., Smith, E.R., Davidson, J.M. and Peroutka, S.J. Differential interactions of "prosexual" drugs with 5-hydroxytryptamine$_{1A}$ and alpha$_2$-adrenergic receptors. *Behav. Neurosci.* (In press).

Middlemiss, D.N., Neill, J., and Tricklebank, M.D. Subtypes of the 5-HT receptor involved in hypothermia and forepaw treading induced by 8-OH-DPAT. *Br. J. Pharmacol.*, 85:251P, 1985.

Moon, S.L., and Taylor, D.P. *In vitro* autoradiography of ^{3}H-buspirone and ^{3}H-2-deoxyglucose after buspirone administration. *Soc. Neurosci. Abs.*, 11:114, 1985.

Norman, A.B., Battaglia, G., Morrow, A.L., and Creese, I. [^{3}H]WB4101 labels S_1 serotonin receptors in rat cerebral cortex. *Eur. J. Pharmacol.*, 106:461–462, 1985.

Pazos, A., and Palacios, J.M. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-$_1$ receptors. *Brain Res.*, 346:205–230, 1985.

Pazos, A., Engel, G., and Palacios, J.M. Beta-adrenoceptor blocking agents recognize a subpopulation of serotonin receptors in brain. *Brain Res.*, 343:403–408, 1985.

Pazos, A., Hoyer, D., and Palacios, J.M. The binding of serotonergic ligands to the porcine choroid plexus: Characterization of a new type of serotonin recognition site. *Eur. J. Pharmacol.*, 106:539–546, 1984.

Pedigo, N.W., Yamamura, H.I., and Nelson, D.L. Discrimination of multiple [^{3}H]5-hydroxytryptamine binding sites by the neuroleptic spiperone in rat brain. *J. Neurochem.*, 36:220–226, 1981.

Peroutka, S.J. 5-HT$_1$ receptor sites and functional correlates. *Neuropharmacology*, 23:1487–1492, 1984.

Peroutka, S.J. Pharmacological differentiation and characterization of 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1C}$ binding sites in rat frontal cortex. *J. Neurochem.* (In press).

Peroutka, S.J. Selective labeling of 5-HT$_{1A}$ and 5-HT$_{1B}$ binding sites in bovine brain. *Brain Res.*, 344:167–171, 1985.

Peroutka, S.J., Huang, S., and Allen, G.A. Canine basilar artery contractions mediated by 5-hydroxytryptamine$_{1A}$ agents. *J. Pharmacol. Exp. Ther.* (In press).

Peroutka, S.J., Mauk, M.D., and Kocsis, J.D. Modulation of hippocampal neuronal activity by 5-hydroxytryptamine and 5-hydroxytryptamine$_{1A}$ selective drugs. *Neuropharmacology* (In press).

Sanders-Bush, E., and Conn, P.J. Effector systems coupled to serotonin receptors in brain: Serotonin stimulated phosphoinositide hydrolysis. *Psychopharmacol. Bull.*, 22(3): 829–836, 1986.

Schlegel, J.R., and Peroutka, S.J. Nucleotide interactions with 5-HT$_{1A}$ binding site directly labeled by ^{3}H-8-OH-DPAT. *Biochem. Pharmacol.* (In press).

Shenker, A., Maayani, S., Weinstein, H., and Green, J.P. Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. *Eur. J. Pharmacol.*, 109:427–429, 1985.

Smith, L.M., and Peroutka, S.J. Differential effects of 5-hydroxytryptamine$_{1A}$ selective drugs on the 5-HT behavioral syndrome. *Pharmacol. Biochem. Behav.* (In press).

Taylor, E.W., Duckles, S.W., and Nelson, D.L. Dissociation constants of serotonin agonists in the canine basilar artery correlate to K$_i$ values at the 5-HT$_{1A}$ binding site. *J. Pharmacol. Exp. Ther.*, 236:118–125, 1986.

Tricklebank, M.D., Middlemiss, D.N., and Neill, J. Pharmacological analysis of the behavioral and thermoregulatory effects of the putative 5-HT$_1$ receptor agonist, RU 24969, in the rat. *Neuropharmacology*. (In press).

Yagaloff, K.A., and Hartig, P.R. ^{125}I-LSD binds to a novel serotonergic site on rat choroid plexus epithelial cells. *J. Neurosci.*, 6:3178–3183, 1985.

Labeling of the 5-HT_{1A} Receptor Subtype

Jean C. Shih, Ph.D.,[1] Kenneth B. Asarch, Pharm.D., Ph.D.,[1] and Richard Ransom, Ph.D.[1]

Introduction

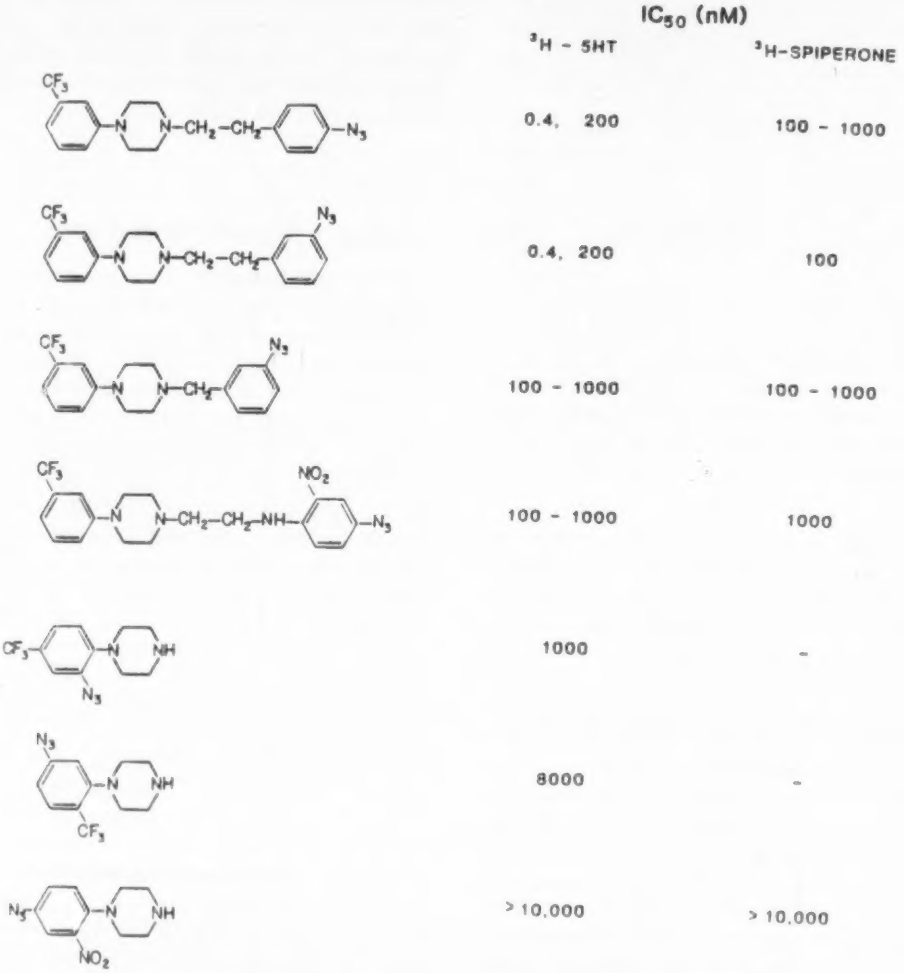
We have been searching for an affinity ligand suitable for labeling the serotonin (5-HT) receptor protein in order to characterize and purify the receptor. Initial ligands studied were two serotonin derivatives, N-(2-nitro-4-azidophenyl)-serotonin (NAP-serotonin) (Cheng and Shih, 1979) and 3-[β-(4-azidobenzamidino) ethyl] -5-hydroxyindole (serotonin azidobenzamidine) (Ransom et al., 1985a). The high nonspecific binding of these two compounds prevents them from serving as useful receptor probes. NAP-serotonin is however useful as a photoaffinity probe for monoamine oxidase (Chen et al., 1984, 1985a, 1985b) and serotonin azidobenzamidine can cause a specific photoinactivation of synaptosomal uptake of serotonin (Ransom et al., 1985a). Dr. Ray Fuller at Eli Lilly and Co. had studied a series of phenylpiperazine derivatives which displayed high affinity for serotonin receptors (Fuller, 1980). We obtained four derivatives and synthesized numerous others. These derivatives were then converted into photoactivatable azido derivatives and their potencies determined at 5-HT_1 sites labeled with [^{3}H]5-HT and 5-HT_2 sites labeled with [^{3}H] spiperone. A partial listing of these compounds is presented in Figure 1. It was found that some of the most potent phenylpiperazines possessed phenethyl substituents on the piperazine nitrogen (Ransom et al., 1985b) and that substitution on the phenyl ring of the phenethyl substituent was not critical in determining potency at 5-HT_{1A} binding sites. It was also determined that displacement of [^{3}H]5-HT by certain of these compounds was distinctly biphasic (Ransom et al., 1985b). Extensive work has been performed to demonstrate that 1-[2-(4-aminophenyl) ethyl]-4 -(3-trifluoromethylphenyl) piperazine (LY 165163; p-NH_2-PE-TFMPP or PAPP) is a selective 5-HT_{1A} ligand and 1-[2-(4-azidophenyl) ethyl]-4-(3-trifluoromethylphenyl) piperazine (p-azido-PAPP) is a selective 5-HT_{1A} photoprobe (structures shown in Figure 2).

Discrimination of 5-HT_1 Subtypes by PAPP

[^{3}H]5-HT binding assays were conducted as previously described (Asarch et al., 1985). Binding assays were carried out at 37°C in 50 mM Tris-HCl, pH 7.4, containing 1 mM EDTA, 5 mM $CaCl_2$, 10 μM pargyline, and 0.1 percent ascorbic acid. We have found that the $CaCl_2$ in the binding medium minimizes lipid peroxidation (Muakkassah-Kelly et al., 1983) and the ascorbic acid prevents oxidation of the [^{3}H]5-HT during the assay (Andresen & Shih, in press). As shown in Figure 3 and Table 1, PAPP discriminates a similar proportion of high and low affinity sites as does spiperone and displays selectivity for the 5-HT_{1A} subtype (Asarch et al., 1985). In the presence of 1 μM spiperone, a concentration that blocks the 5-HT_1 binding sites without affecting 5-HT_{1B} binding sites (Pedigo et al., 1981), PAPP displays only a single low affinity (213 nM) in the rat cortex (Table 1). Interestingly, the trifluoromethylphenyl piperazine (TFMPP) portion of the molecule displays an opposite selectivity to PAPP (Table 1, Asarch et al., 1985). In addition, TFMPP binds to subsets of binding sites of 5-HT_{1B} binding sites as evidenced by the statistically significant 2 site fit for the displacement of [^{3}H]5-HT binding to rat cortical membranes in the presence of a 1 μM spiperone mask of the 5-HT_{1A} binding sites (Table 1).

---

[1] Division of Biological Sciences and Institute for Toxicology, School of Pharmacy, University of Southern California, Los Angeles, CA 90033.



	IC$_{50}$ (nM)	
	^{3}H - 5HT	^{3}H-SPIPERONE
1	0.4, 200	100 - 1000
2	0.4, 200	100
3	100 - 1000	100 - 1000
4	100 - 1000	1000
5	1000	-
6	8000	-
7	> 10,000	> 10,000

FIGURE 1. Potency of photoaffinity labeling probes for [^{3}H]5-HT and [^{3}H]spiperone binding sites. All compounds were synthesized in our laboratory. IC$_{50}$ values were determined from competition experiments in rat cortical membranes in the dark using either 2 nM [^{3}H]5-HT or 1 nM [^{3}H]spiperone as described previously (Ransom et al., 1985). Two IC$_{50}$ values are reported when a two-site model provided a statistically significant better fit than a single site model.

[^{3}H]PAPP Binding

[^{3}H]PAPP was obtained through the catalytic reduction of a ring-brominated analog of PAPP as previously described (Ransom et al., 1986). [^{3}H]PAPP binding assays were carried out under the same conditions as the [^{3}H]5-HT binding assays after appropriate validation (Ransom et al., 1986). [^{3}H]PAPP bound to a single population of sites with a K$_D$ of 1.6 nM and a B$_{max}$ of 162 fmol/mg protein. The Hill coefficient was not statistically different from 1. [^{3}H]PAPP binding in different brain areas was compared with the density of 5-HT$_{1A}$ sites present in various regions. As shown in Table 2, the density of [^{3}H]PAPP sites in hippocampus, cortex, striatum, and cerebellum were very similar to the density of 5-HT$_{1A}$ receptors in these areas.

Several drugs were used to characterize the pharmacology of [^{3}H]PAPP binding to rat cortical membranes. The potency of these agents as inhibitors of [^{3}H]PAPP binding and at 5-HT$_{1A}$ binding sites compare very well

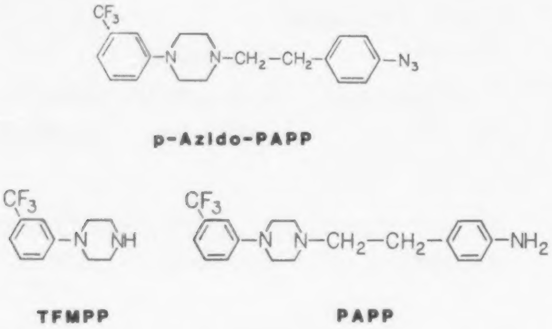


FIGURE 2. Chemical structure of 1-(*m*-trifluoromethylphenyl)-piperazine (TFMPP); 1-[2-(4-aminophenyl) ethyl]-4-(3-trifluoromethylphenyl) piperazine (PAPP); and 1-[2-(4-azidophenyl) ethyl]-4-(3-trifluoromethylphenyl) piperazine (p-Azido-PAPP).

(Table 3). Competition by each drug, including the selective agents spiperone and 8-hydroxy-2-N, N-(di-propylamino)tetralin (8-OH-DPAT), were best modeled as a single site displacement. Further support for the association of [^{3}H]PAPP binding to a 5-HT$_1$ receptor is provided by the very low affinity (K_D = 1,000 nM) exhibited by ketanserin (Janssen) in competition experiments. Because ketanserin has a very high affinity for the 5-HT$_2$ receptor (Leysen et al., 1982), this result also demonstrates that [^{3}H]PAPP at 1 nM does not bind to 5-HT$_2$ receptors. The inhibition of [^{3}H]PAPP binding by maximal doses of all drugs tested was not increased in the presence of 10 μM 5-HT indicating that the displacement observed for every drug occurred from the same population of sites. [^{3}H]PAPP binding was not affected by nonserotonergic agents such as norepinephrine, phenylephrine, prazosin, isoproterenol, dopamine, haloperidol, histamine, pyrilamine, atropine, imipramine, and desmethylimipramine at concentrations which would occupy their specific receptors.

Coupling of [^{3}H]PAPP Binding Sites

[^{3}H]5-HT binding sites have been demonstrated to be regulated by guanosine triphosphate (GTP) and divalent cations (Mallat and Hamon, 1982). It was therefore of interest to determine if 5-HT$_{1A}$ binding sites measured by [^{3}H]PAPP were similarly affected. GTP produces a parallel inhibition of [^{3}H]5-HT and [^{3}H]PAPP specific binding in rat hippocampus measured at K_D concentrations of each radioligand (data not shown). Under the same conditions, 5 mM $MgCl_2$, $CaCl_2$, or $MnCl_2$ produces a 99 percent, 66 percent, or 82 percent increase in [^{3}H]PAPP specific binding in rat hippocampus similar to the increases reported for [^{3}H]5-HT specific binding in rat hippocampus (Hamon et al., 1983). Similar effects of GTP and divalent cations on 5-HT$_{1A}$ binding sites have been ported using other radioligands (Hall et al., 1985; Norman et al., 1985). In the presence of both GTP and divalent cations 5-HT will stimulate adenylate cyclase in the adult rat hippocampus (Barbaccia et al., 1983). Under similar conditions PAPP produces about one-half the stimulation of adenylate cyclase (EC_{50} = 30 nM) produced by serotonin (EC_{50} = 100 nM). This finding is consistent with the results of Shenker et al. (1985) who report in the adult guinea pig hippocampus that 5-HT

TABLE 1. Binding Parameters for Displacement of [^{3}H]5-HT by Spiperone, TFMPP, and PAPP.

Drug	K_H (nM)	B_H (%)	K_L (nM)	B_L (%)
			Cortex	
Spiperone	19.3 ± 4.2	38 ± 1.0	36700 ± 5200	62 ± 1.0
TFMPP	5.6 ± 2.7	52 ± 3.7	172 ± 75	48 ± 3.7
PAPP	2.9 ± 0.5	44 ± 2.7	328 ± 73	56 ± 2.7
		Cortex in Presence of 1 μM Spiperone		
TFMPP	6.0 ± 2.0	63 ± 2.5	273 ± 6.2	37 ± 2.5
PAPP	213 ± 27	100		

The values listed were obtained in rat cortex from at least three competition experiments for each inhibitor. K_H and K_L are the apparent dissociation constants for the high and low affinity sites (± S.E.M.) and were calculated by taking the geometric mean of the computer derived parameters for individual experiments. B_H and B_L are the proportions of high and low affinity sites (± S.E.M.) calculated by taking the arithmetic mean of the computer generated parameters for individual experiments. These parameters were determined at 2 nM [^{3}H]5-HT using 10 μM unlabeled 5-HT to define 100 percent displacement.

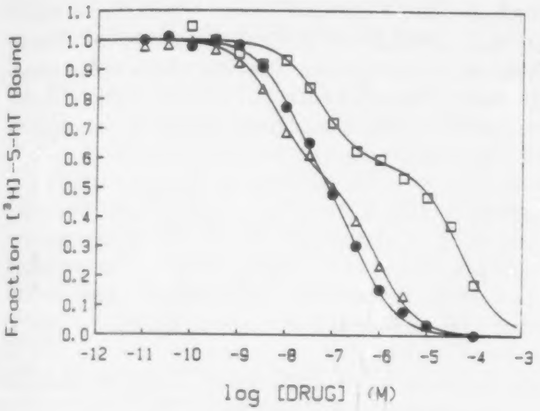


FIGURE 3. Inhibition of [^{3}H]5-HT binding in rat cortex. The data for each curve are from one experiment in rat cortex which was replicated at least three times. Each point is the mean of triplicate determinations which varied by less than 5 percent at each concentration tested. The curves were fitted to the data by computer according to a two-site model (spiperone □, TFMPP ●, and PAPP Δ.

stimulates adenylate cyclase via the 5-HT$_{1A}$ receptor at low concentrations and at higher concentrations further stimulates adenylate cyclase via a yet to be characterized non-5-HT$_{1A}$ receptor.

p-Azido-PAPP Binding Properties

p-Azido-PAPP is readily synthesized from PAPP via a diazotization reaction described previously (Ransom et al., in press). p-Azido-PAPP displays selectivity for the 5-HT$_{1A}$ ing site similar to PAPP. Inhibition of [^{3}H]5-HT binding in the rat hippocampus by both p-azido-PAPP and spiperone fit a two-site model significantly better than a single site model, discriminate the same fraction of sites, and both have higher affinity for 5-HT$_{1A}$ sites (Table 4).

TABLE 2. Regional Densities of 5-HT$_{1A}$ Receptors and [^{3}H]PAPP Binding Sites.

	B$_{max}$ (fmole/mg of protein)	
Brain Region	5-HT$_{1A}$	[^{3}H]PAPP
Hippocampus	366 ± 39	399 ± 38
Cerebral Cortex	123 ± 14	162 ± 20
Corpus Striatum	44 ± 5	52 ± 8
Cerebellum	None	None

5-HT$_{1A}$ receptor densities were determined from [^{3}H]5-HT binding isotherms by the method of Scatchard (1949) using 1 μM 8-OH-DPAT to define nonspecific binding. [^{3}H]PAPP site densities were similarly quantitated in the same synaptic membrane preparation in three separate experiments. Data are mean ± S.E.M. values of the triplicate determinations.

TABLE 3. Affinities of Serotonergic Drugs for 5-HT$_{1A}$ and [^{3}H]PAPP Binding Sites.

	K$_i$ (nM)	
Drug	5-HT$_{1A}$	[^{3}H]PAPP
8-OH-DPAT	2.5	2.8
PAPP	2.9	2.9
d-LSD	3.6	2.5
5-HT	10	18
Spiperone	26	40
Ketanserin	471	1,000

5-HT$_{1A}$ affinities were determined at 2 nM [^{3}H]5-HT by nonlinear regression analysis. PAPP, 8-OH-DPAT and spiperone discriminated two [^{3}H]5-HT binding subpopulations, with the higher affinity site corresponding to the 5-HT$_{1A}$ receptor. 5-HT, d-LSD, and ketanserin displaced [^{3}H]5-HT from a single site. [^{3}H]PAPP binding sites were determined at 1 nM. Ten micromolar 5-HT was used to define nonspecific binding for each radioligand. The values are representative of multiple experiments for each competitor in which at least 12 concentrations of inhibitor were examined in each experiment.

Reversible [^{3}H]p-Azido-PAPP Binding

[^{3}H]p-Azido-PAPP was synthesized from [^{3}H]PAPP (Ransom et al., in press). [^{3}H]p-Azido-PAPP binding experiments were performed in the dark in a similar manner to that previously described for [^{3}H]PAPP and [^{3}H]5-HT (Ransom et al., in press). The binding in the dark was completely reversible as demonstrated by the complete disappearance of specific binding within 4 minutes after addition of 10 μM 5-HT. Saturation binding isotherms showed that [^{3}H]p-azido-PAPP labels a single class of binding sites in rat hippocampal membranes with a K$_D$ of about 1 nM and a B$_{max}$ of 370 fmol/mg protein. The density of [^{3}H]p-azido-PAPP sites in hippocampus agrees with the density of 5-HT$_{1A}$ receptors in this tissue (Ransom et al., in press). Serotonergic drugs were used to compare their potency at [^{3}H]p-azido-PAPP binding sites in the dark with their potency at the 5-HT$_{1A}$ receptors (Table 5). For all compounds studied there is a strong correlation between their affinities for the 5-HT$_{1A}$ receptors and [^{3}H]p-azido-PAPP binding sites. In addition, high concentrations (10 μM) of other monoamine neurotransmitters such as dopamine, norepinephrine, and histamine did not inhibit [^{3}H]p-azido-PAPP binding to hippocampal membranes.

Photodependent Irreversible Binding of [^{3}H]p-Azido-PAPP

Photolysis experiments with [^{3}H]p-azido-PAPP were designed to take advantage of the compound's high affinity for the 5-HT$_{1A}$ receptor. Membranes were incubated with 10 nM [^{3}H]p-azido-PAPP at 37°C, cooled on ice, and then washed in order to reduce the nonspecific binding prior to photolysis (Ransom et al., in press). The washed membranes were resuspended at a concentration of approximately 100 μg protein/ml in photolysis buffer. Photolysis was then carried out by irradiation of the samples on ice for 2 minutes using an Hanovia 450 watt medium pressure mercury lamp at a distance of 20 cm through a filter of Kimax glass (2 mm). Following irradiation the membranes were centrifuged at 50,000 × g for 10 min, solubilized in 20 mM Tris-HCl, pH 7.4, containing 1 percent sodium dodecyl sulfate (SDS), and then subjected to SDS-polyacrylamide gel electrophoresis using a 3 percent stacking gel and a separating gel of 7.5 percent acrylamide. The incorporation of radioactivity into membrane polypeptides upon irradiation in the presence and absence of 1 μM 5-HT is shown in Figure 4. A single peak of radioactivity representing 10 percent incorporation migrates as a 55,000 dalton polypeptide and is completely protected by 5-HT. No incorporation of radioactivity into the 55 kD polypeptide occurs if membranes are incubated with [^{3}H]p-azido-PAPP but not irradiated. Evidence that this polypeptide is associated with the 5-HT$_{1A}$ receptor is indicated by the ability of the following agents with high affinity for 5-HT$_{1A}$ sites to completely block incorporation of radioactivity into the 55 kD band at a concentration of 1 micromolar: 5-HT, 8-OH-DPAT, d-LSD (National Institute of Drug Abuse), metergoline (Farmitalia), spiperone (Janssen Pharmaceutica), TVX Q 7821 (Troponwerke), and buspirone (Bristol). Evidence of the specificity of the incorporation is the inability of the following nonserotonergic agents to block the photodependent incorporation at a concentration of 10 micromolar: norepinephrine, dopamine, haloperidol (Janssen), histamine, pyrilamine, and atropine. In addition ketanserin failed to block incorporation at a concentration of 1 micromolar thus indicating that the 5-HT$_2$ binding site was not labeled.

Conclusions

The results presented indicate that both [^{3}H]PAPP and [^{3}H]p-azido-PAPP can reversibly label the 5-HT$_{1A}$ receptor site and that [^{3}H]p-azido-PAPP, upon irradiation, covalently labels a polypeptide that is, or is a subunit of, the 5-HT$_{1A}$ receptor. We intend to use PAPP as an affinity column ligand with which to try to purify the serotonin receptor, and to use [^{3}H]p-azido-PAPP to identify the purified 5-HT$_{1A}$ receptor.

Acknowledgments

This work was supported by Grants No. MH37020 and No. MH39085 from the National Institute of Mental Health, Department of Health and Human Services, and by Grant No. BRSG S07RR05792, awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health, Department of Health and Human Services. We thank

TABLE 4. Binding Parameters for Displacement of [^{3}H]5-HT by p-Azido-PAPP and Spiperone in Rat Hippocampus.

Drug	K_H (nM)	B_H (%)	K_L (nM)	B_L (%)
p-Azido-PAPP	0.9 ± 1.2	69 ± 2	230 ± 38	31
Spiperone	45 ± 5	71 ± 4	42,000 ± 6,100	29

The values listed were obtained from three competition experiments for each inhibitor. Experiments were carried out in rat hippocampus as described in Table 1.

TABLE 5. Affinities of Serotonergic Drugs for 5-HT$_{1A}$ and [^{3}H]p-Azido-PAPP Binding Sites.

	K_i (nM)	
Drug	5-HT$_{1A}$	[^{3}H]p-Azido-PAPP
d-LSD	2.9	6.1
8-OH-DPAT	4.2	6.7
TVX Q 7821	5.1	8.4
5-HT	7.5	5.2
Metergoline	12	20
Buspirone	16	23
Spiperone	45	38
Mianserin	700	550
Ketanserin	912	1,589

5-HT$_{1A}$ affinities were determined at 2 nM [^{3}H]5-HT in rat hippocampus. The concentration of [^{3}H]p-azido-PAPP was 1 nM. At least 16 concentrations of each inhibitor were used to determine the K_i values which represent the results from at least three experiments for each competitor.

Dr. Bryan B. Molloy at Eli Lilly and Company for initially providing LY 165163, the compound referred to here as PAPP. We are grateful to the Neurosciences Branch, National Institute of Mental Health, for synthesizing the PAPP and p-azido-PAPP.

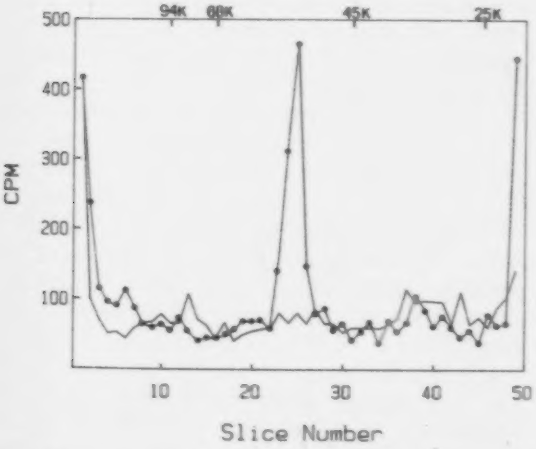


FIGURE 4. SDS-PAGE of [^{3}H]p-azido-PAPP labeled hippocampal membranes. The membranes were incubated with 10 nM [^{3}H]p-azido-PAPP at 37°C for 5 min and then washed and irradiated. The marked (●) line represents incorporation of the label in the absence of an additional agent. The unmarked line is the polypeptide labeling pattern when 1 μM 5-HT was present during the 37°C incubation. The molecular weight markers used were: 94,000, phosphorylase b; 68,000, reindeer serum albumin; 45,000, ovalbumin; 25,000, α-chymotrypsinogen.

References

Andresen, J.W., and Shih, J.C., Necessity of ascorbic acid in [^{3}H]5-hydroxytryptamine radioligand binding assay. *Neuropharmacol.* (In press.)

Asarch, K.B., Ransom, R.W., and Shih, J.C. 5-HT$_{1A}$ and 5-HT$_{1B}$ selectivity of two phenylpiperazine derivatives: Evidence for 5-HT$_{1B}$ heterogeneity. *Life Sci.*, 36:1265–1273, 1985.

Barbaccia, M.L., Brunello, N., Chuang, D.M., and Costa E. Serotonin-elicited amplification of adenylate cyclase activity in hippocampus membranes from adult rat. *J. Neurochem.*, 40:1671–1679, 1983.

Chen, S., Shih, J.C., and Xu, Q.-P. Interaction of N-(2-nitro-4-azidophenyl)-serotonin with two types of monoamine oxidase in rat brain. *J. Neurochem.*, 43(6):1680–1687, 1984.

Chen, S., Shih, J.C., and Xu Q.-P. 4-fluoro-3-nitrophenyl azide, a selective photoaffinity label for type B monoamine oxidase. *Biochem. Pharmacol.*, 34:781–788, 1985a.

Chen, S., Shih, J.C., and Xu Q.-P. The inhibition of monoamine oxidase by phenyl azides. *J. Neurochem.*, 45:940–945, 1985b.

Cheng, S.H., and Shih, J.C. Photoaffinity labeling of serotonin-binding proteins. *Life Sci.*, 25:2197–2203, 1979.

Fuller, R.W., Mason, N.R., Molloy, B.B. Structural relationships in the inhibition of [^{3}H]serotonin binding to rat brain membranes in vitro by 1-phenyl-piperazines. *Biochem. Pharmacol.*, 29:833–835, 1980.

Hall, M.D., Mestikawy, S. El, Emerit, M.B., et al. [^{3}H]8-Hydroxy-2-(di-n-propylamino)tetralin binding to pre- and postsynaptic 5-hydroxytryptamine sites in various regions of the rat brain. *J. Neurochem.*, 44(6):1685–1695, 1985.

Hamon, M., Goetz, C., and Gozlan, H. Reciprocal modulations of central 5-HT receptors by GTP and cations. In: *Advances in Biochemical Psychopharmacology*, Vol. 37. New York: Raven Press, 1983, pp. 349–359.

Leyesen, J.E., Neimegeers, J.E., Van Neuten, J.M., and Laduron, P.M. [^{3}H]Ketanserin (R41 468), a selective [^{3}H]-ligand for serotonin$_2$ receptor binding sites: binding properties, brain distribution, and functional role. *Mol. Pharmacol.*, 21: 301–314, 1982.

Mallat, M., and Hamon, M. Ca^{+2}-guanine nucleotide interactions in brain membranes. I. Modulation of central 5-hydroxytryptamine receptors in the rat. *J. Neurochem.*, 38(1):151–161, 1982.

Muakkassah-Kelly, S.F., Andresen, J.W., Shih, J.C., and Hochstein, P. Dual effects of ascorbate on serotonin and spiperone binding in rat cortical membranes. *J. Neurochem.*, 41(5):1429–1439.

Nelson, D.L., Weck, B., and Taylor, W. Discrimination of heterogeneous serotonin-1 receptors by indoleakylamines. In: *Advances in Biochemical Psychopharmacology*, Vol. 37. New York: Raven Press, 1983, pp. 337–347.

Norman, A.B., Battaglia, G., Creese, I. [^{3}H]WB4101 labels the 5-HT$_{1A}$ serotonin receptor subtype in rat brain. Guanine nucleotide and divalent cation sensitivity. *Mol. Pharmacol.*, 28:487–494, 1985.

Pedigo, N.W., Yamamura, H.I., and Nelson, D.L. Discrimination of multiple [^{3}H]5-hydroxytryptamine binding sites by the neuroleptic spiperone in rat brain. *J. Neurochem.*, 36:220–226, 1985.

Ransom, R.W., Asarch, K.B., and Shih, J.C. A trifluoromethylphenyl piperazine derivative with high affinity for 5-hydroxytryptamine$_{1A}$ sites in rat brain. *J. Neurochem.*, 44:875–880, 1985.

Ransom, R.W., Asarch, K.B., and Shih, J.C. [^{3}H]-1-[2-(4-aminophenyl)ethyl]-4-(3-trifluoromethylphenyl) piperazine: a selective radioligand for 5-HT$_{1A}$ receptors in rat brain. *J. Neurochem.*, 46:68–75, 1986.

Ransom, R.W., Asarch, K.B., and Shih, J.C. Photoaffinity labeling of the serotonin$_{1A}$ receptor in rat hippocampus. *J. Neurochem.* (In press).

Ransom, R.W., Lee, J.D., Bolger, M.B., and Shih, J.C. Photoinactivation of serotonin uptake by an arylazido derivative of 5-hydroxytryptamine. *Mol. Pharmacol.*, 28:185–190, 1985.

Scatchard, G. The attractions of proteins for small molecules and ions. *Ann. NY Acad. Sci.*, 51:660–672, 1949.

Shenker, A., Maayani, S., Weinstein, H., and Green, J.P. Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. *Eur. J. Pharmacol.*, 109(3):427–429, 1985.

Substituted Phenylpiperazines as Serotonin Agonists: Structural Determinants of Potency and Interaction With Receptor Subtypes

Ray W. Fuller, Ph.D.[1]

1-(*m*-Trifluoromethylphenyl)piperazine (TFMPP) and 1-(m-chlorophenyl)piperazine (mCPP) are centrally acting serotonin agonists (Fuller et al., 1978; Samanin et al., 1979). They have structural similarity to quipazine (Hong et al., 1969) and to MK-212 [6-chloro-2-(1-piperazinyl)-pyrazine] (Clineschmidt, 1979), two arylpiperazines previously known to be serotonin agonists. Several other phenylpiperazines besides TFMPP and mCPP also interact with serotonin receptors, and within the chemical series are compounds having markedly different selectivity for serotonin receptor subtypes. Selected phenylpiperazines (structures in Figure 1) and their characteristics in interacting with central and peripheral serotonin receptors are described in this paper.

TFMPP and mCPP moieties are present in the structures of several drugs, and TFMPP and mCPP have been identified as metabolites of some of the drugs listed at the bottom of Figure 1 (Caccia et al., 1985). TFMPP and mCPP may contribute to some of the pharmacologic actions of those drugs. For instance, mCPP is a metabolite of trazodone and has been shown to account for some of the pharmacologic actions of trazodone in laboratory animals; its possible involvement in the pharmacologic actions of trazodone, including antidepressant efficacy clinically, has been considered (Caccia et al., 1982; Maj et al., 1979).

Radioligand Binding

The structure-activity relationship studies of phenylpiperazines as serotonin agonists in the Lilly Research Laboratories were initially based on tritiated serotonin binding to rat brain 5–HT1 receptors (Fuller et al., 1980). Subsequently it was recognized that TFMPP and mCPP had preferential affinity for the 5-HT1B receptor subtype (Sills et al., 1984). This characteristic distinguished them from trazodone, which had preferential affinity for 5-HT2 receptors (*see* Fuller et al., 1984). Recently the study of LY 165163, which was being evaluated as a promising precursor to a photoaffinity label—the azido derivative, was found to have selective affinity for the 5-HT1A site (Asarch et al., 1985). With only a relatively few phenylpiperazines characterized in terms of serotonin receptor subtype selectivity, compounds selective for 5-HT1A,

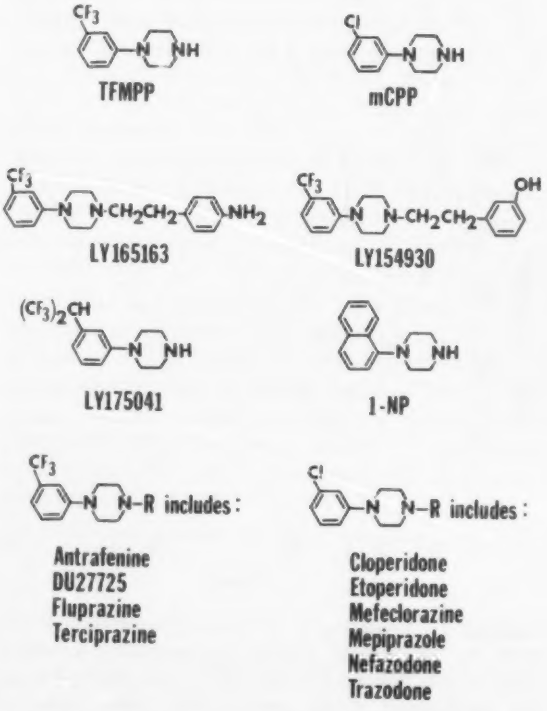


FIGURE 1. Chemical structures of some m-halophenylpiperazines that affect serotonergic function and/or have psychotropic actions.

---

[1] Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

5-HT1B, and 5-HT2 receptors have already been found. A more complete study of the receptor subtype selectivity of phenylpiperazines is likely to be a fruitful area of research.

Effects on Brain Serotonin Turnover

Serotonin agonists that act centrally cause a decrease in serotonin turnover. Such a decrease has been measured as a reduction in steady-state concentrations of 5-hydroxyindole-acetic acid (5-HIAA), the major metabolite of serotonin, and a reduction in the rate of 5-HIAA accumulation after probenecid administration to inhibit its efflux from brain (Figure 2). Table 1 shows that TFMPP caused a decrease in 5-HIAA concentration in mouse brain (as reported earlier for rat brain [Fuller et al., 1978]), along with small increases in serotonin concentration. Apparently the compound acts centrally as a serotonin agonist in mice as it does in rats. The decrease in serotonin turnover also has been measured as a reduction in the rate of serotonin depletion after inhibition of its synthesis and a reduction in the rate of 5-hydroxytryptophan (5-HTP) accumulation after decarboxylase inhibition. The latter effect of TFMPP is shown by the data in Table 2. The accumulation of 5-HTP was reduced by TFMPP, both in hypothalamus and in striatum, in rats.

TABLE 1. Effect of TFMPP on 5-Hydroxyindole Concentrations in Mouse Brain.

Dose of TFMPP mg/kg (i.p.)	5-Hydroxyindoles, pmol/g	
	Serotonin	5-HIAA
0	1249 ± 59	737 ± 35
1	1343 ± 31	648 ± 32
3	1582 ± 109 *(+27%)	540 ± 40 *(−27%)
10	1479 ± 39 *(+18%)	501 ± 26 *(−32%)
30	1561 ± 36 *(+25%)	455 ± 31 *(−38%)

Mean values ± standard errors for 5 mice per group treated 2 hrs before they were killed are shown.

* indicates significant ($p < .05$) drug effects.

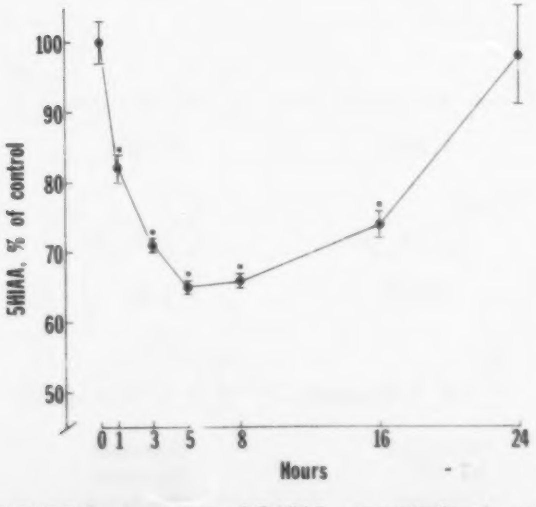


FIGURE 2. Lowering of 5-HIAA concentration in rat brain by LY 165163. 5-HIAA concentration in whole brain of rats treated with LY 165163 (20 mg/kg i.p.) at the designated times before rats were killed is expressed as percentage of the control mean (5 rats per group). Asterisks indicate significant differences ($p<.05$) from the control group.

Neuroendocrine Effects

Since brain serotonin neurons appear to participate in the regulation of pituitary hormone secretion, it is not surprising that central serotonin agonists including phenylpiperazines affect the secretion of pituitary hormones. Table 3 shows that mCPP administration increased serum concentrations both of corticosterone and of prolactin in rats. The increases are like those produced by TFMPP, which also has been shown to increase adrenocorticotropin (ACTH) levels in rat plasma and to decrease hypothalamic content of corticotropin releasing factor (CRF) (Hashimoto et al., 1982), supporting the idea that stimulation of central serotonin receptors in rats leads to increased CRF release from hypothalamus as the cause of the increased blood levels of ACTH and corticosterone.

TABLE 2. Effect of TFMPP on 5-HTP Accumulation After Decarboxylase Inhibition in Rat Brain.

Dose of TFMPP mg/kg s.c.	5–HTP accumulated, nmol/g	
	Hypothalamus	Striatum
0	1.64 ± .13	0.89 ± .006
10	0.65 ± .06*	0.38 ± .04*

Mean values ± standard errors for 5 rats per group are shown. The decarboxylase inhibitor, NSD 1015 (100 mg/kg i.p.), was injected 35 min before rats were killed and 30 min after TFMPP.

*Indicates significant difference from control group ($p < .05$).

mCPP has now been shown to elevate prolactin and glucocorticoid concentrations in primates, including rhesus monkeys and humans, and may be useful in clinical studies to evaluate the functional state of central serotonin receptors (Mueller et al., 1985).

Other Central Effects

Substituted phenylpiperazines are reported to have a variety of other central effects, probably as a consequence of serotonin receptor stimulation. Appetite suppressant activity was the basis for an early patent on mCPP (U.S. Patent 3,253,989, May 31, 1966) before its mechanism of action was known; reduction of food intake by mCPP, TFMPP, and other phenylpiperazines has been observed in several types of animal experiments (e.g., Fuller et al., 1981; Samanin et al., 1979). TFMPP serves as a discriminative stimulus in drug discrimination procedures (Glennon et al., 1984) and suppresses locomotor activity in rats (Lucki & Frazer, 1982). mCPP stimulates the flexor reflex in spinal rats (Maj & Lewandowska, 1980), blocks jumping and paw licking in the rat hot-plate test for analgesia (Rochat et al., 1982), and has anti-aggressive effects (Hahn et al., 1982).

Peripheral Serotonin Receptors

TFMPP and mCPP have little agonist activity at serotonin receptors mediating contraction of the rat jugular vein and instead are antagonists at these receptors (Cohen & Fuller, 1983), which have been characterized as 5-HT2 receptors (Cohen et al., 1981). Other phenylpiperazines, such as 1-naphthylpiperazine (1-NP) (refer to Figure 1), also are serotonin agonists centrally but are antagonists at vascular serotonin receptors (Cohen et al., 1983). TFMPP antagonizes rather than mimics the diarrhea-producing effects of 5-HTP in mice, suggesting it is an antagonist at gut serotonin receptors mediating that effect (Warrick et al., 1981). TFMPP and mCPP also have high affinity for the serotonin receptor that mediates contraction of the rat fundus but have relatively low efficacy as agonists; LY 165163 has affinity for this receptor but no efficacy as an agonist (Cohen & Wittenauer, 1986).

TABLE 3. Effect of mCPP on Serum Hormone Concentrations in Rats.

Dose of mCPP mg/kg (i.p.)	Corticosterone µg/100 ml	Prolactin ng/ml
0	4.6 ± 0.7	7.2 ± 1.8
5	13.1 ± 2.3*	35.5 ± 8.0*
10	47.2 ± 7.0*	55.8 ± 15.8*

Mean values ± standard errors for 5 rats per group are shown. Measurements were made 1 hr after mCPP treatment.

* indicate significant increases ($p < .05$).

Perhaps TFMPP and mCPP act primarily as antagonists at 5-HT2 receptors whether they occur centrally or peripherally; the central serotonin agonist properties of these compounds may be mediated by serotonin receptors other than 5-HT2 receptors. Further evidence bearing on this possibility is needed.

Summary

Several phenylpiperazines are known to affect serotonergic neuronal systems. Among these compounds, some act predominantly as serotonin agonists centrally (e.g., TFMPP and mCPP), whereas others act predominantly as serotonin antagonists (e.g., trazodone). Phenylpiperazines have shown preferential affinity by radioligand displacement for 5-HT1A (LY 165163), 5-HT1B (TFMPP and mCPP), or 5-HT2 (trazodone) receptors. Phenylpiperazines (such as TFMPP and mCPP) may act centrally as serotonin agonists but act peripherally (vascular and gut receptors) as serotonin antagonists; these differences might relate to different subtypes of serotonin receptors being involved in the effects studied. Further characterization of phenylpiperazines may identify additional compounds as useful pharmacologic tools and potential therapeutic agents.

References

Asarch, K. B., Ransom, R. W., and Shih, J. C. 5-HT-1a and 5-HT-1b selectivity of two phenylpiperazine derivatives: evidence for 5-HT-1b heterogeneity. *Life Sci.*, 36:1265–1273, 1985.

Caccia, S., Fong, M. H., Garattini, S., and Zanini, M. G. Plasma concentrations of trazodone and 1-(3-chlorophenyl)piperazine in man after a single oral dose of trazodone. *J. Pharm. Pharmacol.*, 34:605–606, 1982.

Caccia, S., Fong, M. H., Garattini, S., and Notarnicola, A. 1-Aryl-piperazine as active metabolites of drugs with an aryl-piperazine side-chain. *Biochem. Pharmacol.*, 34:393–394, 1985.

Clineschmidt, B. V. MK-212: A serotonin-like agonist in the CNS. *Gen. Pharmacol.*, 10:287–290, 1979.

Cohen, M. L., and Fuller, R. W. Antagonism of vascular serotonin receptors by m-chlorophenylpiperazine and m-trifluoromethylphenylpiperazine. *Life Sci.*, 32:711–718, 1983.

Cohen, M. L., Fuller, R. W., and Kurz, K. D. Evidence that blood pressure reduction by serotonin antagonists is related to alpha receptor blockade in spontaneously hypertensive rats. *Hypertension*, 5:676–681, 1983.

Cohen, M. L., Fuller, R. W., and Wiley, K. S. Evidence for 5-HT2 receptors mediating contraction in vascular smooth muscle. *J. Pharmacol. Exp. Ther.*, 218:421–425, 1981.

Cohen, M. L., and Wittenauer, L. A. Further evidence that the serotonin receptor in the rat stomach fundus is not 5-HT1A or 5-HT1B. *Life Sci.*, 38:1–5, 1986.

Fuller, R. W., Mason, N. R., and Molloy, B. B. Structural relationships in the inhibition of [3H]serotonin binding to rat brain membranes *in vitro* by 1-phenylpiperazines. *Biochem. Pharmacol.*, 29:833–835, 1980.

Fuller, R. W., Snoddy, H. D., and Cohen, M. L. Interactions of trazodone with serotonin neurons and receptors. *Neuropharmacology*, 23:539–544, 1984.

Fuller, R. W., Snoddy, H. D., Mason, N. R., and Molloy, B. B. Effect of 1-(m-trifluoromethylphenyl)-piperazine on 3H-serotonin binding to membranes from rat brain in vitro and on serotonin turnover in rat brain in vivo. *Eur. J. Pharmacol.*, 52:11–16, 1978.

Fuller, R. W., Snoddy, H. D., Mason, N. R., and Owen, J. E. Disposition and pharmacological effects of m-chlorophenylpiperazine in rats. *Neuropharmacology*, 20:155–162, 1981.

Glennon, R. A., McKenney, J. D., and Young, R. Discriminative stimulus properties of the serotonin agonist 1-(3-trifluoromethylphenyl)piperazine (TFMPP). *Life Sci.*, 35:1475–1480, 1984.

Hahn, R. A., Hynes, M. D., and Fuller, R. W. Apomorphine-induced aggression in rats chronically treated with oral clonidine: modulation by central serotonergic mechanisms. *J. Pharmacol. Exp. Ther.*, 220:389–393, 1982.

Hashimoto, K., Ohno, N., Murakami, K., et al. The effect of serotonin agonist 1-(trifluoromethylphenyl)-piperazine on corticotropin releasing factor and arginine vasopressin in rat hypothalamic nuclei. *Endocrinol. Jpn.*, 29:383–388, 1982.

Hong, E., Sancilio, L. F., Vargas, R., and Pardo, E. G. Similarities between the pharmacological actions of quipazine and serotonin. *Eur. J. Pharmacol.*, 6:274–280, 1969.

Lucki, I., and Frazer, A. Behavioral effects of indole- and piperazine-type serotonin receptor agonists. *Soc. Neurosci. Abstr.*, 8:101, 1982.

Maj, J., and Lewandowska, A. Central serotonin mimetic action of phenylpiperazines. *Pol. J. Pharmacol. Pharm.*, 32:495–504, 1980.

Maj, J., Palider, W., and Rawlow, A. Trazodone, a central serotonin antagonist and agonist. *J. Neural Transm.*, 44:237–248, 1979.

Mueller, E. A., Murphy, D. L., and Sunderland, T. Neuroendocrine effects of m-chlorophenylpiperazine, a serotonin agonist, in humans. *J. Clin. Endocrinol. Metab.*, 61:1179–1184, 1985.

Rochat, C., Cervo, L., Romandini, S., and Samanin, R. Evidence that m-chlorophenylpiperazine inhibits some nociceptive responses of rats by activating 5-hydroxytryptamine mechanisms. *J. Pharm. Pharmacol.*, 34:325–327, 1982.

Samanin, R., Mennini, T., Ferraris, A., Bendotti, C., et al. m-Chlorophenylpiperazine: A central serotonin agonist causing powerful anorexia in rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 308:159–163, 1979.

Sills, M. A., Wolfe, B. B., and Frazer, A. Determination of selective and nonselective compounds for the 5-HT1A and 5-HT1B receptor subtypes in rat frontal cortex. *J. Pharmacol. Exp. Ther.*, 231:480–487, 1984.

Warrick, M. W., Dinwiddie, W. G., Lin, T.-M., and Fuller, R. W. Antidiarrheal effects of quipazine and 1-(m-trifluoromethylphenyl)-piperazine in mice. *J. Pharm. Pharmacol.*, 33:675–676, 1981.

Effector Systems Coupled to Serotonin Receptors in Brain: Serotonin Stimulated Phosphoinositide Hydrolysis

Elaine Sanders-Bush, Ph.D.,[1] and
P. Jeffrey Conn, Ph.D.[1]

Central serotonin (5HT) receptors have been classified into two major subtypes, 5HT-1 and 5HT-2, based on radioligand binding studies (Peroutka & Snyder, 1979). Recent evidence suggests that the 5HT-1 binding site can be further subdivided into three subtypes, 5HT-1A, 5HT-1B, and 5HT-1C (Pedigo et al., 1981; Pazos et al., 1984; Yagaloff & Hartig, 1985). The challenge of the future is to determine if these various binding sites are functional receptors which mediate the synaptic action of 5HT. Identification of the biochemical transducing systems which are linked to these recognition sites is one important way to evaluate their role.

Two major transducing mechanisms which mediate signal transmission for neurotransmitters and hormones are the adenylate cyclase/cyclic AMP signal cascade and phospholipase C mediated hydrolysis of polyphosphoinositides. Neurotransmitter mediated activation of adenylate cyclase leads to an increase in intracellular cyclic AMP levels, which serves as a second messenger. The signal cascade then proceeds via cyclic AMP protein kinase mediated protein phosphorylations to final physiological responses (Browning et al., 1985). The second major signaling pathway, the phospholipase C/phosphoinositide hydrolysis mechanism, utilizes inositol lipids [phosphatidylinositol (PI), phosphatidylinositiol-4-phosphate (PIP), and phosphatidylinositol-4, 5-bisphosphate (PIP2)] in the membrane as a first step in the transducing mechanism (Figure 1). It is generally thought that activation of phospholipase C leads to the hydrolysis of PIP2 and the formation of two products, which act as second messengers to elicit cellular responses. One of these products, inositol-1,4,5-trisphosphate (IP3), elevates cytosol calcium levels by releasing intracellular storage pools. Calcium ions then serve as a "third messenger," activating specific protein kinases to evoke responses such as muscle contraction and neurotransmitter release. The second product, diacylglycerol, stimulates protein kinase C, an enzyme which in turn regulates the activity of enzymes by phosphorylating them. The physiological consequences of protein kinase C activation have not been completely worked out, but evidence is emerging that this enzyme is involved in a number of processes, including heterologenous receptor desensitization and control of cell division and differentiation. Another important consequence of the rise in diacylglycerol is the release of arachidonic acid, which leads to the formation of prostaglandins and leukotrienes. These "icosanoids" have numerous cellular effects. The phospholipase C/phosphoinositide hydrolysis cascade mediates signal transduction for a variety of neurotransmitter and hormone receptors, including muscarinic cholinergic, alpha-1 adrenergic, and H-1 histaminergic sites. Interested readers are referred to recent reviews for additional information about this important signaling pathway (Berridge, 1984; Hirasawa & Nishizuki, 1985). 5HT receptors in brain are apparently linked to both the adenylate cyclase and the phosphoinositide hydrolysis pathways. Because of space limitations, this article focuses on the recent studies of 5HT stimulated phosphoinositide hydrolysis. Studies of 5HT activated adenylate cyclase have been extensively reviewed by Middlemiss (1982), Fillion (1983), and Sanders-Bush and Conn (1986).

5HT stimulated phosphoinositide hydrolysis was first characterized in insect salivary gland, where it is involved in the regulation of saliva secretion (Berridge & Heslop, 1981). Limited studies by Berridge et al. (1982) sug-

---

[1] Departments of Pharmacology and Psychiatry, Vanderbilt University School of Medicine, Nashville, TN 37232.

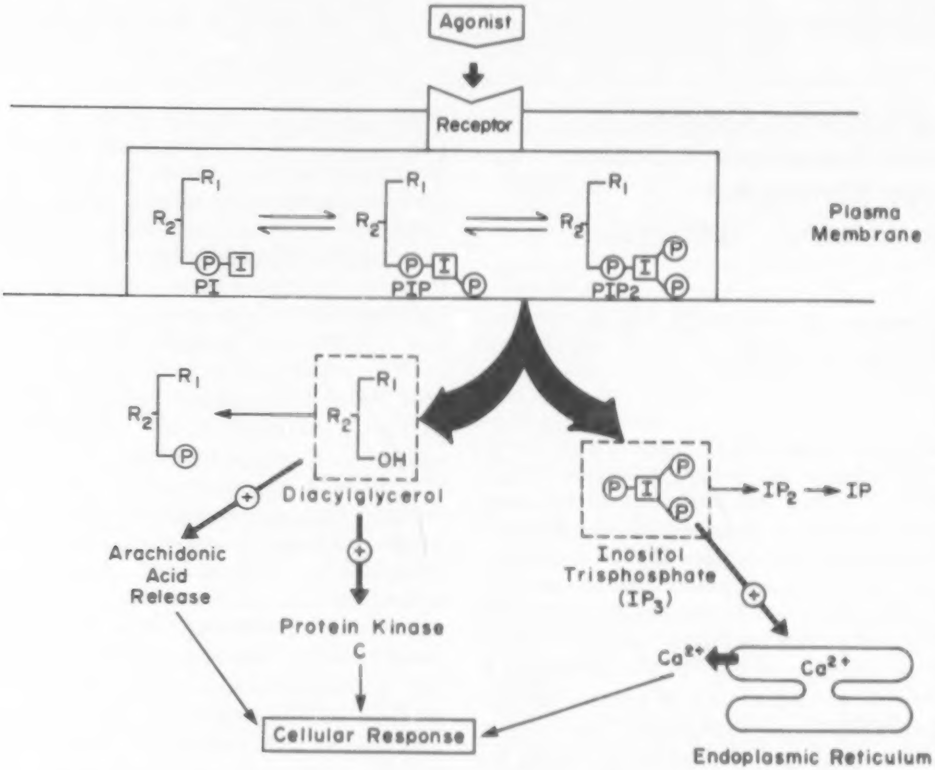


FIGURE 1. Schematic illustration of the phospholipase C/phosphoinositide hydrolysis signal cascade. Phosphatidylinositol (PI) is sequentially phosphorylated to phosphatidylinositol-4-phosphate (PIP) and then to phosphatidylinositol-4,5-bisphosphate (PIP2) by specific kinases. Agonist interaction with membrane receptors leads to the activation of phospholipase C, which catalyzes the hydrolysis of PIP2 to form inositol-1,4,5-trisphosphate (IP3) and diacylglycerol. Pathways of inactivation and second messenger functions are shown.

gested that 5HT also activates phosphoinositide hydrolysis in mammalian brain. We have recently extended these studies with the aim of determining which receptor(s) mediates the 5HT phosphoinositide effect in rat brain (Conn & Sanders-Bush, 1984; 1985). For these studies, slices of cerebral cortex were prelabelled with [3H]-inositol and the method of Berridge et al. (1982) was used to measure the accumulation of [3H]-inositol-1-phosphate (IP) as an index of the hydrolysis of radiolabelled phosphoinositides. IP is formed by the sequential dephosphorylation of IP3 to IP2 and then to IP (Figure 1). Further metabolism of IP is prevented by the addition of lithium, which amplifies the response and makes it possible to study 5HT stimulated phosphoinositide hydrolysis in brain which has a relatively weak signal.

The addition of increasing concentrations of 5HT to prelabelled cortical slices results in the accumulation of increasing amounts of IP (Figure 2). The response is maximum at 10 µM and has an EC50 value of 1 µM. A number of 5HT agonists, including quipazine, MK212, and 5-fluorotryptamine, stimulate phosphoinositide hydrolysis, but the selective 5HT-1 agonist, 8-hydroxy-2-(di-N-propylamino)tetralin, is inactive. Concentration-effect studies of several 5HT agonists showed that the EC50 values and the rank order of potencies at stimulating phosphoinositide hydrolysis in cerebral cortex agree with their potencies at the 5HT-2 binding site (Conn & Sanders-Bush, 1985). Furthermore, a number of 5HT-2 antagonists, including spiperone, ketanserin, LY 53857, pizotifen, pipamperone, and cinanserin, block 5HT ac-

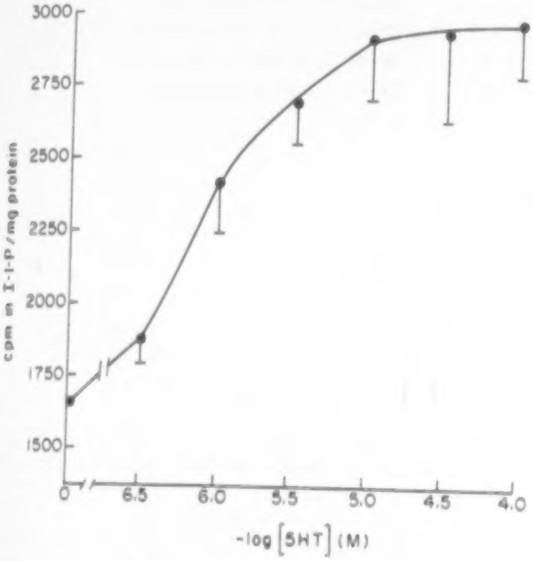


FIGURE 2. 5HT stimulated phosphoinositide hydrolysis in rat cerebral cortex. Cortical slices were prelabelled by incubating with [3H]-inositol. Increasing concentrations of 5HT were added and the release of [3H]-inositol phosphate (IP) was measured as described in Conn and Sanders-Bush (1985). Values plotted are means ± SEM for three determinations.

tivation of phosphoinositide hydrolysis in cortical slices (Conn & Sanders-Bush, 1984; 1985; Kendall & Nahorski, 1985). In order to obtain an estimate of the absolute affinity (K_d) of antagonists for the phosphoinositide hydrolysis linked receptor, concentration-response curves of 5HT's effect were measured in the presence of increasing concentrations of antagonist, as illustrated in Figure 3 for ketanserin. Dose ratios were determined and analyzed by the method of Arunlakshana and Schild (1959). The slope of the Schild plot (inset, Figure 3) is not different from unity, which suggests that ketanserin is a simple competitive antagonist of the phosphoinositide hydrolysis linked receptor. The pA_2 value of ketanserin is −7.93, corresponding to an estimated K_d of 12 nM, which is consistent with the K_d value (3 nM) of [3H]-ketanserin for the 5HT-2 binding site when determined in the presence of physiological salts. A number of other antagonists were analyzed in this manner and for those that gave results consistent with competitive antagonism, K_d values were determined. A plot of the K_d values determined by Schild analyses versus K_i values at the 5HT-2 binding site is linear (Figure 4). Regression analysis showed a significant correlation between the potencies of these drugs at inhibiting 5HT stimulated phosphoinositide hydrolysis and at inhibiting the binding of [3H]-ketanserin to the 5HT-2 site (correlation coefficient = 0.99; $p < 0.001$). Furthermore, antagonists of H-1 histaminergic, alpha-adrenergic, and cholinergic muscarinic receptors do not block the effect of 5HT, which suggests that these receptors are not involved in this response. Based on these data, we hypothesized that 5HT stimulated phosphoinositide hydrolysis in rat cerebral cortex is linked to the 5HT-2 binding site. However, the finding that activation of a given receptor stimulates phosphoinositide hydrolysis does not necessarily mean that the receptor is directly linked to phosphoinositide hydrolysis. The phosphoinositide hydrolysis response to certain agonists is secondary to receptor mediated neurotransmitter release (Bone & Michell, 1985) or to arachidonate metabolism (Rittenhouse, 1984). We have shown, however, that the 5HT-2 mediated phosphoinositide hydrolysis response in cerebral cortex is not dependent upon either of these indirect mechanisms (Conn & Sanders-Bush, 1986). Taken together, our studies in brain suggest that the 5HT-2 binding site is a functional receptor which utilizes phosphoinositide hydrolysis as its transducing mechanism. Studies of 5HT stimulated phosphoinositide hydrolysis in two peripheral tissues, platelets (deChaffoy de Courcelles et al., 1985) and aorta (Roth et al., 1984), are consistent with this conclusion.

Studies of the actions of trifluoromethylphenylpiperazine (TFMPP) and *m*-chlorophenylpiperazine (mCPP) on the 5HT-2 linked phosphoinositide hydrolysis system in the cerebral cortex have yielded some surprising findings. These compounds are generally thought to be agonists at all central 5HT receptors with which they interact. However, the efficacy at the various 5HT receptor subtypes has not been rigorously tested. Using the cortical phosphoinositide hydrolysis system, we have characterized the actions of these as well as other piperazines at central 5HT-2 receptors. Quipazine and MK-

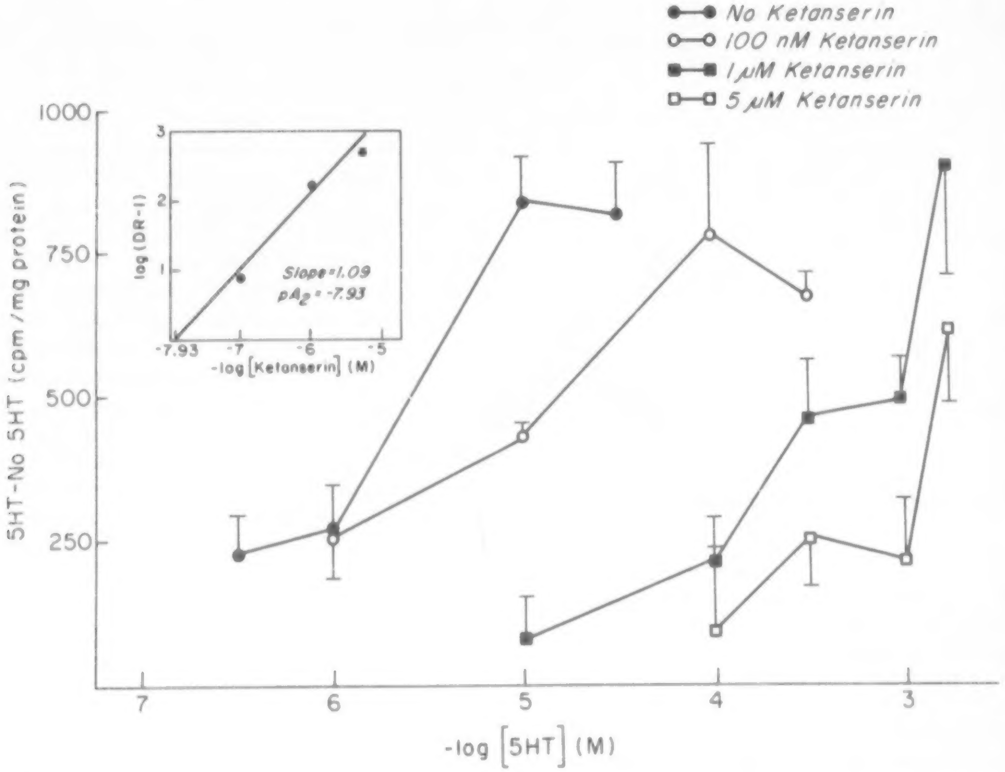


FIGURE 3. Schild analysis of ketanserin's antagonism of 5HT stimulated phosphoinositide hydrolysis in cortical slices. 5HT concentration response curves were generated in the presence of increasing concentrations of ketanserin. Inset shows the Schild plot of the same data. The dose ratio (DR) was calculated by dividing the concentration of 5HT needed to elicit a response of 600 cpm/mg of protein in the presence of ketanserin by the concentration of 5HT needed to elicit the same response in the absence of ketanserin. The pA2 (log K) value was obtained by extrapolation of the line to the *x*-axis. Each point represents the mean of two separate experiments, each done in triplicate. Vertical bars represent the SEM. Reproduced with permission from Conn and Sanders-Bush (1985).

212 function as partial agonists at these receptors. In contrast, TFMPP and mCPP fail to stimulate phosphoinositide hydrolysis at concentrations which completely inhibit the response to 5HT (Figure 5). Concentration-effect studies show that these drugs decrease 5HT's EC50 value without changing the maximum response. Thus, TFMPP and mCPP act as pure antagonists of the 5HT-2 receptor. This finding is consistent with the report that these drugs antagonize the contractile effects of 5HT in vascular smooth muscle (Cohen & Fuller, 1983), a response which is clearly mediated by the 5HT-2 site (Cohen et al., 1981). Since it is unlikely that responses to 5HT which are mimicked by mCPP and TFMPP are mediated by the 5HT-2 binding site, these compounds will be useful in future studies aimed at determining which 5HT receptor subtype mediates different central effects of 5HT.

5-HT-stimulated phosphoinositide hydrolysis in subcortical regions of rat brain is apparently mediated by mechanisms other than activation of the 5HT-2 receptor (Janowsky et al., 1984; Conn & Sanders-Bush, 1985), but the pharmacology of these effects has not yet been worked out. We have recently identified a unique 5HT receptor in the choroid plexus which is coupled to phosphoinositide hydrolysis (Conn et al., 1986). The effect of 5HT on IP formation in choroid plexus (5-fold stimulation, Figure 6) is much larger than in cerebral cortex (2-fold stimulation,

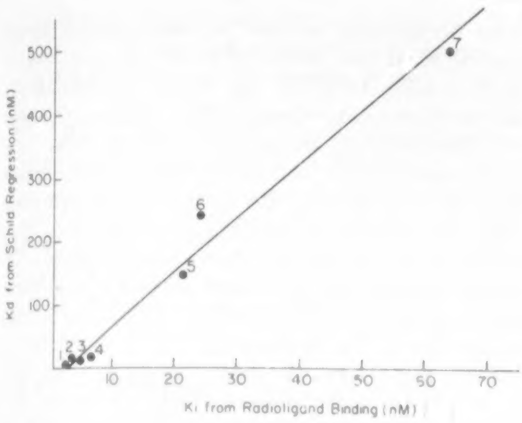


FIGURE 4. Correlation between inhibition of 5HT stimulated phosphoinositide hydrolysis and inhibition of [^{3}H]-ketanserin binding to the 5HT-2 site. The K_d values at the phosphoinositide hydrolysis linked receptor in cerebral cortex were determined by Schild analyses as described in the text. K_i values at the 5HT-2 binding site were determined by competition for 0.6 nM [^{3}H]-ketanserin binding to cortical membranes as described in Conn and Sanders-Bush (1985). 1. spiperone; 2. ketanserin; 3. pizotifen; 4. mianserin; 5. cinanserin; 6. trazodone; 7. promethazine.

Figure 2). Furthermore, the potency of 5HT is about tenfold higher in the choroid plexus. With such a robust signal in choroid plexus, it was possible to follow the time course of the formation of all three inositol sugars (Figure 7). Both IP3 and inositol bisphosphate (IP2) increase early and peak at about 5 minutes. These data demonstrate that PIP2 hydrolysis is activated by 5HT, but do not exclude the possibility that the hydrolysis of the other phosphoinositides is also increased since the three sugars increase simultaneously. The finding that the affinity of 5HT at the choroid plexus receptor (EC50 = 46 nM) is much higher than at the cerebral cortex 5HT-2 receptor (EC50 = 1000 nM) suggests that different receptor sites may mediate these effects. We therefore compared the pharmacology of the response in choroid plexus with the pharmacology of the 5HT-2 binding sites. Furthermore, the recently described 5HT-1C binding site is highly localized in the choroid plexus (Pazos et al., 1984; Yagaloff & Hartig, 1985), so the possibility that this site might mediate the effects of 5HT in this tissue was examined. The K_i value of 5HT at competing for the 5HT-1C binding site (94 nM) is similar to its EC50 at the phosphoinositide-linked receptor in choroid plexus, but not in cerebral cortex. Furthermore, the rank order and absolute potencies of antagonists in blocking phosphoinositide hydrolysis and 5HT-1C binding are in excellent agreement (Table 1). Based on the pharmacological similarity of the phosphoinositide hydrolysis response and the 5HT-1C binding site, we have concluded that the 5HT-1C binding site on choroid plexus epithelial cells is a functional receptor

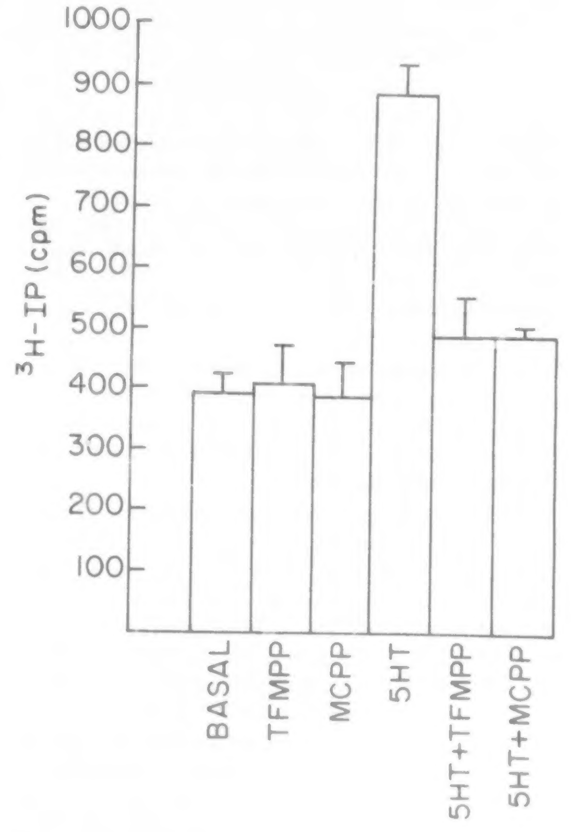


FIGURE 5. Antagonism of 5HT stimulated phosphoinositide hydrolysis by piperazines. Prelabelled rat cerebral cortical slices were incubated with 25 μM concentrations of trifluoromethylphenylpiperazine (TFMPP) or m-chlorophenylpiperazine (mCPP) in the presence or absence of 5 μM 5HT. The piperazines had no effect on the basal release of [^{3}H]-IP, but blocked the stimulatory effect of 5HT.

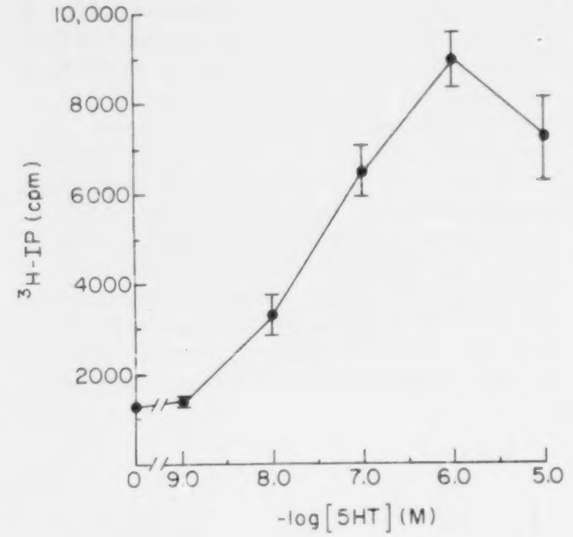


FIGURE 6. 5HT stimulated phosphoinositide hydrolysis in rat choroid plexus. Individual whole choroid plexus were prelabelled by incubating with [^{3}H]-inositol. Increasing concentrations of 5HT were added and release of [^{3}H]-inositol phosphate (IP) was measured as described in Conn et al. (1986). Values plotted are means ± SEM for three determinations.

which is linked to phosphoinositide hydrolysis. It remains to be determined if this receptor mediates any of the known physiological effects of 5HT, such as inhibition of CSF production (Maeda, 1983).

The "selective" 5HT-2 antagonist, ketanserin, has a moderately high affinity for the 5HT-1C receptor (Table 1). Frequently, the finding that a single dose of ketanserin blocks a response to 5HT is taken as evidence that the response is mediated by the 5HT-2 receptor. However, caution should be taken in making such a conclusion since the 5HT-1C receptor is also blocked by ketanserin. Mianserin, another antagonist with selectivity for the 5HT-2 versus the 5HT-1A and 5HT-1B sites, has equal affinity for the 5HT-1C (Table 1) and the 5HT-2 sites (Figure 4). Spiperone, on the other hand, distinguishes between 5HT-1C and 5HT-2 sites with more than three orders of magnitude difference in its affinities for the two sites. It remains to be determined if other "selective" 5HT-2 antagonists remain selective when evaluated at this new receptor site.

In summary, evidence has accumulated that at least two 5HT receptor subtypes, the 5HT-2 and the 5HT-1C sites, are linked to phosphoinositide hydrolysis. Although the pharmacological properties differ, there are many similarities between these two receptor sites. It remains to be determined whether these receptors are different proteins or the same gene product with posttranslational modifications or different physical environments which are responsible for the different properties. The availability of *in vitro* functional correlates of these binding sites has permitted a more precise classification of the actions of drugs. Obviously, binding studies do not differentiate whether drugs bind as agonists or as antagonists; such classifications depend on functional analyses. There is a tendency, however, to categorize drugs at all 5HT receptor subtypes as agonists or antagonists based on functional studies of a single subtype. Our finding that TFMPP and mCPP, drugs which are commonly considered to be 5HT agonists, actually function as pure antagonists of 5HT-2 receptors illustrates the need for functional studies of specific 5HT receptor subtypes.

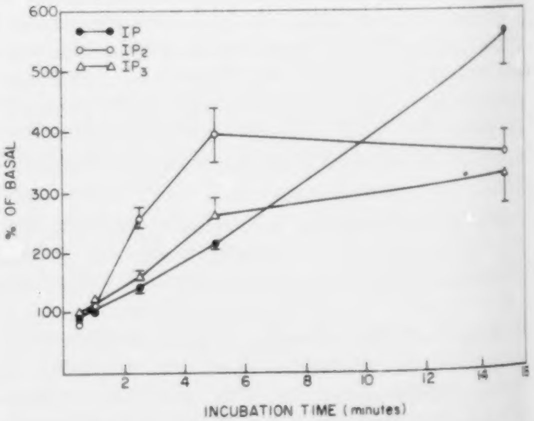


FIGURE 7. Time course of the formation of inositol sugars after the addition of 5HT. Individual choroid plexus were prelabelled with [^{3}H]-inositol. 5HT (10 µM) was added at time zero and the incubation was continued for the indicated times. The levels of radioactive IP, IP2, and IP3 were measured after purification by anion-exchange chromatography (Berridge et al., 1982). Values are presented as percent of basal levels of sugars and are mean ± SEM of 5 to 6 determinations.

TABLE 1. K_d Values (nM) at Choroid Plexus Phosphoinositide Hydrolysis Linked Receptor and at 5HT-1c and 5HT-2 Binding Sites.

Antagonist	Response[a]	Radioligand Binding	
		5HT-2[b]	5HT-1c[c]
Mianserin	12	7	5
Ketanserin	130	3	195
Spiperone	6200	2	4600

[a] Adapted from Conn et al. (1986).

[b] Competition with [3H]-ketanserin, from Conn and Sanders-Bush (1985).

[c] Competition with [125I]-LSD, from Conn et al. (1986).

Acknowledgments

The original investigations reported in this article were supported in part by USPHS grant MH 34007 and by a fellowship from Lilly Research Laboratories to P. Jeffery Conn, Ph.D.

References

Arunlakshana, O., and Schild, H.O. Some quantative uses of drug antagonists. *Brit. J. Pharmacol.*, 14:48–58, 1959.

Berridge, M.J. Inositol trisphosphate and diacylglycerol as second messengers. *Biochem. J.*, 220:345–360, 1984.

Berridge, M.J., and Heslop, J.P. Separate 5-hydroxytryptamine receptors on the salivary gland of the blowfly are linked to the generation of either cyclic adenosine 3',5' monophosphate or calcium signals. *Brit. J. Pharmacol.*, 73:729–738, 1981.

Berridge, M.J., Downes, P.C., and Hanley, M.R. Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. *Biochem. J.*, 206:587–595, 1982.

Bone, E.A., and Michell, R.H. Accumulation of inositol phosphates in sympathetic ganglia: Effects of depolarization and of amine and peptide neurotransmitters. *Biochem. J.*, 227:263–269, 1985.

Browning, M.D., Huganir, R., and Greengard, P. Protein phosphorylation and neuronal function. *J. Neurosci.*, 45:11–23, 1985.

Cohen, M.L., and Fuller, R.W. Antagonism of vascular serotonin receptors by m-chlorophenylpiperazine and m-trifluoromethylphenylpiperazine. *Life Sci.*, 32:711–718, 1983.

Cohen, M.L., Fuller, R.W., and Wiley, K.S. Evidence for 5-HT_2 receptors mediating contraction in vascular smooth muscle. *J. Pharmacol. Exp. Ther.*, 218:421–425, 1981.

Conn, P.J., and Sanders-Bush, E. Selective 5HT-2 antagonists inhibit serotonin stimulated phosphatidylinositol metabolism in cerebral cortex. *Neuropharmacology*, 23:993–996, 1984.

Conn, P.J., and Sanders-Bush, E. Serotonin-stimulated phosphoinositide turnover: mediation by the S_2 binding site in rat cerebral cortex but not in subcortical regions. *J. Pharmacol. Exp. Ther.*, 234:195–203, 1985.

Conn, P.J., and Sanders-Bush, E. Biochemical characterization of serotonin stimulated phosphoinositide turnover. *Life Sci.*, 38:663–669, 1986.

Conn, P.J., Sanders-Bush, E., Hoffman, B.J., and Hartig, P.R. A unique serotonin receptor in choroid plexus is linked to phosphoinositide hydrolysis. *Proc. Natl. Acad. Sci.* (In press, 1986).

de Chaffoy de Courcelles, D., Leysen, J.E., De Clerck, F., et al. Evidence that phospholipid turnover is the signal transducing system coupled to serotonin-S_2 receptor sites. *J. Biol. Chem.*, 260:7603–7608, 1985.

Fillion, G. 5-Hydroxytryptamine receptors in brain. In: Iversen, L.L., Iversen, S.D., and Snyder, S.H. (eds.), *Handbook of Psychopharmacol.*, Vol. 17. New York: Plenum Press, 1983, pp. 139–166.

Hirasawa, K., and Nishizuka, Y. Phosphatidylinositol turnover in receptor mechanisms and signal transduction. *Ann. Rev. Pharmacol. Toxicol.*, 25:147–170, 1985.

Janowsky, A., Labarca, R., and Paul, S.M. Characterization of neurotransmitter receptor-mediated phosphatidylinositol hydrolysis in the rat hippocampus. *Life Sci.*, 35:1953–1961, 1984.

Kendall, D.A., and Nahorski, S.R. 5 Hydroxytryptamine-stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: Pharmacological characterization and effects of antidepressants. *J. Pharmacol. Exp. Ther.*, 233:473–479, 1985.

Maeda, K. Monoaminergic effect on cerebrospinal fluid production. *Nihon Univ. J. Med.*, 25:155–174, 1983.

Middlemiss, D.N. Multiple 5-hydroxytryptamine receptors in the central nervous system of the rat. In: de Bolleroche, J. (ed.), *Presynaptic Receptors: Mechanism and Function*, Ellis-Harwood, 1982, pp. 46–74.

Pazos, A., Hoyer, D., and Palacios, J.M. The binding of serotonergic ligand to the porcine choroid plexus: characterization of a new type of serotonin recognition site. *Eur. J. Pharmacol.*, 106:539–546, 1985.

Pedigo, N.W., Yamamura, H.I., and Nelson, D.L. Discrimination of multiple ^{3}H-5-hydroxytryptamine binding sites by the neuroleptic spiperone in rat brain. *J. Neurochem.*, 36:220–226, 1981.

Peroutka, S.J., and Snyder, S.H. Multiple serotonin receptors: differential binding of [3-H]5-hydroxytryptamine, [3-H]lysergic acid diethylamide and [3-H]spiroperidol. *Mol. Pharmacol.*, 16:687–699, 1979.

best copy available

Rittenhouse, S.E. Activation of human platelet phospholipase C by ionophore A23187 is totally dependent upon cyclo-oxygenase products and ADP. *Biochem. J.*, 222:103–110, 1984.

Roth, B.L., Nakaki, T., Chuang, D.M., and Costa, E. Aortic recognition sites for serotonin (5HT) are coupled to phospholipase C and modulate phosphatidylinositol turnover. *Neuropharmacology*, 23:1223–1225, 1984.

Sanders-Bush, E, and Conn, P.J. Neurochemistry of serotonin neuronal systems: Consequences of serotonin receptor activation. In: ***Psychopharmacology: Third Generation of Progress***. New York: Raven Press. (In press.)

Yagaloff, K. A. and Hartig, P. R. [125I]-LSD binds to a novel serotonergic site on rat choroid plexus epithelial cells. *J. Neurosci.*, 5:3178–3183, 1985.

Serotonin Receptor Subtype Agonists: Differential Effects on Sensorimotor Reactivity Measured With Acoustic Startle

Michael Davis, Ph.D.,[1] James V. Cassella, Ph.D.,[1] William H. Wrean,[1] and John H. Kehne, Ph.D.[1]

Investigating how serotonin receptor subtypes interact with behavior may be simplified by analyzing how serotonergic drugs alter a simple reflex. The acoustic startle reflex in the rat offers a number of advantages in the analysis of drug effects on behavior (cf. Davis, 1980). Startle amplitude is dependent upon the characteristics of the eliciting stimulus, allowing a non-zero baseline against which both inhibitory and excitatory drug effects can be analyzed.

Drugs can act on neurotransmitters that either mediate or modulate a simple reflex behavior. A neurotransmitter that mediates startle is one that would be released within one of the four possible synapses comprising the startle pathway (Davis et al., 1982). If 5-HT containing neurons mediate this reflex then depletion of 5-HT should eliminate startle by preventing transmission from one neuron to the next within the startle pathway. However, depletion of 5-HT does not eliminate startle (cf. Davis, 1980) indicating that 5-HT is not a mediating neurotransmitter for the startle reflex.

On the other hand, considerable evidence does indicate that 5-HT modulates the startle reflex. It is clear from Table 1, however, that treatments that affect 5-HT produce complex effects on the startle reflex. Several studies have suggested that 5-HT tonically inhibits startle, since treatments that deplete the brain of 5-HT elevate startle. For example, lesions of the dorsal and median raphe nuclei (Davis & Sheard, 1974; Geyer et al., 1976), administration of *p*-chlorophenylalanine (Conner et al., 1970; Carlton & Advokat, 1973), *p*-chloroamphetamine (Davis & Sheard, 1976), or 5,7-dihydroxytryptamine (Geyer et al., 1980), or tryptophan-free diets (Walters et al., 1979) increase startle amplitude. In contrast, other studies indicate that activation of 5-HT receptors can substantially increase startle amplitude, suggesting that 5-HT is excitatory to startle. For example, increasing the levels of 5-HT by systemic administration of L-tryptophan, 5-hydroxytryptophan, or lithium (each in combination with a monoamine oxidase inhibitor) markedly increase startle (M. Davis, unpublished findings; Fechter, 1974; Svensson, 1985). Moreover, direct 5-HT agonists such as 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) or 8-hydroxy-2-(di-n-propylamine) tetralin (8-OH-DPAT) increase startle substantially (Davis et al., 1980a; Svensson, 1985; Svensson & Ahlenius, 1983).

Closer examination of these data indicate, however, that 5-HT may have differential actions on startle depending upon whether it acts primarily in the forebrain or spinal cord. For example, Geyer et al. (1976) found that lesions of the median raphe nuclei depleted 5-HT in the hippocampus which correlated with increased startle. Moreover, local administration of 5-HT into the lateral ventricle (Geyer et al., 1975) or into the hippocampus itself depressed startle amplitude (Geyer,

TABLE 1. Effects of Treatments That Alter 5-HT on Startle.

Treatment	Effect	Conclusion
Raphe Lesions	Startle Increase	5-HT—Inhibitory
PCPA	Startle Increase	5-HT—Inhibitory
5,7-DHT	Startle Increase	5-HT—Inhibitory
Tryptophan Free Diet	Startle Increase	5-HT—Inhibitory
p-Chloroamphetamine	Startle Decrease	5-HT—Inhibitory
Tryptophan + MAOI	Startle Increase	5-HT—Excitatory
5-HTP + MAOI	Startle Increase	5-HT—Excitatory
Lithium + MAOI	Startle Increase	5-HT—Excitatory

---

[1] Department of Psychiatry, Yale University School of Medicine, and The Ribicoff Research Facilities of the Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06508.

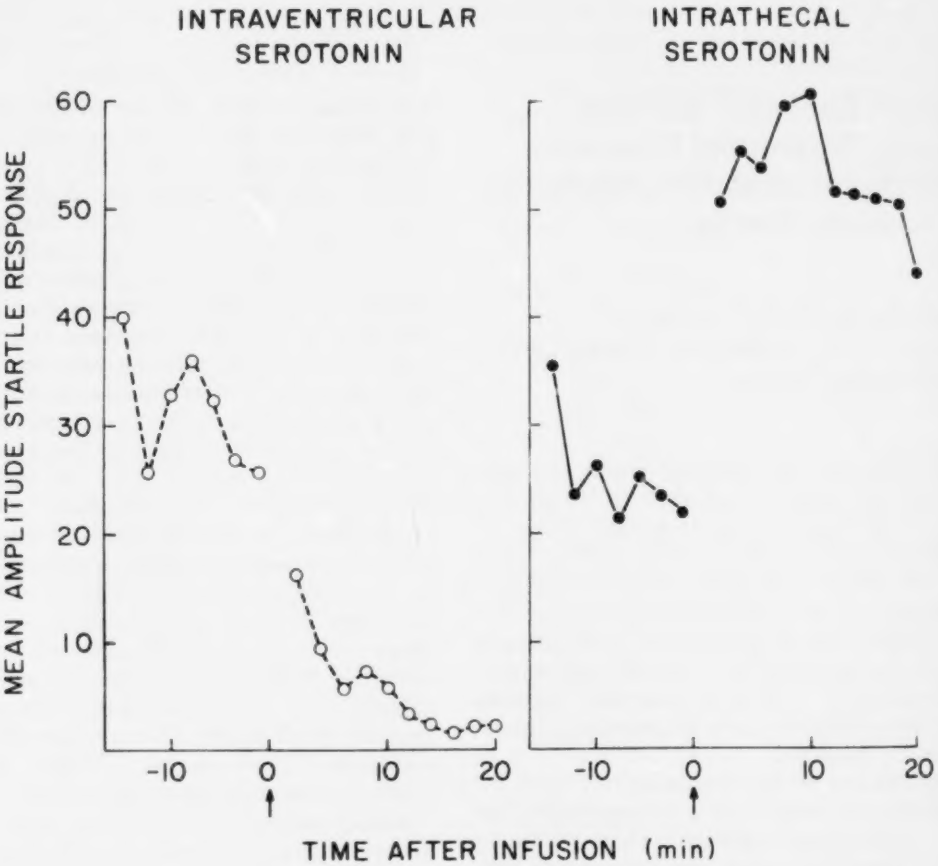


FIGURE 1. Mean amplitude startle over 2-min periods before and after infusion (arrow) of 200 μg of serotonin into the lateral ventricle (left panel) or onto the spinal cord (right panel). Reproduced with permission from Davis et al., 1980b, *Science*, copyright 1980, American Association for the Advancement of Science.

1975). On the other hand, treatments that increase startle by elevating 5-HT also produce a characteristic "serotonin syndrome," which involves structures in the brainstem and spinal cord (Jacobs & Klemfuss, 1975). Therefore it is possible that 5-HT might increase startle by actions in the spinal cord but depress startle via actions in the forebrain.

Effects of Intraventricular or Intrathecal 5-HT on Startle

To test forebrain-inhibitory and spinal-excitatory effects of 5-HT, rats were implanted with either intraventricular or intrathecal catheters, allowing for the infusion of drugs into the forebrain or spinal cord, respectively (Davis et al., 1980b). One week later all rats were injected intraperitoneally (ip) with 25 mg/kg pargyline (to retard the degradation of 5-HT) and then tested for startle before and after infusion of 200 μg of 5-HT. Figure 1 shows that 5-HT depressed startle after intraventricular administration, but increased startle after intrathecal administration. Figure 2 shows that each of these effects was directly related to the amount of 5-HT infused.

Taken together these data suggest that 5-HT depresses startle by actions in the forebrain but enhances startle by actions in the spinal cord. These findings are consistent with electrophysiological data indicating that 5-HT generally has a depressant action in a number of forebrain structures including the hippocampus (e.g., Haigler & Aghajanian,

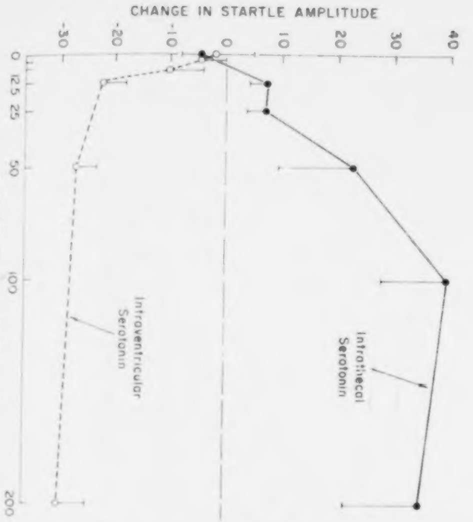


FIGURE 2. Mean change in startle, computed as the mean amplitude of startle during the 20-min period after infusion minus the mean amplitude of startle during the 15-min period before infusion, for each dose of serotonin infused onto the spinal cord (intrathecal) or into the lateral ventricle (intraventricular). Vertical bars represent the standard error of the mean. Reproduced with permission from Davis et al., 1980b, *Science*, copyright 1980, American Association for the Advancement of Science.

1974). In contrast, 5-HT facilitates motor neuron excitability (e.g., McCall & Aghajanian, 1979; White & Neuman, 1980), which may account for its excitatory effects on startle after intrathecal administration, since the motor neurons involved in startle are located in the spinal cord.

Effects of Systemically Administered 5-HT Agonists on Startle

Recent evidence indicates that 5-HT$_1$ receptors may be differentiated into 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes (Nelson et al., 1981; Pedigo et al., 1981; Schellman et al., 1984). To test the possibility that the differential effects of 5-HT on startle result from actions of 5-HT at different 5-HT$_1$ receptor subtypes, we compared the effects on startle of the selective 5-HT$_{1A}$ agonist 8-OH-DPAT (Doods et al., 1985; Middlemiss & Fozard, 1983; Peroutka, 1985) with those of 1-(m-chlorophenyl) piperazine (mCPP) which along with other short-chain phenylpiperazines, has some specificity for 5-HT$_{1B}$ receptor subtypes (Asarch et al., 1985; Sills et al., 1984). In these experiments 80 rats were matched into 8 groups of 10 animals each so that each group had equivalent baseline startle levels. Two days later, each group was tested following ip injection of one of four doses of 8-OH-DPAT (0.15, 0.63, 2.50, or 10.0 mg/kg) or one of four doses of mCPP (1.25, 2.5, 5.0, or 10.0 mg/kg). Within each group, half the rats were injected with the drug on their first test day, while the other half received saline. Immediately after testing, all rats were presented with the first of 120 startle stimuli at a 20-sec interstimulus interval (i.e., 40 min of testing). Two days later, these test procedures were repeated, except rats previously injected with the drug were now injected with saline and vice versa. Hence each rat served as its own control with respect to the drug vs. saline, while drug dosage varied between groups.

Figure 3 shows that 8-OH-DPAT markedly increased startle almost immediately after injection (left panel), and that the magnitude of the effect was directly related to the dose of 8-OH-DPAT (right panel). An overall analysis of variance indicated a highly significant excitatory effect of 8-OH-DPAT ($p < .001$) which was dose dependent ($p < .005$). In contrast, Figure 4 shows that mCPP decreased startle immediately after injection (left panel) and that this depressant effect was directly related to the dose of mCPP (right panel). An overall analysis of variance indicated a significant depressant effect of mCPP ($p < .001$) that was dose dependent ($p < .05$).

Effects of 5-HT$_{1A}$ or 5-HT$_{1B}$ Agonists Given Intraventricularly or Intrathecally on Acoustic Startle.

The systemic data indicate that the 5-HT$_{1A}$ agonist 8-OH-DPAT increases startle whereas the 5-HT$_{1B}$ agonist mCPP depresses startle. Since 5-HT in the spinal cord elevated startle and 5-HT in the forebrain depressed startle, it is likely that excitatory effects of 8-OH-DPAT following systemic administration might result from actions in the spinal cord, whereas the depressant effects of systemically administered mCPP might result from actions in the forebrain. To test this hypothesis,

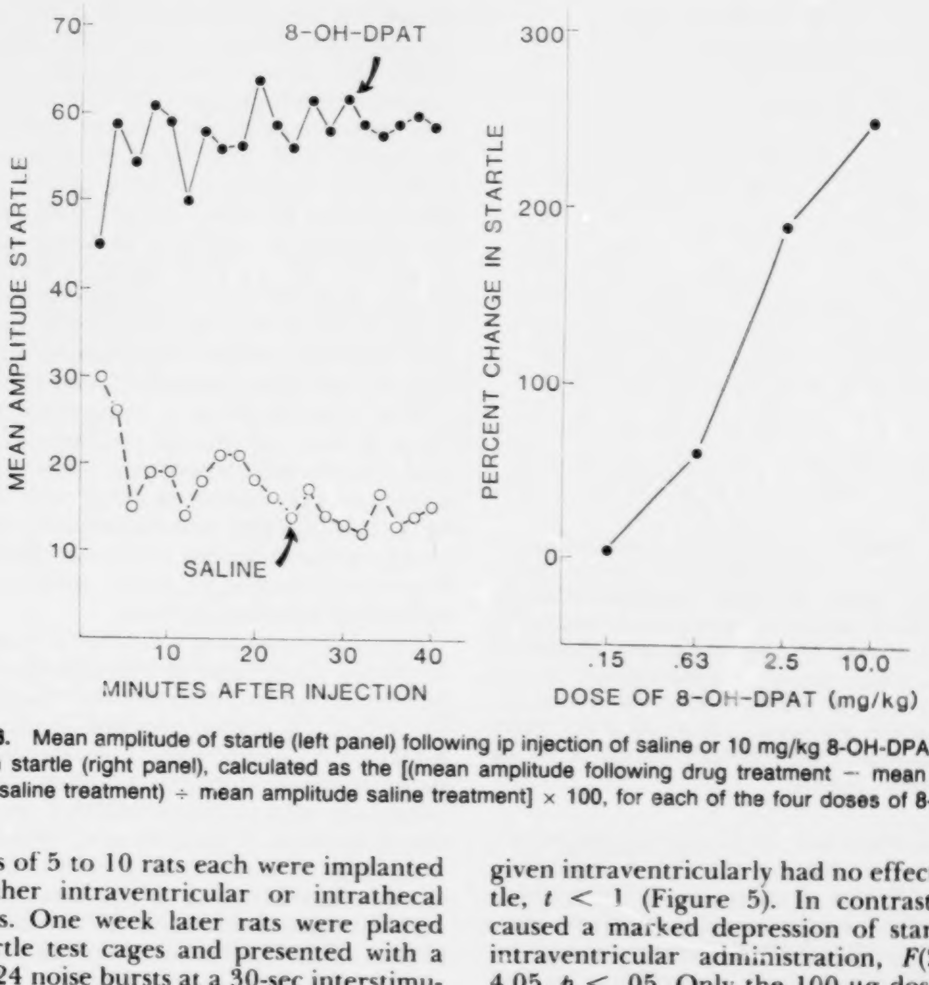


FIGURE 3. Mean amplitude of startle (left panel) following ip injection of saline or 10 mg/kg 8-OH-DPAT. Percent change in startle (right panel), calculated as the [(mean amplitude following drug treatment − mean amplitude following saline treatment) ÷ mean amplitude saline treatment] × 100, for each of the four doses of 8-OH-DPAT (ip).

8 groups of 5 to 10 rats each were implanted with either intraventricular or intrathecal catheters. One week later rats were placed into startle test cages and presented with a total of 24 noise bursts at a 30-sec interstimulus interval. The rats were then removed and infused with either 8-OH-DPAT or mCPP, using different groups of rats for different doses. Immediately thereafter the rats were returned to the test cages and presented with the first of 60 noise bursts at a 30-sec interstimulus interval (i.e., 30 min of testing).

Figure 5 shows the change in startle amplitude from the pre-infusion to the post-infusion period for the various groups. Overall analysis of these difference scores revealed that 8-OH-DPAT markedly increased startle after intrathecal administration, $F(2,17) = 6.07$, $p < .01$. Both the 50 µg and 100 µg doses significantly increased startle relative to vehicle, $t(12) = 2.13$, $p < .05$ and $t(12) = 4.26$, $p < .001$, respectively. On the other hand, even the highest dose of 8-OH-DPAT given intraventricularly had no effect on startle, $t < 1$ (Figure 5). In contrast, mCPP caused a marked depression of startle after intraventricular administration, $F(2,19) = 4.05$, $p < .05$. Only the 100 µg dose significantly depressed startle relative to vehicle, $t(11) = 2.56$, $p < .05$. Although mCPP tended to depress startle after intrathecal administration (Figure 5), this effect was not statistically significant, $t(11) = 1.16$, $p > .10$).

Summary and Future Directions

Figure 6 summarizes our present understanding of the way in which 5-HT modulates sensorimotor reactivity measured with the acoustic startle reflex. Activation of 5-HT$_{1B}$ receptors in the forebrain appears to depress startle. At the present time we do not know where these receptors might be located. As mentioned earlier, local administration of 5-HT into the hippocampus depressed startle (Geyer, 1975). However, the hippocampus

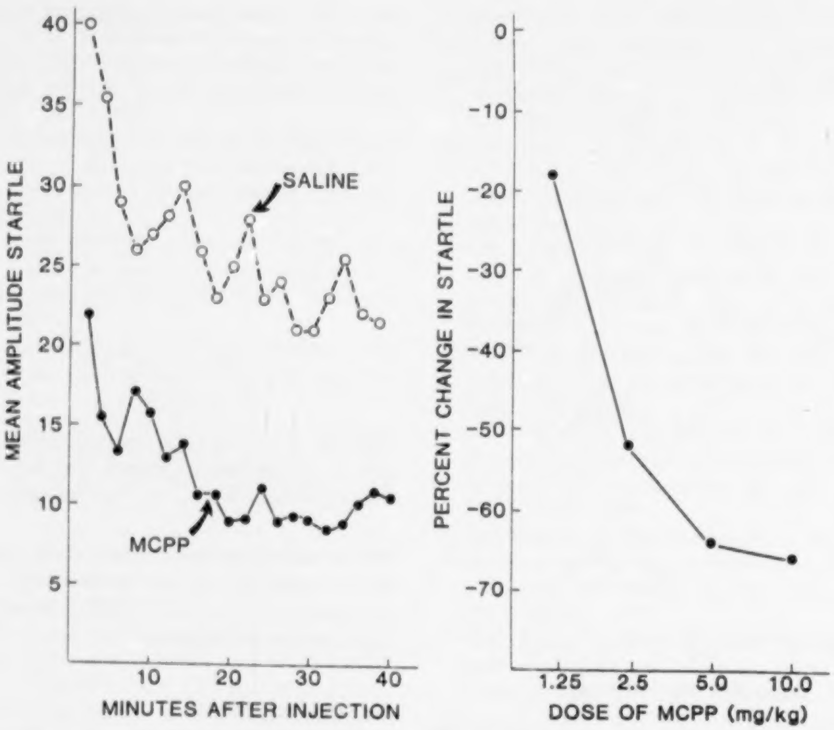


FIGURE 4. Mean amplitude of startle (left panel) following ip injection of saline or 2.5 mg/kg mCPP. Percent change in startle (right panel), calculated as the [(mean amplitude following saline treatment − mean amplitude after mCPP treatment) ÷ mean amplitude saline treatment] × 100, for each of the four doses of MCPP (ip).

contains predominantly the 5-HT$_{1A}$ receptor subtype, whereas the caudate nuclei contains a much higher density of 5-HT$_{1B}$ receptors (Deshmukh et al., 1983; Pazos & Palacios, 1985). Future studies comparing the effects of local infusion of selective 5-HT agonists into forebrain areas containing different densities of 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes might determine the location of the 5-HT$_1$ receptor subtype that mediates the depressant effect on startle.

Activation of 5-HT$_{1A}$ receptors in the spinal cord increases the amplitude of the startle reflex. Electrophysiological studies indicate that 5-HT increases the response of motor neurons to excitatory input (McCall & Aghajanian, 1979; White & Neuman, 1980). Hence the excitatory effects of intrathecal 5-HT or 8-OH-DPAT may result from facilitating the response of motor neurons in the spinal cord to the afferent volley initiated by the startle-eliciting stimulus. Our behavioral data suggest that 5-HT$_{1A}$ agonists might be especially effective in facilitating the response of motor neurons when measured electrophysiologically.

Thus far we have not systematically investigated whether different 5-HT antagonists preferentially block the excitatory effects of 8-OH-DPAT vs. the inhibitory effects of mCPP on startle. Metergoline has been reported to antagonize the depressant effects of mCPP on locomotor activity (Lucki et al., 1984) whereas it does not block the excitatory effects of 8-OH-DPAT on startle (Svensson, 1985). Thus it is possible that metergoline might show selectivity for 5-HT$_{1B}$ vs. 5-HT$_{1A}$ receptors, thereby preferentially blocking the depressant effect of mCPP on startle. On the other hand, methiothepin did block the excitatory effects of 8-OH-DPAT on startle (Svensson, 1985) although methiothepin's antidopaminergic and antinoradrenergic effects (e.g., Lloyd & Barth-

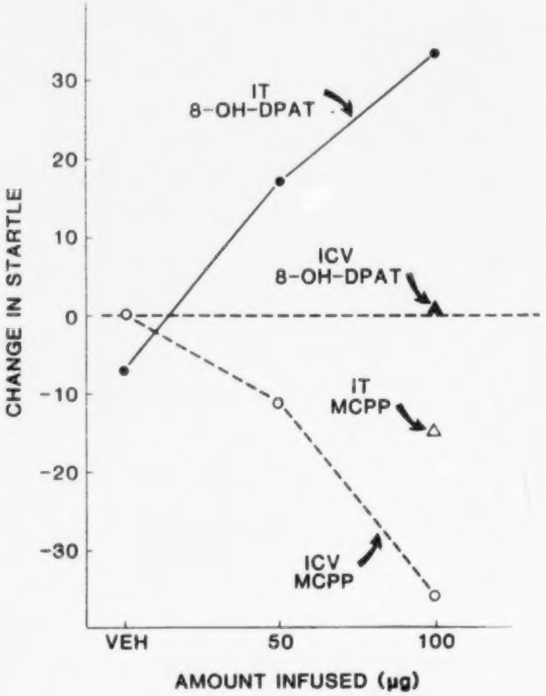


FIGURE 5. Mean change in startle, computed as the mean amplitude of startle during the 30-min period after infusion minus the mean amplitude of startle during the 12-min period before infusion, for each dose of MCPP or 8-OH-DPAT administered intraventricularly (ICV) or intrathecally (IT).

olini, 1974) may have contributed to this blockade.

Interestingly, propranolol has been reported to block the serotonin syndrome produced by L-tryptophan plus a MAOI (Green & Graham-Smith, 1976) or produced by 8-OH-DPAT (Goodwin & Green, 1985), with the 1-isomer being considerably more potent than the d-isomer. The 1-isomer is also more potent in binding to 5-HT receptors (Middlemiss et al., 1977). Previously we found that d,1-propranolol completely blocked the excitatory effect of another 5-HT$_{1A}$ agonist, 5-MeODMT, on startle (Davis, et al., 1980a). Therefore propranolol might also block the effects of either systemically or intrathecally administered 8-OH-DPAT and the 1-isomer might produce a more potent blockade than the d-isomer. In fact, the differential actions on startle of 5-HT or mCPP given intraventricularly vs. 5-HT or 8-OH-DPAT given intrathecally may provide a sensitive test procedure to evaluate the specificity of newly developed 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor subtype agonists or antagonists.

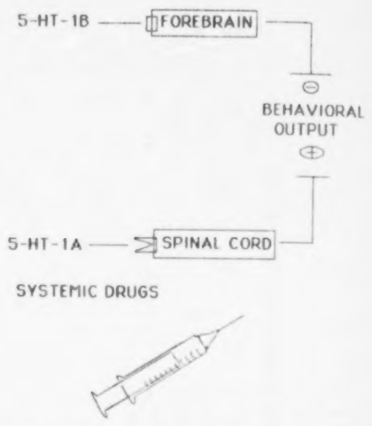


FIGURE 6. Schematic representation of behavioral effects of serotonin agonists that act on receptors in the spinal cord (5-HT$_{1A}$) or the forebrain (5-HT$_{1B}$).

Acknowledgments

This research was supported by NSF Grant BNS–81–20476, NIMH Grant MH–25642, NINCDS Grant NS–18033, Research Scientist Development Award MH–00004 to Michael Davis and the State of Connecticut. James Cassella was supported by Biological Sciences Training Grant MH–14276. We thank Leslie Fields for secretarial assistance and Lee Schlesinger for technical help.

References

Asarch, K.B., Ransom, R.W., and Shih, J.C. 5-HT-1a and 5-HT-1b selectivity of two phenylpiperazine derivatives: Evidence for 5-HT-1b heterogeneity. *Life Sci.*, 36:1265–1273, 1985.

Carlton, P.L., and Advokat, C. Attenuated habituation due to parachlorophenylalanine. *Pharmacol. Biochem. Behav.*, 1:657–663, 1973.

Conner, R.J., Stolk, J.M., Barchas, J.D., and Levine, S. Parachlorophenylalanine and habituation to repetitive auditory startle stimuli in rats. *Physiol. Behav.*, 5:1215–1219, 1970.

Davis, M. Neurochemical modulation of sensory-motor reactivity: Acoustic and tactile startle reflexes. *Neurosci. Biobehav. Rev.*, 4:241–263, 1980.

Davis, M., Astrachan, D.I., Gendelman, P.M., and Gendelman, D.S. 5-Methoxy-N,N-dimethyltryptamine: Spinal cord and brainstem mediation of excitatory effects on acoustic startle. *Psychopharmacology (Berlin)*, 70:123–130, 1980a.

Davis, M., Astrachan, D.I., and Kass, E. Excitatory and inhibitory effects of serotonin on sensorimotor reactivity measured with acoustic startle. *Science*, 209:521–523, 1980b.

Davis, M., Gendelman, D.S., Tischler, M.D., and Gendelman, P.M. A primary acoustic startle circuit: Lesion and stimulation studies. *J. Neurosci.*, 2:791–805, 1982.

Davis, M., and Sheard, M.H. Habituation and sensitization of the rat startle response: Effects of raphe lesions. *Physiol. Behav.*, 12:425–431, 1974.

Davis, M., and Sheard, M.H. p-Chloroamphetamine (PCA): Acute and chronic effects on habituation and sensitization of the acoustic startle response in the rat. *Eur. J. Pharmacol.*, 35:261–273, 1976.

Deshmukh, P.P., Yamamura, H.I., Woods, L., and Nelson, D.L. Computer-assisted autoradiographic localization of subtypes of serotonin$_1$ receptors in rat brain. *Brain Res.*, 288:338–343, 1983.

Doods, H.N., Kalkman, H.O., DeJonge, A., et al. Differential selectivities of RU 24969 and 8-OH-DPAT for the purported 5-HT$_{1A}$ and 5-HT$_{1B}$ binding sites. Correlation between 5-HT$_{1A}$ affinity and hypotensive activity. *Eur. J. Pharmacol.*, 112:363–370, 1985.

Fechter, L.D. Central serotonin involvement in the elaboration of the startle reaction in rats. *Pharmacol. Biochem. Behav.*, 2:161–171, 1974.

Geyer, M.A. Functional heterogeneity within neurotransmitter systems. *Psychopharmacol. Commun.*, 1:675–685, 1975.

Geyer, M.A., Petersen, L.R., and Rose, G.J. Effects of serotonergic lesions on investigatory responding by rats in a holeboard. *Behav. Neural. Biol.*, 30:160–177, 1980.

Geyer, M.A., Puerto, A., Menkes, D.B., Segal, D.S., and Mandell, A.J. Behavioral studies following lesions of the mesolimbic and mesostriatal serotonergic pathways. *Brain Res.* 106:257–270, 1976.

Geyer, M.A., Warbritton, A.J.D., Menkes, D.B., et al. Opposite effects of intraventricular serotonin and bufotenin on rat startle responses. *Pharmacol. Biochem. Behav.*, 3:687–691, 1975.

Goodwin, G.M., and Green, A.R. A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT$_1$ and 5-HT$_2$ receptors. *Br. J. Pharmac.*, 84:743–753, 1985.

Green, A.R., and Grahame-Smith, D.G. (-)-Propranolol inhibits the behavioural responses of rats to increased 5-hydroxytryptamine in the central nervous system. *Nature*, 262:594–596, 1976.

Jacobs, B.L., and Klemfuss, H. Brain stem and spinal cord mediation of a serotonergic behavioral syndrome. *Brain Res.*, 100:450–457, 1975.

Haigler, H.J., and Aghajanian, G.K. Lysergic acid diethylamide and serotonin: A comparison of effects on serotonergic neurons and neurons receiving a serotonergic input. *J. Pharmacol. Exp. Ther.*, 188:688–699, 1974.

Lloyd, K.G., and Bartholini, G. The effect of methiothepin on cerebral monoamine neurons. In: *Advances in Biochemical Psychopharmacology*, Vol. 10. New York: Raven Press, 1974, pp. 305–309.

Lucki, I., Nobler, M.S., and Frazer, A. Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. *J. Pharmacol. Exp. Ther.*, 228:133–139, 1984.

McCall, R.B., and Aghajanian, G.K. Serotonergic facilitation of facial motoneuron excitation. *Brain Res.*, 169:11–27, 1979.

Middlemiss, D.N., and Fozard, J.R. 8-Hydroxy-2-(di-n-propylamino)-tetralin discriminates between subtypes of the 5-HT$_1$ recognition site. *Eur. J. Pharmacol.*, 90:151–153, 1983.

Middlemiss, D.N., Blakeborough, L., and Leather, S.R. Direct evidence for an interaction of β-adrenergic blockers with the 5-HT receptor. *Nature*, 267:289–290, 1977.

Nelson, N.L., Pedigo, N.W., and Yamamura, H.I. Multiple ^{3}H-5-hydroxytryptamine binding sites in rat brain. *J. Physiol. (Paris)*, 77:369–372, 1981.

Pazos, A., and Palacios, J.M. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. *Brain Res.*, 346:205–230, 1985.

Pedigo, N.W., Yamamura, H.I., and Nelson, D.L. Discrimination of multiple ^{3}H-5-hydroxytryptamine binding sites by neuroleptic spiperone in rat brain. *J. Neurochem.*, 36:220–226, 1981.

Peroutka, S.J. Selective labeling of 5-HT$_{1A}$ and 5-HT$_{1B}$ binding sites in bovine brain. *Brain Res.*, 344:167–171, 1985.

Schnellman, R.G., Waters, S.J., and Nelson, D.L. [^{3}H]5-hydroxytryptamine binding sites: species and tissue variation. *J. Neurochem.*, 42:65–70, 1984.

Sills, M.A., Wolfe, B.B., and Frazer, A. Determination of selective and nonselective compounds for the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes in rat frontal cortex. *J. Pharmacol. Exp. Ther.*, 231:480–487, 1984.

Svensson, L. Effects of 8-OH-DPAT, lisuride and some ergot-related compounds on the acoustic startle response in rat. *Psychopharmacology*, 85:469–475, 1985.

Svensson, L., and Ahlenius, S. Enhancement by the putative 5-HT receptor agonist 8-OH-2-(di-n-propylamino)tetralin of the acoustic startle response in the rat. *Psychopharmacology*, 79:104–107, 1983.

Walters, J.K., Davis, M., and Sheard, M.H. Tryptophan free diet: Effects on the acoustic startle reflex in rats. *Psychopharmacology*, 62:103–109, 1979.

White, S.R., and Neuman, R.S. Facilitation of spinal motoneurone excitability by 5-hydroxytryptamine and noradranaline. *Brain Res.*, 185:1–9, 1980.

Influences of Pharmacologic and Psychosocial Factors on the Course of Schizophrenia

Co-Chairs:

Nina R. Schooler, Ph.D. — *National Institute of Mental Health*
Rockville, MD 20857

John M. Kane, M.D. — *Hillside Hospital*
Glen Oaks, NY 11004

Prediction of Relapse in Schizophrenia

Jeffrey A. Lieberman, M.D.,[1] John M. Kane, M.D.,[1] Stavros Sarantakos, M.D.,[1] Dominick Gadaletta, M.D.,[1] Margaret Woerner, Ph.D.,[1] Jose Alvir, Dr. P.H.,[1] and Jorge Ramos-Lorenzi, M.D.[1]

Schizophrenia is acknowledged to be a heterogeneous illness (Bleuler, 1950). Its clinical heterogeneity is manifest in the marked variability that patients within the schizophrenic syndrome have in their courses of illness (Bleuler, 1974), presentation and evolution of psychopathology (Pfohl & Winokur, 1982; Pogue-Geile & Harrow, 1984; Johnstone et al., 1978), pharmacologic treatment response (Davis, 1975; Cole et al., 1966; Klein & Davis, 1969), and vulnerability to drug side effects (Baldessarini et al., 1980). Despite this broad heterogeneity, the pharmacotherapeutic approach to treatment is surprisingly uniform.

A major deficiency in the clinical management of schizophrenia is the lack of proven methods by which to predict the subsequent course of illness and to identify patients who really require neuroleptic maintenance to prevent relapse or alternatively would remain stable for substantial periods of time without drug treatment. If such methods existed it might be possible to individualize maintenance neuroleptic pharmacotherapy for schizophrenic patients in a way that improves the benefit to risk ratio. Previous studies have suggested the utility of various measures as predictors of relapse in schizophrenia including serum or plasma prolactin (PRL) (Brown & Laughren, 1981; Zander et al., 1981) and neuroleptic levels (Brown et al., 1982; Brown & Silver, 1985), growth hormone (GH) response to apomorphine (Cleghorn et al., 1984; Mueller-Spahn et al., 1984) and behavioral response to a psychostimulant provocative test (Angrist et al., 1981; vanKammen et al., 1982; Lieberman et al., 1984).

---

[1] Hillside Hospital, division of Long Island Jewish Medical Center, P.O. Box 38, Glen Oaks, NY 11004.

This work was supported by PHS grants MH-38880 and MH-00537 to Dr. Lieberman. The authors wish to acknowledge the assistance of Drs. Howard Green and Steven Geisler in this project. Endocrine hormones were assayed in the laboratory of Mr. Thomas Cooper under the direction of Ms. Hana Novachenko at New York State Psychiatric Institute. Neuroleptic assays were performed in the Neuropharmacology Laboratory of Dr. Bruce Kinon, Long Island Jewish Medical Center.

The study on which we report was designed to evaluate predictors of outcome in stable outpatients with schizophrenia undergoing neuroleptic maintenance treatment.

Method

Subjects

Subjects came from the aftercare services of Hillside Hospital's department of psychiatry and met the following criteria:

1) Diagnosis of subacute, subchronic, or chronic schizophrenia or schizoaffective disorder according to Research Diagnostic Criteria.

2) Between 18 and 50 years old.

3) No history of serious neurologic disorder, endocrine disorder, or current serious medical condition.

4) A remission of their last acute episode as defined by the following items on the Schedule for Affective Disorders and Schizophrenia-Psychosis and Disorganization items (SADS-PD): a) a rating no greater than two for severity and presence of delusions (only "suspected" as being present by the rater); b) a rating no greater than two for severity and presence of hallucinations (only "suspected" as being present by the rater); c) a rating no greater than three for incoherence ("a few definite instances of impairment in understandability but they are never gross"); d) a rating no greater than three for bizarre behavior (strange behavior but not obviously "crazy"); and e) catatonic motor behavior not present.

5) Their total score on factors III, IV, and V of the Brief Psychiatric Rating Scale (BPRS) was less than 24.

6) They had been stable at their current level of remission for at least 6 months and were receiving neuroleptic maintenance treatment.

7) They were willing and able (as judged by a psychiatrist not involved with the project) to give informed consent.

Infusion Procedure

All subjects received two infusions, one of methylphenidate and one of placebo, in randomized order, 1 week apart. The drug and placebo administrations were double blind. Subjects (*N* = 11) who entered the study before a design change received a set of infusions following neuroleptic discontinuation and a 20-day washout period (42 days if the subject had been receiving fluphenazine decanoate). Those (*N* = 28) entering after the design change received a set of infusions before neuroleptic withdrawal and a set following withdrawal and the washout period.

A standardized protocol was used for all infusions (Lieberman et al., 1984).

Infusion responses were classified as positive or negative by predetermined quantitative changes in specified rating scale item scores. A positive response was defined quantitatively as an increase of at least two scale points above the thresholds of any of the critical SADS-PD items used to define remission or an eight point or more increase from the pre-infusion BPRS score of the critical items (items 4, 7, 8, 10, 11, 12, 14, and 15). (An increase of one scale point above the SADS-PD item threshold or a six point BPRS critical items increase was called a questionable response.) True positive responders were those patients who had positive change scores in responses to methylphenidate only. True negative responders were defined as having had negative responses to all infusions.

Followup

Patients were seen weekly by their treating psychiatrists, during the drug washout period and for 10 weeks following completion of the infusions. Thereafter, patients were seen biweekly. Patients were evaluated for prodromal (Herz & Melville, 1979) and formal psychopathologic symptoms at each clinic visit.

Relapse was defined as an increase of at least 2 scale points above the thresholds on any of the critical SADS-PD items used to define remission and/or a 10-point or more increase from the baseline scores of the critical BPRS items Whenever clinically possible, patients were not considered relapsed unless the symptoms persisted at this level of severity for 1 week.

Upon relapse, patients were treated with a fixed dose regimen of fluphenazine decanoate (1.0 cc IM weekly) and clinical response was evaluated for 8 weeks.

Results

Data from 34 patients were used in the analyses. The sample consisted of 21 males and 13 females with a mean (± S.D.) age of 29.1 ± 2.5 years. Twenty-three of the patients were diagnosed as having schizophrenia and 11 as having schizoaffective disorder (predominantly schizophrenic, RDC) (Spitzer et al., 1977). The patients were relatively early in their course of illness (mean ± S.D. age at onset was 20.5 ± 2.5 years), had a mean (± S.D.) of 2.8 ± 1.1 previous episodes and had achieved a level of remission sufficient for them to live in the community as outpatients (mean ± S.D. duration of remission before study entry was 109.7 ± 61 weeks) and to participate in ongoing vocational activities (e.g., a job, rehabilitation program, or school). Though stable and well functioning the sample was characterized by residual symptoms. Mean (± S.D.) item scores for the different rating scales at baseline were as follows: BPRS (all items) 1.28 ± .26; SADS-PD 1.25 ± 1.7; T & A .2 ± .4; CGI 1.94 ± .81. Sixteen of the 34 subjects had TD (overall global rating of mild on the Simpson Dyskinesia Scale). Sixteen of the 34 subjects entered the study on long acting injectable medication (fluphenazine decanoate).

Behavioral, neurologic, and endocrine responses to methylphenidate and placebo are shown in Figure 1. BPRS critical item scores were significantly increased by methylphenidate in both the on ($\bar{X}$ Δ BPRS = 1.93, t = 2.88, df = 27, p = 0.008) and off neuroleptic infusions ($\bar{X}$ Δ BPRS = 2.04, t = 2.40, df = 27, p = 0.02), but not altered by placebo. Taylor and Abrams scale scores were reduced by methylphenidate in both the on ($\bar{X}$ Δ T & A = −0.13, t = 1.93, df = 27, p = 0.06) and off neuroleptic infusions ($\bar{X}$ Δ T & A = −0.19, t = 2.58, df = 27, p = 0.02). No change was observed with placebo. Symptoms of TD and blink rate were significantly increased by methylphenidate in the on ($\bar{X}$ Δ SDS = 2.10, t = 3.68, df = 18, p = 0.002; $\bar{X}$ Δ blinks = 10.7, t = 2.45, df = 20, p = 0.02); and off ($\bar{X}$ Δ SDS = .380, t = 4.61, df = 14, p = 0.0005; $\bar{X}$ Δ blinks = 13.5, t =

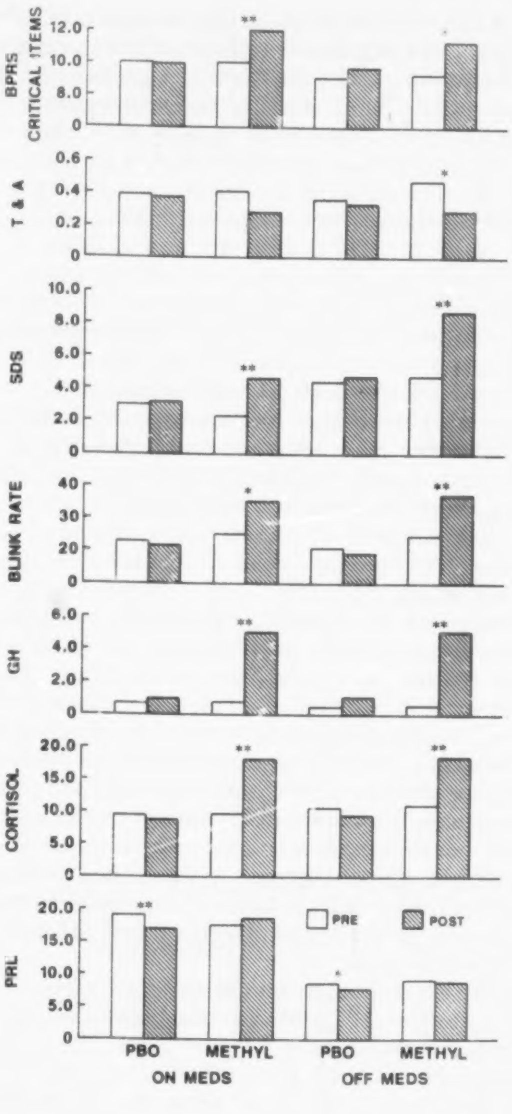


FIGURE 1. Behavioral (BPRS Critical Items Score, Taylor and Abrams Score), neurologic (tardive dyskinesia rating scale score and blink rate), and endocrine (prolactin, growth hormone, and cortisol levels) responses to infusions with placebo and methylphenidate while on and off neuroleptic medications. (* $p < .05$. ** $p < .01$.) There were no significant main effects for neuroleptic treatment or significant interactions on any of these measures. Significant methylphenidate effects were seen for BPRS critical items (F = 8.70, df = 17, p = .009), SDS (F = 36.10, df = 8, p = .00), PRL (F = 5.14, df = 18, p = .04), GH (F = 19.09, df = 16, p = .00), and cortisol (F = 42.34, df = 11, p = .00).

3.15, $df = 16$, $p = 0.006$) neuroleptic infusions but not altered significantly by placebo. Plasma GH and cortisol were significantly increased by methylphenidate during the on neuroleptic infusion ($\bar{X}\ \Delta$ GH $= 4.38$, $t = 4.82$, $df = 25$, $p = 0.0001$; $\bar{X}\ \Delta$ cortisol $= 8.19$, $t = 6.67$, $df = 18$, $p = 0.0001$) and during the off neuroleptic infusion ($\bar{X}\ \Delta$ GH $= 4.79$, $t = 5.71$, $df = 23$, $p = 0.0001$; $\bar{X}\ \Delta$ cortisol $= 7.42$, $t = 5.41$, $df = 13$, $p = 0.0001$). No change was observed with placebo. Plasma PRL significantly declined during the on neuroleptic placebo infusion ($\bar{X}\ \Delta$ PRL $= -1.89$, $t = 6.15$, $df = 27$, $p = 0.0001$) and during the off neuroleptic placebo infusion ($\bar{X}\ \Delta$ PRL $= -.93$, $t = 2.61$, $df = 24$, $p = 0.02$) but was not significantly changed during either methylphenidate infusion.

For subjects who underwent all four infusions repeated measures ANOVAs were done to test for the effects of neuroleptic treatment with methylphenidate challenge on pre-post infusion change scores on the behavioral, neurologic, and neuroendocrine measures. A significant neuroleptic treatment effect would indicate differences in pre-post infusion change scores on and off neuroleptics. A significant methylphenidate challenge effect would indicate differences in response to the methylphenidate challenge compared to the placebo challenge. A significant interaction effect would indicate differential methylphenidate challenge effects on and off neuroleptics.

BPRS critical items (neuroleptic effect $F = 1.50$, $df = 17$, $p = .24$; methylphenidate effect $F = 8.70$, $df = 17$, $p = .009$; interaction $F = .06$, $df = 17$, $p = .80$): T&A (neuroleptic effect $F = 2.10$, $df = 18$, $p = .16$; methylphenidate effect $F = 1.49$, $df = 18$, $p = .24$; interaction $F = .37$, $df = 18$, $p = .55$); SDS (neuroleptic effect $F = 3.77$, $df = 8$, $p = .09$; methylphenidate effect $F = 36.10$, $df = 8$, $p = .00$; interaction $F = 3.77$, $df = 8$, $p = .09$); blink rate (neuroleptic effect $F = 1.98$, $df = 6$, $p = .21$; methylphenidate effect $F = 1.65$, $df = 6$, $p = .25$; interaction $F = .64$, $df = 6$, $p = .46$); PRL (neuroleptic effect $F = .38$, $df = 18$, $p = .55$; methylphenidate effect $F = 5.14$, $df = 18$, $p = .04$; interaction $F = 2.83$, $df = 18$, $p = .11$); GH (neuroleptic effect $F = .14$, $df = 16$, $p = .71$; methylphenidate effect $F = 19.09$, $df = 16$, $p = .00$; interaction $F = .13$, $df = 16$, $p = .72$); cortisol (neuroleptic effect $F = .00$, $df = 11$, $p = .96$; methylphenidate effect $F = 42.34$, $df = 11$, $p = .00$; interaction $F = .27$, $df = 11$, $p = .62$).

Using the criteria for behavioral response to the infusions previously described, 6 patients were classified as positive responders, 5 as questionable responders, and 23 as negative responders (Table 1). No patient had a positive or questionable response to placebo. The highest rate of positive response was found in the off neuroleptic methylphenidate infusion (19%). No patient (who had both sets of infusions) who had a positive or questionable response to the on neuroleptics infusion had a negative response off neuroleptics, while two patients who had negative responses in the on neuroleptic infusion had positive or questionable responses to the off neuroleptics infusion. Because BPRS critical item increments during methylphenidate infusions clearly differentiated between the positive and questionable responders on one hand and the negative responders on the oth-

TABLE 1. Challenge Test Response Rates.

	Patients' Peak Response to Challenge Tests		Patients' Response to Methyl Challange		Response of Patients Who Had Methyl Challenges in Both Conditions	
	Pbo ($N = 34$)	Meth ($N = 34$)	On Meds ($N = 28$)	Off Meds ($N = 27$)	On Meds ($N = 21$)	Off Meds ($N = 21$)
%Negative	100	71	72	78	80	76
%Positive	0	18	14	15	10	19
%Questionable	0	11	14	7	10	5

Behavioral response rates reflecting classification of patients by all infusions are shown in the first two columns. Response rates of all patients to methylphenidate infusions by neuroleptic status are shown in the third and fourth columns. The last two columns show the response rates to methylphenidate infusions when on and off neuroleptics of patients who underwent both sets of infusion procedures.

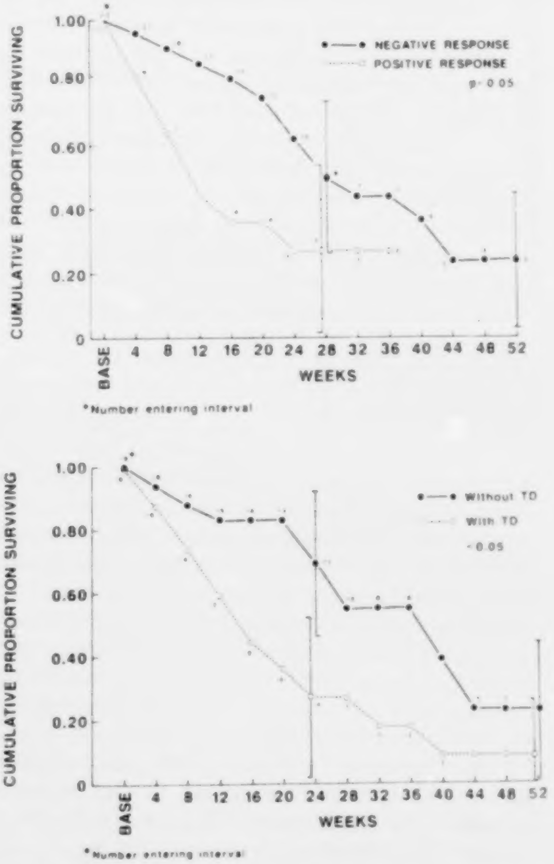
er hand, the positive and questionable responses were combined for the purposes of outcome analyses. Positive (and questionable) and negative responders were comparable on demographic and clinical measures. Positive responders had nonsignificantly higher psychopathology scores than negative responders, and had a nonsignificantly higher proportion of females (50% to 33.3%).

The 34 patients were followed for periods ranging from 1 to 52 weeks (mean 21.4, S.D. 16.6 weeks). Survival curves for patients by behavioral response class are shown in Figure 2 (top). Periods of follow-up for the positive responders ranged from 1 to 38 weeks (median 11); for negative responders it ranged from 1 to 52 weeks (median 30). A survival analysis used to compare time to relapse as a function of infusion response indicated that positive responders were likely to relapse sooner (Wilcoxon Stat = 6.41, $df = 1$, $p = 0.01$). Ten of eleven positive responders relapsed. The 10th had been assigned to active (double blind) neuroleptic treatment after exhibiting prodromal symptoms as per the study protocol. Thirteen of twenty-three negative responders have relapsed.

The sample was divided into patients with and without tardive dyskinesia (TD) using a global score of 2 (mild) on the SDS as the criterion. This is a fairly conservative measure of TD, and since patients were examined while on and off neuroleptics there could be no false negative subjects with covert TD. Patients with TD had a median survival period of 19 weeks (range 1 to 52); patients without TD had a median survival period of 32 weeks (range 1 to 52) (Figure 2, bottom). A survival analysis used to compare time to relapse as a function of TD status indicated that patients with TD relapsed sooner (Wilcoxon Stat = 4.8, $df = 1$, $p = .028$). A chi-square analysis prompted by the similarity between the behavioral response class and TD variables' relationship to outcome revealed that patients with TD were significantly more likely to have a positive or questionable methylphenidate response ($\chi^2 = 7.58$, $df = 2$, $p = .02$).

To examine the relationship of TD response and blink rate response to outcome, we dichotomized the sample at the median of the methylphenidate infusion increment in SDS scores (three scale point increase in the sum of the seven body area global items) and blink rate (7 blinks/min) and compared the survival curves (Figure 3). There was a significant relationship between TD response to methylphenidate and outcome in the off neuroleptic infusion. Patients with the greater increases in SDS scores relapsed sooner (Wilcoxon Stat = 4.0, $df = 1$, $p = .045$); and there was a close to significant trend toward earlier relapse for patients with greater blink rate increments (Wilcoxon Stat = 3.7, $df = 1$, $p = .056$).

To examine the relationship between endocrine response and outcome, the sample was divided at the median of the distribution of the dependent variable in question. Endocrine response was defined as the difference



*Number entering interval

*Number entering interval

FIGURE 2. Outcome by behavioral response classification to methyphenidate infusions (top); and for patients with and without tardive dyskinesia (bottom).

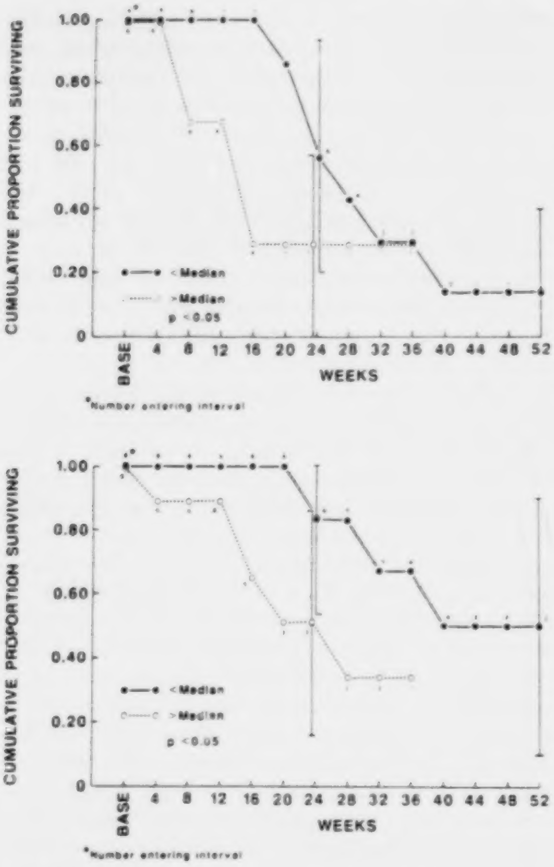


FIGURE 3. Outcome to methylphenidate infusion while off medication by tardive dyskinesia (top) and by blink rate response (bottom).

between the mean of the post-infusion values (four samples) and the mean of the pre-infusion values (three samples). Response was also defined as the difference between the maximum post-infusion values and the mean of the three pre-infusion values. Significant relationships were found between time to relapse and mean PRL response to placebo infusions both on and off neuroleptics (Figure 4), mean and maximum GH response to the methylphenidate infusion on neuroleptics and maximum GH response to the placebo infusion off medication (Figure 5). Patients whose PRL declined less than 1.4 ng/ml or increased in the placebo infusion on neuroleptics relapsed sooner (Wilcoxon Stat = 3.94, *df* = 1, *p* = .047). This did not appear to be a function of neuroleptic effects as neither basal PRL levels (on or off neuroleptics) nor neuroleptic dosage or serum neuroleptics levels correlated with relapse. Moreover, this same finding was more significant during the off medication placebo infusion. Patients whose PRL increased or declined less than .9 ng/ml relapsed more rapidly (Wilcoxon Stat = 5.88, *df* = 1, *p* = .015). Patients who had larger GH increases to methylphenidate (> 3.2 ng/ml) during the on neuroleptic infusion relapsed sooner (Wilcoxon Stat = 4.91, *df* = 1, *p* = .028); while patients who had larger GH increases to placebo (>-.2 ng/ml) during the off neuroleptic infusion relapsed sooner (Wilcoxon Stat = 7.84, *df* = 1, *p* = .005).

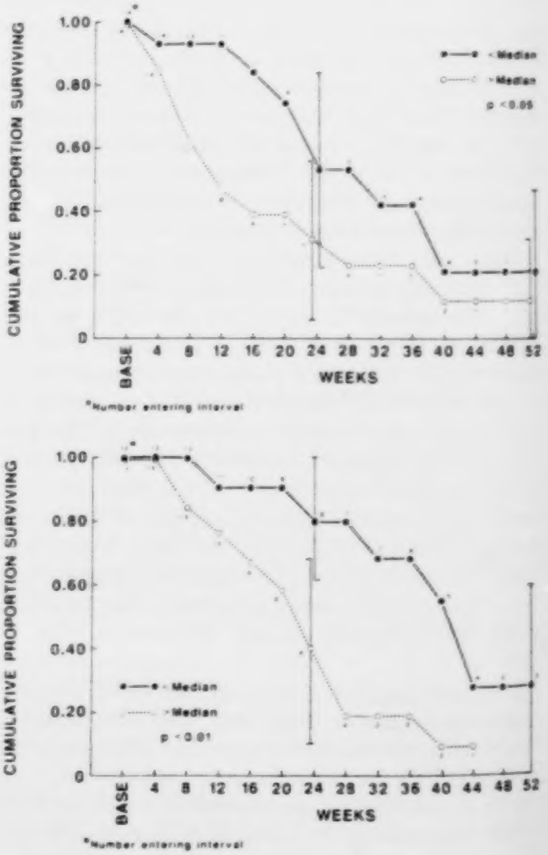


FIGURE 4. Outcome by prolactin response to placebo infusion while on medication (top) and off medication (bottom).

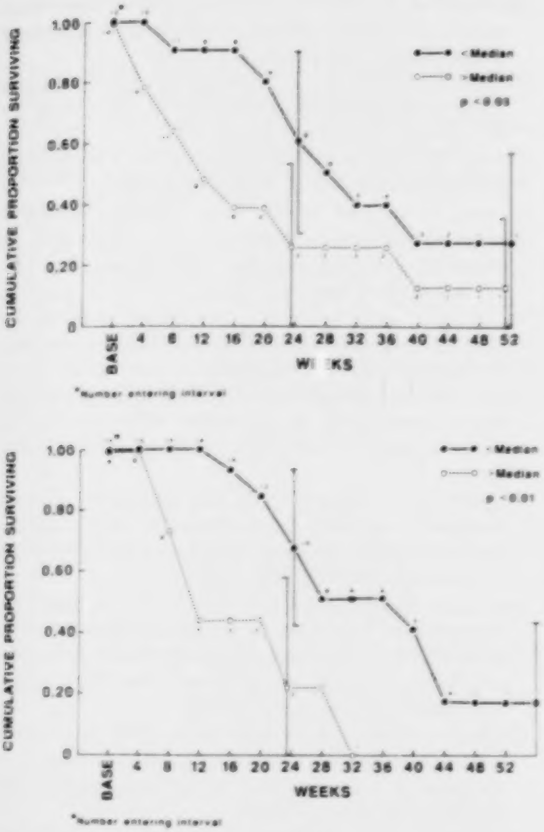


FIGURE 5. Outcome by growth hormone response to methylphenidate infusion while on medication (top) and to placebo infusion while off medication (bottom).

Discussion

The rate and pattern of relapse in this study are comparable to those previously reported in similar studies (Davis, 1975; Hogarty et al., 1974; Kane et al., 1982). The fact that specific biologic and clinical variables were significantly correlated with outcome in some cases was predicted and in other cases was unexpected. The significant relationship between behavioral response to methylphenidate was consistent with our initial hypothesis and confirms and extends the findings of Angrist et al. (1981) and VanKammen et al. (1982). It is interesting that positive and negative responders to methylphenidate were not different clinically, nor could relapse be predicted by any clinical or demographic variable. The exception to this was TD. The fact that patients with TD relapsed to a significantly greater extent than patients without TD raises the possibility of an interaction between treatment and course of illness. Comparisons of clinical characteristics between patients with and without TD, including duration of illness and number of prior episodes, however, revealed no significant differences. The fact that patients with TD were significantly more likely to be positive responders to methylphenidate suggests that these were overlapping measures. To further evaluate this, a survival analysis using a Cox proportional hazards regression model was done to assess the joint effects of TD and behavioral response classification on outcome. Both variables lost significance in this analysis, indicating that a factor common to both was affecting outcome. There are several ways to interpret this. Patients who have a certain, more severe course of illness may be susceptible to developing TD with sufficient neuroleptic exposure and sensitivity to the psychotogenic effects of methylphenidate. Another possibility is that patients who develop TD are, consequently, more sensitive to the behavioral effects of methylphenidate. The fact that TD and blink rate responses during the off neuroleptic infusion were also significantly associated with relapse provides further support for dopamine system involvement. Blink rate behavior has been described as mediated by dopaminergic systems (Stevens, 1978; Karson et al., 1982). That neuroleptic therapy diminished the apparent relationship among behavioral, TD, and blink rate response to outcome would indicate pharmacologic interference with behavior mediated by physiologic dopamine systems.

Although PRL response to methylphenidate showed no significant relationship to outcome, PRL response to placebo did. Patients with little or no decreases or absolute increases in post-placebo infusion PRL levels from pre-infusion levels were more likely to relapse. The PRL placebo response could be viewed as the secretory pattern of resting PRL over a 3-hour period, reflecting the patient's adaptation to the laboratory environment and procedure, and the diurnal rhythm of PRL (MacLeod, 1976). In this context, the lack of a decline or an increase in PRL levels could be viewed as a stress effect.

Growth hormone response to methylphenidate while patients were on neuroleptics was significantly correlated with outcome. Since this relationship was not found during the off neuroleptic methylphenidate infusion, it suggests that GH response was not a measure of endogenous physiologic dopamine activity, but possibly a functional measure of neuroleptic efficacy.

Growth hormone response to the off neuroleptic placebo infusion was significantly correlated with outcome. Davis et al. (1983) have reported that patients with schizophrenia have an irregular secretory pattern with more spontaneous peaks in secretion than is seen normally and that this may be the result of a regulatory dysfunction. This abnormal pattern was dampened by neuroleptic treatment. The increased GH response to placebo in this study may have been a reflection of these increased secretory peaks. However, when the coefficient of variation of GH values in the course of the placebo infusions was calculated, no correlation with outcome was found. Another possibility is that they also represent a stress effect.

In summary, specific biologic and clinical variables, including behavioral response to methylphenidate, presence of TD, blink rate response to methylphenidate, and anterior pituitary hormone response to methylphenidate and placebo under specific pharmacologic conditions, are associated with outcome in terms of relapse following neuroleptic withdrawal. As outcome predictors, these measures appear to have the clinically useful potential for identifying candidates for neuroleptic withdrawal and/or dose reduction treatment strategies.

References

Angrist, B., Peselow, E., Rotrosen, J., and Gershon, S. Relationship between responses to dopamine agonists, psychopathology, neuroleptic maintenance in schizophrenic subjects. In: Angrist, B., et al. (eds.), *Recent Advances in Neuropsychopharmacology*, Vol. 31. New York: Pergamon Press, 1981, pp. 49–54.

Baldessarini, R., Cole, J., Davis, J., et al. Task force report on late neurological effects of antipsychotic drugs. APA, Washington, D.C., 1980.

Bleuler, E. In: Zinkin, J. (translator), *Dementia Praecox or the Group of Schizophrenias* (1911). New York: International Universities Press, 1950.

Bleuler, M. The long-term course of the schizophrenic psychosis. *Psychol. Med.*, 4:244–254, 1974.

Brown, W.A., and Silver, M.A. Serum neuroleptic levels and clinical outcome in schizophrenic patients treated with fluphenazine decanoate. *J. Clin. Psychopharm.*, 5:143–147, 1985.

Brown, W., and Laughren, T. Low serum prolactin and early relapse following neuroleptic withdrawal. *Am. J. Psychiatry*, 138:237–239, 1981.

Brown, W., Laughren, T., Chisholm, E., et al. Low serum neuroleptic level predict relapse in schizophrenic patients. *Arch. Gen. Psychiatry*, 39:998–1000, 1982.

Cleghorn, J.M., Brown, G.M., and Brown, P.J. Growth hormone responses to apomorphine HCl in schizophrenic patients on drug holidays and at relapse. *Br. J. Psychiatry*, 142:482–488, 1984.

Cole, J.O., Goldberg, S.C., and Davis, J.M. Drugs in the treatment of psychosis. Controlled studies. In: Solomon, P. (ed.), *Psychiatric Drugs*, Proceedings of a Research Conference held in Boston. New York: Grune and Stratton, 1966, pp. 153–180.

Davis, K.L., Davis, B.M., and Mohs, R.C. Neuroendocrine dysregulation in schizophrenia. Presented at the American College of Neuropsychopharmacology Meetings, San Juan, 1983.

Herz, M.I., and Melville, C. Relapse in schizophrenia. *Am. J. Psychopharmacol.*, 64:337–340, 1979.

Hogarty, G.E., Goldberg, S.C., Schooler, N.R., et al. Drug and sociotherapy in the aftercare of schizophrenic patients II. Two year relapse rates. *Arch. Gen. Psychiatry*, 31:603–608, 1974.

Johnstone, E.C., Frith, C.D., Crow, T.J., et al. The dementia of dementia praecox. *Acta Psychiat. Scand.*, 57:305–324, 1978.

Kane, J.M., Weinhold, P., Kinon, B., et al. Prevalence of abnormal involuntary movements (spontaneous dyskinesia) in the normal elderly. *Psychopharmacology*, 77:105–108, 1982.

Karson, C.N., Bigelow, L.B., Kleinman, J.E., et al. Haloperidol-induced changes in blink rates correlate with changes in BPRS score. *Br. J. Psychiatry*, 140:503–507, 1982.

Klein, D., and Davis, J. *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore: Williams and Wilkins, 1969, pp. 52–138.

Lieberman, J.A., Kane, J.M., Gadaleta, D., et al. Methylphenidate challenge as a predictor of relapse in schizophrenia. *Am. J. Psychiatry*, 141:633–638, 1984a.

MacLeod, R.W. Regulation of prolactin secretion. In: Martini, L. and Ganong, W.F. (eds.), *Frontiers in*

Neuroendocrinology, Vol. 4. New York: Raven Press, 1976, pp. 169–194.

Mueller-Spahn, F., Ackenheil, M., Albus, M., et al. Neuroendocrine effects of apomorphine in chronic schizophrenic patients under long-term neuroleptic therapy and after drug withdrawal: relations to psychopathology and tardive dyskinesia. *Psychopharmacology*, 84:436–440, 1984.

Pfohl, B., and Winokur, G. The evolution of symptoms in institutionalized hebephrenic/catatonic schizophrenics. *Br. J. Psychiatry*, 141:567–572, 1982.

Pogue-Geile, M.F., and Harrow, M. Negative and positive symptoms in schizophrenia and depression: A followup. *Schizophr. Bull.*, 10:371–387, 1984.

Spitzer, R.L., Endicott, J., and Robins, E. Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, third edition. New York State Psychiatric Institute, New York, 1977.

Stevens, J.R. Eye blink and schizophrenia: psychosis or tardive dyskinesia? *Am. J. Psychiatry*, 135:223–225, 1978.

VanKammen, D.P., Docherty, J.P., and Bunney, W.E., Jr. Prediction of early relapse after pimozide discontinuation by response to *d*-amphetamine during pimozide treatment. *Biol. Psychiatry*, 17:233–242, 1982.

Zander, K., Fischer, B., Zimmer, R., et al. Long-term neuroleptic treatment of chronic schizophrenic patients: Clinical and biochemical effects of withdrawal. *Psychopharmacology*, 73:43–47, 1981.

Interpersonal and Pharmacologic Treatment in Schizophrenia: A Comparative Study of New Approaches

William T. Carpenter, Jr., M.D.,[1] Douglas W. Heinrichs, M.D.,[1] and Thomas E. Hanlon, Ph.D.[1]

Introduction

Current thinking regarding the interpersonal therapeutics of schizophrenia favors the use of a number of therapeutic strategies designed to address practical problems encountered by the schizophrenic patient and his (her) family. Only minimally derived from theory, these strategies tend to eschew etiologic relevance and consider pharmacological approaches as indispensable. Those receiving recent emphasis can be briefly described as follows:

1. Individual treatment aimed at establishing a close interpersonal bond between the schizophrenic patient and clinician for purposes of gathering information, offering support and encouragement, identifying the beginning of relapse, and otherwise helping the patient deal with the complex social demands that are so overwhelming for many individuals with this illness (Heinrichs & Carpenter, 1981, 1982).
2. An educational approach intended to inform patient and family regarding the nature of schizophrenia and the various treatments available and to form a link for establishing and coordinating joint therapeutic efforts (Anderson et al., 1980; Heinrichs & Carpenter, 1983).
3. Behavioral techniques aimed at reducing stress and environmental stimulation and at enhancing patient and familial coping behaviors (Wallace et al., 1980).

The present paper is a report on two open comparative trials involving the treatment of outpatient schizophrenics with two methods of drug administration and two levels of interpersonal interaction, one of which incorporated features of the above innovative strategies. The expectation in the first trial was that a targeted drug, high psychosocial intervention would be superior to a standard maintenance medication approach in terms of longer-term outcome on selected criteria (e.g., deficit symptoms). The second trial involved a comparison of standard maintenance medication with a maintenance medication approach utilizing a high level of psychosocial interaction. The expectation in this instance was that the latter approach would be superior to standard maintenance procedures on measures of deficit symptoms and overall functioning. These trials represent the preliminary phase of a research program concerned with the utility of reduced medication strategies in the treatment of schizophrenic outpatients. Because of the heuristic nature of the trials, analyses of the findings, which were *t* tests unless otherwise noted, were undertaken for exploratory rather than hypothesis-testing purposes.

General Methods

Subjects. Patients between the ages of 18 and 50 were accepted for evaluation and treatment on discharge from a psychiatric hospital unit, or less frequently, from a community clinic or practicing psychiatrist. All had had a recent psychotic episode and were in some intermediate stage of recovery. Preadmittance screening was undertaken to assure a patient cohort with a clinical diagnosis of schizophrenia. Patients who had less than 2 weeks of psychosis with no evidence of prodromal or residual symptoms and those with a longstanding, unchanging deterioration were not accepted for study. Other exclusion criteria included evidence of an organic brain disorder, recent evidence of alcoholism or clinically significant drug abuse, poor physical health, or a major medical illness requiring treatment.

---

[1] Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228.

Baseline and Treatment Procedure. Initial clinic visits were devoted to evaluation and stabilization, which generally involved the administration of neuroleptic medication for periods lasting 4 to 8 weeks. When a patient was clinically stabilized, medication was withdrawn to allow a 4-week drug-free period, during which baseline assessments were completed. Neuroleptic medication was administered only when there was an obvious need for symptom control. At the completion of the drug-free trial, the patient was randomly assigned, within sex, age, and prognostic status, to a 2-year experimental treatment course. A patient failing to complete the drug-free period on two attempts was admitted to the experimental phase while on medication.

Assessment Measures. Case history and prognostic instruments completed in the stabilization period included the *Overall Brief Psychiatric History* and the *Prognostic Scale.* Diagnostic instruments included a modified version of the *Psychiatric Assessment Inventory* (PAI) and the *Research Diagnostic Criteria* (RDC). Criterion instruments included the *Brief Psychiatric Rating Scale* (BPRS), the *Global Assessment Scale* (GAS), the *Level of Functioning Scale* (LFS), and the *Quality of Life Scale* (QLS). Criterion instruments were completed initially and at 6-month intervals by an evaluator who was independent of the treatment team. Interrater agreement on major criterion measures tended to be high, with intraclass correlations (ICC) for total scores invariably over .70 and generally within the mid .80 to mid .90 range.

Trial I Procedures and Results

Experimental Treatments

Maintenance Medication (MM). This approach was equivalent to the standard maintenance medication treatment offered to recently hospitalized schizophrenic patients by most outpatient aftercare services. Treatment was designed to provide continuous pharmacotherapy, utilizing daily chlorpromazine equivalent dosages of 300 mg or greater combined with brief visits with a pharmacotherapist on alternate weeks. Contacts with nursing personnel were also scheduled to provide medication, evaluate side effects, monitor medication use, etc. Adjustments in medication dosage level above 300 mg were made on the basis of symptom change and/or side effect manifestation. No systematic attempt was made to incorporate family members into the treatment strategy, nor were the brief clinical contacts utilized in implementing more extensive or individualized treatment plans.

Targeted Medication (TM). Patients assigned to the targeted medication approach were treated within the context of high psychosocial intervention. In this approach, medication was administered on an as-needed basis over the 2-year experimental period. Ordinarily, patients assigned to the targeted medication group remained drug-free. However, medication was initiated at moderate- to high-dosage levels on the occurrence of prodromal experiences, i.e., symptoms or signs that in the past had characteristically preceded psychotic decompensation. Medication was subsequently discontinued when the patient had returned to a stable clinical state. In effect, the targeted strategy was one of minimizing exposure to antipsychotic medication by maintaining the patient off medication during periods of clinical stability.

Psychosocial intervention consisted of assignment to a primary therapist (e.g., a psychiatric social worker) who was available for weekly sessions of approximately 45 minutes. The primary focus of these sessions was on the development of a shared view of the illness and the careful delineation of the early prodromal symptoms characteristic of the patient's prior course. The patient and therapist thereafter remained alert for the development of such symptoms so that prompt drug intervention could be made. The therapist also helped the patient identify environmental stressors and provided direction and support for minimizing their impact. This program has been described elsewhere (Carpenter & Heinrichs, 1983).

Early in the treatment course, the therapist saw the patient and family (or significant others) for six weekly sessions organized around the educational approach of Goldstein et al. (1978). The nature of the psychosis was discussed, precipitants and stressors identified, and practical suggestions for reducing stressors and their impact offered. Particular attention was paid to educating families as to the early signs of relapse and enlisting their participation in prompt intervention when these signs appeared.

Results

Sample Characteristics. The sample for Trial I consisted of 42 (20 male, 22 female) schizophrenic outpatients with a mean age of 30.7 years. Thirty-four of the patients were Black, and 8 White. Most (76%) were considered chronic (RDC) and approximately one-half were diagnosed as paranoid schizophrenic, with the remaining diagnoses fairly evenly distributed between undifferentiated and schizoaffective. Characteristics of the 2 treatment subsamples of 21 patients each are presented under Trial I in Table 1. The subsamples did not differ significantly on any of the measures involved.

With respect to initial global pathology, means for the 2 subsamples on the GAS were not significantly different, both falling in the 41 to 50 score range, reflecting "serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention." Also nondifferentiating, mean LFS total scores revealed "moderate" impairment, with work functioning generally reflecting extensive unemployment and social functioning indicating limited interpersonal engagement.

Dropouts. Over the 2-year study period, 16 of the 42 study patients dropped from the study; 9 of these were MM patients and 7 TM patients. Two of the nine MM patients refused assignment to this regimen, six discontinued treatment (two after having been hospitalized), and one was noncompliant. Of the seven TM patients who failed to continue, two discontinued treatment after they were hospitalized, two were discontinued from the study while hospitalized, and three discontinued while off medication. For the two treatment groups, mean ***Prognostic Scale*** scores for dropouts were not significantly different. Further illustrating the comparability of the treatment subgroups, resulting mean prognosis scores for MM vs TM completers were nearly identical.

TABLE 1. Demographic Characteristics of the Treatment Subsamples.

	Trial I		Trial II
Characteristic	TM	MM	MM+
Mean Age	29.7	31.7	25.8
Sex			
Female	12	10	9
Male	9	11	12
Race			
Black	17	17	12
White	4	4	8
Oriental	—	—	1
Mean Education	11.9	13.1	13.0
Mean Age at 1st Hospitalization	23.9	27.8	21.9
RDC Diagnosis			
Acute	5	5	5
Chronic	16	16	16
Schizophrenic			
Paranoid	10	11	10
Undifferentiated	5	6	5
Disorganized	1	—	—
Schizoaffective			
Depressed	5	4	4
Manic	—	—	2

Medication. In examining the prescription of medication over successive phases of the treatment course, it is clear that the goal of effecting a substantial reduction in the usual prescription of medication through the use of a targeted strategy was attained (Table 2). While the average daily dosage for MM actually increased over 6-month blocks during the 2-year period, that for TM decreased, with a resulting differential treatment dose that was significant for the final 6-month period (980 vs. 183 mg). The average daily dosage over the entire 2-year period was 720 mg for MM and 196 mg for TM ($p < .05$). On the average, TM patients were on medication approximately one-third of the time (31.2%) over the course of treatment.

Outcome. By the end of the 2-year course, 11 of 21 TM patients and 9 of 21 MM patients had been hospitalized. Most of the hospitalizations for TM, i.e., 8 of 11, were during the first 6 months of treatment, while those for MM tended to occur during the second year of treatment. The differential hospitalization rate for the first 6-month period was significant.

Hospitalization did not constitute the end of a patient's involvement in the study, and most of the patients returned to the study on

TABLE 2. Medication for Successive 6-Month Periods.

	0–6 Mos.	7–12 Mos.	13–18 Mos.	19–24 Mos.
Average Daily Dose (mg.)				
MM	453	565	643	980
TM	239	222	151	183
	(p = .16)	(p = .059)	(p = .054)	(p = .031)
Time on Medication				
TM	32.0%	29.7%	26.5%	41.0%

discharge. Additional comparative analyses of number of hospitalizations over the 2-year course therefore included both first and subsequent hospitalizations for each patient. Other than for the initial 6 months of treatment, none of these analyses yielded statistically significant results. Averages for number of hospitalizations for TM patients (N = 15 and 14) were .67 and .57 for years 1 and 2, respectively, while those for MM (N = 17,13) were .29 and .69. These figures again reflect the poorer performance for TM during the early stage of treatment. Duration of hospitalizations for completed cases in the two treatment groups was also examined (Table 3). Though MM patients tended to be hospitalized longer than TM patients (e.g., an average of 55 vs. 43 days, respectively), analyses of treatment differences with respect to duration of hospitalization were uniformly nonsignificant for every time interval examined.

Outcomes for the two groups in terms of ratings of symptoms and psychosocial functioning at both the 1- and 2-year evaluation points were virtually indistinguishable. Table 3 contains Trial I data for the 2-year period for those patients completing the program. Results for both groups were generally indicative of the maintenance of status quo with respect to levels of psychopathology, with fairly adequate symptom control being characteristic (i.e., "mild" BPRS symptoms on the average). The GAS and LFS still evidenced "need for treatment" and "moderate" impairment, respectively. Levels of psychosocial functioning, including the QLS, tended to favor TM patients, but not significantly so. The only measures approaching significance ($p < .10$) in this respect were those for an LFS measure combining the frequency and quality of social contacts and for the LFS score "Fullness of Life."

Trial II Procedures and Results

Experimental Treatments

This trial involved a comparison of the standard maintenance group of Trial I (MM) with the first 21 patients assigned to maintenance medication plus psychosocial intervention (MM+) in a subsequently conducted TM/MM+ comparison. The MM+ approach utilized in Trial II was developed to function as the control procedure for the principal comparison (to be reported later) involving targeted and maintenance medication, with psychosocial procedures held constant. The present trial intended, first, to establish the level of effectiveness for standard neuroleptic drug maintenance and, second, to determine the extent to which maintenance plus high psychosocial intervention dif-

TABLE 3. Mean Scores for Outcome Variables—2 Years.

Variable	Trial I TM	Trial I MM	Trial II MM+
N	14	12	17
Level of Functioning Scale*	23.1	20.6	22.4
Brief Psychiatric Rating Scale			
Factor 1	2.3	2.1	1.9
Total	1.9	1.8	2.1
Global Adjustment Scale*	46.4	42.8	48.4
Quality of Life Scale*	3.5	2.8	3.1
Year 1			
Hospitalizations	.67	.29	.28
Days hospitalized	18.27	18.35	6.50
N	15	17	18
Year 2			
Hospitalizations	.57	.69	.33
Days hospitalized	23.28	30.84	12.50
N	14	13	18
Cumulative Years 1–2			
Days hospitalized	42.86	54.84	19.00
N	14	13	18

*Higher scores indicative of better status.

fered from standard maintenance procedures with respect to outcome.

As in the standard maintenance procedure, patients assigned to MM + treatment received medication on a continuous basis, utilizing a daily chlorpromazine equivalent dosage of 300 mg as the base level. The prescription of medication, however, was performed within the context of a high level of psychosocial intervention. Besides the involvement of a primary therapist, this included the enlistment of both patients and families in the early identification of prodromal symptoms to insure prompt drug intervention and/or the reduction of stress. The criteria for both the prescription and reduction of medication were the same as those in the targeted procedure.

Results

Sample Characteristics. The sample for Trial II consisted of 42 patients (23 male, 19 female) with a mean age of 28.8 years. Twenty-nine patients were Black, 12 were White, and 1 was Oriental. Again, most (76%) were chronic and approximately one-half were diagnosed paranoid schizophrenic according to RDC, with the remaining diagnoses fairly evenly distributed between undifferentiated and schizoaffective, mainly schizophrenic. Consisting of 21 patients each, the treatment subsamples differed with respect to mean age (MM + patients younger than MM patients) and mean age at first hospitalization (MM + patients first hospitalized at a younger age than MM patients). Although proportionately more white patients were administered MM + than MM (eight vs. four), this discrepancy was not significant. As in the case of Trial I, the two subsamples did not differ with respect to initial global pathology.

Dropouts. Over the 2-year period, 3 of the 21 MM + patients dropped from the study, compared to 9 of the MM patients (*see* above). Of the 3 MM + dropouts, one refused to be placed on continuous medication, one discontinued treatment, and one moved out of the area. The difference in treatment-related dropouts (2 of 20 for MM + vs. 9 of 21 for MM) was significant ($\chi^2 = 5.63$, $p < .05$). As in the case of Trial I, lack of differentiation with respect to mean *Prognostic Scale* scores for both dropout and completer subsets was indicative of treatment group comparability.

Outcome. Over the experimental treatment course, 6 of the 21 MM + patients were hospitalized vs. 9 of 21 MM patients. Averages for number of hospitalizations for completed MM + cases ($N = 18$) were .28 and .33 for years 1 and 2, respectively, vs. .29 and .69 for MM (Table 3). Although in the expected direction, the second year difference was not significant. Average number of days hospitalized over the 2-year period for completed cases were 19 for MM + and 55 for MM ($p = .11$, Mann Whitney U Test).

Global criterion measures of psychopathology were undifferentiating with respect to treatment at both the 1- and 2-year evaluation points (Table 3). Among several measures of psychosocial functioning examined at the 2-year period, only the "Fullness of Life" item of the LFS tended to favor MM + over MM ($p = .08$).

Discussion

In the present study of the comparative efficacy of targeted vs. standard maintenance medication (Trial I), results consistently revealed that outcomes, as measured by positive symptoms, social and work performance, and negative symptom course, were essentially similar in the two treatment groups over a 2-year course of treatment. As to the need for hospitalization, the targeted drug patients required more frequent hospital admissions initially, but hospital stay was shorter, resulting in similar overall hospital utilization in the two groups over the 2-year period.

In Trial I, the targeted approach was applied to a range of schizophrenic outpatients without incurring the dire consequences often presupposed, such as extending hospitalization, disruption of living and work arrangements, harm to self and others, and progressive deterioration. Although there was little to no indication of a differentially beneficial action of TM with respect to negative symptoms, it is evident that the strategy yielded a significant reduction in exposure to neuroleptic drugs for schizophrenic patients and thereby presumably reduced the risks inherent in such exposure. (The relative incidence of untoward effects, including tardive dyskinesia, will be examined in a larger scope comparison of TM and MM + to be reported on completion of the program.)

Trial II revealed that maintenance plus psychosocial treatment was at least equivalent to standard maintenance treatment, if not superior. Results for a few key dimensions, including days hospitalized, tended to favor MM + but fell short of significance in this small sample. Also, there was indication in dropout data that MM + had more "holding" power than MM.

Some mention should be made of the sequence for implementing the psychosocial component of this research. Procedures for this component were in the early developmental stage when data were being collected on the TM sample. Although the extent to which this obscured the effectiveness of the TM approach is a matter of conjecture, it may have been a limiting factor. The MM + procedure was undertaken after 5 months experience with the psychosocial technique, during which psychosocial routines concerned with the administration of medication were perfected.

Acknowledgments

Acknowledgments are due Sue Parks and Ann Summerfelt for their contributions to this report.

References

Anderson, C.M., Hogarty, G.E., and Reiss, D.J. Family treatment of adult schizophrenic patients: A psychoeducational approach. *Schizophr. Bull.*, 6:490–505, 1980.

Carpenter, W.T., and Heinrichs, D.W. Early intervention, time-limited, targeted pharmacotherapy of schizophrenia. *Schizophr. Bull.*, 9:533–542, 1983.

Goldstein, M., Rodnick, E., Evans, J.R., et al. Drug and family therapy in the aftercare treatment of acute schizophrenia. *Arch. Gen. Psychiatry*, 35:1169–1217, 1978.

Heinrichs, D.W., and Carpenter, W.T. The efficacy of individual psychotherapy: A perspective and review emphasizing controlled outcome studies. In: Arieti, S. (ed.), *American Handbook of Psychiatry, Vol. VII.* New York: Basic Books, 1981, pp. 586–613.

Heinrichs, D.W., and Carpenter, W.T. The psychotherapy of the schizophrenic disorders. In: *Psychiatry 1982: The American Psychiatric Annual Review.* Washington, D.C.: American Psychiatric Press, 1982, pp. 154–166.

Heinrichs, D.W., and Carpenter, W.T. The coordination of family therapy with other treatment modalities for schizophrenia. In: McFarlane, W.R. (ed.), *Family Therapy in Schizophrenia.* New York: The Guilford Press, 1983, pp. 267–287.

Wallace, C.J., Nelson, C.J., Liberman, R.P., et al. A review and critique of social skills training with schizophrenic patients. *Schizophr. Bull.*, 6:42–63, 1980.

Medication, Family Psycho-Education, and Social Skills Training: First Year Relapse Results of a Controlled Study[1]

Gerard E. Hogarty, M.S.W.,[2] and Carol M. Anderson, Ph.D.[2]

Approximately 40 percent of schizophrenic patients maintained on antipsychotic medication experience a psychotic relapse in the first year following hospital discharge (Hogarty, 1984). Evidence from psychobiology and environmental psychology suggested that stimulation from the therapeutic and natural environments of vulnerable schizophrenic patients might often be sufficient to provoke underlying psychobiological deficits in the form of psychosis, even among patients who receive appropriate doses of maintenance chemotherapy.

A program of family psychoeducation/management and social skills training was developed based upon these theoretical notions as either a more direct (family psychoeducation) or less direct (social skills training) attempt to modify highly stimulating [expressed emotion (EE)] family environments (Anderson, Reiss, & Hogarty, 1986). The goal was to develop a safe and protected setting for patient and family which, in the context of maintenance chemotherapy, would lead to reduced rates of schizophrenic relapse.

Method

At hospital admission, 131 consecutively admitted patients were identified as potential candidates for this aftercare study. Following refusals and administrative terminations, 103 patients who resided in high EE households were randomly assigned to either (1) family psychoeducation and management; (2) social skills training; (3) the combination of these treatments; or (4) to a drug-maintained control group. All patients received antipsychotic medication; a majority maintained with fluphenazine decanoate. Two-thirds of the sample was male, predominantly white (81%), never married (76%), living with parent(s) (69%), and young (mean age 27). These characteristics follow upon selecting high EE subjects who live with family.

Results

For patients meeting criteria for treatment exposure, the following first year's relapse results (Hogarty et al., 1986) were observed:

1) there was a significant main effect for family psychoeducation in forestalling relapse (19% relapse);

2) there was a significant main effect for social skills training in forestalling relapse (20% relapse);

3) in the absence of evidence that treatment main effects occurred only when combined (i.e., a nonsignificant interaction), the effects of family psychoeducation and social skills training were judged to be additive (0% relapsed);

4) the international relapse rate among medicated controls was again confirmed (41% relapsed).

These results were also observed when only patients were included in the analyses who were known to be faithful medication compliers (i.e., the effect of psychosocial treatment was not simply an artifact of greater medication compliance). Further, we explored the effects of treatment on EE and subsequent relapse by means of repeated EE evaluations. We concluded that: (1) no patient relapsed in any household which changed from high EE to low EE, independent of treatment condition; (2) among households which remained high in EE, relapse continued to be elevated and was not

---

[1] Study supported by USPHS Grant MH-30750.

[2] Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

Reprint requests: Gerald E. Hogarty.

different among controls (42% relapsed) and those who received family psychoeducation alone (33% relapsed), or social skills training alone (29% relapsed); (3) only the combination of family psychoeducation and social skills training provided a significant prophylactic effect (0% relapsed) in households which remained high in EE.

It appeared that the family psychoeducation main effect could be explained, in part, by its relatively greater ability, as hypothesized, to lower EE in 16 of the 41 families who were treated (39%). However, lowered EE also occurred in a subsample of households not exposed to family treatment (i.e., controls and social skills training alone), where 11 of 44 households (25%) changed from high EE to low EE. An examination of patterns of EE at admission and follow-up, by treatment, for all individual relatives revealed no significant associations between the components of EE and outcome. Nor did the amount of face-to-face contact between the patient and relative explain relapse rates. Caution is suggested in making causal inferences regarding the relationship between EE and relapse. It is possible that the high EE status of households which contained a relapsed patient was due to the relapse event itself. In the absence of interim EE evaluations, it is unknown to us whether some or all of these households had, in fact, changed from high to low EE and then returned to high EE at the time of the patient's relapse. Preliminary analyses of the adjustment of non-relapsed patients suggest that better adjusted patients were found in households who changed from high to low EE. This being the case, it is possible that some families change their EE status because the patient's condition improves, rather than that lowering EE causes the better patient outcome.

Unfortunately, contrary to predictions, rates of relapse in the second post-discharge year have increased significantly. At the end of 2 years there remains a significant, but modest, main effect of family psychoeducation in forestalling relapse.

Discussion

The results of this study are essentially in agreement with those reported by Leff et al. (1982, 1985) and Falloon et al. (1982, 1985) in their studies of family treatment and medication among patients residing in high EE households. The low relapse rate of patients in families treated with psychoeducation and management strategies is consistent across studies and remains less than 10 percent at 9 months and equal to or less than 20 percent at 12 months. Relapse rates among drug treated controls at 9 months was 50 percent in the Leff et al. (1982) study and 44 percent in the Falloon et al. (1982) study. Thus, we are able to conclude that following many decades of study, there is increasing evidence that psychosocial interventions do add something more to the maintenance treatment of schizophrenic patients than drug therapy alone, at least in the first year following hospital discharge. Unfortunately, the rise in relapse rates over time indicates that important treatment challenges remain:

1) strategies are needed for recovered patients (and their families) which would sustain compliance with maintenance chemotherapy and psychosocial programs over time; and

2) more patient specific interventions need to be developed which would respond to the sources of *internal* stimulation among recovered patients, particularly as these patients move toward a fuller life beyond the clinic and family.

At the moment our greatest success seems to be in the early convalescent months when family life can be tempered and the patient trained to accommodate and respond to this protected environment. Later attempts by the recovered patient for a more complete and autonomous life beyond clinic, home, and sheltered workshop seem associated with noncompliance and/or exposure to sources of stimulation with which the patient is unable to cope.

References

Anderson, C.M., Reiss, D.J., and Hogarty, G.E. *Schizophrenia in the Family: A Practitioner's Guide to Psychoeducation and Management.* New York: Guilford Press, 1986.

Falloon, I.R.H., Boyd, J.L., McGill, C.W., Razoni, J., Moss, H.B., and Gilderman, H.A. Family management in the prevention of exacerbations of schizophrenia. *N. Engl. J. Med.*, 306:1437–1444, 1982.

Falloon, I.R.H., Boyd, J.L., McGill, C.W., Williamson, M., Razoni, J., Moss, H.B., Gilderman, A.M., and Simpson, G.M. Family management in the prevention of morbidity of schizophrenia. *Arch. Gen. Psychiatry*, 42:887–896, 1985.

Hogarty, G.E. Depot neuroleptics: the relevance of psycho-social factors. *J. Clin. Psychiatry*, 45(sec. 2):36–42, 1984.

Hogarty, G.E., Anderson, C.M., Reiss, D.J., Kornblith, S.J., Greenwald, D.P., Javna, C.D., and Madonia, M.J. Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare of schizophrenia. *Arch. Gen. Psychiatry*, 43:633–642, 1986.

Leff, J., Kuipers, L., Berkowitz, R., Eberlein-Vries, R., and Sturgeon, D. A controlled trial of social intervention in the families of schizophrenic patients. *Brit. J. Psychiatry*, 141:121–134, 1982.

Leff, J., Kuipers, L., Berkowitz, R. and Sturgeon, D. A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. *Brit. J. Psychiatry*, 146:594–600, 1985.

Nicotine as a Psychoactive Drug: Anxiety and Pain Reduction, Arousal, and Appetite Regulation

Co-Chairs:

Murray E. Jarvik, M.D., Ph.D.
Brentwood VA Medical Center
Los Angeles, CA 90024

Ovide F. Pomerleau, Ph.D.
University of Michigan School of Medicine
Ann Arbor, MI 48105

Introduction

Nicotine is the principal psychoactive agent in smoking. The pharmacological actions of this drug are complex and, in some ways, paradoxical. Though highly toxic, nicotine in small doses is reinforcing, maintaining self-administration with remarkable tenacity. Though neither dramatic intoxication nor dramatic withdrawal effects are associated with chronic nicotine use, nicotine self-administration, particularly from cigarettes, occurs in nearly half of the world's adult population; no culture to which the tobacco habit has been introduced has eradicated it. Over the years, there has been some disagreement about the nature of reinforcement mechanisms in smoking. Researchers can be divided into two main camps—those who believe that the smoking habit is largely the result of psychological factors (i.e., learning and conditioning); and those who emphasize pharmacological factors (i.e., the addictive nature of nicotine). The panel reviewed research on some of the effects of nicotine that seem to provide reinforcement for smoking and attempted to integrate psychological and pharmacological phenomena.

Dr. Pomerleau reviewed research indicating pain- and anxiety-reduction from nicotine administration. He pointed out that various studies on motives for smoking and on recidivism have established a strong relationship between dysphoric mood states and smoking. He described his own research, using anxiety and cold-pressor pain as well-defined indicators of psychologically relevant nicotine activity, demonstrating antinociception and anxiety reduction after nicotine administration in minimally deprived smokers. Cold-pressor pain reduction was also observed in ex-smokers, who are no longer pharmacologically dependent on nicotine. These findings suggest that reinforcement for smoking is not exclusively the result of relief of nicotine withdrawal but also involves effects independent of the nicotine addiction cycle.

Dr. Domino reviewed animal and human research on nicotine-produced electrocortical arousal and enhanced psychological alertness. He observed that a large percentage of smokers claim that smoking helps them to think more clearly and to concentrate, thereby enhancing performance on tasks like visual surveillance and rapid information processing as well as long-term memory (recall). Animal research has demonstrated critical EEG desynchronization accompanied by waking after nicotine injection, followed by slow-wave sleep that is more profound than before nicotine administration. Other effects of nicotine include inhibition of phasic stretch reflexes and facilitation of orienting reflexes as well as biphasic effects on the cardiovascular and respiratory systems.

Dr. Grunberg reviewed animal and human research on the effects of nicotine on appetite regulation. He noted that many smokers specify control of body weight as an important reason for continuing to smoke. In fact, cigarette smokers weigh less than nonsmokers of comparable age. Recent findings in his laboratory indicate that nicotine administration is accompanied by decreased consumption of sweet-tasting substances in both animals and humans, with corresponding decreases in total caloric intake. The issue of whether this effect is attributable to reduction of hunger for carbohydrates or to modification of taste for sweet foods by nicotine administration was considered.

Dr. Jarvik integrated these themes, presenting new data on the role of enhanced alertness as a reinforcer for smoking and on postprandial smoking. He also discussed the biphasic effects of nicotine (i.e., arousal followed by calming), different responses associated with nicotine dosage/speed of administration, and the role of personality and situational variables in determining reinforcement value.

Ovide F. Pomerleau

Nicotine as a Psychoactive Drug: Anxiety and Pain Reduction

Ovide F. Pomerleau, Ph.D.[1]

Smoking is often characterized as negatively reinforced behavior—i.e., as escape from or avoidance of an aversive state of withdrawal in an addictive cycle (Russell, 1977). Withdrawal from smoking is associated with increased anxiety and pain sensitivity, disruption of performance, and various dysphoric states such as irritability (Schachter, 1978). An important implication of the addiction model of smoking is that the probability of smoking/nicotine self-administration is linked to the time since the last cigarette and the current plasma nicotine level.

A number of studies confirm basic elements of the addiction model (*see* Jarvik, 1979). Work in my laboratory (Pomerleau, Fertig, & Shanahan, 1983) comparing heavy and light smokers (using plasma cotinine as the basis for classification) found that heavy smokers: 1) took in more nicotine from research cigarettes (which were used to eliminate the confounding effects of brand preference); 2) exhibited greater physiological tolerance to nicotine (attenuated heart rate increase and skin temperature decrease per plasma nicotine increment); 3) demonstrated more nicotine withdrawal symptoms when deprived of cigarettes overnight; and 4) showed closer regulation of plasma nicotine (that is, proportionally less variation in plasma nicotine when smoking cigarettes of differing strengths)—attributes consistent with an addiction model.

The addiction model in its extreme form (e.g., Schachter, 1978) holds that the principal consequence of smoking is the relief of withdrawal symptoms created by its absence. Such a formulation has limitations as a comprehensive explanation of smoking. With the exception of the first cigarette of the day or of cigarettes smoked after an extended period of deprivation, much *ad libitum* cigarette smoking seems to be prompted by various environmental events (interoceptive or exteroceptive stimuli) that are independent of the time since the last cigarette—e.g., various dysphoric states, performance demands, etc. (*see* Pomerleau & Pomerleau, 1984). Moreover, there are no clear demonstrations of smoking withdrawal prior to *ad libitum* smoking at intervals that are representative of ordinary smoking (half an hour to an hour since the last cigarette). Even at its peak at 24 hours of deprivation, the withdrawal state is variable, idiosyncratic responses being the rule (Hatsukami et al., 1984; Shiffman & Jarvik, 1976).

Nearly half the world's adult population smokes, and even in industrial nations such as the United States, 30 percent of the population continues to smoke despite well-publicized adverse health effects and increasingly restrictive societal and legislative proscriptions. The line of experimentation described herein is an attempt to characterize some of the reinforcing stimuli for *ad libitum* smoking and to understand how nicotine, a drug that produces neither dramatic intoxication nor marked withdrawal, can control behavior so powerfully.

Behavioral responses—pain reduction and anxiety relief—were selected as representative of the reinforcing consequences of smoking, a choice supported by numerous investigations involving nicotine administration in both animals and humans (Battig, 1980; Gilbert, 1979). The choice of pain and anxiety reduction, known markers of endogenous opioid activity, was also influenced by this laboratory's demonstration of nicotine-stimulated beta-endorphin release in circulating plasma (Pomerleau et al., 1983; Seyler et al., 1986). Pain was induced using a cold pressor apparatus (immersing an arm into freezing water); anxiety was induced by having subjects attempt to solve a puzzle (a six-letter

---

[1] Professor of Psychology in Psychiatry, University of Michigan School of Medicine, Behavioral Medicine Program, Riverview Building, 900 Wall Street, Ann Arbor, MI 48105.

The research was supported by National Cancer Institute grant CA 42730.

anagram) they had previously failed to complete.

In an initial set of experiments (Pomerleau et al., 1984), habitual smokers (who had smoked in excess of a pack a day for more than 5 years) served as paid subjects. Each experiment involved a screening session followed by experimental sessions with and without nicotine available. The screening sessions provided a 5-minute exposure to freezing (4.0 ± 0.5°C) water to allow subjects to set a criterion for cold pain in subsequent sessions (Experiment I) or exposure to failure at solving an (unsolvable) anagram to provide a means of inducing anxiety in subsequent sessions (Experiment II). (Subjects were told that they would receive a $10 bonus if they solved the anagram in 60 seconds or a $5 bonus if they solved it in 5 minutes.)

Subjects smoked a usual-brand cigarette half an hour before each experimental session to insure comparable, minimal levels of deprivation. In experimental sessions, subjects smoked either usual-brand cigarettes with brand markings deleted (mean nicotine content, 1.2 mg/cigarette) or zero nicotine cigarettes ("Free," International Brands, Inc., Los Gatos, CA) for 5 minutes. In Experiment I, after completion of the cigarette, subjects were exposed to freezing water for 5 minutes; pain awareness and endurance thresholds were determined, and the McGill Pain Questionnaire was administered. In Experiment II, subjects were told prior to consuming a cigarette that in 5 minutes they would have another opportunity to solve the anagram. The Spielberger State Anxiety Inventory was administered before and after completion of the cigarette.

In Experiment I, all five subjects showed increased pain awareness thresholds after they smoked a usual-brand cigarette (related-measures *t*-test; $p < .05$, one-tailed). Four of five subjects showed increased pain endurance (the fifth kept his arm immersed for the 5-minute limit in both sessions) and three of five reported decreased perception of pain (as indicated by lower scores on the McGill Pain Rating Index [PRI]; *see* Table 1). In Experiment II, all five subjects showed a greater decrease in anxiety when they were allowed to smoke their usual-brand nicotine-containing cigarette, as shown in Figure 1. [Analysis of Variance, prepost × nicotine condition; $F(1,4) = 14.38, p < .05$.]

The initial experiment left unanswered the question of whether antinociception and anxiety reduction were attributable to the smoking of a usual-brand cigarette or to the intake of nicotine. Accordingly, the findings were replicated in an additional 10 male smokers (Fertig et al., in press). The general procedure resembled that of the first experiment. Instead of smoking usual-brand cigarettes, however, subjects did the following on 4 successive days: 1) smoked two high-nicotine (2.87 mg) research cigarettes (Tobacco and Health Research Institute, Lexington, KY) 5 minutes apart (to remove the contribution of brand preference); 2) self-administered fine tobacco snuff ("Sweet Scotch" snuff, Helme Tobacco Company, Helmetta, NJ) intranasally over two 5-minute periods (to provide nicotine by a novel route of administration); 3)

TABLE 1. Pain Responses in the Cold-Pressor Test after Smoking.

Subject	Nicotine Content of Usual Cigarette (mg)	Cigarette Condition	Cold-Pressor Pain Thresholds (sec)		McGill Pain Questionnaire PRI (R)
			Awareness	Tolerance	
S 02		0-nicotine	13	27	15
	0.8	usual	17	28	25
S 36		0-nicotine	7	19	30
	1.3	usual	16	25	27
S 52		0-nicotine	16	300	28
	1.3	usual	27	300	18
S 72		0-nicotine	81	172	20
	1.2	usual	124	300	13
S 89		0-nicotine	20	47	29
	1.3	usual	41	64	33

Reprinted with permission from *Addictive Behaviors*, Vol. 9, Pomerleau, Turk, and Fertig, The effects of cigarette smoking on pain and anxiety, Copyright 1984, Pergamon Press, Ltd.

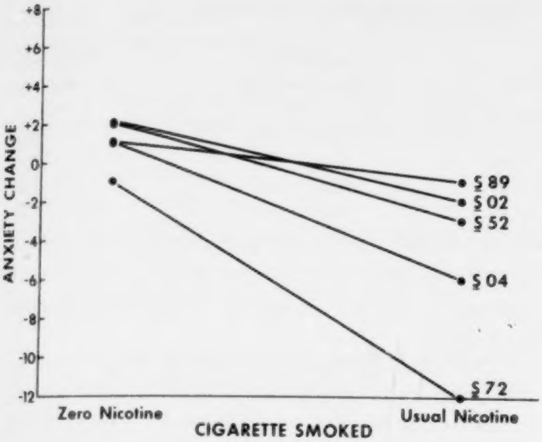


FIGURE 1. Anxiety scores before and after a usual nicotine or a zero-nicotine cigarette. Reproduced with permission from *Addictive Behaviors*, Vol. 9, Pomerleau, Turk, and Fertig. The effects of cigarette smoking on pain and anxiety. Copyright 1984, Pergamon Press, Ltd.

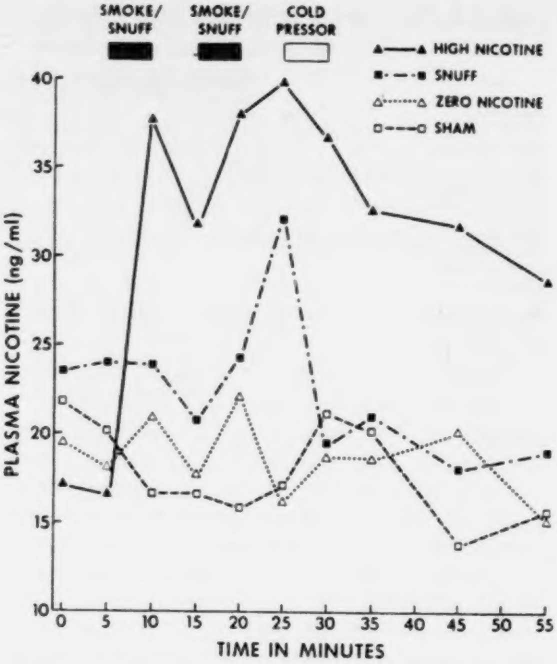


FIGURE 2. Plasma nicotine as a function of time for the two nicotine and no-nicotine conditions; means for ten subjects. Reprinted with permission from *Addictive Behaviors*, Fertig, Pomerleau, and Sanders, Nicotine-produced antinociception in minimally deprived smokers and ex-smokers, in press, Pergamon Press, Ltd.

smoked two zero-nicotine cigarettes (to control for smoke inhalation); and 4) sham-smoked two unlit cigarettes (to control for psychological effects and motor behavior). Nicotine and no-nicotine conditions were counterbalanced to control for order effects. Blood was withdrawn unobtrusively from the median antecubetal vein.

As shown in Figure 2, the two nicotine conditions resulted in marked increases in plasma nicotine, whereas in the no-nicotine conditions plasma nicotine decayed slightly over the 55-minute session. Table 2 presents the effects of nicotine intake on antinociception: Smoking high-nicotine cigarettes significantly increased pain awareness thresholds compared with sham-smoking [F (1,8) = 66.28, $p < .0001$], as did administration of tobacco snuff [F (1,8) = 21.5, $p < .005$]. Similar increases were found for pain endurance thresholds following high-nicotine cigarettes [F (1,8) = 21.15, $p < .005$] and following snuff [F (1,8) = 17.09, $p < .005$]. High-nicotine cigarettes also reduced significantly the perception of pain on the McGill Pain Rating Index (PRI) [F (1,8) = 7.56, $p < .05$], although snuff did not. Estimation of cold-pressor pain at its worst (Worst Pain Index; WPI) was significantly reduced (as indicated by lower scores) following the administration of snuff [F (1,8) = 8.33, $p < .05$] but not following the smoking of high-nicotine cigarettes.

In the above experiment, no observable differences in nicotine withdrawal were found in minimally deprived subjects prior to smoking nicotine or no-nicotine cigarettes, but the possibility that nicotine administration caused relief of withdrawal unrecognized by the subject could not be ruled out. In response to this ambiguity, 15 male ex-smokers (no cigarettes in the last year, as validated by the absence of detectable nicotine in plasma) were exposed to one session in which they snuffed a single dose of tobacco (about one-fourth the dose used for smokers) and another in which they snuffed an inert substance ("Postum," General Foods, White Plains, NY). As shown in Table 3, pain awareness and endurance thresholds increased and McGill scores decreased following administration of tobacco snuff, though only endur-

TABLE 2. Pain Responses in the Cold-Pressor Test: Means (± SEM) for 10 Smokers.

Condition	Cold-Pressor Pain Thresholds (sec) Awareness	Cold-Pressor Pain Thresholds (sec) Endurance	McGill Pain Questionnaire PRI	McGill Pain Questionnaire WPI
High Nicotine	24.2 (± 8.6)	59.0 (± 26.7)	31.8 (± 4.6)	3.1 (± 0.3)
Snuff	25.8 (± 11.6)	56.9 (± 23.5)	32.5 (± 4.5)	2.7 (± 0.2)
Zero Nicotine	14.2 (± 4.6)	46.8 (± 19.0)	33.5 (± 4.6)	3.0 (± 0.2)
Sham	11.7 (± 3.4)	35.0 (± 16.6)	35.9 (± 4.8)	3.2 (± 0.2)

Reprinted with permission from *Addictive Behaviors*, Fertig, Pomerleau, and Sanders, Nicotine-produced antinociception in minimally deprived smokers and ex-smokers, in press, Pergamon Press, Ltd.

ance reached significance $[F\ (1,13) = 7.65,\ p < .05]$.

These studies demonstrated that antinociception was not the result of brand preference, smoking as a ritual behavior, or inhaling smoke *per se*, but rather was a consequence of nicotine intake independent of route of administration. Since smokers were minimally deprived and exhibited no significant differences on the Shiffman Withdrawal Inventory prior to the nicotine/no-nicotine conditions as compared with *ad libitum* smoking at the screening session, we infer that antinociception following smoking is not simply the result of relief of withdrawal (the simple addiction model hypothesized by Schachter, 1978). The argument is strengthened by the observation that ex-smokers, who are no longer pharmacologically dependent on nicotine and do not exhibit any withdrawal symptoms, also showed reduced pain in the nicotine condition. It should be noted, however, that in pilot studies, ex-smokers were able to take in larger doses of tobacco snuff than people who had never smoked before, suggesting that some residual tolerance (and, theoretically, some degree of withdrawal) might exist. Thus, while the above studies and previous research with nicotine-naive animals strongly support the existence of nicotine effects that are independent of relief of nicotine withdrawal, the definitive test at the human level may have to be conducted with people who have never been nicotine-dependent.

The above research, along with findings from other laboratories, has led to the formulation of a biobehavioral model emphasizing the neuroregulatory mediation of key reinforcing consequences in smoking (Pomerleau & Pomerleau, 1984). As shown in Table 4, a compilation of numerous investigations on the behavioral and subjective consequences of smoking suggests that smoking produces effects that can be seen as favorable or adaptive, at least from a short-term perspective. Salient among these effects is reduction of negative affect (e.g., anxiety relief; McKennell, 1970; Shiffman, 1982). Depending on the antecedent conditions (exteroceptive or interoceptive stimuli defining either a neutral or aversive state), these consequences can be defined as either positive or negative reinforcers. Under this formulation, various exteroceptive or interoceptive stimuli, such as demands for task performance, dysphoric states (including pain and anxiety), socializing, or even completion of a meal, serve as discriminative stimuli for smoking, setting the occasion for nicotine self-administration because in the past, smoking/nicotine intake produced temporary improvements in performance or affect. The model further proposes that in the heavy smoker, these "extra" cigarettes are superimposed on a nicotine addiction cycle in which smoking relieves aver-

TABLE 3. Pain Responses in the Cold-Pressor Test: Means (± SEM) for 15 Ex-Smokers.

Condition	Cold-Pressor Pain Thresholds (sec) Awareness	Cold-Pressor Pain Thresholds (sec) Endurance	McGill Pain Questionnaire PRI	McGill Pain Questionnaire WPI
Snuff	34.3 (± 11.8)	68.3 (± 15.4)	21.3 (± 12.0)	2.9 (± 0.9)
Placebo	28.8 (± 8.9)	54.2 (± 11.0)	25.1 (± 14.4)	3.1 (± 0.9)

Reprinted with permission from *Addictive Behaviors*, Fertig, Pomerleau, and Sanders, Nicotine-produced antinociception in minimally deprived smokers and ex-smokers, in press, Pergamon Press, Ltd.

TABLE 4. Commonly Reported Behavioral and Subjective Effects of Smoking.

Consequences of smoking in habitual smokers
↑ concentration/ ↑ ability to tune out irrelevant stimuli
↑ memory (recall)
↑ psychomotor performance
↑ alertness/ ↑ arousal
↓ anxiety/ ↓ tension
↑ pleasure/ ↑ facilitation of pleasure
↓ body weight (↓ preference for sweet-tasting substances)

Adapted from Pomerleau and Pomerleau, 1984.

sive withdrawal symptoms experienced when the inter-cigarette interval becomes sufficiently long.

The above formulation begins to provide an explanation for the remarkable strength of the smoking habit. Evidence suggests that the number of affective states or performance demands that can be modified by nicotine is quite large (Pomerleau & Pomerleau, 1984), providing a plausible explanation for the thorough interweaving of smoking into the fabric of daily life. Moreover, from the perspective of learning theory (*see* Pomerleau, 1981), the immediacy of the consequences of smoking (one quarter of the nicotine inhaled in smoke crosses the blood/brain barrier in 7 to 10 seconds) and the sheer number of repetitions (a pack a day smoker receives over 70,000 puffing reinforcements per year) can be seen as adding considerably to the persistence of the habit (Jarvik, 1979). What is needed now is systematic research directed toward elucidation of the neuroregulatory concomitants of the reinforcement of smoking, taking into account interactions between the stimulus context for smoking and its behavioral and subjective consequences.

References

Battig, K. The smoking habit and psychopharmacological effects of nicotine. *Activitas Nervosa Superior,* 22:274–288, 1980.

Fertig, J.B., Pomerleau, O.F., and Sanders, B. Nicotine-produced antinociception in minimally deprived smokers and ex-smokers. *Addict. Behav.* (In press.)

Gilbert, D.G. Paradoxical tranquilizing and emotion-reducing effects of nicotine. *Psychol. Bull.,* 86:643–661, 1979.

Hatsukami, D.K., Hughes, J.R., Pickens, R.W., and Svikis, D. Tobacco withdrawal symptoms: An experimental analysis. *Psychopharmacology,* 84:231–236, 1984.

Jarvik, M. Biological influences on cigarette smoking. In: Krasnegor, N. (ed.), *The Behavioral Aspects of Smoking* (NIDA Research Monograph 26). Rockville, MD: National Institute on Drug Abuse, 1979, pp. 7–45.

McKennell, A. Smoking motivation factors. *Br. J. Soc. Clin. Psychol.,* 9:8–22, 1970.

Pomerleau, O.F. Underlying mechanisms in substance abuse: Examples from research on smoking. *Addict. Behav.,* 6:187–196, 1981.

Pomerleau, O.F., Fertig, J.B., Seyler, L.E., and Jaffe, J. Neuroendocrine reactivity to nicotine in smokers. *Psychopharmacology (Berlin),* 83:61–67, 1983.

Pomerleau, O.F., Fertig, J.B., and Shanahan, S.O. Nicotine dependence in cigarette smoking: An empirically-based, multivariate model. *Pharmacol. Biochem. Behav.,* 19:291–299, 1983.

Pomerleau, O.F., and Pomerleau, C.S. Neuroregulators and the reinforcement of smoking: Towards a biobehavioral explanation. *Neurosci. Biobehav. Rev.,* 8:503–513, 1984.

Pomerleau, O.F., Turk, D., and Fertig, J.B. The effects of cigarette smoking on pain and anxiety. *Addict. Behav.,* 9:265–271, 1984.

Russell, M.A.H. Smoking problems: An overview. In: Jarvik, M., et al. (eds.), *Research on Smoking Behavior* (NIDA Research Monograph 17). Rockville, MD: National Institute on Drug Abuse, 1977, pp. 13–34.

Schachter, S. Pharmacological and psychological determinants of smoking. *Ann. Inter. Med.,* 88:104–114, 1978.

Seyler, L.E., Pomerleau, O.F., Fertig, J.B., et al. Pituitary hormone response to cigarette smoking. *Pharmacol. Biochem. Behav.,* 24:159–162, 1986.

Shiffman, S. Relapse following smoking cessation: A situational analysis. *J. Consult. Clin. Psychol.,* 50:71–86, 1982.

Shiffman, S., and Jarvik, M. Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacologia,* 50:35–39, 1976.

Nicotine: A Unique Psychoactive Drug—Arousal With Skeletal Muscle Relaxation[1]

Edward F. Domino, M.D.[2]

Introduction

From a molecular point of view, nicotine has many common elements with the neurotransmitter acetylcholine (ACh). If one examines the positive and negative charges and the distance between them for both molecules, they are very similar, as shown in Figure 1.

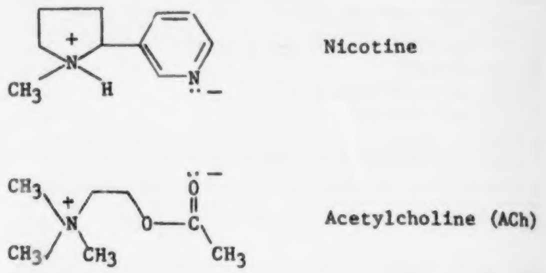


FIGURE 1. Chemical structure of nicotine and acetylcholine.

This is especially true at pH 7.4 because the pyrrolidine nitrogen of nicotine is partially ionized. Likewise, the pyridine nitrogen has two electrons that line up with the electrons of the oxygen at the esteratic site of ACh. Thus, it turns out that nicotine precisely mimics ACh from an electronic and structural point of view. This is the molecular basis of the nicotinic actions of ACh. Nicotine has an appropriate set of pKas so that at body pH of 7.4 about 69 percent is ionized at a temperature of 37°C. About 31 percent of nicotine molecules can penetrate a large variety of lipophilic membranes including the blood-brain barrier, the blood-placental barrier, etc. Since nicotine is a substance that exists both in ionized as well as un-ionized forms, it can act both extracellularly as well as penetrate various lipophilic barriers.

Multiple Actions of Nicotine

In tobacco-smoking concentrations nicotine is a remarkable psychoactive drug (Domino, 1973). A wide variety of complex stimulant and depressant effects are observed in animals and humans that involve the central and peripheral nervous, cardiovascular, endocrine, gastrointestinal, and skeletal motor systems. These heterogeneous effects are further intermingled with personality and other behavioral variables that result in self-administration, tobacco dependence, and withdrawal phenomena upon abrupt cessation of tobacco smoking. The following are among the key issues related to the pharmacology of nicotine:

1) *Nicotine Receptors.* There are multiple nicotinic receptors in the brain including very high, high, and low affinity types. Their relation to nicotinic ganglionic and skeletal muscle receptor types needs elaboration. Extensive research in the past 10 years has shown the existence of nicotinic cholinergic binding sites in the brain. Although α-bungarotoxin is a very useful ligand to study peripheral nicotinic cholinergic receptors at the neuromuscular junction, its use in labeling functional nicotinic receptors in the brain has been unrewarding. There is no question that α-bungarotoxin binding sites exist in the brain, but those sites differ from those to which nicotine binds. Some investigators have stressed the noncholinergic binding of ^{3}H-labeled nicotine, while many others have emphasized that ^{3}H-nicotine can bind to specific nicotine cholinergic receptors in the brain. This literature has been summarized in the recent publication by Shimohama et al. (1985) who have characterized two saturable

---

[1] Supported in part by the Psychopharmacology Research Fund.

[2] Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-0010.

Address all correspondence concerning this manuscript to: E.F. Domino, M.D., Department of Pharmacology, M6414 Medical Science Bldg. I, University of Michigan, Ann Arbor, MI 48109-0010.

binding sites for (–)^{3}H-nicotine in human brain, one with a K_d of 8.1 and the other 86 nM, and a B_{max} of 36 and 90 fmole/mg protein, respectively. Sloan et al. (1984) have stressed that ^{3}H-nicotine binding is extremely complex, involving very high, high, and low affinity sites.

Perhaps the most unexpected findings regarding nicotinic cholinergic binding sites are those described by Schwartz and Kellar (1985). They reported that nicotine tartrate equivalent to 1 mg/kg s.c. of (–) nicotine base given *b.i.d.* for up to 21 days caused a progressive up-regulation (30–40% increase) in regional rat brain ^{3}H-ACh binding sites measured in the presence of atropine to occupy the muscarinic sites. In contrast, the binding of ^{3}H-3-quinuclidinyl benzilate (QNB) to the muscarinic sites was unaffected by the nicotine treatment. Chronic isofluorophate (DFP) administration caused the expected down-regulation of both nicotinic and muscarinic receptor binding (Russell et al., 1981; Schwartz and Kellar, 1983b). Marks et al. (1983) reported an up-regulation of ^{3}H-nicotine binding sites to continuous nicotine infusions in mice. Clarke et al. (1986) have shown that in the rat brain the autoradiographic distribution of ^{3}H-ACh and ^{3}H-nicotine are essentially identical. Therefore, up-regulation of nicotine cholinergic binding sites to chronic nicotine appears to be an established fact, at least in mice and rats. Both Marks et al. (1983) and Schwartz and Kellar (1985) have suggested a functional blockade of the nicotinic cholinergic receptors with sufficient recovery that would allow enhanced behavioral responses to low doses of nicotine within 24 hours, as has been shown behaviorally by Clarke and Kumar (1983) and Ksir et al. (1985).

London et al. (1985b) have used *in vitro* autoradiography to identify ^{3}H-nicotine binding sites in the rat brain. The most intense localization of ^{3}H-label was in the interpeduncular nucleus and medial habenula. Other nuclei of the brain showed some binding, but it was not detected in the hippocampus or the periaqueductal grey matter. The relative absence of nicotine binding in the hippocampus is surprising. Miner et al. (1985) have shown that mice sensitive to the convulsant effects of nicotine have greater α-bungarotoxin binding in the hippocampus than seizure insensitive mice.

2) *Acetylcholine Release*. In the past 23 years there has been accumulating evidence to support the hypothesis that some of the actions of nicotine are due to the release of ACh and other neurotransmitters, especially NE. Chiou and Long (1969) and Chiou (1973) obtained evidence that nicotinic cholinergic agonists including nicotine, carbachol, and 1,1-dimethyl-4-phenylpiperazinium (DMPP) release endogenous ACh from the presynaptic cholinergic nerve terminals rather than stimulating postsynaptic nicotinic receptors. This was shown using a chick nerve-muscle preparation. Chiou et al. (1970) also showed that these same nicotinic agonists could release ACh from rat cerebral cortical synaptic vesicles. Briggs and Cooper (1982) showed that nicotine and DMPP release newly synthesized ^{3}H-ACh from synaptosomes prepared from the myenteric plexus of guinea pig ileum. The release of ^{3}H-ACh was Ca^{++} dependent and was blocked by C_6 and curare. More recently, Rowell and Winkler (1984) showed that newly synthesized ^{3}H-ACh was also released from mouse cortical synapses by both nicotine and DMPP. The release of ^{3}H-ACh by nicotine was Ca^{++} dependent and was blocked by C_6. Thus there is good evidence that nicotine releases ACh by a presynaptic mechanism. In contrast, presynaptic muscarinic receptors (mostly M_2) inhibit ACh release.

3) *EEG Activation*. There is considerable evidence that in animals nicotine causes EEG activation (Domino, 1967). The EEG activating effects of small doses of nicotine occur in intact as well as brainstem transected animals. These effects of nicotine are directly on brainstem neuronal circuits. However, stimulation of peripheral afferents and release of catecholamines and possibly other neurotransmitters and modulators (serotonin, histamine) enhances the direct central effects of nicotine.

4) *Behavioral Arousal*. The EEG activating effects of nicotine result in behavioral arousal (Domino et al., 1967). In tobacco smokers, depending on circumstances, nicotine can have either sedative or stimulant effects (Kumar and Lader, 1981). Aceto and Martin (1982) have reviewed the large variety of nic-

otine effects on behavior including facilitation of memory, the increase in spontaneous activity, its antinociceptive properties, and its suppression of irritability as well as appetite.

5) *REM Sleep*. Nicotine increases the amount of REM sleep, an effect also seen with arginine vasopressin (Domino & Yamamoto, 1965). This observation in cats has not been pursued. It has many important implications regarding the sleep cycle of tobacco smokers and should be studied further.

6) *Cerebral Metabolism*. Inasmuch as both behavioral arousal and REM sleep increase cerebral metabolism, it would be expected that nicotine would also produce important alterations in cerebral metabolism. It would be of special interest to compare the location of ^{3}H-nicotine binding in the brain with its effects on local cerebral glucose utilization. London et al. (1985a) have done such a study using the rat. Nicotine stimulated local cerebral glucose utilization 139 percent over control in the medial habenula and 50 to 100 percent in the superior colliculus and the anteroventral thalamic and interpeduncular nuclei. Other areas of the brain showed moderate to no significant changes. These effects of nicotine were blocked by mecamylamine. Furthermore, they correlated well with the distribution of ^{3}H-nicotine in the brain except in layer IV of the neocortex which showed nicotine binding, but no change in local cerebral glucose utilization.

7) *Skeletal Muscle*. Nicotine and tobacco smoking dramatically reduce phasic stretch reflexes such as the patellar reflex in human volunteers (Domino & Von Baumgarten, 1969). Both central and peripheral mechanisms are involved. Not all skeletal muscles are relaxed by nicotine. Skeletal muscles involved in the orienting reflex (trapezius) show enhanced tension (Fagerström & Götestam, 1977).

8) *Cardiovascular, Respiratory, and Gastrointestinal Systems*. Nicotine and tobacco smoking have profound effects on these systems. These effects have been described in detail elsewhere (*see* textbook, Gilman et al., 1985).

9) *Conditioned-Avoidance and Self-Stimulation Behavior*. Conditioned-avoidance behavior is selectively depressed by nicotine (Domino, 1965). Its effects on self-stimulation behavior are complex (Olds and Domino, 1969) but usually depressant on single dose administration.

10) *Stimulus Discrimination*. The stimulus discrimination properties of nicotine have been extensively studied by Rosecrans and Chance (1977). Romano et al. (1981) compared a number of nicotinic agonists as cues in rats using a T-maze paradigm. (+) Nicotine which is the enantiomer of natural or (−) nicotine was much less potent, and both position isomers (2- and 4-nicotine) were inactive. Anabasine provided a nicotine cue, but subcutaneous cytisine did not. However, intraventricular (i.v.t.) cytisine was a partially effective cue. The cue effects were blocked by low doses of mecamylamine and pempidine and high doses of C_6. Their findings suggest that the cue receptor is in the brain, and is pharmacologically similar to the nicotinic cholinergic ganglionic receptor.

11) *Self-Administration*. Nicotine self-administration readily occurs in both animals and man (*see* Henningfield, 1984) which probably accounts for the habit of tobacco smoking. Most of the earlier reports on intravenous nicotine self-administration indicate that the reinforcing properties of nicotine are generally weak compared to other classes of drugs of abuse such as stimulants, opiates, and sedative-hypnotics when continuous reinforcement or fixed ratio schedules are used. However, recent studies using interval and second order schedules of nicotine produce persistent behavior at high rates (Dougherty et al., 1981; Goldberg et al., 1981).

12) *Endocrine System*. Nicotine produces profound neuroendocrine changes, including elevated plasma catecholamines, glucose, glucagon, cortisol, insulin, and vasopressin (*see* Domino, 1979, and textbook, Gilman et al., 1985).

13) *Tachyphylaxis, Tolerance, Sensitization*. Nicotine produces tachyphylaxis, tolerance, and sensitization which vary in different organs and systems. Initially in animals nicotine depresses locomotor activity, but when given chronically nicotine markedly stimulates locomotor activity. In chronic nicotine treated rats Clarke and Kumar (1983) have shown that (−) nicotine is 10 times as potent as (+) nicotine in stimulating motor activity. Mecamylamine prevented the locomotor stimulant effects of nicotine, while chlorisonda-

mine only partially reduced it, suggesting that nicotine was acting centrally. When given i.v.t., chlorisondamine blocked the stimulant actions of nicotine for at least 3 weeks.

14) *Pharmacogenetic and Personality Factors.* Considerable individual variability occurs in response to nicotine, suggesting important pharmacogenetic and personality factors.

15) *Up-Regulation of Cholinergic Receptors.* Contrary to expectations, chronic nicotine tends to cause up-regulation of cholinergic receptors. Schwartz and Kellar (1983) showed, as expected from the findings of Russell et al. (1981), that 10 days after the daily administration of DFP, ^{3}H-ACh binding is down-regulated in the rat brain. In contrast, after 10 days of nicotine administration twice daily, ^{3}H-ACh binding is increased. In both cases the affinity was not altered, but only the B_{max}. Subsequently, Schwartz and Kellar (1985) extended their findings to a high affinity ^{3}H-ACh binding site. Furthermore, the nicotinic antagonists mecamylamine and dihydro-β-erythroidine did not alter ^{3}H-ACh binding after 10 to 14 days of treatment alone or with concurrent nicotine. They suggest that ^{3}H-ACh binding sites on nicotinic receptors are subject to up- as well as down-regulation, probably through protracted desensitization of the recognition site. However, if continuous desensitization were the primary mechanism, one would not expect behaviors like locomotor stimulation to be enhanced after chronic nicotine. Marks et al. (1983) have pursued this issue using chronic nicotine infusions on tolerance development and number of nicotine receptors using mice. They conclude that chronic nicotine results in tolerance to a variety of physiological endpoints such as rotarod performance, heart rate, and body temperature. At the same time, there is an increase in brain nicotine receptors. Ksir et al. (1985) also have shown, using rats, that daily administration of nicotine enhances its locomotor stimulant effects and increases ^{3}H-ACh binding to brain nicotinic receptors. They suggest that the data imply the two phenomena are functionally linked. Marks and Collins (1985) also studied tolerance, cross-tolerance, and the number of M and N receptors after chronic nicotine or oxotremorine given to mice. Chronic oxotremorine caused down-regulation of M-receptors, while chronic nicotine caused up-regulation of N-receptors. Some cross-tolerance occurred to the effects of nicotine in the oxotremorine treated mice which did not appear related to changes in nicotinic receptors. Nicotine treated mice were tolerant to six different physiologic measures as were the oxotremorine treated mice.

Conclusions

Nicotine produces a most complex series of effects at multiple sites throughout the body. It is indeed a most remarkable psychoactive substance. Nicotine alters the complex of balance of functions of muscarinic and nicotinic pre- and postsynaptic cholinergic receptors, as well as acting through noncholinergic mechanisms.

References

Aceto, M.D., and Martin, B.R. Central actions of nicotine. *Medicinal Res. Rev.*, 2:43–62, 1982.

Briggs, C.A., and Cooper, J.R. Cholinergic modulation of the release of [^{3}H] acetylcholine from synaptosomes of the myenteric plexus. *J. Neurochem.*, 38:501–508, 1982.

Chiou, C.Y. Mechanism of acetylcholine release by drugs and its blockade. *Arch. Int. Pharmacodyn. Therap.*, 201:170–181, 1973.

Chiou, C.Y., and Long, J.P. Acetylcholine-releasing effects of some nicotinic agents on chick biventer cervias muscle preparation. *Proc. Soc. Exper. Biol. Med.*, 132:732–737, 1969.

Chiou, C.Y., Long, J.P., Potrepka, R., and Spratt, J.L. The ability of various nicotinic agents to release acetylcholine from synaptic vesicles. *Arch. Int. Pharmacodyn. Therap.*, 187:88–96, 1970.

Clarke, P.B.S., and Kumar, R. The effects of nicotine on locomotor activity in non-tolerant and tolerant rats. *Br. J. Pharmacol.*, 78:329–337, 1983.

Clarke, P.B.S., Schwartz, R.D., Paul, S.M., et al. Nicotinic binding in rat brain: autoradiographic comparison of [^{3}H] acetylcholine, [^{3}H] nicotine and [^{125}I] alpha-bungarotoxin. *J. Neurosci.*, 1986. (In press.)

Domino, E.F. Some behavioral actions of nicotine. In: Von Euler, U.S. (ed.), *Tobacco Alkaloids and Related Compounds*. London: Pergamon Press, 1985, pp. 145–166.

Domino, E.F. Electroencephalographic and behavioral arousal effect of small doses of nicotine: A neuropsychopharmacological study. *Ann. N.Y. Acad. Sci.*, 142:216–244, 1967.

Domino, E.F. Neuropsychopharmacology of nicotine and tobacco smoking. In: Dunn, W.J., Jr. (ed.), *Smoking Behavior: Motives and Incentives*. Washington, D.C.: V.M. Winston and Son, 1973, pp. 5–31.

Domino, E.F. Behavioral, electrophysiological, endocrine, and skeletal muscle actions of nicotine and tobacco smoking. In: Remond, A., and Izard, C. (eds.), *Electrophysiological Effects of Nicotine*. Amsterdam: Elsevier/North Holland Biomedical Press, 1979, pp. 133–146.

Domino, E.F., Dren, A.T., and Yamamoto, K. Pharmacologic evidence for cholinergic mechanisms in neocortical and limbic activating systems. *Progress in Brain Research*, Vol. 27. Amsterdam: Elsevier Publishing Co., 1967, pp. 337–362.

Domino, E.F., and Von Baumgarten, A.M. Tobacco cigarette smoking and patellar reflex depression. *Clin. Pharmacol. Ther.*, 10:72–79, 1969.

Domino, E.F., and Yamamoto, K. Nicotine: Effect on the sleep cycle of the cat. *Science*, 150:637–638, 1965.

Dougherty, J., Miller, D., Todd, G., and Kosterbauder, H.B. Reinforcing and other behavioral effects of nicotine. *Neurosci. Behav. Rev.*, 5:487–495, 1981.

Fagerström, K.O., and Götestam, K.G. Increase in muscle tonus after tobacco smoking. *Addictive Behaviors*, 2:203–206, 1977.

Gilman, A.G., Goodman, L.S., Rall, T.W., and Murad, F. (eds.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics 7th Edition*. New York: MacMillan Publishing Co., 1985.

Goldberg, S.R., Spealman, R.D., and Goldberg, D.M. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science*, 214:573–575, 1981.

Henningfield, J.E. Behavioral pharmacology of cigarette smoking. *Adv. Behav. Pharmacol.*, 4:131–210, 1984.

Ksir, C., Hakan, P., Hall, D.P., Jr., and Kellar, K.J. Exposure to nicotine enhances the behavioral stimulant effect of nicotine and increases binding of ^{3}H-acetylcholine to nicotine receptors. *Neuropharmacology*, 24:527–531, 1985.

Kumar, R., and Lader, M. Nicotine and smoking. In: Essman, W.B., and Valzelli, L. (eds.), *Current Developments in Psychopharmacology*, Vol. 6. New York: Spectrum, 1981, pp. 127–164.

London, E.D., Connolly, R.J., Szikszay, M., and Wamsley, J.K. Distribution of cerebral metabolic effects of nicotine in the rat. *Eur. J. Pharmacol.*, 110:391–392, 1985a.

London, E.D., Waller, S.B., and Wamsley, J.K. Autoradiographic localization of [^{3}H] nicotine binding sites in the rat brain. *Neuroscience Lett.*, 53:179–184, 1985b.

Marks, M.J., Burch, J.B., and Collins, A.C. Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. *J. Pharmacol. Exp. Ther.*, 226:817–825, 1983.

Marks, M.J., and Collins, A.C. Tolerance, cross-tolerance and receptors after chronic nicotine or oxotremorine. *Pharmacol. Biochem. Behav.*, 22:283–291, 1985.

Miner, L.L., Marks, M.J., and Collins, A.C. Relationships between nicotine-induced seizures and hippocampal nicotinic receptors. *Life Sci.*, 37:75–83, 1985.

Olds, M.E., and Domino, E.F. Comparison of muscarinic and nicotinic cholinergic agonists on self-stimulation behavior. *J. Pharmacol. Exp. Ther.*, 166:189–204, 1969.

Romano, C., Goldstein, A., and Jewell, N.P. Characterization of the receptor mediating the nicotine discriminative stimulus. *Psychopharmacology*, 74:310-315, 1981.

Rosecrans, J.A., and Chance, W.T. Cholinergic and non-cholinergic aspects of the discriminative stimulus properties of nicotine. *Adv. Behav. Biol.*, 22:155–185, 1977.

Rowell, P.P., and Winkler, D.L. Nicotinic stimulation of [^{3}H] acetylcholine release from mouse cerebral cortical synaptosomes. *J. Neurochem.*, 43:1593–1598, 1984.

Russell, R.W., Carson, V.G., Booth, R.A., and Jenden, D.J. Mechanisms of tolerance to the anticholinesterase, DFP: acetylcholine levels and dynamics in rat brain. *Neuropharmacology*, 20:1197–1201, 1981.

Schwartz, R.D., and Kellar, K.J. Nicotinic cholinergic receptor binding sites in the brain: regulation *in vivo*. *Science*, 220:214–216, 1983.

Schwartz, R.D., and Kellar, K.J. *In vivo* regulation of [^{3}H] acetylcholine recognition sites in brain by nicotinic cholinergic drugs. *J. Neurochem.*, 45:427–433, 1985.

Shimohama, S., Taniguchi, T., Fujiwara, M., and Kameyama, M. Biochemical characterization of the nicotinic cholinergic receptors in human brain: binding of (–)-[^{3}H] nicotine. *J. Neurochem.*, 45:604–610, 1985.

Sloan, J.W., Todd, G.D., and Martin, W.R. Nature of nicotine binding to rat brain P$_2$ fraction. *Pharmacol. Biochem. Behav.*, 20:899–909, 1984.

Nicotine as a Psychoactive Drug: Appetite Regulation

Neil E. Grunberg, Ph.D.[1]

Introduction

Cigarette smokers weigh less than comparably aged nonsmokers, and habitual smokers who quit smoking generally gain weight (Grunberg, 1982; 1985; Wack & Rodin, 1982). Three major explanations have been proposed to account for these phenomena: (1) changes in consumption of all foods; (2) changes in energy utilization; (3) changes in consumption of particular foods. More specifically, the first postulate holds that smokers eat less than do nonsmokers and that smoking cessation is accompanied by increased food consumption. These changes in eating behavior may result from changes in hunger or a need to substitute food for cigarettes. The second explanation is that some component of tobacco (probably nicotine) increases metabolism and thereby results in decreased body weight without changes in caloric intake. Abstinence from smoking may result in a relative decrease in metabolism so that body weight increases without changes in food consumption. The third hypothesis is that cigarette smoking is accompanied by decreased consumption of sweet-tasting high caloric foods and that consumption of these particular foods increases when smokers kick their habit. Changes in caloric intake from these foods is thought to cause changes in body weight. Although these ideas are all quite reasonable, until recently there was little empirical reason to believe any one of them. A series of human and animal studies was begun in 1979 to investigate the relationship between smoking and body weight and between nicotine and body weight. Some of these studies are reviewed in this paper and the results of these studies are discussed in terms of clinical implications and future research directions.

General or Specific Food Consumption?

In a human laboratory study smokers and nonsmokers (18–36 years old; males and females) participated in a taste judgment study (Grunberg, 1982). Smokers (individuals who smoked at least 15 cigarettes per day for at least 2 years) abstained from smoking during the morning of the experiment. The study was run around lunchtime. The smokers were divided into two equal groups: smokers allowed to smoke immediately before tasting foods and smokers not allowed to smoke before the taste test. Subjects were presented with nine different foods (three sweet, three salty, and three bland) that were provided as bite-sized pieces in separate bowls. Subjects were instructed to taste each food and to rate each food on a series of taste-judgment scales. Water was provided for mouth-rinsing between tastes. Subjects were told that when they finished tasting and rating the foods, they could eat whatever they wanted, but that they should first be sure that all foods were carefully rated. Subjects were left with the foods for 20 minutes to allow time for the taste ratings and still plenty of time to nibble. All bowls of food were weighed before and after the study. After tasting the foods, subjects picked three foods to taste again for another part of the study. These procedures provided data on taste preferences based on actual food consumption and self-reports.

The results of this study are presented in Figure 1. Smokers allowed to smoke ate significantly less sweets than did nonsmokers and less sweets than did smokers not allowed to smoke. Consumption of the salty and bland foods were similar in all three groups of sub-

---

[1] Uniformed Services University of the Health Sciences, Medical Psychology Department, 4301 Jones Bridge Road, Bethesda, MD 20814–4799.

This work was supported by the Uniformed Services University of the Health Sciences Protocol No. C07223. The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Department of Defense or the Uniformed Services University of the Health Sciences.

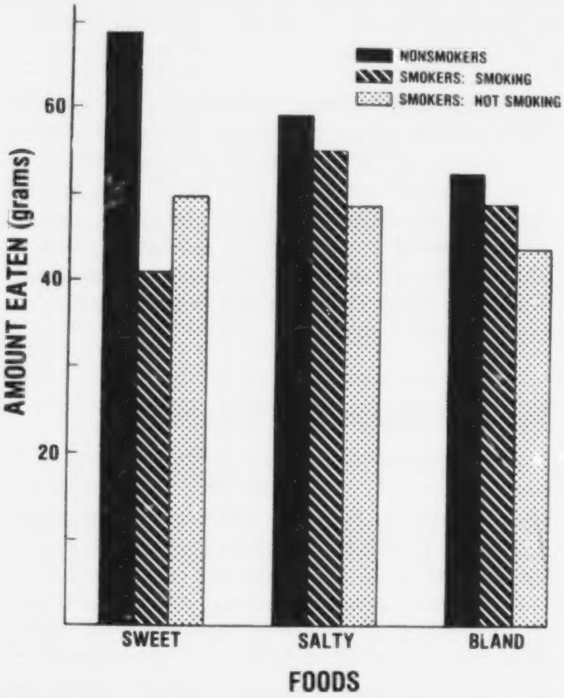


FIGURE 1. Average amount of food eaten within each taste class. (Reprinted with permission from *Addictive Behaviors*, Vol. 7, Grunberg, N.E., The effects of nicotine and cigarette smoking on food consumption and taste preferences, 1982, Pergamon Press, Ltd.)

jects. Based on self-reports, smokers not allowed to smoke expressed the greatest preference for sweets and smokers smoking expressed the least preference for sweets.

An animal study was designed to complement the human laboratory study (Grunberg, 1982). In the animal study nicotine administration was manipulated in order to determine whether this pharmacologic agent, which is generally accepted to be the dependence-producing component of tobacco, also alters body weight. Male Sprague-Dawley rats were the subjects. Animals received subcutaneous administration via Alzet osmotic minipumps of either 0, 2.5, 5.0, or 10.0 mg nicotine per kg body weight per day. Subjects were individually housed and were provided with a standard laboratory chow, three sugar solutions (35%, 25%, and 10% w/v d-glucose), and water. Body weight, food, water, and sugar solution consumption were measured daily for 2-week periods before, during, and after nicotine administration. The within and between subjects design of this study allowed for careful evaluation of the effects of nicotine on general food consumption, specific taste preferences for sweet versus nonsweet foods, and body weight.

Figure 2 presents the mean body weights for each group of animals for each phase of the study. Individual data points represent a composite of the data from each experimental group averaged over many days. Comparing the changes in body weight from before to during drug administration, animals receiving nicotine gained significantly less weight than did control animals. After cessation of nicotine, animals in the experimental groups gained more weight than did animals receiving saline.

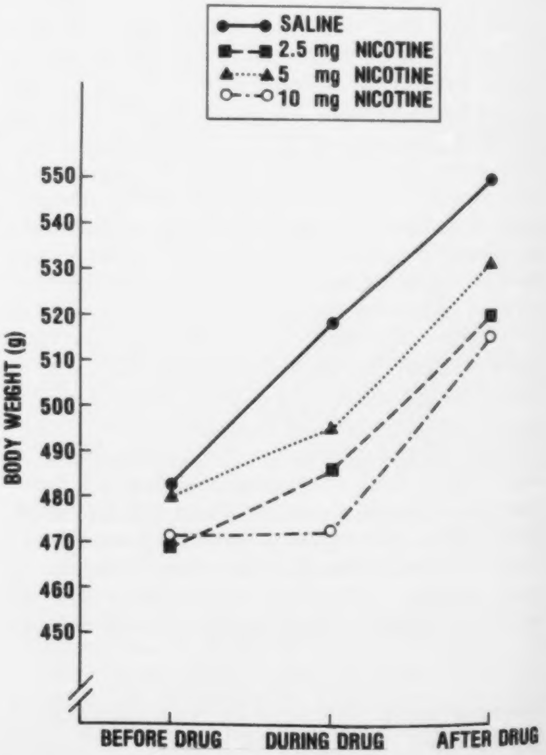


FIGURE 2. Average body weights before, during, and after drug administration. (Reprinted with permission from *Addictive Behaviors*, Vol. 7, Grunberg, N.E., The effects of nicotine and cigarette smoking on food consumption and taste preferences, 1982, Pergamon Press, Ltd.)

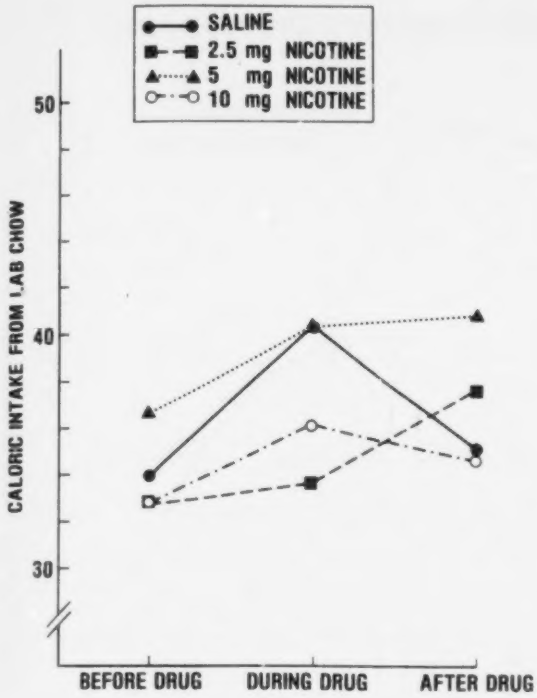


FIGURE 3. Average caloric intake from lab chow before, during, and after drug administration. (Reprinted with permission from *Addictive Behaviors*, Vol. 7, Grunberg, N.E., The effects of nicotine and cigarette smoking on food consumption and taste preferences, 1982, Pergamon Press, Ltd.)

Figure 3 indicates that there were no consistent effects of nicotine administration or cessation of nicotine on consumption of the bland laboratory chow. In marked contrast, Figure 4 indicates that animals receiving nicotine significantly decreased consumption of the sugar solutions during drug administration. After cessation of nicotine, animals significantly increased their consumption of sugar solutions. These changes in sweet food consumption resulted in significant changes in caloric intake that could account for the changes in body weight.

Are These Laboratory Findings Generalizable?

An archival epidemiological study was conducted to determine whether the laboratory results regarding nicotine and sweet foods were a robust phenomenon that also appeared in the entire United States population (Grunberg & Morse, 1984). United States per capita consumption of cigarettes was compared to U.S. per capita consumption of all major food groups during a 14-year period. Figure 5 presents the data for cigarettes and sugar. Consistent with the laboratory studies, there was a significant inverse relationship between cigarette and sugar consumption.

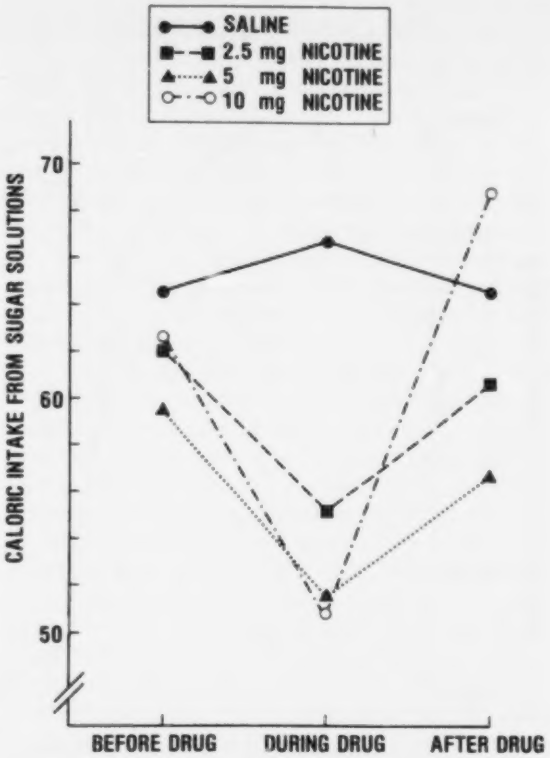


FIGURE 4. Average caloric intake from sugar solutions. (Reprinted with permission from *Addictive Behaviors*, Vol. 7, Grunberg, N.E., The effects of nicotine and cigarette smoking on food consumption and taste preferences, 1982, Pergamon Press, Ltd.)

What Happens if Only Bland Foods Are Available?

The preceding data are consistent with the proposition that changes in specific food consumption (sweets) accompany smoking and abstinence from smoking and that these changes may account for changes in body weight. There were no changes in consumption of nonsweet foods in the animal and

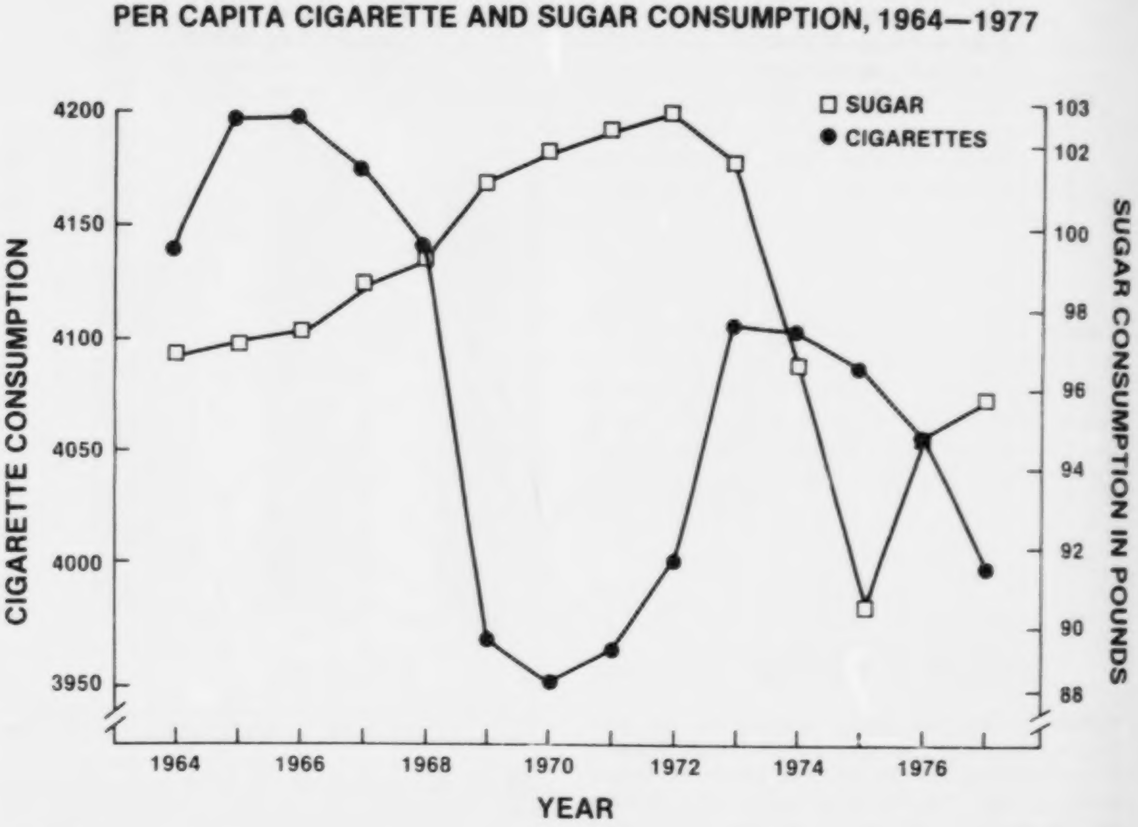


FIGURE 5. United States per capita cigarette and sugar consumption. (Reprinted with permission from *Journal of Applied Social Psychology*, Vol. 14, Grunberg, N.E., and Morse, D.E., Cigarette smoking and food consumption in the United States, 1984, V.H. Winston & Sons, Inc.)

human studies. These results suggest that if only bland food is available, there will be no changes in caloric intake during or after nicotine administration and there will be no changes in body weight. Animal studies were performed to examine directly the effects of nicotine on body weight and bland food consumption (Grunberg, Bowen, & Morse, 1984).

The animal paradigm described previously was followed except that only bland laboratory chow and water were available and the nicotine dosages were slightly different (0, 4, 8, and 12 mg/kg/day). Figure 6 presents the mean body weight values for each group of animals for 6-day periods before, during, and after drug administration. There was an inverse dose-effect relationship between nicotine administration and body weight. These effects of nicotine on body weight were slightly attenuated compared to the previous study when sugar solutions were available. After cessation of nicotine administration, all groups of animals gained similar amounts of weight as did control animals. That is, in contrast to the previous study, animals that had received nicotine did *not* gain excessive amounts of weight. Analyses of food and water consumption revealed that there were no differences between experimental groups during any phase of the study and for either of these variables. To summarize, when only bland food was available, there were no effects of nicotine or cessation of nicotine on eating behavior; the effects of nicotine administration on body weight were slightly attenuated; and there was no excessive gain in body weight after cessation of nicotine. To

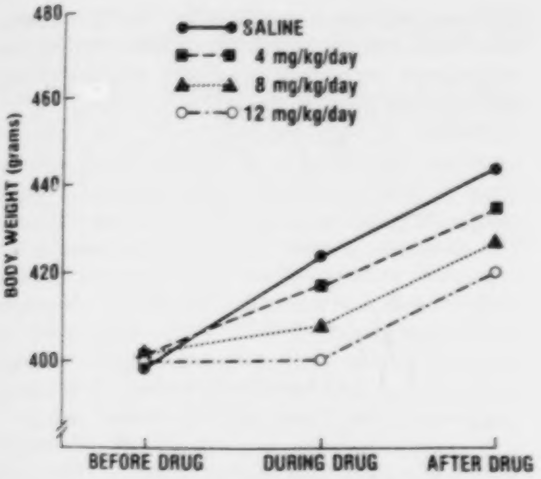


FIGURE 6. Average body weights before, during, and after drug administration when only nonsweet foods were available. (Reprinted with permission from *Psychopharmacology*, Vol. 83, Grunberg, N.E., Bowen, D., and Morse, D.E., Effects of nicotine on body weight and food consumption of rats, 1984, Springer-Verlag.)

double check these findings, a similar study was run with a longer nicotine administration period. All results were identical. Therefore, it seems that nicotine only affects consumption of sweet foods and this effect is particularly important in post-nicotine excessive body weight gains.

Sweet Taste vs. Caloric Content

In the animal and human studies of sweet food consumption, the foods that had sweet taste also were high in caloric content and carbohydrate content. Therefore, it is impossible to know which of these factors is responsible for nicotine's effects in changing specific food consumption. A series of animal studies was conducted to separate these factors (Grunberg, Bowen, Maycock, & Nespor, 1985). In one study, rats had continuous access to water and two foods: a sweet-tasting (saccharin flavored), low-calorie food and a nonsweet, low-calorie food. The foods were identical in nutrient constituents. Three groups of animals (0, 6, 12 mg nicotine/kg/day) were examined for weeks before, during, and after drug administration. There was an inverse dose-effect relationship between nicotine and body weight during drug administration and a positive relationship between nicotine and body weight gain after cessation of nicotine. Animals receiving nicotine decreased consumption of the sweet food compared to controls during the drug administration period. After the drug administration phase, animals that had received nicotine increased sweet-food consumption compared to controls. Consumption of the nonsweet foods showed opposite effects as the animals clearly switched their preferences during and after drug administration.

In a related animal study the two foods were both nonsweet but one had high-caloric value (by increasing carbohydrate content) and the other had low-caloric value. Again, there was an inverse relationship between nicotine and body weight during drug administration and a positive relationship between nicotine and body weight gain after cessation of nicotine. The effects of nicotine on consumption of the high-caloric carbohydrate food were similar to, but substantially weaker than, the effects on sweet-food consumption. Therefore, both sweet taste and caloric content contributed to the effects of nicotine on specific food consumption but sweet taste was particularly important.

Males vs. Females

Women seem to be more concerned than men about weight gains after cessation of smoking. This concern may reflect society-induced gender differences in attention to body weight and physical appearance. Alternatively, cigarette smoking and nicotine may have different effects on women and men. All of the animal studies cited above used male subjects. Therefore, female rats were used as subjects in a study designed to be comparable to the studies of nicotine, body weight, and bland food consumption (Grunberg, Bowen, & Winders, 1985). Animals were used as subjects for all of the reasons described earlier. In addition, it was assumed that animals would not be self-conscious about their body weight and eating behavior. Therefore, the effects of nicotine could be evaluated without concern for such psychological variables as restraint in eating. The effects of every dose of nicotine (adjusted for initial body weight) were greater on the body weight, food consumption, and water consumption of the females compared to similar studies with males. In fact, the highest dosage of nicotine decreased consumption of the bland food. After cessation of nicotine, eating behavior increased. These effects were markedly different from previous studies of male animals. Also, there was an inverse relationship between nicotine and water consumption. In male animal studies, water consumption was never affected by nicotine. These sex differences are currently under additional examination and, so far, continue to show up. It seems that women's concerns about body weight gains after abstaining from cigarettes may reflect biobehavioral differences in the effects of nicotine.

Possible Implications

The results of these studies have both clinical and basic science implications. Taken together, these studies suggest that smokers who quit smoking should especially avoid sweet-tasting, high caloric foods; and might try using noncaloric sweeteners on foods. Women who quit smoking also should monitor consumption of nonsweet foods (but addition of noncaloric sweeteners may help control excessive food consumption). These suggestions are, of course, extrapolations from the data discussed and therefore require careful clinical assessment before any of these approaches can be touted as effective.

On a theoretical level, it is worth considering why preferences for sweet tastes and carbohydrates are altered by nicotine. Perhaps nicotine alters glucose availability in the body and hedonic preference for sweet tastes is altered in response to this biochemical mechanism (Grunberg, 1985; Grunberg et al., 1985). This possibility is currently under investigation. The altered preference for foods based on carbohydrate content is another issue that merits further investigation. Possibly, smokers who give up cigarettes experience the marked and almost unbearable unpleasantness of abstinence and eat carbohydrates to modulate and improve mood. In effect, the specific food consumption might be considered as self-administration of a psychopharmacologic agent to regulate affect. This conjecture is speculative, but it is consistent with recent research evidence that carbohydrate consumption alters mood (Spring, Lieberman, Swope, & Garfield, 1984).

Finally, it may be interesting to consider whether the effects of nicotine on specific food consumption reflects general mechanisms common to other drugs of dependence. For example, sweet-tasting carbohydrates are reported to help offset the unpleasantness of withdrawal from alcohol (Griffiths, Bigelow, & Henningfield, 1980). Also, anecdotal reports indicate that narcotics addicts crave sugar when they kick their habits. It has been suggested that these effects reflect underlying commonalities among drugs of dependence (Grunberg & Baum, 1985). This possibility also deserves careful empirical attention.

Conclusion

Classic studies using nicotine have provided critical knowledge about general physiological processes involving nicotinic vs. muscarinic receptors. More recently, the role of nicotine as the pharmacologic agent of dependence to tobacco has emerged as a central topic in smoking research and treatment. Now, it is clear that nicotine alters body weight and that studies of nicotine's effects on specific food consumption may reveal useful clinical knowledge and may provide theoretical insights regarding the biological bases for specific food cravings.

References

Griffiths, R.R., Bigelow, G.E., and Henningfield, J.E. Similarities in animal and human drug-taking behavior. In: Mello, N.K. (ed.), *Adv. in Substance Abuse.* Greenwich, CT: JAI Press, 1980, pp. 1–90.

Grunberg, N.E. The effects of nicotine and cigarette smoking on food consumption and taste preferences. *Addict. Behav.*, 7:317–331, 1982.

Grunberg, N.E. Nicotine, cigarette smoking, and body weight. *Br. J. Addict.*, 80:369–377, 1985.

Grunberg, N.E., and Baum, A. Biological commonalities of stress and substance abuse. In: Shiffman, S., and Wills, T.A. (eds.), *Coping and Substance Use.* Orlando: Academic Press, 1985, pp. 25–62.

Grunberg, N.E., Bowen, D.J., Maycock, V.A., and Nespor, S.M. The importance of sweet taste and caloric content in the effects of nicotine on specific food consumption. *Psychopharmacology*, 87:198–203, 1985.

Grunberg, N.E., Bowen, D.J., and Morse, D.E. Effects of nicotine on body weight and food consumption in rats. *Psychopharmacology*, 83:92–98, 1984.

Grunberg, N.E., Bowen, D.J., and Winders, S.E. Nicotine, body weight and food consumption in female rats. Presented at the meeting of the American Psychological Association, Los Angeles, CA, 1985.

Grunberg, N.E., and Morse, D.E. Cigarette smoking and food consumption in the United States. *J. Appl. Soc. Psychol.*, 14:310–317, 1984.

Spring, B.J., Lieberman, H., Swope, G., and Garfield, G. Effects of carbohydrates on mood and behavior. Presented at meeting on Diet and Behavior: A Multidisciplinary Evaluation, Arlington, VA, 1984.

Wack, J.T., and Rodin, J. Smoking and its effects on body weight and the systems of caloric regulation. *Am. J. Clin. Nutr.*, 35:366–388, 1982.

Nicotine as a Psychoactive Drug—Panel Summary

Murray E. Jarvik[1]

The four members of this panel have emphasized some of the more important reinforcing properties of nicotine, the major pharmacological agent in tobacco. People smoke for at least five reasons: to increase arousal, improve attention, reduce anxiety, control aggression, and decrease appetite. Another important impetus to smoking is withdrawal relief. On the other hand, people desist from smoking for very different and primarily nonpharmacological reasons. A combination of social pressure and fear of deleterious health consequences has profoundly decreased the incidence of smoking in the United States and in certain other parts of the world. Relapse after smoking cessation is a particularly interesting psychological phenomenon illustrating the conflict between the positive reinforcing actions of nicotine and the social and intellectual forces tending to diminish smoking.

Many studies have unequivocally shown that stress increases the rate of smoking cigarettes. Pomerleau, Domino, and Jarvik are particularly interested in possible mechanisms underlying this effect. There are probably many components to this phenomenon. First, the nonspecific activating action of stress may have a tendency to increase all types of habitual behavior, and particularly drug taking, whether of sedative or stimulant drugs. Nevertheless, most smokers do report an anxiety-reducing effect of smoking in everyday life. It has been much more difficult to demonstrate anxiety reduction from experimentally induced stress in the laboratory by either nicotine or cigarette smoking. Nonetheless, in some studies induction of both mental and physical distress has been shown to be relieved by nicotine administration. Reduction of aggression by nicotine may be a related phenomenon. The pathways involving the induction of dysphoria are diverse, but there is presumably some final common pathway which is acted upon by nicotine. Physiological explanations of the antianxiety effects of nicotine are still forthcoming, but it is well known that nicotine induces a complex cascade of neural hormones, including peptides such as endogenous opioids, components of the hypothalamic pituitary axis, and a variety of biogenic amines, among others. Analysis of the relative importance of each of these components has begun in various laboratories utilizing agonists and antagonists to these compounds.

The peculiar stimulant properties of nicotine have been used by millions of smokers to improve the quality of intellectual work. Evidence from a variety of laboratories indicates that performance in a variety of tasks of concentration, vigilance, and perception are indeed improved by appropriate doses of nicotine both in smokers and (more importantly) nonsmokers. The electrophysiological changes in the brain and other parts of the nervous system which might be responsible for such effects have been reviewed by Dr. Domino to illustrate how this drug might facilitate intellectual performance such as perception, learning, and memory.

The reduction of anxiety and irritability may also contribute to enhanced performance and euphoria. The work of Dr. Don Cherek on the ability of nicotine to reduce aggression is particularly pertinent in this respect and may involve some of the same mechanisms implicated in anxiety reduction.

The homeostatic mechanisms of feeding have been perhaps more intensively studied by psychophysiologists than any other form of reinforcement. The analogies between eating and smoking are so strong that it is hard to ignore the similarities and to assume that somewhere there must be either intersecting or final common pathways involved. Both smoking and eating are forms of oral gratification, a point early recognized by psychodynamic theorists. Of more empirical importance is the fact that smoking unequivocally results in weight reduction, and as Dr. Grunberg has pointed out, there are probably two factors involved: a metabolic enhancement by nicotine and a selective depression of desire for sweet, caloric foods. Again, the mechanisms and particularly the involvement of specific anatomical sites have not been clarified. A related important paradoxical finding by Edythe London and collaborators at the National Institute on Drug Abuse has indicated that the hypothalamus is virtually devoid of nicotinic receptors, so that the interaction between feeding and smoking must somehow be indirectly mediated. Another aspect of eating and smoking which Jarvik and collaborators have been particularly concerned with is the highly reinforcing nature of the postprandial cigarette. This is a very robust phenomenon which almost all smokers experience, but the mechanism of which has not yet been revealed.

---

[1] Professor of Psychiatry and Pharmacology, School of Medicine, University of California, Los Angeles, CA 90024.

In summary, we would have to conclude that although the evidence linking smoking to disease is incontrovertible, nonetheless nicotine has some positive virtues which are worth pursuing for their own sake. If nicotine could be administered free of the harmful effects of tobacco, many of the deleterious effects could be eliminated. In fact, nicotine has been given orally, by inhalation, nasally, sublingually, intravenously, and transdermally. While this alkaloid does have intrinsically harmful cardiovascular effects, further research might reveal ways of dealing with these so that this drug might still have promise as a pharmacologically useful therapeutic agent.

Basic and Clinical Aspects of Prefrontal Cortex Physiology in Neuropsychiatry

Chair:

Daniel R. Weinberger, M.D.

National Institute of Mental Health
Saint Elizabeths Hospital
Washington, DC 20032

Electrophysiological Evidence Implicating Frontal Lobe Dysfunction in Schizophrenia

John M. Morihisa, M.D.[1]

The importance of the frontal lobes in the pathogenesis of schizophrenia has its roots in the neuroanatomic foundations of modern psychiatry (Morihisa & Weinberger, 1986). Indeed, Alzheimer (1913) felt that pathology in layers II and III of the frontal lobes had a significant role in the etiology of schizophrenia (dementia praecox). In addition, phenomenological studies of this disorder have highlighted a number of clinical manifestations that yield a constellation of symptoms that is strikingly similar to what we have come to associate with neurologic cases of frontal lobe disease. This symptom complex would include: poor insight, social withdrawal, decreased behavioral spontaneity, ineffectiveness, inattentiveness, and lack of interest in personal hygiene (Morihisa & Weinberger, 1986). This is not to say that the entire spectrum of symptoms that can be associated with schizophrenia is congruent with those demonstrated by neurologic patients with clear frontal lobe disease. Instead, we would suggest that a subgroup of schizophrenic patients often exhibit a subset of symptoms that are quite reminiscent of a frontal-lobe syndrome. In schizophrenia, this grouping of symptoms has had sufficient heuristic value to form the basis for several clinical subtyping strategies in schizophrenia. The clinical categorizations of "negative symptom" type or "defect symptom state" schizophrenia would appear closest in content to those that might support an involvement of frontal lobe pathology. Encouraged by these theoretical suspicions and circumstantial clinical evidence, interest has focused on techniques that might provide direct measurement of frontal lobe abnormalities in schizophrenia.

The earliest findings were derived from pneumoencephalography which suggested structural pathology of the central nervous system in schizophrenia. However, it would require an evolutionary step in radiology to allow more specific structural investigations in the form of computed tomography. During this period, a parallel avenue of investigation was developing. This was the introduction of topographic electrophysiologic approaches to examine brain function. Pioneering work was led by Walter and Shipton (1951), Petsche (1954), and Remond

---

[1] Psychiatrist-in-Chief, Veterans Administration Medical Center, 50 Irving Street N.W., Washington, DC 20422. Professor of Psychiatry, Georgetown University School of Medicine.

(1955) and extended by Estrin and Uzgalis (1969), Lehman (1971), Bickford and colleagues (1972), and Gotman & Gloor (1975). In 1979, Duffy et al. introduced a computerized topographic mapping system, brain electrical activity mapping, which built upon several decades of work in the field.

Our study employed a Duffy system that utilized a standard convention for the placement of electroencephalograph (EEG) electrodes, the International 10–20 System. All electrodes were referenced to linked ears and additional electrodes were attached to monitor eye movements. The data from these leads were amplified through Grass 7P511 amplifiers and recorded on a Honeywell 5600E 28 channel FM analog tape recorder for off-line processing by a DEC PDP 11–60 computer. Prior to analysis all data were visually inspected and segments containing eye blinks, eye movements, muscle potentials, movement artifacts, or 60 Hz interference were eliminated. A spectral analysis was performed using the Fast Fourier Transform algorithm (Cooley & Tukey, 1976). Topographic maps of this spectral analysis were used to present condensed and summarized EEG data. These maps can also demonstrate epochs of simple visual (flash) or auditory (click) evoked potentials or display statistical information in topographic format (Duffy et al., 1979, 1981).

In 1983 this computerized topographic technique was systematically applied to the study of schizophrenia (Morihisa et al., 1983). This study compared drug-free schizophrenic patients and medicated schizophrenic patients to normal controls. Schizophrenic patients fulfilled *DSM–III* and Research Diagnostic Criteria and drug-free patients were unmedicated for at least 4 weeks and medicated patients were on a standardized dose of haloperidol (0.4 mg/kg) for at least 4 weeks. The patients were not significantly different from the controls for age, gender, or handedness. The major finding of this study was that schizophrenic patients demonstrated more delta activity over the entire cortical surface than did controls. Furthermore, the drug-free patients demonstrated greater delta activity than the medicated patients. Thus, the greater delta activity in schizophrenic patients does not appear to be an acute effect of medication. The increased delta activity in schizophrenia was seen over the entire cortical surface. This finding contributes further evidence of brain abnormalities in this disorder. In order to further refine our pathophysiological focus we must complement this approach with techniques which measure brain metabolism and structure (Morihisa, 1985*b*). The importance of using multiple complementary brain imaging techniques is emphasized by the vulnerability of EEG studies to artifactual contamination and the fact that EEG studies are generally limited to recordings from the cortical surface (Morihisa, in press).

Supporting Evidence From Positron Emission Tomography (PET)

Recent studies using positron emission tomography support the involvement of frontal lobe abnormalities in schizophrenia. Buchsbaum et al. (1982, 1984) reported abnormalities of the anteroposterior gradient of glucose metabolism in schizophrenic patients compared to controls. Although these findings have been also reported in affective disorders and other groups have failed to replicate this result, one of the most recent investigations using positron emission tomography (Wolkin et al., 1985) has taken the argument a step further by demonstrating a finding of specifically decreased absolute glucose metabolism in the frontal lobes of schizophrenic patients.

Supporting Structural Evidence

Recent structural evidence has been reported using computerized tomography (Weinberger, 1984; Shelton et al., 1985) that found subtle atrophy of the frontal cortex in schizophrenic patients. Andreasen and colleagues (1986) have introduced a new brain imaging strategy in the investigation of frontal lobe pathology in schizophrenia, magnetic resonance imaging (MRI). Andreasen and her co-workers report (1986) that schizophrenic patients had significantly smaller frontal lobes than normal controls.

Supporting Evidence From Regional Cerebral Blood Flow (rCBF)

This evidence of frontal lobe dysfunction is consistent with the work of Ingvar and colleagues (1974) who reported a relative decrease in frontal cerebral blood flow in schizophrenic patients compared to alcoholic controls. Although there were a number of limitations to Ingvar's original studies (Berman et al., 1984), recent work by Weinberger and colleagues using xenon-133 regional cerebral blood flow has refocused attention on frontal lobe dysfunction in schizophrenia.

Weinberger and colleagues (Berman et al., 1984; Weinberger et al., 1986; Berman et al., 1986) used a cognitive activation test, the Wisconsin Card Sort, to place a specific demand on the dorsolateral prefrontal cortex. Neuroscience findings have suggested that this activation task will selectively test the functional integrity of the dorsolateral prefrontal cortex (Weinberger et al., 1986). Weinberger found that normal subjects demonstrated the expected increase in blood flow in the prefrontal region but schizophrenic patients failed to do so. Thus, this application of rCBF adds further evidence implicating frontal lobe pathology in schizophrenia and suggests that we refine our focus to the dorsolateral prefrontal cortex.

We next hope to use the Wisconsin Card Sort paradigm as a cognitive activation task in an investigation of schizophrenia using computerized topographic mapping (Morihisa, in press). This would represent an important next step in the computerized topographic EEG investigation of frontal lobe dysfunction in schizophrenia. First, this strategy uses a cognitive activation task as opposed to measuring the difficult-to-control resting alert cognitive state. Second, this particular cognitive activation task selectively places a demand upon a specific component of the frontal lobes and thereby may allow greater resolution of pathologic localization (Morihisa & Weinberger, 1986).

Combining EEG Topographic Approaches With Other Brain Imaging Techniques

The utility of matching complementary brain imaging techniques reflects the fact that each of these approaches has specific limitations and measures quite different parameters of brain function. Thus, by combining the strengths and information of different imaging techniques we can build the strongest case for hypothesizing specific patterns of pathophysiology (Morihisa, 1984).

Our most recent computerized topographic study (Morihisa & McAnulty, 1985) of EEG and evoked potentials employed computed tomography to provide a structural basis for the electrophysiological comparison of two groups of schizophrenic patients. In this pilot study we explored the relationship of anatomic pathology and electrophysiological differences between a group of schizophrenic patients with frontal atrophy versus a group of schizophrenic patients without frontal atrophy. This preliminary investigation delineated four regional differences between these two groups, all of which overlay frontal cortical regions (Figure 1). These findings suggest that, in schizophrenia, differences in electrophysiological function may be associated with definable gross morphologic abnormalities of the brain (Morihisa & McAnulty, 1985).

Conclusion

Thus, a compelling body of evidence has been reported implicating frontal lobe dysfunction as a process that may be important to our understanding of schizophrenia. However, despite some convergence in findings, caution must be exercised in the interpretation of this seemingly meaningful constellation of findings from clinical observation and functional and structural brain imaging techniques. First, a number of contradictory results have been reported using rCBF, PET scan, and computerized topographic EEG approaches. Second, these findings suggestive of frontal pathology have not been found in all patients with schizophrenia and, perhaps even more confounding, PET studies have reported similar abnormalities in patients with affective disorders. Finally, schizophrenia encompasses a wide range of clinical manifestations which suggest a heterogeneity of pathology and perhaps etiology.

Although computerized topographic electrophysiological studies are consistent with

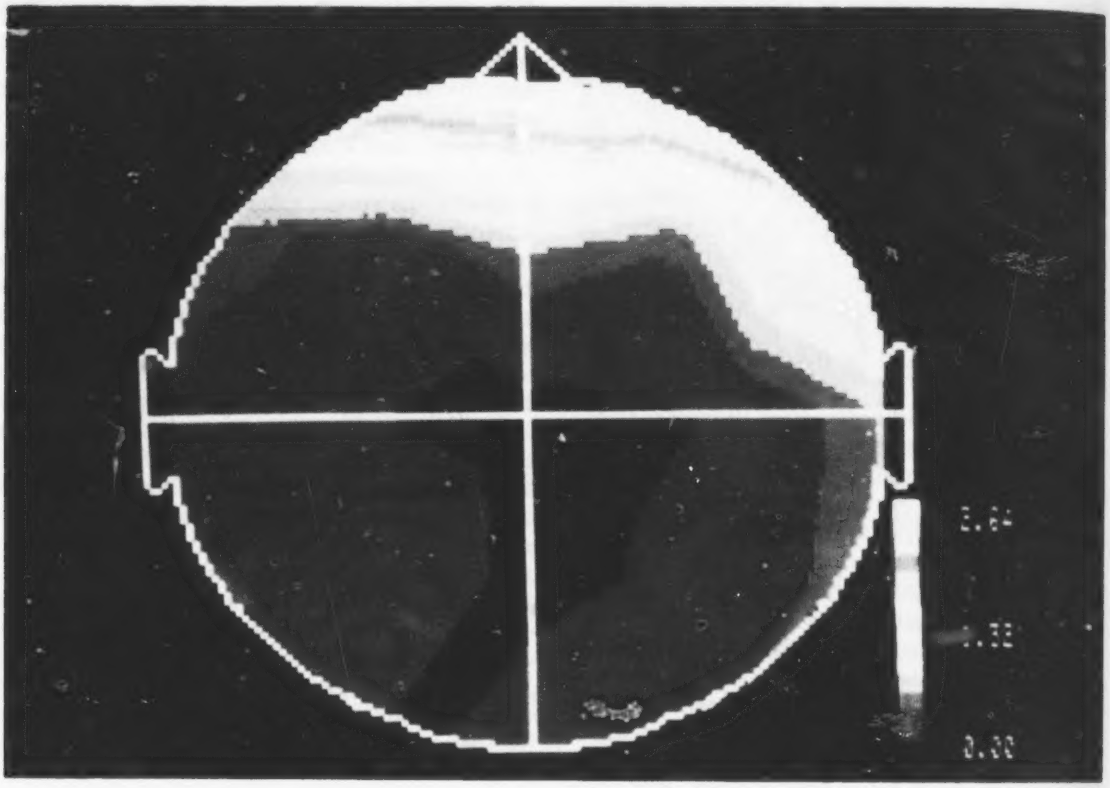


FIGURE 1. This is a brain electrical activity map that compares electrophysiological data (visual evoked potential) for two groups of schizophrenic patients: schizophrenic patients who demonstrate frontal atrophy on computed tomography scan versus schizophrenic patients who show no evidence of frontal atrophy. Greatest difference is presented in white and overlies the frontal lobes. This is one of four maps that were elucidated in this study, all of which involved regions overlying the frontal lobes.

the hypothesis of frontal lobe pathology in schizophrenia, the inherent limitations of these approaches and the lack of a unitary body of findings emphasize the urgency for further studies, especially those employing complementary brain imaging approaches in concert to enlarge and enhance our scientific window of investigation (Morihisa, in press).

References

Alzheimer, A. Beitrage zur pathologischen Anatomie der Dementia Praecox. *Allgemeine Z. Psychiatrie*, 70:810–812, 1913.

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Washington, DC: American Psychiatric Association, 1980.

Andreasen, N., Nasrallah, H.A., Dunn, V., et al. Structural abnormalities in the frontal system in schizophrenia. *Arch. Gen. Psychiatry*, 43:136–144, 1986.

Berman, K.F., Weinberger, D.R., Morihisa, J.M., et al. Regional cerebral blood flow in psychiatry: Application to clinical research. In: Morihisa, J.M. (ed.), *Brain Imaging in Psychiatry*. Washington, D.C.: American Psychiatric Press, 1984.

Berman, K.F., Zec, R.F., and Weinberger, D.R. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: II. Role of neuroleptic treatment, attention and mental effort. *Arch. Gen. Psychiatry*, 43:126–135, 1986.

Bickford, R.G., Billinger, T.W., Fleming, N.I.I., et al. The compressed spectral array (CSA): A pictorial EEG. *Proc. San Diego Biochem. Symp.*, 11:365–470 1972.

Buchsbaum, M.S., Ingvar, D.H., Kessler, R., et al. Cerebral glucography with positron tomography: Use in normal subjects and in patients with schizophrenia. *Arch. Gen. Psychiatry*, 39:251–259, 1982.

Buchsbaum, M.S., DeLisi, L.E., Holcomb, H.H., et al. Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch. Gen. Psychiatry*, 41:1159–1166, 1984.

Cooley, J.W., Tukey, J.W. An algorithm for the machine calculation of complex Fourier series. *Math Comput.*, 19:297–301, 1976.

Duffy, F.H., Burchfiel, J.L., Lombroso, C.T. Brain electrical activity mapping (BEAM): A method for extending the clinical utility of EEG and evoked potential data. *Ann. Neurol.*, 5:309–332, 1979.

Duffy, F.H., Bartels, P.H., Burchfiel, J.L. Significance probability mapping: An aid in the topographic analysis of brain electrical activity. *Electroencephalogr. Clin. Neurophysiol.*, 51:455–462, 1981.

Estrin, T., Uzgalis, R. Computer display of spatio-temporal EEG patterns. *IEEE Trans. Biomed. Eng.*, 16:192–196, 1969.

Gotman, J., Gloor, R., Ray, W.G. A quantitative comparison of traditional reading of the EEG and interpretation of computer extracted features in patients with supratentorial brain lesions. *Electroencephalogr. Clin. Neurophysiol.*, 38:623–639, 1975.

Ingvar, D.H., Franzen, G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr. Scand.*, 50:425–462, 1974.

Lehman, D. Multichannel topography of human alpha EEG fields. *Electroencephalogr. Clin. Neurophysiol.*, 31:439–449, 1971.

Morihisa, J.M., Duffy, F.H., Wyatt, R.J. Brain electrical activity mapping (BEAM) in schizophrenic patients. *Arch. Gen. Psychiatry*, 40:719–728, 1983.

Morihisa, J.M. (ed.), *Brain Imaging in Psychiatry*. Washington, D.C.: American Psychiatric Press, 1984.

Morihisa, J.M., McAnulty, G.B. Structure and function: Brain electrical activity mapping and computed tomography in schizophrenia. *Biol. Psychiatry*, 20:3–19, 1985*a*.

Morihisa, J.M. Computerized topographic mapping of electrophysiologic data in psychiatry. *Psychiatric Annals*, 15(4):250–253, 1985*b*.

Morihisa, J.M., Weinberger, D.R. Is schizophrenia a frontal lobe disease? An organizing theory of relevant anatomy and physiology. In: Andreasen, N. (ed.), *Can Schizophrenia Be Localized in the Brain?* Washington, D.C.: American Psychiatric Press, 1986, Chapter 2.

Morihisa, J.M. Computerized EEG and Evoked Potential Mapping. In: Andreasen, N. (ed.), *Brain Imaging for Psychiatrists*. Washington, D.C.: American Psychiatric Press (in press).

Petsche, H., and Marko, A. Das Photozellentoposkop, eine einfache Methode zur Bestimmung der Feldverteilung und Ausbreitung hirnelektrischer. *Vorgange. Arch. Psychiat.*, 192:447–452, 1954.

Remond, A. Orientations et tendences des methodes topographiques dans l'etude de l'activite electrique du cerveau. *Rev. Neurol.*, 93:399–410, 1955.

Shelton, R.C., Ingraham, L., and Weinberger, D.R. Cerebral structural pathology in schizophrenia: A new cohort. Scientific exhibit at the annual meeting of the Society of Biological Psychiatry, Dallas, Texas, May 17, 1985.

Spitzer, R.L., Endicott, J., and Robins, E. *Research Diagnostic Criteria for Selected Group of Functional Disorders*. 3rd ed. New York: Biometrics Research Division, New York State Psychiatric Institute, 1977.

Walter, W.G., and Shipton, H.W. A new toposcopic display system. *Electroencephalogr. Clin. Neurophysiol.*, 3:281–292, 1951.

Weinberger, D.R. CAT scan findings in schizophrenia: Speculation on the meaning of it all. *J. Psychiatr. Res.*, 18:477–490, 1984.

Weinberger, D.R., Berman, K.F., and Zec, R.F. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow (rCBF) evidence. *Arch. Gen. Psychiatry*, 43:114–124, 1986.

Wolkin, A., Jaeger, J., Brodie, J.D., Wolf, A.P., et al. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by Positron Emission Tomography. *Am. J. Psychiatry*, 142:564–571, 1985.

Neuroleptic-Induced Psychological Supersensitivity Syndromes: Are These Syndromes Myth or Reality?

Co-Chairs:

Philip A. Berger, M.D.
Stanford University School of Medicine
Stanford, CA 94305

Kenneth L. Davis, M.D.
Bronx VA Medical Center
Bronx, NY 10468

Supersensitivity Psychosis and Tardive Dyskinesia: A Survey in Schizophrenic Outpatients

Guy Chouinard, M.D., M.Sc. (Pharmacol), F.R.C.P.(C),[1,2,3] Lawrence Annable, B.Sc., Dip. Stat.,[1,2] and Andree Ross-Chouinard, M.D. (Neurology), F.R.C.P.(C)[1,2]

Long-term administration of neuroleptics is currently the most efficacious treatment for chronic schizophrenia. However, this type of treatment is not without serious risk, particularly for the central nervous system. Abnormal movements of choreoathetoid type called tardive dyskinesia have been reported to occur in 20 to 40 percent of patients receiving neuroleptics (American Psychiatric Association Task Force Report, 1979) and can be potentially irreversible, especially after the age of 40. We reported another long-term side effect of neuroleptic treatment which we called supersensitivity psychosis (Chouinard et al., 1978; Chouinard & Jones, 1980). Receptor changes in the dopaminergic pathways of the mesolimbic (Davis & Rosenberg, 1979) or other nonstriatal dopaminergic regions of the brain could explain the disorder in the same way that changes in the neostriatum are thought to be responsible for tardive dyskinesia.

There are difficulties associated with the diagnosis of supersensitivity psychosis (Chouinard & Jones, 1982). The symptoms of the latter are nearly the same as the disease process itself; the distinctions being that only positive symptoms of schizophrenia are exhibited, that the symptoms fluctuate according to the masking effect of increased neuroleptic dose or unmasking effect of decreased dose, and that relapses occur more rapidly than would be expected from the normal course of the illness. In this respect, perhaps it is worth mentioning that the symptoms of tardive dyskinesia have also been mistaken for mannerisms of schizophrenia, hyperkinetic parkinsonian side effects (akathisia or tremors), and senile choreic movements.

As with tardive dyskinesia, clinical symptoms of supersensitivity psychosis are masked by neuroleptics. Since all the neuroleptics presently available have prolonged half-lives,

---

[1] Clinical Psychopharmacology Unit, Allan Memorial Institute. Royal Victoria Hospital, Montreal, Quebec, Canada.

[2] Department of Psychiatry, McGill University, Montreal, Canada.

[3] Research Department, Hopital Louis-H, Lafontaine, Montreal, Canada.

recognition of the disorder is difficult. One would predict that metaclopramide, a short-acting dopamine (DA) receptor blocking agent, when given in doses effective in treating schizophrenia, would give clear evidence of supersensitivity relapse upon abrupt withdrawal. Cases of supersensitivity psychosis have been reported following withdrawal of clozapine (Ekholm et al., 1984; Perenyi et al., 1985), a drug with a short half-life and a greater affinity for mesolimbic than striatal DA receptors. Other cases have been reported following withdrawal of neuroleptics in manic-depressive illness (Witschy et al., 1984; Duff et al., in preparation), and reserpine (Kent & Wilber, 1982).

The disorder may be less readily apparent in inpatient populations since, like tardive dyskinesia, supersensitivity psychosis is identified most readily in patients under stress. Tardive dyskinetic symptoms are exacerbated during periods of increased concentration or anxiety. Similarly, the most potent stressors for supersensitivity psychosis are the normal activities of the patient's life which are difficult to recreate in a hospital setting.

Given the difficulties in diagnosing supersensitivity psychosis, we carried out a survey of the disorder in an outpatient population for which conditions of treatment optimized the possibility of observing its presence. At the same time, we carried out a 5-year follow-up study of tardive dyskinesia (Chouinard et al., 1979; Chouinard et al., in press).

Method

For the purposes of this study, the clinical presentation of supersensitivity psychosis was defined as follows: sudden relapse upon neuroleptic dosage decrease or discontinuation with rapid improvement upon re-establishment of neuroleptic treatment, and evidence of CNS tolerance to antipsychotic effect as manifested through a need for a gradual increase in neuroleptic dosage to maintain constant therapeutic effect. Using these criteria, we carried out a cross-sectional survey of supersensitivity psychosis in 224 schizophrenic outpatients chronically maintained on neuroleptic treatment. The patients studied attended an outpatient clinic in which all patients have a diagnosis of schizophrenia according to the Research Diagnostic Criteria (Spitzer et al., 1977). Within the clinic, pharmacotherapy was under strict control and, at the time of the study, the following principles were applied: the minimum therapeutic dose was given; a single neuroleptic was prescribed whenever possible; very few patients received low-potency neuroleptics; drugs were administered in a single daily dose or twice-daily regimen; procyclidine was the only antiparkinsonian drug used; attempts were made to withdraw the antiparkinsonian after 3 months; fluphenazine enanthate, an injectable long-acting drug was given to patients who did not respond to other neuroleptics, those who could not be relied upon to take medication, and those with frequent relapses; polypharmacy was avoided and antidepressant drugs, minor tranquilizers, and hypnotics were not prescribed; medication was reviewed each time the patient came to the clinic.

Patients were rated during their regular visit to the clinic by a psychiatrist (GC) who had been in charge of their treatment for 10 years. The following ratings were carried out: 1) The presence of supersensitivity psychosis, rated on a 3-point rating scale (0 = absent, 1 = doubtful or borderline, 2 = definite). The principal clinical characteristic used for the diagnosis of definite supersensitivity psychosis was a greater relapse rate during continuous neuroleptic treatment than when not continuously treated. Doubtful or borderline cases were classified as such if: a) a patient had developed definite drug tolerance but no definite relapse when medication was decreased; b) patients had showed definite relapse upon decrease or discontinuation of medication, but the relapse occurred shortly after 6 weeks for oral medication or 3 months for depot injectable neuroleptics. 2) Therapeutic response to treatment, rated on a 5-point rating scale (1 = marked improvement and 5 = worse); and 3) Overall severity of illness, rated on a 7-point rating scale (1 = normal and 7 = extremely ill).

The patient's illness was also classified as good or poor prognosis according to criteria similar to those of Robins and Guze (1970) (age of onset and presence of significant residual symptoms being the main criteria). *Independently, patients underwent an extra-*

TABLE 1. Patient Characteristics.

	Men (n = 113)		Women (n = 111)		All Patients (n = 224)	
	Mean	(S.D.)	Mean	(S.D.)	Mean	(S.D.)
Age	41.9	(10.9)	48.4	(11.0)	45.1	(11.4)
Neuroleptic dose (CPZ units)*	706	(885)	454	(552)	587	(750)
Years on neuroleptics	12.7	(6.3)	14.9	(5.8)	13.8	(6.1)

*Neuroleptic medications were converted to mg/day chlorpromazine units according to the equivalency given by Davis (1980). Fluphenazine enanthate was converted to chlorpromazine units on the basis of an equivalency of a dose of 25 mg I.M. every 2 weeks to 150 mg chlorpromazine daily.

pyramidal symptom assessment, using a standardized examination procedure for parkinsonian symptoms and tardive dyskinesia, and were rated on the Extrapyramidal Symptom Rating Scale by a neurologist (AR-C). Blood was drawn for determination of plasma prolactin concentration and was analyzed for neuroleptic activity using a neuroleptic radioreceptor assay (Creese & Snyder, 1977; Lader, 1980; Cohen et al., 1980). Also, various demographic variables were recorded by review of the patient's chart: age, number of years treated with neuroleptics, length of previous psychiatric hospitalizations, current dosage of neuroleptics, number of ECT treatments, number of insulin treatments, presence of brain damage, history of alcoholism, history of antidepressant treatment.

Results

The characteristics of the population studied are shown in Table 1. Women tended to be older but required a lower neuroleptic maintenance dose than men. Table 2 shows the prevalence of tardive dyskinesia, using the Research Diagnostic Criteria of Schooler and Kane (1982) (which require presence of at least "moderate" dyskinetic movements in one or more body areas or at least "mild" dyskinetic movements in two or more body areas), and supersensitivity psychosis. The prevalence of definite cases of supersensitivity psychosis (22%) was about one half that of tardive dyskinesia (45%) and did not vary with sex.

Table 3 compares the age and neuroleptic dosage of patients with and without supersensitivity psychosis and tardive dyskinesia. Patients with supersensitivity psychosis were receiving a larger mean neuroleptic dose than patients without this syndrome ($t = 4.07, p < .001$), but there was no difference with respect to mean age. Patients with tardive dyskinesia, on the other hand, tended to be older than patients without tardive dyskinesia ($t = 4.05, p < .001$), but there was no difference with respect to mean neuroleptic dose.

Patients receiving low-potency neuroleptics tended to have different characteristics from those receiving high potency neuroleptics and were considered as a separate group. Table 4 shows the results for different variables according to the rating given for supersensi-

TABLE 2. Prevalence of Tardive Dyskinesia and Supersensitivity Psychosis.

	Men (n = 113)		Women (n = 111)		All Patients (n = 224)	
	No.	%	No.	%	No.	%
Tardive dyskinesia (Research Diagnostic Criteria)	51	45	49	44	100	45
Supersensitivity Psychosis (2=definite only)	26	23	24	22	50	22
Supersensitivity Psychosis (2=definite; 1=doubtful or borderline)	48	42	49	44	97	43

TABLE 3. Characteristics of Patients With and Without Supersensitivity Psychosis (Definite), and Tardive Dyskinesia (Research Diagnostic Criteria): Mean (S.D.).

	Supersensitivity Psychosis		Tardive Dyskinesia	
	Present (n = 50)	Absent (n = 174)	Present (n = 100)	Absent (n = 124)
Age (yrs)	44 (12)	46 (14)	48 (11)[a]	42 (11)
Neuroleptic dose (mg/day CPZ units)	940 (1002)[b]	472 (614)	625 (854)	526 (632)

[a] Statistically significant ($p < .001$) difference in mean age between patients with and without tardive dyskinesia.
[b] Statistically significant ($p < .01$) difference in mean neuroleptic dose between patients with and without supersensitivity psychosis.

tivity psychosis in patients receiving high-potency neuroleptics only. Patients with a definite diagnosis of supersensitivity psychosis were receiving significantly greater neuroleptic doses ($t = 4.35$, $p < .001$) and had significantly higher prolactin levels (men: $t = 1.68$, $p < .10$; women: $t = 2.38$, $p < .05$) than those without supersensitivity psychosis. There was also a nonsignificant trend for higher neuroleptic radioreceptor assay levels in patients with supersensitivity psychosis than those without the disorder (these were measured in 71 patients only so there was less statistical power to detect differences).

Table 5 shows similar results for patients receiving low-potency neuroleptics. Although the numbers of subjects in this group are small the same trend for increasing neuroleptic dose and radioreceptor assay levels is present in patients with supersensitivity psychosis. In general, patients treated with low-potency drugs tended to be older and have more tardive dyskinesia than the high-potency group.

Table 6 compares patients with supersensitivity psychosis and those without the syndrome with respect to schizophrenic prognosis. There was a tendency ($p < .10$) for supersensitivity psychosis to be more frequent in patients diagnosed as "good prognosis" (atypical, schizophreniform, paranoid subtype) than in those diagnosed as "poor prognosis" (other subtypes).

Discussion

The prevalence of tardive dyskinesia meeting the Schooler and Kane research criteria (1982) in these schizophrenic outpatients was 45 percent, about twice that of diagnosed cases of supersensitivity psychosis, 22 percent. We have elsewhere reported

TABLE 4. Supersensitivity Psychosis, Tardive Dyskinesia, and Patient Characteristics: Patients Treated With High-Potency Neuroleptics ($N = 191$).

	Mean (S.D.) Supersensitivity Psychosis			
	Not Present 0 ($n = 93$)	Doubtful or Borderline 1 ($n = 39$)	Definite 2 ($n = 45$)	Not Assessable 3 ($n = 14$)
Age	44.5 (11.4)	42.2 (12.1)	43.4 (11.5)	46.5 (8.7)
Neuroleptic dose (CPZ units)	399 (473)	699 (810)	913 (917)***	421 (271)
Neuroleptic-RRA level[a]	14.2 (31.8)	15.3 (16.5)	23.5 (35.9)	6.2 (5.9)
CGI of therapeutic effect	1.5 (0.6)	1.5 (0.7)	1.5 (0.5)	1.1 (0.4)
CGI of severity of illness	4.4 (0.9)	4.4 (1.0)	4.7 (1.2)†	4.6 (0.6)
Prolactin female ng/ml	33.2 (25.6)	42.5 (33.8)	52.5 (38.1)*	44.7 (38.1)
Prolactin male ng/ml	17.8 (11.4)	21.6 (14.6)	23.5 (16.1)†	16.4 (9.6)
T.D. (research criteria)	45.2%	33.3%	42.2%	50.0%

[a] Measured in 99 subjects only, classified according to supersensitivity psychosis as follows: not present n=43; borderline n=19; definite n=28; not assessed n=9.
† Significantly different (p<.10) from corresponding mean value for patients without supersensitivity psychosis (*t* test).
* Significantly different (p <.05) from corresponding mean value for patients without supersensivity psyhcosis (*t* test).
*** Significantly different (p<.001) from corresponding mean value for patients without supersensitivity psychosis (*t* test).

TABLE 5. Supersensitivity Psychosis Rating, Tardive Dyskinesia and Patient Characteristics: Patients Treated With Low-Potency Neuroleptics ($n = 33$).

	Mean (S.D.) Supersensitivity Psychosis			
	Not Present 0 ($n = 14$)	Doubtful or Borderline 1 ($n = 8$)	Definite 2 ($n = 5$)	Not Assessable 3 ($n = 6$)
Age	52.9 (9.8)	50.3 (8.9)	52.8 (10.0)	52.8 (10.3)
Neuroleptic dose (CPZ units)	216 (169)	681 (684)	1190 (1718)	725 (1483)
Neuroleptic-RRA level*	13.1 (6.9)	34.3 (24.6)	41.9 (63.0)	55.1 (0.4)
CGI of therapeutic effect	1.1 (0.3)	1.3 (0.5)	1.8 (0.8)	1.8 (0.8)
CGI of severity of illness	4.0 (0.8)	4.5 (0.8)	4.4 (0.5)	3.3 (0.8)
Prolactin level (ng/ml)	21.2 (23.3)	24.5 (25.6)	19.3 (10.5)	21.4 (14.3)
T.D. (research criteria)	50.0%	50.0%	60.0%	83.3%

*Measured in 14 patients only, classified according to supersensitivity psychosis as follows: not present $n = 6$; borderline $n = 3$; definite $n = 3$; not assessed $n = 2$.

(Chouinard et al., in press) that over a 5-year period the annual incidence rate of tardive dyskinesia corrected for remissions in these patients was 2.9 percent, similar to that reported by Kane et al. (1982) from a prospective study of tardive dyskinesia development.

A diagnosis of supersensitivity psychosis was associated with a higher maintenance dose of neuroleptics, high prolactin levels and a "good" schizophrenic prognosis. No relationship was seen, however, between tardive dyskinesia and supersensitivity psychosis. The trend for a higher dose and prolactin level to be seen in patients with supersensitivity psychosis may reflect the development of dopamine supersensitivity in areas of the brain responsible for the appearance of psychotic symptoms. The latter would necessitate increased neuroleptic dosage to maintain clinical improvement. Of course, it could be argued that one of the features used to make the diagnosis was evidence of drug tolerance. However, not all patients were diagnosed based on the presence of this feature and drug tolerance was defined as the need for dosage increases over time after a patient had been stable on a lower dose, and not simply the presence of a large absolute dose of neuroleptic unchanged from the dose needed to control a previous acute relapse of the illness. Thus these indirect measures of increased dopaminergic antagonist activity in patients diagnosed as having supersensitivity psychosis do provide some measure of support for the diagnosis.

TABLE 6. Supersensitivity Psychosis and Schizophrenic Prognosis: Patients Treated With High-Potency Neuroleptics.

	Supersensitivity Psychosis	
Prognosis	Present	Absent
Good prognosis	37	7
Poor prognosis	62	29

$\chi^2 = 3.12$, $p < .10$ (Yates' correction applied).

That patients with good prognosis schizophrenia show a tendency towards greater susceptibility to supersensitivity psychosis could explain the lack of correlation with tardive dyskinesia. Tardive dyskinesia is more often seen in poor prognosis patients (Chouinard et al., 1979) and a different susceptibility based on prognosis could obscure any relationship between these two supersensitivity disorders in an individual patient. In an earlier study carried out with chronically hospitalized inpatients having poor prognosis schizophrenia, we found an association between tardive dyskinesia and supersensitivity psychosis. But, in this outpatient study including both poor and good prognosis patients, such a relationship was not found. It should be mentioned that the great majority of patients included in this study were receiving fluphenazine, given either orally or in the long-acting injectable form (decanoate or enanthate). Further cross-sectional studies involving neuroleptics with more selective D_2 dopamine receptor blocking properties (greater D_2-D_1 ratios than phenothiazines or thioxanthenes) are now under way with the same group of patients.

References

American Psychiatric Association Task Force Report. *Tardive Dyskinesia*, 18:43–56, 1979.

Chouinard, G., Annable, L., Mercier, P., and Ross-Chouinard, A. Five-year follow-up study of tardive dyskinesia. *Psychopharmacol. Bull.* (in press).

Chouinard, G., Annable, L., Ross-Chouinard, A., and Nestoros, J.N. Factors related to tardive dyskinesia. *Am. J. Psychiatry*, 136:79–83, 1979.

Chouinard, G., and Jones, B.D. Neuroleptic-induced supersensitivity psychosis: Clinical and pharmacologic characteristics. *Am. J. Psychiatry*, 137:16–21, 1980.

Chouinard, G., Jones, B.D., and Annable, L. Neuroleptic-induced supersensitivity psychosis. *Am. J. Psychiatry*, 135:1409–1410, 1978.

Chouinard, G., and Jones, B.D. Neuroleptic-induced supersensitivity psychosis, the hump course and tardive dyskinesia. *J. Clin. Psychopharmacol.*, 2:143–144, 1982.

Cohen, B.M., Herschel, M., Miller, E., et al. Radioreceptor assay of haloperidol tissue levels in the rat. *Neuropharmacology*, 19:663–668, 1980.

Creese, I., Snyder, S.H. A simple and sensitive radioreceptor assay for antischizophrenic drugs in blood. *Nature*, 270:180–182, 1977.

Davis, K.L., Rosenberg, G.S. Is there a limbic system equivalent of tardive dyskinesia? *Biol. Psychiatry*, 14:699, 1979.

Davis, J.M. Antipsychotic drugs. In: Freedman, A.M., Kaplan, H.I. and Sadock, B.J. (eds.), *Comprehensive Textbook of Psychiatry*, 3rd edition, Vol. 3. Baltimore: Williams and Wilkins Co., 1980, pp. 2257–2289.

Duff, V., Steiner, W., Laporta, M., et al. Neuroleptic-induced supersensitivity psychosis in patients with bipolar affective disorder (in preparation).

Ekholm, B., Eriksson, K., Lindstrom, L.H.H. Supersensitivity psychosis in schizophrenic patients after sudden clozapine withdrawal. *Psychopharmacology*, 83:293–294, 1984.

Kane, J.M., Woerner, M., Weinhold, P., et al. A prospective study of tardive dyskinesia development: preliminary results. *J. Clin. Psychopharmacol.*, 2:345–349, 1982.

Lader, S.R. A radioreceptor assay for neuroleptic drugs in plasma. *J. Immunoassay*, 2:57–75, 1980.

Kent, T.A., and Wilber, R.D. Reserpine withdrawal psychosis: the possible role of denervation supersensitivity of receptors. *J. Nerv. Ment. Dis.*, 170:502–504, 1982.

Perenyi, A., Kuncz, E., and Bagdy G. Early relapse after sudden withdrawal or dose reduction of clozapine. *Psychopharmacology*, 86:244, 1985.

Robins, E., and Guze, S.B. Establishment of diagnostic validity in psychiatric illness: its application to psychiatry. *Am. J. Psychiatry*, 126:983–992, 1970.

Schooler, N.R., and Kane, J.M. Research diagnoses for tardive dyskinesia. *Arch. Gen. Psychiatry*, 39:486–487, 1982.

Spitzer, R.L., Endicott, J., and Robins, E. Research Diagnostic Criteria, 3rd edition, Biometrics Research, New York State Psychiatric Institute, New York, 1977.

Witschy, J.K., Malone, G.L., and Holden, L.D. Psychosis after neuroleptic withdrawal in a manic-depressive patient. *Am. J. Psychiatry*, 141:105–106, 1984.

Associations Among Plasma Prolactin Levels, Tardive Dyskinesia, and Paranoia in Treated Schizophrenics: Relevance to Supersensitivity Psychosis

John G. Csernansky, M.D.,[1] Sophia Vinogradov, M.D.,[1] Elisabeth Prosser, M.D.,[1] Jonathan Kaplan, M.D.,[1] Philip A. Berger, M.D.,[1] and Leo E. Hollister, M.D.[1]

Introduction

Schizophrenics who are exposed to chronic neuroleptic treatment may develop supersensitivity of their brain dopamine (DA) receptors. This is thought to occur when increases in the number of DA receptors develop as an adaptation to neuroleptic-induced receptor blockade (Burt et al., 1977). No significant change in receptor affinity occurs. Choreoform movements of the face, jaw, tongue, and extremities, termed tardive dyskinesia, are felt to be the clinical consequence of DA receptor supersensitivity (DS) development in the nigrostriatal DA pathway, (Klawans et al., 1980). Rapid relapse following neuroleptic dose decrease or withdrawal and the need for steadily increasing neuroleptic doses to maintain remission (i.e., supersensitivity psychosis) may be the result of an analogous development of DS in the mesolimbic DA pathway, (Ungerstedt & Ljundberg, 1977; Davis & Rosenberg, 1979; Chouinard & Jones, 1980). Finally, if DS develops in the tuberoinfundibular DA pathway, tolerance to the prolactin-elevating effects of neuroleptics might occur (Brown, 1983).

Changing Prolactin Levels as a Marker for Supersensitivity Psychosis

A peripheral marker for the putative supersensitivity psychosis syndrome is needed because the clinical characteristics of the syndrome are difficult to distinguish from the natural course of schizophrenia. Decreasing blood prolactin levels during chronic neuroleptic treatment (i.e., tolerance to neuroleptic-induced elevation) may be such a marker. However, it remains controversial whether or not tolerance develops to the prolactin-elevating effects of neuroleptics.

Many investigators have observed that chronic schizophrenics despite continuing treatment have prolactin levels within the normal range (Beumont et al., 1974; De Rivera et al., 1976; Csernansky et al., 1983). This suggests that tolerance does occur; however, prospective studies have yielded mixed results. Both Meltzer and Fang (1976) and Gruen et al. (1978) have found continued elevation of blood prolactin levels after 1 to 3 months of neuroleptic treatment. However, Brown and Laughren (1981) found that prolactin levels rose and then fell during 4 months of neuroleptic treatment. Prospective studies lasting 6 months or more may be needed to resolve this conflict.

Correlations Among Prolactin, Tardive Dyskinesia, and Clinical Symptoms During Treatment

If DS develops concurrently in the various brain DA pathways, correlations among prolactin levels, tardive dyskinesia, and clinical symptoms suggestive of supersensitivity psychosis may occur. We measured plasma prolactin levels, neuroleptic activity (using a radioreceptor assay), abnormal movements, and clinical symptoms in 33 male Research Diagnostic Criteria-positive schizophrenics during neuroleptic treatment.

The patients' plasma prolactin levels were almost entirely within the normal range for males (mean ± SD, 4.4 ± 2.8 ng/ml, highest value 15.2 ng/ml). Prolactin index values, calculated on the ratio of plasma prolactin to

---

[1] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, and the Palo Alto VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

neuroleptic activity (measured by radioreceptor assay), were used as individual patient measures of tuberoinfundibular DA sensitivity corrected for a given amount of circulating neuroleptic activity. Prolactin levels ($r(s) = -.38$, $p < .03$) and prolactin index values ($r(s) = -.56$, $p < .001$) were inversely correlated with age, a variable we interpreted as an indirect measure of neuroleptic exposure. Plasma prolactin levels were not significantly correlated with either tardive dyskinesia or clinical symptoms in any of these patients. However, in a subgroup of these patients less than 45 years of age ($n = 19$), prolactin index values were inversely correlated with tardive dyskinesia ($r(s) = -.56$, $p < .03$), assessed using the Gerlach (1979) scale, and the hostility-suspiciousness subscale of the Brief Psychiatric Rating Scale (Overall, 1974) ($r(s) = -.56$, $p < .03$). We interpreted the presence of residual paranoid symptoms in these treated patients as consistent with the presence of supersensitivity psychosis. A more detailed report of this experiment is published elsewhere (Csernansky et al., 1986). In summary, a lower ratio of blood prolactin to neuroleptic levels may be a useful marker to identify patients during treatment who have tardive dyskinesia or characteristics of supersensitivity psychosis. Further research is needed.

TABLE 1. Operational Criteria for Supersensitivity Psychosis (A through C are required).

A.______ At least 6 months of uninterrupted neuroleptic treatment.

B.______ At least one of the following is present for probable, two for definite:

______1) Maintenance neuroleptic dose has steadily increased.

______2) Psychotic symptoms develop repeatedly during uninterrupted neuroleptic treatment and improve after dose increase.

______3) Psychotic symptoms develop rapidly when neuroleptics are withdrawn or the dose is decreased and improve upon restitution of previous therapy.

C.______ None of the following is present:

______1) Non-compliance with neuroleptic medication or substance abuse are usual precipitants of psychotic relapse.

______2) The patient has a neurological disorder, such as a progressive dementia.

Supersensitivity Psychosis: ___Definite ___No
___Probable ___Not determinable

Dates covered
by chart review: ___/___/___ to ___/___/___

Operational Criteria for Supersensitivity Psychosis

As a further adjunct to the study described above we examined the hospital records of 26 of the 33 schizophrenic patients. Using the operational criteria shown in Table 1, we attempted to classify the patients as having definite, probable, or no supersensitivity psychosis. In addition, we allowed the chart examiner to note if the record was incomplete and classification impossible. The criteria emphasized two major components of the supersensitivity psychosis syndrome: need for increasing neuroleptic dose (tolerance) and rapid relapse (dependence).

The two raters (one psychiatrist and one trained research assistant) scored the records independently. To determine the interrater reliability of these classification criteria, numerical scores were assigned to the various groups as follows (definite = 3, probable = 2, no = 1). Then a Spearman rank order correlation was calculated for the two raters. This indicated a surprisingly good agreement ($r(s) = .67$, $p < .001$, $n = 24$). Only 2 records could not be classified by the raters.

However, no significant correlation was found between each patient's supersensitivity psychosis criteria score and tardive dyskinesia, paranoia, or prolactin levels when the entire group, or when only patients less than 45 years of age ($n = 13$) were examined. Thus, a review of hospital records using these criteria for supersensitivity psychosis did not appear to identify patients with current evidence of DS characteristics (i.e., paranoia, tardive dyskinesia, lower prolactin, or prolactin index values). Further research is needed to validate the existence of the supersensitivity psychosis syndrome, and to identify patients who have it.

Acknowledgments

This work was supported by National Institutes of Health grant MH-03030 (LEH), a VA Career Development Award to JGC, National Institute of Mental Health grant MH-30854 to the Norris Mental Health Clinical Research Center at Stanford University, and a grant from the Research Service of the Veterans Administration to the Schizophrenia Biologic Research Center at Palo Alto VA Medical Center. The authors thank Sherry J. Riney for her excellent technical assistance.

References

Beumont, P.J.V., Corker, C.S., Friesen, H.G., et al. The effects of phenothiazines on endocrine function: II. Effects in men and post-menopausal women. *Brit. J. Psychiatry.*, 124:420–430, 1974.

Brown, W.A. Prolactin levels and effects of neuroleptics. *Psychosomatics*, 24:569–581, 1983.

Brown W.A., and Laughren, T.P. Tolerance to the prolactin-elevating effect of neuroleptics. *Psychiatry Res.*, 5:317–322, 1981.

Burt, D.R., Creese, I., Snyder, S.H. Antischizophrenic drugs: Chronic treatment elevates dopamine receptor binding in brain. *Science*, 196:326–327, 1977.

Chouinard, G., and Jones, B.D. Neuroleptic-induced supersensitivity psychosis: Clinical and pharmacologic characteristics. *Am. J. Psychiatry*, 137:16–21, 1980.

Csernansky, J.G., Prosser, E., Kaplan, J., et al. Possible associations among plasma prolactin levels, tardive dyskinesia, and paranoia in treated schizophrenics, *Biol. Psychiatry*, 1986 (In press.)

Davis, K.L., Rosenberg, G.S. Is there a limbic system equivalent of tardive dyskinesia? *Biol. Psychiatry*, 14:699–703, 1979.

Gerlach, J. Tardive dyskinesia. *Dan. Med. Bull.*, 26:209–254, 1979.

Klawans, H.L., Goetz, C.G., and Perlik, S. Tardive dyskinesia: Review and update. *Am. J. Psychiatry*, 137:900–908, 1980.

Meltzer, H.Y., and Fang, V.S. The effect of neuroleptics on serum prolactin in schizophrenic patients. *Arch. Gen. Psychiatry*, 33:279–286, 1976.

Overall, J.E. The Brief Psychiatric Rating Scale in psychopharmacology research. In: Pichot, P. (ed.), *Psychiatry*. Basel: Karger, 1974, pp. 67–78.

Ungerstedt, U., and Ljundberg, T. Behavioral patterns related to dopamine neurotransmitters: Effect of acute and chronic antipsychotic drugs. *Adv. Biochem. Pharmacol.*, 16:193–220, 1977.

Basic and Clinical Studies of Neuroleptic-Induced Supersensitivity Psychosis and Dyskinesia

Bruce I. Diamond, Ph.D.,[1] and Richard L. Borison, M.D., Ph.D.[1]

Introduction

Chronic neuroleptic treatment can induce a supersensitivity psychosis either when dosage is decreased or discontinued (Chouinard et al., 1978). Analogous to striatal dopamine (DA) receptor supersensitivity underlying tardive dyskinesia supersensitivity psychosis have been postulated to result from mesolimbic DA receptor supersensitivity (Chouinard & Jones, 1980; Davis & Rosenberg, 1979). In animals, striatal DA supersensitivity in response to chronic neuroleptics has been demonstrated behaviorally (Christensen et al., 1976) and by receptor binding studies (Burt et al., 1977). Davis et al. (1978) has shown that DA receptor supersensitivity after chronic neuroleptic treatment also occurs in the mesolimbic system in animals.

Clinically, if neuroleptic treatment results in mesolimbic DA supersensitivity then, according to Davis and Rosenberg (1979), tolerance should develop to antipsychotic drug effects, withdrawal of neuroleptics should result in a rapid relapse, and psychosis should develop in nonschizophrenic patients treated with neuroleptics. Tolerance (Chouinard et al., 1978), rapid relapse (Chouinard & Jones, 1980; Ekblom et al., 1984), and psychosis in nonschizophrenic individuals as a result of neuroleptic treatment have been shown (Sale & Dristall, 1978; Witschy et al., 1984).

Other issues surrounding supersensitivity psychosis include the effects of anticholinergic drug activity on withdrawal symptomatology, the association of supersensitivity psychosis with tardive dyskinesia, and the development of DA supersensitivity in the tuberoinfundibular system. Luchins et al. (1980) and LaCoursiere et al. (1976) attribute the withdrawal symptoms of restlessness, agitation, insomnia, and anxiety to cessation of anticholinergic effects. However, there is no doubt that high potency neuroleptics without anticholinergic activity can produce withdrawal symptoms (LaCoursiere et al., 1975) and, in fact, neuroleptics with anticholinergic properties may show even less withdrawal symptoms due to a cholinergic rebound (Chouinard & Jones, 1982).

The proposal that both supersensitivity psychosis and tardive dyskinesia are the result of neuroleptic-induced supersensitive DA receptor sites in different brain regions argues in favor of their coexistence within the same individual. Notwithstanding, it has been suggested (Chouinard & Jones, 1982) that supersensitivity psychosis occurs in good prognostic patients while tardive dyskinesia occurs more often in patients with poor prognosis. Moreover, high prolactin levels have been proposed to be associated with supersensitivity psychosis (Chouinard & Jones, 1980). Thus, in this paper both basic and clinical studies were performed to help elucidate neuroleptic-induced DA supersensitivity psychosis.

Methods

Basic Studies

In order to determine the effectiveness of different neuroleptics to act on striatal and mesolimbic DA receptor functions, animal studies were performed. Sprague-Dawley male rats (250–300 g) housed individually with free access to food and water were used. Under pentobarbital anesthesia (35 mg/kg; i.p.) bilateral stainless steel cannulae were placed into either the caudate nucleus or nu-

---

[1] Medical College of Georgia, Department of Psychiatry, Augusta, GA 30912, and Veterans Administration Medical Center, Augusta, GA 30910.

Send correspondence to: Bruce I. Diamond, Ph.D., Department of Psychiatry, Medical College of Georgia, Augusta, GA 30912.

cleus accumbens using the coordinates from the atlas of Pelligrino and Cushman (1967). Drug infusions (0.5 ml/min) were made using a microliter syringe in freely moving animals and behavior quantitated by rating scales (Diamond et al., 1984).

In other studies 14–day (i.p.) treatment with either clozapine (20 mg/kg) or chlorpromazine (30 mg/kg) to rats receiving amphetamine (AMP) (3.7 mg/kg; i.p.) for 6 weeks (3 weeks prior to, 2 weeks during, and 1 week after neuroleptic treatment) was conducted. Stereotype behavior was quantitated before, during, and after neuroleptic treatment.

Clinical Studies

Twenty-three chronic schizophrenic male patients, after signing informed consents, participated in these studies. The patients were stable for at least 2 months on various neuroleptics. The age range was 34 to 56 years with a mean age of 42.6 years. In one study antipsychotic medication was abruptly discontinued in 12 patients. After a week washout clozapine was administered for 9 weeks which included a 5-day buildup to 200 mg daily. Another 1-week washout period followed the clozapine treatment.

In the other study seven patients were receiving thioridazine and four were receiving haloperidol. Four patients were on 800 mg/day, one on 400 mg/day, and two on 150 mg/day of thioridazine while one was on 25 mg/day, two on 15 mg/day, and one on 2 mg/day of haloperidol. Thioridazine and haloperidol were discontinued by gradually reducing the dosage. Patients remained drug-free for 5 days followed by reinstatement of the original drug and dosage.

In both studies psychopathology was evaluated and rated using the Brief Psychiatric Rating Scale (BPRS) and tardive dyskinesia by the Abnormal Involuntary Movement Scale (AIMS). In some patients serum prolactin was measured using radioimmunoassay.

Results

Basic Studies

The administration of DA (100 mcg) into the nucleus accumbens of rats produced an increase in locomotor behavior. These animals made 35 ± 6 crossings in 10 minutes compared to 12 ± 3 crossings for saline controls. When DA was applied to the caudate nucleus animals exhibited stereotyped grooming, sniffing, headbobbing, and gnawing. They were rated 3.5 ± 0.4 during the subsequent 30-minute period. Pretreatment with systemic clozapine and thioridazine inhibited, in a dose related manner, intralimbic locomotion induced by DA (Table 1). Haloperidol (0.2 to 1 mg/kg) did not demonstrate this dose effect with the doses used. In contrast, haloperidol did show a dose-related inhibition of stereotypy when DA was applied to the caudate nucleus (Table 1). Similar results (Table 1) also were observed for clozapine and thioridazine in striatal DA mediated stereotyped behavior. Thus, as can be readily observed from Table 1 all three neuroleptic drugs preferentially inhibit limbic before striatal DA effects.

In animals treated chronically with AMP, stereotypy scores before neuroleptic administration were 3.5 ± 0.2. Chlorpromazine treatment inhibited AMP stereotypy less effectively over the 14-day period (Table 2). Thus, tolerance appeared to develop. Although clozapine failed to significantly inhibit, AMP stereotypy the trend of tolerance was apparent (Table 2). Upon cessation of chlorpromazine there was a significant increase in AMP behavioral scores over pre-chlorproma-

TABLE 1. Percent Inhibition of Intracerebral Dopamine Effects.

Site	Clozapine			Thioridazine			Haloperidol		
	10	20 (mg/kg)	30	15	30 (mg/kg)	60	0.2	0.5 (mg/kg)	1
Nucleus Accumbens	50	80	100	47	60	100	100	100	100
Caudate Nucleus	20	45	70	23	48	100	50	72	100

TABLE 2. Inhibition (%) of Chronic Amphetamine Stereotypy.

	Pre-Drug Days	Drug Days			Drug Washout Days		
Treatment	1	1	7	14	1	3	7
Chlorpromazine (30 mg/kg)	0	76	59	40	+ 18	+ 15	0
Clozapine (20 mg/kg)	0	10	4	0	+ 3	0	0

+ Potentiation

zine ratings. This lasted for 3 days (Table 2). Clozapine withdrawal did not affect significantly AMP stereotypy (Table 2).

Clinical Studies

The mean BPRS score of the 12 clozapine patients during the washout period preceding the administration of clozapine was 26.2 ± 6.3. By the end of the first 2 weeks of clozapine treatment the mean score had fallen to 20.7 ± 6.8. This level of improvement continued throughout the clozapine treatment phase. At the end of the 1-week clozapine withdrawal period, the BPRS score was 30.3 ± 14.4. None of these mean BPRS scores were significantly different from each other. However, when the data were separated into those that exhibited a worsening of symptomatology following clozapine withdrawal, half the patients were worse after clozapine withdrawal. In fact, five of six patients that did not worsen had lower BPRS scores after clozapine withdrawal which ranged from 10 to 27 percent improvement over pre-clozapine scores. However, the average improvement was not statistically significant. In contrast, the group with higher post-clozapine BPRS scores from pre-clozapine scores showed a significant difference ($p \leq 0.05$). Four of these six patients demonstrated a greater than 20 percent worsening. The percent of worsening ranged from 17 to 126 percent. There were only 2 of 12 patients that had tardive dyskinesia. The AIMS score of these two patients was not modified by either clozapine treatment or withdrawal.

In Figures 1 and 2 the results of seven patients on thioridazine are shown. Only two patients had their BPRS score increase 20 percent or more when the dose of thioridazine was decreased. However, in six of seven patients, ratings of psychosis were worse during the drug washout period ($p \leq 0.025$). When the original dose of thioridazine was reinstated the mean BPRS score was within 6 percent of the original thioridazine baseline score. In fact, only two patients who got worse had scores above 10 percent of their original score. Patient G had an unusual and opposite effect when thioridazine was discontinued and reinstated (Figure 2).

Table 3 shows the mean and standard deviation of the BPRS score in four patients receiving haloperidol. When haloperidol was withdrawn, there was a significant increase ($p \leq 0.05$) in the BPRS score which returned to the pre-drug score when haloperidol was reinstated. Within this group of four patients reinstatement of the original dose of haloperidol did not modify the psychopathology observed during the washout period in one patient.

The discontinuation and reinstatement of thioridazine and haloperidol on dyskinesias

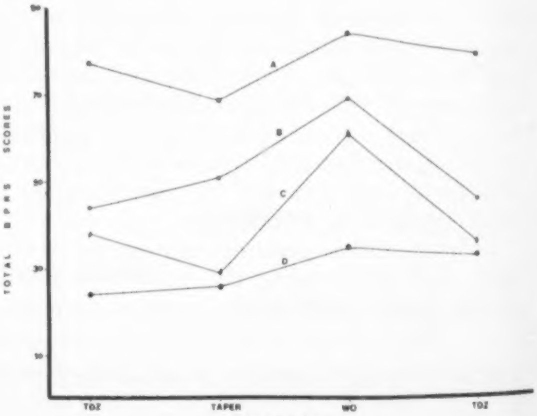


FIGURE 1. The total Brief Psychiatric Rating Scale (BPRS) score of four patients (A,B,C,D) on thioridazine (TDZ), during dose reduction (taper), washout (WO), and thioridazine reinstatement (TDZ).

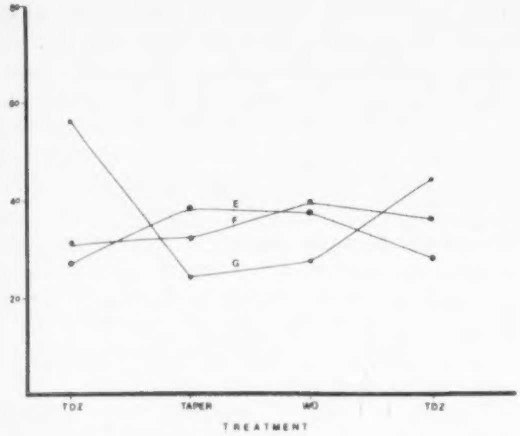


FIGURE 2. Patients (E,F,G) total Brief Psychiatric Rating Scale (BPRS) score on thioridazine, during dosage reduction (taper), washout (WO), and reinstatement of thioridazine (TDZ).

was not unusual except for two patients who improved when haloperidol was discontinued. These results are presented in Table 4.

If one compares the AIMS against the BPRS scores, there are only three cases where both did not worsen during drug withdrawal: two patients on haloperidol where the dyskinesias improved and one patient on thioridazine whose psychosis improved.

Serum prolactin was measured in patients on thioridazine, during washout and when the original thioridazine dose was reinstated. The mean serum prolactin level while on thioridazine was 20.0 ng/ml range 4.6 to 32.6 ng/ml. During the washout period mean prolactin levels fell to 5.5 ng/ml with a range between 4.6 to 6.6 ng/ml. When thioridazine was readministered at its original dose, serum prolactin levels were higher than the original drug period (32.7; range 9.9 to 51.7; ($p \leq 0.05$).

TABLE 3.

Treatment	BPRS ($\bar{X}$ ± S.D.) Scores
Haloperidol	33 ± 3.6
Dosage Taper	39 ± 12
Washout	51.2 ± 15
Reinstatement	35.5 ± 1.7

TABLE 4. Effect of Haloperidol and Thioridazine on Dyskinesia.

		AIMS Score		
Drug	Patient	Initial Dose	Washout	Reinstated Dose
Haloperidol	1	5	24	6
	2	5	7	5
	3	4	0	5
	4	2	0	2
Thioridazine	A	23	25	22
	B	3	10	2
	C	3	12	3
	D	6	10	5
	E	0	2	0
	F	0	4	0
	G	0	0	0

Discussion

Supersensitivity psychosis has been postulated to be the result of an underlying DA receptor site sensitivity in the mesolimbic system, whereas in tardive dyskinesia DA supersensitivity within the extrapyramidal system probably is the causative factor. Since neuroleptic drugs are dopamine receptor blockers, supersensitivity psychosis and dyskinesia should be produced equally by all neuroleptics. However, Chouinard and Jones (1982) suggest that neuroleptics with anticholinergic activity should mask the withdrawal psychosis and demonstrated that supersensitivity psychosis occurs with high potency neuroleptics (Chouinard & Jones, 1980). Notwithstanding, it has been reported (Ekblom et al., 1984) that clozapine, an antipsychotic drug with high anticholinergic activity, produces supersensitivity psychosis in schizophrenic patients. This same argument about the anticholinergic activity of neuroleptics or lack of it in individuals predisposed to tardive dyskinesia is often cited (APA Task Force, 1980). Thus, clozapine usage leads to few cases of tardive dyskinesia in contrast to high potency neuroleptics (Gerlack & Summelsgaard, 1978). The administration of clozapine, thioridazine, or haloperidol to the mesolimbic and striatal brain areas of rats, in this paper, demonstrated that the anticholinergic property of a neuroleptic is not important in blocking the effects of DA. The only difference between these three drugs was potency. However, clozapine never completely blocked DA in the striatal system. By extrapolation higher doses should, but in likelihood would exceed those concentrations used clinically. These results support receptor binding studies in human and rat brain where these neuroleptics, within a similar concentration range, inhibited ^{3}H-spiroperidol binding in the limbic system but not the extrapyramidal system (Borison et al., 1981). The failure of clozapine to significantly block chronic AMP stereotypy where striatal DA receptor site numbers are increased (Borison et al., 1979) supports the differential action of clozapine. Further evidence to support the fact that low and high potency neuroleptics are equipotent in inducing supersensitivity or mesolimbic psychosis are the results that clozapine, thioridazine, and haloperidol were capable of doing so in this study and clozapine (Ekblom et al., 1984) and fluphenazine (Chouinard & Jones, 1980) in other studies.

Features of supersensitivity psychosis include tolerance to antipsychotic drug effects and relapse after drug withdrawal (Davis & Rosenberg, 1979). Both of these effects were observed in rats chronically treated with AMP and administered either clozapine or chlorpromazine for 14 days (Table 2). The lack of significant antagonism and subsequent rebound increase in AMP stereotypy observed with clozapine is probably due to its absence of significant striatal DA blocking properties, since chronic amphetamine is known to produce striatal DA supersensitivity (Klawans & Rubovits, 1972). If one examines the effect of chlorpromazine withdrawal on AMP stereotypy there is not only a relapse but a rebound increase of behavioral stereotypy compared to pre-chlorpromazine scores. This rebound worsening or relapse occurs in the mesolimbic system and is supported clinically by the clozapine results whereby 50 percent of the patients exhibited worse BPRS scores after clozapine withdrawal.

The issue of relapse as a feature of supersensitivity psychosis is one surrounded by controversy, since a differentiation between the active underlying psychopathology and the drug effect has to be made. In Figures 1 and 2 patients A, B, and G had initial BPRS scores above 40 while on drug, indicative of active pathology. However, upon drug withdrawal patient G improved dramatically and worsened when thioridazine was reinstated. Obviously this patient did not have supersensitivity psychosis but a psychosis due to the drug. One patient after haloperidol withdrawal continually worsened even after haloperidol was reinstated. Ideally, supersensitivity psychosis drug withdrawal studies should be extended in a drug-free condition for as long as possible so that its course can be observed (Weinberger et al., 1981).

Tolerance was observed in patients (A,B,D,E,F) on thioridazine and one patient on haloperidol if one assumes that when the original dose was reinstated the BPRS scores were slightly higher than before drug discontinuation. This phenomenon of higher values on the same drug and dosage after washout compared to before washout was observed for prolactin levels in patients on thioridazine. Thus, it appears that in these patients supersensitivity develops in the tuberoinfundibular system as well.

If the pathology of tardive dyskinesia and supersensitivity psychosis differs only in the anatomical area involved, then patients with both should have concomitant changes in their BPRS and AIMS scores. Except for three patients this occurred. Unlike tardive dyskinesia, reports of supersensitivity psychosis are rare in individuals without schizophrenia. This may be due to the lack of knowledge about supersensitivity psychosis or that an abnormal DA state in the mesolimbic system is a necessary prerequisite for this to develop. However, animal studies argue against this latter point of view. There are several questions that are often asked about tardive dyskinesia, on the reversibility, incidence and other characteristics, that need to be also answered for supersensitivity psychosis by future studies.

References

American Psychiatric Association. *Tardive Dyskinesia.* Task Force report No. 18. Washington, D.C.: American Psychiatric Association, 1980.

Borison, R.L., Hitri, A., Klawans, H.L., and Diamond, B.I. A new animal model for schizophrenia: Behavioral and receptor binding studies. In: Usdin, E. (ed.), *Catecholamines: Basic and Clinical Frontiers*. New York: Pergamon Press, 1979, pp. 719–721.

Borison, R.L., Hitri, A., Blowers, A.J., and Diamond, B.I. Anti-psychotic drug action; clinical, biochemical, and pharmacological evidence for site specificity of action. *Clin. Neuropharm.*, 6(2):137–150, 1983

Burt, D.R., Creese, I., and Snyder, S.H. Antischizophrenic drugs: Chronic treatment elevates dopamine receptor binding in brain. *Science*, 196:321–326, 1977.

Chouinard, G., Jones, B.D., and Annable, L. Neuroleptic-induced supersensitivity psychosis. *Am. J. Psychiatry*, 135:1409–1410, 1978.

Chouinard, G., and Jones, B.D. Neuroleptic-induced supersensitivity psychosis: Clinical and pharmacological characteristics. *Am. J. Psychiatry*, 137(1):16–21, 1980.

Chouinard, G., and Jones, B.D. Neuroleptic-induced supersensitivity psychosis, the "Hump Course," and tardive dyskinesia. *J. Clin. Psychopharmacol.*, 2(2):143–144, 1982.

Christensen, A.V., Fjalland, G., and Moller-Nielsen, I. On the supersensitivity of dopamine receptors, induced by neuroleptics. *Psychopharmacol.*, 48:1–6, 1976.

Davis, K.L., Hollister, L.E., and Futz, W.C. Induction of dopaminergic mesolimbic receptor supersensitivity by haloperidol. *Life Sci.*, 23:1543–1546, 1978.

Davis, K.L., and Rosenberg, G.S. Is there a limbic system equivalent of tardive dyskinesia? *Biol. Psychiatry*, 14(4):699–703, 1979.

Diamond, B.I., Hitri, A., Shah, C., and Borison, R.L. Differentiation of phenylethylamine (PE)- and amphetamine (AMPH)-induced behaviors. In: Boulton, A.A., Baker, G.B., Dewhurst, W.G., and Sandler, M. (eds.), *Neurobiology of the Trace Amines*. Clifton: The Humana Press, 1984, pp. 375–388.

Ekblom, B., Eriksson, K., and Lindstrom, L.H. Supersensitivity Psychosis in schizophrenic patients after sudden clozapine withdrawal. *Psychopharmacol.*, 83:293–294, 1984.

Gerlach, J., and Simmelsgaard, H. Tardive Dyskinesia during and following treatment with haloperidol, haloperidol + biperiden, thioridazine and clozapine. *Psychopharmacol.*, 59:105–112, 1978.

Klawans, H.L., and Rubovits, R. An extrapyramidal model of tardive dyskinesia. *J. Neural Transm.*, 33:235–246, 1972.

LaCoursiere, R.B., Spohn, H.E., and Thompson, K. Medical effects of abrupt neuroleptic withdrawal. *Compr. Psychiatry*, 17:285–294, 1976.

Luchins, D.J., Freed, W.J., and Wyatt, R.J. The role of cholinergic supersensitivity in the medical symptoms associated with withdrawal of antipsychotic drugs. *Am. J. Psychiatry*, 137(11):1395–1398, 1980.

Pellegrino, L.J., and Cushman, A.J. *A Stereotaxic Atlas of the Rat Brain*. New York: Appleton-Century-Crofts, 1967.

Sale, I., and Kristall, H. Schizophrenia following withdrawal from chronic phenothiazine administration: A Case Report. *Aust. N.Z., J. Med.*, 12:73–75, 1978.

Weinberger, D.R., Llewellyn, B., Bigelow, B., et al. Drug withdrawal in chronic schizophrenic patients: in search of neuroleptic-induced supersensitivity psychosis. *J. Clin. Psychopharmacol.*, 1(3):120–123, 1981.

Witschy, J.K., Malone, G.L., and Holden, D.L. Psychosis after neuroleptic withdrawal in a manic-depressive patient. *Am. J. Psychiatry*, 141(1):105–106, 1984.

Recent Advances in HPA Physiology and Pathophysiology (II)

Chair:

Charles B. Nemeroff, M.D., Ph.D.

Duke University Medical Center
Durham, NC 27710

Corticotropin-Releasing Hormone—A New Tool to Investigate Hypothalamic-Pituitary-Adrenocortical Physiology in Psychiatric Patients

Florian Holsboer, M.D., Ph.D.[1]

The recent sequencing and subsequent synthesis of ovine corticotropin-releasing factor (o-CRF) by Vale et al. (1981) and its human analog by Shibahara et al. (1983) opened the possibility to study pathophysiology underlying several aberrancies of the pituitary-adrenocortical system in psychiatric illness. Since hypersecretion of corticosteroids represents one of the most extensively studied abnormalities among depressed patients, it was intended to investigate by means of o-CRF or human CRH infusions whether hypercortisolemia can be attributed to a central nervous system disturbance.

Clinical Studies Employing Ovine CRF

A dose of 100 µg ovine CRF was infused to eight drug-free patients with endogenous depression. Their maximum corticotropin (ACTH) output was indistinguishable from a comparison sample of normal controls (Holsboer, 1983; Holsboer et al., 1984a). This was taken as support that an enhanced responsiveness of pituitary corticotrophs at the anterior pituitary is not likely to account for excessive pituitary adrenal activity. The failure of a consistent relationship between response of ACTH and a variety of adrenal corticosteroids following 100 µg o-CRF given at 9 a.m. with a multisteroid assessment following synthetic ACTH and subsequently a 1 mg dexamethasone suppression test (DST) further corroborated that a central rather than a peripheral effect is the main factor responsible for HPA-overactivity (Holsboer et al., 1984a). Subsequently o-CRF responses of the pituitary-adrenal system were recorded in 16 depressed patients who were further classified according to their DST status, registered after the o-CRF challenge. The net ACTH and cortisol release pattern between DST suppressors and nonsuppressors was indistinguishable between both groups (Holsboer et al., 1984b). Also, o-CRF induced ACTH, cortisol and corticosterone output in eight depressed nonsuppressors on the DST was unchanged when these individuals were retested after return to euthymia and DST suppression (Holsboer et al., 1985a). Based on these findings, it was hypothesized that neither enhanced responsiveness of the pituitary nor the adrenal gland is a pathophysiological correlate of DST nonsuppression.

---

[1] Research Unit, Department of Psychiatry, University of Mainz, Langenbeckstrasse 1, 6500 Mainz, FRG.

Clinical Studies Employing Human CRH

When the human analog of CRF (h-CRH) became available in 1984 the study protocol was changed and the h-CRH infusions were performed at 7 p.m. This study design promised to reveal more subtle differences in hormonal response, since Copinschi et al. (1983) suggested that CRH stimulation tests performed during the quiescent period of the pituitary-adrenal system may be advantageous to discriminate between normal and subnormal corticotropic function.

After a standard calorie and electrolyte balanced lunch at 11:30 a.m., all depressed patients and normal controls received an intravenous catheter connected with an extension through a sound proof lock into an adjacent room where plasma for cortisol analysis was collected every 20 minutes between 2 p.m. and 7 p.m. At 7 p.m., 100 μg h-CRH reconstituted in 1 ml 0.02 percent HC1 in 0.9 percent saline was directly injected into the cannula and plasma for ACTH and cortisol assessment was sampled according to the time points given in Figure 1. The major finding of this study was a blunted response of ACTH in depressives, which was associated with enhanced release of baseline cortisol levels prior to h-CRH infusion (Holsboer et al., 1984c). Interestingly, the cortisol release patterns remained indistinguishable between both comparison groups, indicating that after prolonged hyperstimulation by ACTH and possibly by other adrenal growth factors the adrenocortical cells may develop a mild functional hyperplasia. Such a phenomenon is also present in endocrine diseases associated with an ACTH excess such as ACTH-dependent Cushing-syndrome or congenital adrenal hyperplasia. These study results were amplified by the data of Gold et al. (1984) who reported in their comprehensive review that following ovine CRF, depressives have an attenuated ACTH response when contrasted to manics, schizophrenics, or normal controls. Since there is evidence that aldosterone regulation is impaired in depression (Hullin et al., 1981; Holsboer et al., 1982) a study was conducted which compared aldosterone response to h-CRH in eight depressives and eight matched controls with ACTH, cortisol, and corticosterone response. In agreement with previous studies from our laboratory (Holsboer et al., 1984c, Holsboer et al., 1986a) and those by Gold et al. (1984) ACTH output was decreased in depressives, while cortisol and corticosterone release was normal. However, we found a significantly blunted aldosterone release induced by h-CRH (Figure 2). Differential effects of h-CRH to glucocorticoid and mineralocorticoid release may provide a clue to understanding the reported disturbance of electrolyte homeostasis in patients with affective disorder.

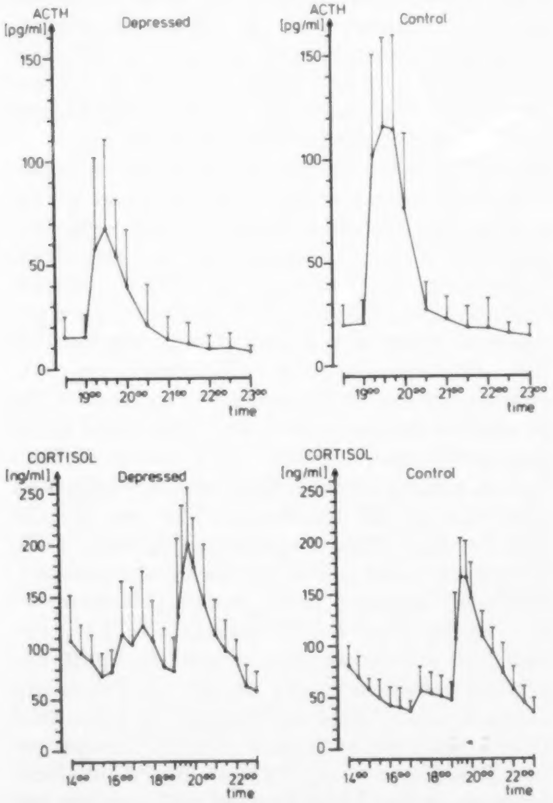


FIGURE 1. Effect of h-CRH on plasma ACTH and cortisol release in normal controls and depressed patients.

h-CRH-Challenges in Dexamethasone Treated Depressives and Controls

DST nonsuppression of ACTH and cortisol was originally regarded as a peripheral outprint of a centrally mediated overdrive of

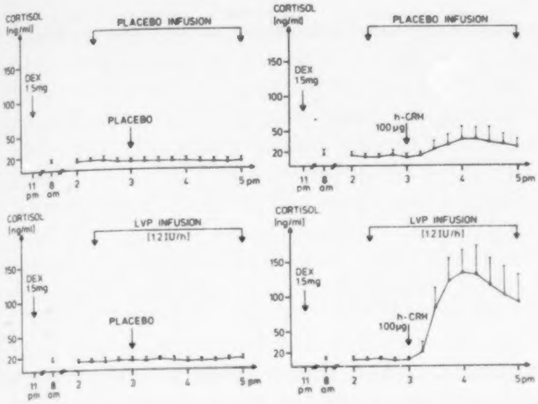


FIGURE 2. Effect of placebo, h-CRH, LVP, and a combined h-CRH/LVP administration upon plasma cortisol in normal controls pretreated with 1.5 mg dexamethasone.

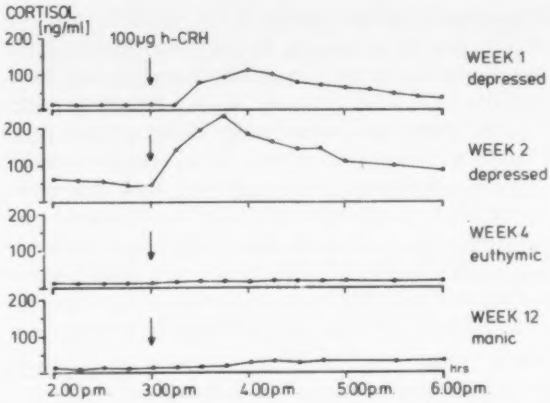


FIGURE 3. Plasma cortisol response in a dexamethasone pretreated patient following h-CRH at different clinical conditions.

CRH (Carroll et al., 1976). To further explore the pathophysiology underlying DST resistant cortisol levels in depression we compared pituitary-adrenal response to placebo, h-CRH or lysine vasopressin (LVP) with a concurrent application of both neuropeptides after pretreatment with 1.5 mg dexamethasone in six normal male controls (von Bardeleben et al., 1985). As shown in Figure 3, LVP infusion (1.2 IU/h) given in the afternoon failed to provoke ACTH and cortisol elevation. Also an h-CRH bolus administered at 3 p.m. induced only a modest release of ACTH and cortisol above hormone levels observed after placebo infusion. However, if both peptides were administered in combination, a substantial escape of plasma cortisol from dexamethasone suppression became apparent. Since ACTH levels increased in parallel with cortisol it was concluded that LVP synergizes the effect of h-CRH at pituitary corticotrophs to override dexamethasone suppression. In line with this finding is a recent study by Nemeroff et al. (1984) who measured CRH in cerebrospinal fluid and observed elevated levels in major depression which were not related to their DST status. This questions that elevation of CRH alone is sufficient to explain DST resistance and suggests that other factors including synergizing neuropeptides, activity of neural pathways and changes at feedback receptor levels are corequired.

In contrast to normal controls, depressed patients pretreated with dexamethasone responded to CRH with increased cortisol release (Figure 4). This phenomenon was observed in DST suppressors as well as in DST resistant patients. When retesting these individuals several times during the course of their illness and again either following recovery or a switch into mania, it was observed that h-CRH gradually failed to produce cortisol surges after depressive symptomatology has entirely resolved. Whereas in normals the dexamethasone bioavailability achieved by administering 1.5 mg dexamethasone is obviously sufficient to prevent pituitary-adrenal stimulation by CRH, this seems not to be the case for depressives, even if dexamethasone plasma concentrations add to nonsuppressed endogenous cortisol levels. This suggested that in depression the negative feedback receptors at the pituitary, the hypothalamus and the hippocampus, become subsensitive to corticosteroids in depressed patients. When central regulation returns to normalcy there is a stepwise increase of receptor sensitivity resulting in an adrenocortical response to CRH which is indistinguishable from that in normal controls. This tentative conclusion is in line with several recent observations. Carr et al. (1984) reported a paradoxical increase in ACTH levels after infusion of cortisol to endogenously depressed patients indicating that glucocorticoids may produce stimulatory as well as inhibitory effects on ACTH release. While active stress or steroid administration is able to decrease the corticotrophic cell sensitivity to CRH, chronic stress leads to normal or increased sensitivity. Young and Akil (1985) employed anterior lobe cultures from chronically stressed rats and showed that subsensitivity to steroid negative feedback at the pituitary can develop since these animals release increased ACTH after CRH and have increased ACTH pituitary contents despite the known inhibitory effects of corticosteroids upon ACTH biosynthesis and release. In addition McEwen (1985) has recently reviewed the diverse regulatory effects which glucocorticoids exert upon brain neurotransmission and emphasized that the hippocampus, which is an important site for glucocorticoid negative feedback, develops subsensitivity to these steroids following prolonged overexposure. Conceivably then, hypercortisolemia may induce a neuronal loss of steroid sensitive receptors reducing its suppressing inputs upon CRH-ACTH release. Mechanisms of this kind may have considerable physiological significance to explain several different though overlapping phenomena of pituitary-adrenocortical disturbance including hypersecretion of cortisol and abnormal responses to dexamethasone or to a combined h-CRH/DST administration.

h-CRH-Induced Changes of Thyroid Function

Multiple endocrine perturbation tests may provide a set of variables which allows profiling of neural function. This rationale is limited if several neuroendocrine systems would be independent from each other. Besides abnormalities of the pituitary-adrenocortical axis, the reduced thyrotropin (TSH) response following infusion of thyrotropin-releasing hormone (TRH) constitutes the most extensively studied endocrine disturbance among depressives (Loosen and Prange, 1982). We compared ACTH responses following 100 μg h-CRH with TSH responses to 500 μg TRH in 11 patients with major endogenous depression and 11 normal controls (Holsboer et al., 1985b). The time difference between both tests was at least 2 days and basal thyroid status revealed euthyroidism. In agreement with current literature lower TSH output expressed as area under time course curve was found in depressives when compared with controls. A Spearman rank correlation of TSH and ACTH output following specific secretagogues revealed statistical significance ($r = 0.65$, $p < 0.01$). After challenging the pituitary-adrenal axis during sleep with a total of 200 μg CRH during 4 hours (10 p.m. – 1 a.m.), TRH-tests, which revealed that after h-CRH prestimulation TSH responses are blunted, were performed the next morning. These data suggest that the thyroid axis is not independent from pituitary-adrenal activity. Both endocrine axes seem to be, at least in part, under a common control.

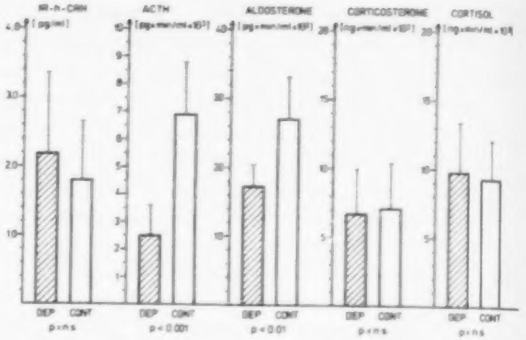


FIGURE 4. ACTH, glucocorticoid, and mineralocorticoid responses (expressed as areas under time course curves ± SD) to h-CRH in normal controls and depressed subjects. Plasma CRH levels measured 15 min after injection were indistinguishable between groups.

h-CRH Induced Sleep-Endocrine Changes

The sleep related secretion of human growth hormone (h-GH) during the first half of total sleep period is regulated by an intrinsic central nervous system mechanism whose precise nature is unknown. At the same time period when nocturnal growth hormone secretion reaches its maximum the cortisol secretion approaches its nadir. Clinical states which are associated with increased levels of endogenous or exogenous corticosteroids are frequently characterized by decreased pituitary growth hormone reserve. To further investigate the interdependency between the physiological growth hormone surge during sleep and pituitary-adrenal activity, 50 μg h-

CRH or placebo was infused four times every hour beginning at 10 p.m. to normal controls, who were adapted to the sleep laboratory and who fell asleep between 11 p.m. and midnight. Blood was drawn every 20 minutes until 7 a.m. to measure cortisol and h-GH. The major finding of this study was a significant blunting of sleep-related h-GH release, indicating that a pituitary-adrenocortical activity may modulate growth hormone release induced by falling asleep. No immediate effects of repetitive h-CRH stimulations upon major sleep characteristics during the first part of the night were observed. However, in the second part of the night, a marked reduction of REM sleep and stages 3 and 4 was recorded, whereas stages 1 and 2 increased. Similarly, Ehlers et al. (1986) showed that in rats an intracerebroventricularly administered dose of h-CRH reduces slow wave sleep drastically and increases the higher frequency contents. The present observation of a more shallow sleep after h-CRH as opposed to placebo suggests that peripheral hormonal overactivity of the pituitary-adrenocortex system contributes to the behavioral phenomena which are experimentally and perhaps also physiologically evoked by central CRH.

References

Carr, D.B., Wool, C., Lydiard, R.B., et al. Rate-sensitive inhibition of ACTH release in depression. *Amer. J. Psychiatry*, 141:590–592, 1984.

Carroll, B.J., Curtis, G.C., and Mendels, J. Neuroendocrine regulation in depression. I. Limbic-system-adrenocortical dysfunction. *Arch. Gen. Psychiatry*, 33:1039–1044, 1976.

Copinschi, G., Beyloos, M., Bosson, D., et al. Immediate and delayed alterations of adrenocorticotropin and cortisol nyctohermal profiles after corticotropin-releasing factor in normal man. *J. Clin. Endocrinol. Metab.*, 57:1287–1291, 1983.

Ehlers, C.L., Reed, T.K., and Henriksen, S.J. Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. *Neuroendocrinology*, 42:467–474, 1986.

Gold, P.W., Chrousos, G., Kellner, C., et al. Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Amer. J. Psychiatry*, 141:619–627, 1984.

Holsboer, F., Doerr, H.G., and Sippell, W.G. Blunted aldosterone response for dexamethasone in female patients with endogenous depression. *Psychoneuroendocrinol.*, 7:155–162, 1982.

Holsboer, F. Prediction of clinical course by dexamethasone suppression test (DST) response in depressed patients—physiological and clinical construct validity of the DST. *Pharmacopsychiat.*, 16:186–191, 1983.

Holsboer, F., Müller, O.A., Doerr, H.G., et al. ACTH and multisteroid responses to corticotropin-releasing factor in depressive illness: Relationship to multisteroid responses after ACTH stimulation and dexamethasone suppression. *Psychoneuroendocrinol.*, 9:147–160, 1984a.

Holsboer, F., Gerken, A., Steiger, A., et al. Corticotropin-releasing factor induced pituitary-adrenal response in depression. *Lancet*, I:55, 1984b.

Holsboer, F., von Bardeleben, U., Gerken, A., et al. Blunted corticotropin and normal cortisol response to human corticotropin releasing factor (h-CRF) in depression. *New Engl. J. Med.*, 311:1127, 1984c.

Holsboer, F., Gerken, A., Stalla, G.K., and Müller, O.A. ACTH, cortisol and corticosterone output after ovine corticotropin-releasing factor challenge during depression and after recovery. *Biol. Psychiatry*, 20:276–286, 1985a.

Holsboer, F., Gerken, A., von Bardeleben, U., et al. Relationship between pituitary responses to human corticotropin-releasing factor and thyrotropin-releasing hormone in depressives and normal controls. *Europ. J. Pharmacol.*, 110:153–154, 1985b.

Holsboer, F., Gerken, A., von Bardeleben, U., et al. Human corticotropin-releasing hormone in depression—correlation with thyrotropin-secretion following thyrotropin releasing hormone. *Biol. Psychiatry*, 21:601–611, 1986.

Hullin, R.P., Levell, M.J., O'Brien, M.J., and Toumba, K.J. Inhibition of in vitro production of aldosterone by manic-depressive sera. *Brit. J. Psychiatry*, 183:373–380, 1981.

Loosen, P.T., and Prange, A.J., Jr. Serum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: A review. *Amer. J. Psychiatry*, 139:405–416, 1982.

McEwen, B.S. Steroids and brain function. *Trends in Pharmacol. Sci.*, 65:23–26, 1985.

Nemeroff, C.B., Widerlöv, E., Bissette, G., et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science*, 226:1342–1344, 1984.

Shibahara, S., Morimoto, Y., Furutani, Y., et al. Isolation and sequence analysis of the human corticotropin-releasing factor precursor gene. *EMBO J.*, 2:775–779, 1983.

Vale, W., Spiess, J., Rivier, C., and Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science*, 213:1341–1397, 1981.

Von Bardeleben, U., Holsboer, F., Stalla, G.K., and Müller, O.A. Combined administration of human corticotropin-releasing factor and lysine vasopressin induces cortisol escape from dexamethasone suppression in healthy subjects. *Life Sciences*, 37:1613–1618, 1985.

Young, E.A., and Akil, H. Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: Effects of acute and chronic stress. *Endocrinol.*, 117:23–30, 1985.

Multiendocrine Assessment in the Dexamethasone Suppression Test

S. Craig Risch, M.D.,[1] David S. Janowsky, M.D.,[1] Lewis L. Judd, M.D.J.,[1] Christian Gillin, M.D.,[1] Mariam Mott,[1] Jeffrey L. Rausch, M.D.,[1] and Leighton Y. Huey, M.D.[1]

Introduction

Adrenal cortisol hypersecretion, as well as flattened cortisol circadian periodicity, and failure to suppress plasma cortisol concentrations with the overnight low-dose Dexamethasone Suppression Test (DST), occur in a significant number of endogenously depressed patients, and have now been well established as substantive neuroendocrine markers highly specific for primary affective disorders (Stokes et al., 1975; Carroll et al., 1976*a*, 1976*b*, 1981; Sachar, 1976; Brown et al., 1979; Sachar et al., 1980; Schlesser et al., 1980). Many investigators also believe that this neuroendocrine abnormality reflects limbic-hypothalamic-hypophyseal hyperactivity.

In this regard, Fang et al. (1981) and Reus et al. (1982) have recently reported that although dexamethasone-resistant depressed patients did not differ statistically from dexamethasone-sensitive depressed patients in pre-dexamethasone plasma adrenocorticotrophic hormone (ACTH) concentrations, the dexamethasone-resistant depressed patients did have significantly higher post-dexamethasone plasma ACTH concentrations than did the dexamethasone-sensitive patients. Kalin et al. (1982) reported that dexamethasone-resistant patients have significantly higher pre- and post-dexamethasone plasma ACTH concentrations than do dexamethasone-sensitive patients.

Yerevanian et al. (1983) failed to demonstrate differences in ACTH plasma concentrations at 4 p.m. or 11 p.m. after dexamethasone in 19 normal volunteers, 10 depressed suppressors, and 19 depressed nonsuppressors. However, they interpreted this lack of significant group differences as reflecting of great interindividual variation in adrenal sensitivity to circulating ACTH among the subjects within each group. In a later study, this group (Yerevanian et al., 1983) reported that among 16 patients with major depressive disorder who were nonsuppressors on the DST upon hospital admission, that there was a significant reduction in plasma ACTH concentrations in patients whose DST normalized with clinical recovery, while ACTH levels remained high in the group that continued to be nonsuppressors.

Thus, these studies suggest that ACTH levels may be elevated in dexamethasone nonsuppressors and that monitoring plasma ACTH concentrations in the DST might be clinically useful.

In addition to suppressing plasma concentrations of cortisol and ACTH, dexamethasone also suppresses plasma concentrations of prolactin. Thus, Meltzer et al. (1982) monitored the plasma prolactin response to dexamethasone in 52 psychiatric patients and reported a significant association between nonsuppression of plasma cortisol and prolactin after administration of dexamethasone.

Thus, we have been studying the clinical utility of monitoring plasma ACTH and prolactin concentrations before and after dexamethasone in psychiatric inpatients on our Affective Disorders Unit at the San Diego Veterans Administration Hospital.

Methods

These studies were conducted with the local human subjects committee approval. All subjects gave written, informed consent. All subjects were male and there were no significant differences in age composition among

---

[1] Department of Psychiatry, School of Medicine, University of California, San Diego, M-003, La Jolla, CA 92093; and San Diego Veterans Administration Medical Center, La Jolla, CA 92161.

experimental and control groups. All subjects received a Schedule of Affective Disorder and Schizophrenia (SADS) and Research Diagnostic Criteria (RDC) diagnosis based on an interview by an experienced diagnostician and collateral information obtained from previous hospitalizations, medical records, and interviews with family members. Diagnostic breakdown of the 28 subjects was as follows: schizoaffective depression = 3, major depression = 10, minor depression = 3, bipolar depression = 4, other = 4, bipolar manic = 3, and schizoaffective manic = 1. No subjects were receiving medications or had medical illness known to interfere with the DST. All subjects were inpatients on the Affective Disorders Clinical Research Unit of the San Diego Veterans Administration Hospital. All subjects received the standard DST as described by Carroll and colleagues (1981). Blood samples for plasma cortisol determinations were obtained at 0800, 1600, and 2300 before and after the 1 mg DST. Blood samples for plasma ACTH and prolactin determinations were only obtained at 0800 and 1600 before and after the DST. Blood was collected in polypropylene EDTA tubes on ice and promptly centrifuged at 10,000 rpm for 20 minutes in a refrigerated centrifuge and plasma was stored in a −80 degree°C freezer until assayed. Subjects whose plasma cortisol concentrations exceeded 5 ug/dl at 0800, 1600, or 2300 after dexamethasone were classified as nonsuppressors.

Assay Procedures

Plasma cortisol concentrations for the DST's were performed in the SDVAMC clinical laboratory using the Becton Dickinson I (125) Cortisol ARIA II System.

Assay sensitivity is 2 μg/dl and upper limit is 64 μg/dl. The intra-assay coefficient of variation is 4.8 to 5.9 percent and the interassay coefficient of variation is 4.9 to 8.6 percent.

Plasma ACTH measurements employed a sensitive RIA system developed and described by Orth and coworkers. This well characterized antiserum has a high affinity ($K_d > 1.07 \times 10^{-12}$ M/liter) and is now commercially available from the IgG Corporation. The antiserum is of polyclonal origin yet it is specifically directed at the steroidogenic NH_2-terminal (1–24) sequence of the whole (1–39) ACTH molecule. Thus, it does not react with nonsteroidogenic COOH-terminal fragments of ACTH that can be found in circulating blood. The optimized RIA system is capable of detecting as little as 5 pg/ml of immunoreactive ATCH while maintaining a working range of 0.5 to 75 pg/tube with excellent precision throughout the standard curve. The working standard ACTH reference preparation for this assay is the synthetic human (1–39) sequence of adrenocorticotropin which is available from Dr. Salvatore Raiti at the National Hormone and Pituitary Program (NIADDK).

Plasma prolactin concentrations were determined in duplicate using a RIA with reagents purchased from Calibiochem Corp. (La Jolla, CA). The double antibody technique was used with human PRL for iodination and standards, and with a rabbit antihuman PRL antibody. The sensitivity of the assay is 0.8 ng/ml with intraassay variation of 5 percent and interassay variation of 8 percent.

Pre-dexamethasone basal and post-dexamethasone changes in neuroendocrine plasma concentrations among groups were determined by mixed analysis of variance. Both raw scores and log transformed neuroendocrine concentrations were analyzed. "Cut-points" using a computerized program derived from Fisher's Exact Test were used to determine sensitivity and specificity of different neuroendocrine changes among groups. Pearson product moment correlations were performed on pre- and post-dexamethasone plasma cortisol, prolactin, and ACTH values.

Results

As expected, in the subject group as a whole, dexamethasone suppressed plasma concentrations of cortisol, prolactin, and ACTH (Table 1).

Subjects were grouped as dexamethasone suppressors or nonsuppressors using post-dexamethasone cortisol values of 5 μg/dl as the discriminating cut-points. Pre- and post-dexamethasone prolactin and ACTH values were compared using a two-factor ANOVA

TABLE 1. Pre- and Post-Dexamethasone Means and Standard Errors for 28 Psychiatric Patients.

	Pre-Dexamethasone			Post-Dexamethasone			
	0800	1600	2300	0800	1600	2300	*p* Value
ACTH pg/ml (N = 25)	25.2 ± 2.9	23.8 ± 2.5	—	14.6 ± 1.7	14.6 ± 1.4	—	.0000
Prolactin ng/ml (N = 22)	16.9 ± 1.3	14.1 ± 1.2	—	12.6 ± 1.1	13.4 ± 1.0	—	.0000
Cortisol µg/dl (N = 24)	17.5 ± 1.2	11.8 ± 1.0	6.4 ± 1.5	3.2 ± 0.7	3.5 ± 0.6	3.2 ± 0.4	.0000

with one repeated measure to assess group differences (suppressors vs. nonsuppressors) over time.

No significant group-by-time interactions for ACTH or prolactin were found when all pre- and post-dexamethasone time points were used.

However, a significant group by time interaction was found for raw ACTH scores when the 2 post-dexamethasone times were compared for the 2 groups (Table 2) ($F(1,25) = 5.56, p < .05$) as well as log-transformed values ($F(1,25) = 10.00, p < .005$). No such significant interaction was found for prolactin.

Simple effects tests were performed post-hoc on ACTH values to determine if changes over time for each group and differences between groups at each time were significant.

No significant positive correlations were noted in pre-dexamethasone basal or post-dexamethasone changes among cortisol, prolactin, and ACTH.

A "cut-point" Fisher's Exact Test of ACTH 19.0 pg/ml at 1600 post-dexamethasone significantly differentiated bipolar depressed and major depressed patients from all other subjects (Table 3). A cut-point of cortisol 8.8 µg/dl, at 1600 pre-dexamethasone significantly differentiated bipolar depressed and major depressed patients from all other subjects (Table 3). Cut-points of prolactin 20.1 ng/ml at 0800 pre-dexamethasone and 14.6 ng/ml at 1600 post-dexamethasone significantly differentiated bipolar depressed and major depressed patients from all other subjects (Table 3).

TABLE 2. Post-Dexamethasone Means and Standard Errors for ACTH in Subjects Who Did and Did Not Suppress Cortisol.

	0800	1600	*N*	*F* Value	*p* Value
Suppressors	16.1 ± 2.3	14.4 ± 1.8	17	5.56*	.0265
Nonsuppressors	12.8 ± 2.0	16.2 ± 2.2	10		

*Reported *F* value (*df* = 1,25) is for the group by time interaction.

Discussion

These results parallel other reports that bipolar depressed and major depressive patients have significant abnormalities of anterior pituitary ACTH and prolactin, as well as adrenal cortisol, secretion. Specifically, abnormalities of ACTH suppressibility to dexamethasone was noted, and 1600 post-dexamethasone ACTH levels were better discriminators of bipolar depressed and major depressive disorder patients from other nosological types of patients in the subject group. Matthews et al. (1982) have similarly reported that post-dexamethasone plasma concentrations of anterior pituitary β-Endorphin-like immunoreactivity were better nosological discriminators than post-dexamethasone cortisol levels. These results also suggest that the abnormality in adrenal cortisol hypersecretion widely noted in melancholia, may

TABLE 3. Cut-points Obtained Using a Fisher's Exact Test That Differentiate Significantly Between Depressed and Nondepressed Patients.

	ACTH—1600 Post-Dexamethasone			
	≤ 19.0	> 19.0	*p* value	
Nondepressed	11	0	.030	Sensitivity = 38.5%
Depressed	8	5		Specificity = 100.0%
	Prolactin—0800 Baseline			
	≤ 20.1	> 20.1	*p* value	
Nondepressed	5	3	.049	Sensitivity = 100.0%
Depressed	12	0		Specificity = 37.5%
	Prolactin—1600 Post-Dexamethasone			
	≤ 14.6	> 14.6	*p* value	
Nondepressed	4	4	.010	Sensitivity = 100.0%
Depressed	14	0		Specificity = 50.0%
	Cortisol—1600 Baseline			
	≤ 8.8	> 8.8	*p* value	
Nondepressed	6	5	.043	Sensitivity = 90.0%
Depressed	1	9		Specificity = 54.5%

represent, at least in part, dysfunction at the pituitary or even more central levels.

Prolactin levels tended to be lower (Table 3) pre- and post-dexamethasone, in bipolar depressed and major depressive disorder patients than other nosological types of patients, as has been reported by others.

These results need replication with much larger sample sizes, but suggest to us that concomitant measurement of pituitary ACTH and prolactin (and β-Endorphin-like immunoreactivity in a previous study, Matthews et al., 1982) may be of clinical utility in improving the sensitivity and specificity of the DST, and in understanding neuroendocrine dysfunction in melancholia.

Summary

Plasma concentrations of ACTH and prolactin were measured at 0800 and 1600 before and after the standard 1 mg overnight DST. Dexamethasone suppressed plasma concentrations of ACTH, prolactin, and cortisol in the subject group as a whole. There was a significant group time interaction when post-dexamethasone ACTH concentrations were compared between DST suppressors and nonsuppressors. "Cut Points" (Fisher's Exact Test) of plasma prolactin at 0800 pre-dexamethasone and at 1600 post-dexamethasone, of plasma ACTH at 1600 post-dexamethasone, and of plasma cortisol at 1600 pre-dexamethasone significantly differentiated patients with bipolar depressive disorder and major depressive disorder from other psychiatric patients. These pilot findings suggest that monitoring plasma prolactin and ACTH concentrations in the DST might increase the sensitivity and specificity of this laboratory test for melancholia.

Acknowledgments

This work was supported, in part, by the San Diego Veterans Administration Hospital, and grants MH 00393, MH 39113, and MH 30914.

References

Brown, W.A., Johnston, R., and Mayfield, D. The 24-hour dexamethasone suppression test in a clinical setting: Relationship to diagnosis symptoms, and response to treatment. *Am. J. Psychiat.*, 136:543–548, 1979.

Carroll, B.J., Curtis, G.C., and Mendels, J. Neuroendocrine regulation in depression: I. Limbic system-adrenocortical dysfunction. *Arch. Gen. Psychiatry*, 33:1039–1044, 1976*a*.

Carroll, B.J., Curtis, G.C., and Mendels, J. Neuroendocrine regulation in depression: II. Discrimination of depressed from nondepressed patients. *Arch. Gen. Psychiatry*, 33:1051–1058, 1976*b*.

Carroll, B.J., Feinberg, M., Greden, J.F., et al. A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. *Arch. Gen. Psychiatry*, 38:15–22, 1981.

Fang, V.S., Tricou, B.J., Robertson, A., and Meltzer, H.Y. Plasma ACTH and cortisol levels in depressed patients: relations to dexamethasone suppression test. *Life Sci.*, 29:931, 1981.

Kalin, N.H., Weiler, S.J., and Shelton, S.E. Plasma ACTH and cortisol concentrations before and after dexamethasone. *Psychiatry Research*, 7:87–91. 1982.

Matthews, J., Akil, H., Greden, J., and Watson, S. Plasma measures of B-Endorphin-Like Immunoreactivity in depressives and other psychiatric subjects. *Life Sci.*, 31:1867–1870, 1982.

Meltzer, H.Y., Fang V.S., Tricou, B.J., et al. Effects of dexamethasone on plasma prolactin and cortisol levels in psychiatric patients. *Am. J. Psychiat.*, 139:763–768, 1982.

Reus, V.I., Joseph, M.S., and Dallman, M.F. ATCH levels after the dexamethsone suppression test in depression. *N. Engl. J. Med.*, 306:238, 1982.

Sachar, E.J. Neuroendocrine dysfunction in depressive illness. *Ann. Rev. Med.*, 27:389, 1976.

Sachar, E.J., Asnis, G., Nathan, R.S., et al. Dextroamphetamine and cortisol in depression. *Arch. Gen. Psychiatry*, 37:755, 1980.

Schlesser, M.A., Winokur, G., and Sherman, B.M. Hypothalamic-pituitary-adrenal axis activity in depressive illness: Its relationship to classification. *Arch. Gen. Psychiatry*, 37:737–743, 1980.

Stokes, P.E., Pick, G.R., Stoll, P.M., and Nunn, W.D. Pituitary-adrenal function in depressed patients: resistance to dexamethasone suppression. *J. Psychiat. Res.*, 12:271, 1975.

Yerevanian, B.I., and Woolf, P.D. Plasma ACTH levels in primary depression: relationship to the 24 hour dexamethasone suppression test. *Psychiatry Research*, 9(1):45–51, 1983.

Yerevanian, B.I., Woolf, P.D., and Iker, H.P. Plasma ACTH levels in depression before and after recovery: relationship to the dexamethasone suppression test. *Psychiatry Research*, 10:175–181, 1983.

Recent Advances in Biomedical Research in Schizophrenia

Chair:

Robert O. Friedel, M.D.

Charter Medical Corporation
and Charter Westbrook Hospital
Richmond, VA 23227

Introduction

The prevalence of schizophrenia has been estimated to be approximately 0.6 to 0.8 percent of the population across most cultures studied. However, these numbers do not reflect the cost in human suffering, lost productivity, and medical and other expenses caused by this illness. In spite of the fact that there has not been a major breakthrough in our understanding of the etiologies or treatments of schizophrenia since the serendipitous discovery of chlorpromazine in 1954, there has been a steady advance in our knowledge in these areas. In addition, as a result of the recent application of sophisticated research methodologies and technologies, there has been a relative burst of new information coming from the field which has created renewed enthusiasm for and increased interest in research in schizophrenia. Most of these data support the contentions that schizophrenia has biological origins, may well involve a disturbance in function of one of the CNS dopaminergic pathways, and appears to result in the disturbance of certain functions of the prefrontal cortex.

The purposes of this panel were to present some of the most provocative and representative data of this type, and to provide a selective state-of-the-art review of the field.

I am indebted to Dr. Seymour Kety for helping me to think through the topics to be covered, though I am responsible for whatever biases and omissions resulted from the final selections.

The Genetics of Schizophrenia: A Current Perspective

Kenneth S. Kendler, M.D.[1]

This review will focus on recent work addressing four questions: 1) *is schizophrenia familial?* If schizophrenia is familial, 2) *to what extent is the familial aggregation of schizophrenia due to environmental versus genetic factors?* and 3) *what is transmitted within families that predisposes members to schizophrenia?* Finally, if genetic factors play an important role in the familial transmission of schizophrenia, 4) *what is their mode of genetic transmission?*

Over 25 family studies published before 1980 have all suggested that schizophrenia strongly aggregates in families. However, nearly all of these studies had three important methodologic limitations: 1) no control groups were used, 2) diagnoses were made nonblind, and 3) neither structured personal interviews nor operationalized diagnostic criteria were used.

These limitations and the demonstration in small uncontrolled samples of low degrees of familial aggregation for schizophrenia have raised questions whether schizophrenia, when carefully or "narrowly" diagnosed, is indeed a familial disorder. Since 1980, four major studies meeting most or all of these methodologic criteria have been performed which permit an evaluation of these claims. These studies, performed in Switzerland (Scharfetter & Nusperli, 1980), Iowa (Tsuang et al., 1980; Kendler et al., 1985), St. Louis (Guze et al., 1983), and New York (Baron et al., 1985), have all found a highly significant excess risk for schizophrenia in the relatives of schizophrenic probands compared to relatives of either psychiatric or normal control groups. Three of these studies used narrow criteria for schizophrenia. Results of recent more methodologically rigorous family studies have replicated earlier findings in suggesting that schizophrenia, even when "narrowly" diagnosed, is indeed a familial disorder.

A major goal of genetic epidemiology is to discriminate for familial disorders the degree to which familial transmission is due to genetic versus nongenetic mechanisms. For schizophrenia the great bulk of our knowledge about this problem comes from twin and adoption studies.

The last 5 years have seen two important advances in our understanding of twin studies of schizophrenia. Twin studies have often been faulted because of the "equal environment assumption," that is, that monozygotic (MZ) and dizygotic (DZ) twins are exposed to approximately equal environments. Studies have shown that for many social variables, the environment is more similar for MZ than for DZ twins. While this may invalidate twin studies, another interpretation is possible. The similarity in behavior of MZ twins might *create* for themselves more similar environments. As recently reviewed (Kendler et al., 1983), these two alternative hypotheses have been subject to empirical test in at least nine different studies. Consistently, these studies suggest that the environmental similarity of MZ twins is the *result* and not the cause of their behavioral similarity. Current evidence supports the validity of the equal environment assumption of twin studies.

Twelve major twin studies of schizophrenia have been performed to date. None of these studies meet all the methodologic criteria outlined above for family studies and an additional criterion that zygosity assignment be made blind with respect to psychiatric diagnosis. A major problem in interpretation of these studies stems from the fact that they vary considerably in the mode of selection of proband twins and diagnostic criteria applied. Taking advantage of the fact that these differences should equally affect MZ and DZ concordance rates, it is possible to compare across twin studies by using genetic models which take into account concordance rates for both twin types. When one such model (the multifactorial threshold model) is applied, substantial agreement was found across all major twin studies of schizophrenia (Kendler, 1983). The heritability of liability of schizophrenia was found to range in nearly all studies from 0.6 to 0.9. Twin studies consistently suggest that genetic factors play a major role in the familial transmission of schizophrenia. These figures are reassuringly similar to those obtained fitting path analytic models to the transmission of schizophrenia in twins and a wide variety of nontwin relationships.

---

[1] Associate Professor, Departments of Psychiatry and Human Genetics, Medical College of Virginia/Virginia Commonwealth University. Mailing address: Dept. Psychiatry, MCV PO Box 710, Richmond VA 23298.

Regarding adoption studies of schizophrenia, the major advance in the last 5 years has been the application of operationalized diagnostic criteria to previously collected samples. The study of the adopted-away offspring of schizophrenic and control parents performed in Denmark by Rosenthal and coworkers has been reanalyzed by Lowing et al. (1983). Excluding many of the parents for whom the diagnosis was not secure, they nonetheless broadly reconfirmed the results of the original investigators. The famous Danish study of biologic and adoptive relatives of schizophrenic and control adoptees of Kety and coworkers has been subject to several reanalyses. The only complete analysis was performed using DSM-III criteria by Kendler and Gruenberg (1984). Their results replicated and extended all the major findings of Kety and coworkers.

Only one new adoption study of schizophrenia has been reported since 1980. Tienari and coworkers in Finland (1985) have collected the largest sample to date of adopted away offspring of schizophrenic and control parents. Preliminary results suggest that psychosis is significantly more common among the adopted away offspring of schizophrenic versus control parents. However, they also find a strong correlation between the psychiatric status of the adoptee and the functioning of the adoptive family. While this may be due to a disturbed adoptive family causing disturbance in the adoptee, it cannot as yet be ruled out that the reverse process is occurring; that is, that a disturbed adoptee is causing disturbance in the adoptive family.

On the level of psychopathological syndromes, four major hypotheses can be articulated about the form of liability to schizophrenia that is transmitted in families: 1) a general liability to all psychiatric illness, 2) a liability to poor psychosocial functioning, oddness, suspiciousness, etc., 3) a liability to psychosis, and 4) a specific liability only to classic schizophrenia. These hypotheses are useful because they generate specific predictions about the pattern of psychopathology that should be observed in families of schizophrenics.

While early family and adoption studies of schizophrenia provided clues to the validity of these four hypotheses, more definitive evaluation had to await the introduction of operationalized criteria, blind diagnosis, and normal control groups. The crucial comparison is between relatives of schizophrenics and a sample representative of the general population. Both of the two recent family studies containing such a control group and using DSM-III criteria (Baron et al., 1985; Kendler et al., 1985) found results clearly inconsistent with the first hypothesis. In both studies, no excess risk for affective illness, anxiety disorders, or alcoholism was found in the relatives of the schizophrenics versus controls. Similar results on a smaller sample size were found in the Copenhagen sample of the Danish adoption study (Kendler & Gruenberg, 1984) and in pilot data from the West of Ireland (Kendler et al., unpublished data). The familial liability to schizophrenia appears to possess some specificity.

As suggested by earlier studies, the more recent application of operationalized criteria has provided considerable support for the second hypothesis. Reanalyses of the Danish adoption samples (Lowing et al., 1983; Kendler & Gruenberg, 1984) found that, as defined by DSM-III, schizotypal, paranoid, and possibly schizoid personality disorder have a strong genetic relationship to schizophrenia. Three further investigations based on intact families have supported these findings. Two were done in New York, one employing the family history method (Kendler et al., 1984) and the other utilizing direct interviews (Baron et al., 1985). Both provided strong evidence for a familial relationship between schizophrenia and schizotypal and paranoid personality disorder. The third study comes from county Roscommon, Ireland (Kendler et al., unpublished data) where pilot data also show a significantly higher risk for schizotypal and paranoid personality disorders in interviewed first-degree relatives of schizophrenic versus control probands. All of these studies, of course, argue against the fourth hypothesis that the transmitted liability to schizophrenia is specific for only the chronic psychotic disorder.

Recent studies have also provided some support for the third hypothesis. In the large Iowa cohort, Kendler et al. (1985) found evidence for a familial link between DSM-III schizophrenia and schizoaffective disorder, atypical psychosis, and psychotic affective illness. Both Baron et al. (1982) and Scharfetter and Nusperli (1980) also found evidence for a familial relationship between schizophrenia and at least certain subgroups of schizoaffective patients.

In summary, results to date strongly suggest that neither the first nor the fourth hypothesis is correct. The familial predisposition to schizophrenia is neither completely nonspecific, nor highly specific. Results are available to strongly support the second hypothesis and also to provide some evidence in favor of the third hypothesis. These findings provide an increasingly complex, but informative picture of the nature of the transmitted liability to schizophrenia.

While evidence in favor of a genetic contribution to schizophrenia has been available for nearly 50 years, we are still largely ignorant about the mode of transmission of this liability. This undesirable state of affairs largely results from 1) the inherent complexity of the "schizophrenic phenotype," 2) the lack, until recently, of sufficiently powerful statistical-analytic tools, and 3) a paucity of large, carefully controlled data sets, collected using the major advances in field techniques in psychiatric epidemiology made in the last decade.

Interest has largely focused on two techniques with incorporate information about family structure with the goal of detecting a single locus that substantially affects liability to illness: complex segregation analysis and linkage analysis.

While developing from a relatively simple method to determine the segregation ratio within sibships, segregation analysis has grown considerably in complexity; and modern techniques will include estimates of gene frequency, penetrance, transmission probabilities, polygenes, common sibling environment and variable age of onset. Despite these advances, applications of this method to schizophrenia have been few and controversial.

Four major segregation analyses of schizophrenia have been published. Two of them (Elston et al., 1978; Tsuang et al., 1982) found evidence for vertical transmission of schizophrenia but strongly rejected a single gene model. The other two (Carter & Chung, 1980; Risch & Baron, 1984) also found strong evidence for vertical transmission of schizophrenia and found the pattern could be explained by polygenes with a relatively high heritability (.62 to .82). However, in both studies a single major gene alone or a single major gene with a modest polygene "background" also gave a good fit to the data. These results should be regarded as very preliminary. Only two of these studies used data sets that would meet the methodologic criteria noted above for family studies (Tsuang et al., 1982; Risch & Baron, 1984) and only one of these included a specific evaluation of the schizophrenia spectrum (Risch & Baron, 1984). Both of these methodologically adequate studies were based on a relatively small number of interviewed first degree relatives (354, Tsuang et al.; 276, Risch & Baron). Power analyses have suggested that the sample size required to detect a major gene for a discontinuous trait like schizophrenia is more likely to be in the range of 1,000 first-degree relatives. Finally, segregation analyses of schizophrenia have not to date incorporated exciting new developments including tests for genetic heterogeneity and the incorporation of environmental risk factors into the analysis.

Given the many complexities that may underlie the genetic transmission of schizophrenia, the ultimate resolving power of segregation analysis remains controversial. In the wake of the scientific revolution spawned by DNA technology, and the spectacular success at locating the genes for Huntington's disease and cystic fibrosis, interest has increased markedly in the application of linkage analysis to psychiatric disorders such as schizophrenia. Linkage analysis used to be limited in man because informative markers could be found in any given pedigree for only a small proportion of the human genome. Using recent developments in molecular genetics, the number of potentially informative markers is now nearly unlimited.

If a sufficient number of large informative pedigrees can be found and a single gene exists which substantially influences liability to schizophrenia in at least a subset of these pedigrees, it is theoretically only a matter of screening a sufficient number of markers to locate the gene. However, there are many reasons why the detection of a major gene for schizophrenia by linkage analysis should be much more difficult than for the typical Mendelian human disorders. Probably the most important such reasons are incomplete penetrance and genetic heterogeneity.

To date, linkage studies of schizophrenia using conventional markers have been few and relatively disappointing. Two early studies reported possible linkage between schizophrenia and the group specific protein (Gc), the immunoglobin Gm locus (Elston et al., 1973), and HLA (Turner, 1979). However, the most carefully done linkage study of schizophrenia to date (McGuffin et al., 1983) could replicate neither of these findings nor find evidence for linkage between schizophrenia and any other of the 17 markers examined. Given the small sample sizes used and the limited number of markers examined, the negative results are not surprising.

In summary, the evidence is relatively strong that schizophrenia is a familial disorder and that the familial aggregation of schizophrenia is due largely to genetic factors. Whatever the familial predisposition that operates for schizophrenia, it not only "codes" for the classic, psychotic disorder but also increases liability to "schizophrenia-like" personality disorders and probably other nonschizophrenic nonaffective psychoses. We remain largely ignorant about the mode of transmission of the genetic liability to schizophrenia. Although previous studies have been inconclusive, newly developed methods of complex segregation and linkage analysis provide a source for cautious optimism regarding the possibility of clarifying this central issue.

References

Baron, M., Gruen, R., Rainer, J.D., et al. A family study of schizophrenia and normal control probands: implications for the spectrum concept of schizophrenia. *Am. J. Psychiatry*, 142:447–455, 1985.

Baron, M., Gruen, R., Asnis, L., and Kane, J. Schizoaffective illness, schizophrenia and affective disorders: morbidity risks and genetic transmission. *Acta. Psychiatr. Scand.*, 65:253–262, 1982.

Carter, C.L., and Chung, C.S. Segregation analysis of schizophrenia under a mixed genetic model. *Hum. Hered.*, 30:350–356, 1980.

Elston, R.C., Kringlen, E., and Namboodiri, K.K. Possible linkage relationships between certain blood groups and schizophrenia or other psychoses. *Behav. Genet.*, 3:101–106, 1973.

Elston, R.C., Namboodiri, K.K., Spence, M.A., and Rainer, J.D. A genetic study of schizophrenia pedigrees. One-locus hypotheses. *Neuropsychobiology*, 4:193–206, 1978.

Guze, S.B., Cloninger, C.R., Martin, R.L., and Clayton, P.J. A follow-up and family study of schizophrenia. *Arch. Gen. Psychiatry*, 40:1273–1276, 1983.

Kendler, K.S. Twin studies of schizophrenia: a current perspective. *Am. J. Psychiatry*, 140:1413–1425, 1983.

Kendler, K.S., and Gruenberg, A.M. An independent analysis of the Copenhagen sample of the Danish adoption study of schizophrenia. VI. pattern of psychiatric illness, as defined by DSM-III in adoptees and relatives. *Arch. Gen. Psychiatry*, 41:555–564, 1984.

Kendler, K.S., Gruenberg, A.M., and Tsuang, M.T. Psychiatric illness in the first-degree relatives of schizophrenia and surgical control patients: a family study using DSM-III criteria. *Arch. Gen. Psychiatry*, 42:770–779, 1985.

Kendler, K.S., Masterson, C., Ungaro, R., and Davis, K. A family history study of schizophrenia related personality disorder. *Am. J. Psychiatry*, 141:424–427, 1984.

Lowing, P.A., Mirsky, A.F., and Pereira, R. The inheritance of schizophrenic spectrum disorders: a reanalysis of the Danish adoptee study data. *Am. J. Psychiatry*, 140:1167–1171, 1983.

McGuffin, P., Festenstein, H., and Murray, R. A family study of HLA antigens and other genetic markers in schizophrenia. *Psychol. Med.*, 13:31–43, 1983.

Risch, N., and Baron, M. Segregation analysis of schizophrenia and related disorders. *Am. J. Hum. Genet.*, 36:1039–1059, 1984.

Scharfetter, C., and Nusperli, M. The group of schizophrenias, schizoaffective psychoses and affective disorders. *Schizophrenia Bull.*, 6:586–591, 1980.

Tienari, P., Sorri, A., Lahti, I., et al. The Finnish adoptive family study of schizophrenia. *Yale J. Biol. Med.*, 58:227–237, 1985.

Tsuang, M.T., Winokur, G., and Crowe, R.R. Morbidity risks of schizophrenia and affective disorders among first-degree relatives of patients with schizophrenia, mania, depression and surgical conditions. *Brit. J. Psychiatry*, 137:497–504, 1980.

Tsuang, M.T., Bucher, K.D., and Fleming, J.A. Testing the monogenic theory of schizophrenia: an application of segregation analysis to blind family study data. *Br. J. Psychiatry*, 140:595–599, 1982.

Turner, W.J. Genetic markers for schizotaxia. *Biol. Psychiatry*, 14:177–206, 1979.

The Dopamine Hypothesis: Variations on a Theme (II)

Richard Jed Wyatt, M.D.[1]

Introduction

The basic dopamine (DA) hypothesis of schizophrenia states that there is a functional excess of DA in the brains of schizophrenic individuals and that the excess is causally related to the disorder. Many investigators have proposed variations to the basic DA hypothesis (Crow, 1981), including that the mechanism of action of neuroleptic drugs is attributable to their blockade of brain DA receptors (Carlson & Lindqvist, 1963). Another variation is that there is a functional decrease in brain DA activity in certain schizophrenics (Wyatt & Weinberger, 1984; Wyatt, 1985; Chounard & Jones, 1979). Below I review some of the evidence relating to these DA hypotheses and propose still further variations. These new models attempt to explain several observations of schizophrenia which, if they are "facts," must be explained by any model proposing a common pathophysiology, if not cause, of schizophrenia.

The DA Hypothesis of Schizophrenia

The notion that there might be an excess of DA in schizophrenia began when it was realized that stimulants, such as amphetamine, when given in high doses, or for prolonged periods, were capable of producing a paranoid psychosis that in many ways was indistinguishable from schizophrenia (Young & Scoville, 1938; Woodrow, Reifman, & Wyatt, 1978). During the 1960's and 1970's some of the mechanisms of action of amphetamine became understood and one of these was that amphetamine releases DA from neuronal terminals. In 1963 Carlson and Lindqvist published their finding that medications that decrease the symptoms of schizophrenia, chlorpromazine and haloperidol, are capable of increasing brain 3-methoxytyramine, a major metabolite of DA. Medications that do not alter the course of schizophrenia did not produce this increase. Based on this finding, they proposed the novel hypothesis that neuroleptics block DA receptors. Several groups of investigators (Creese & Snyder, 1976) demonstrated a striking correlation between the average daily dose of neuroleptics and their ability to displace radiolabeled haloperidol in the striatum. In comparing equivalent clinical potencies of neuroleptics used to treat schizophrenia and affective disorders, however, there is also an equally striking correlation across neuroleptics (Wyatt & Torgow, 1976). This correlation and other findings suggest that any DA alteration in these disorders might be downstream from the cause but still of considerable pathophysiological importance (other explanations also exist).

Additional "Facts" Requiring Explanation

A. *Gender Differences and the Role of Estrogen*: It has been known for a number of years that there are striking gender differences in schizophrenia (Mendelson, Gillin, & Wyatt, 1977; Seeman, 1985). Schizophrenia affects males and females in the same percentages, but females are affected later, have a milder course, have a better response to neuroleptics, and sometimes become worse premenstrually and during the postpartum period. There is often, however, an improvement during pregnancy. Thus there appears to be an association between estrogen concentration and the severity of the illness. Also, in the past estrogens have been used in the treatment of psychosis. Animal data suggest that estrogens behave as neuroleptics; they appear to block DA.

B. *Age of Onset*: The onset of schizophrenia generally begins after puberty. At this time the prefrontal cortex becomes fully myelinated (Yakovlev & LeCours, 1964) and the ability to perform abstract thinking is well established. A number of investigators have found apparent alterations in the prefrontal cortex of schizophrenic patients using psychophysiological and imaging techniques (Weinberger, Berman, & Zec, 1986). Possible prefrontal cortex abnormalities in schizophrenia include abnormal smooth pursuit eye movements, increased electroencephalographic delta wave activity, decreased regional cerebral blood flow, particularly following provocative tests, and increased prefrontal sulci size seen on CT scans.

---

[1] Neuropsychiatry Branch, National Institute of Mental Health, WAW Building, Room 536, Saint Elizabeths Hospital, Washington, D.C. 20032.

C. *Genetics*: Schizophrenia appears to be, at least in part, a genetic disorder. There must be a corresponding genetic alteration in the brain, unless schizophrenia is like phenylketonuria where the primary lesion is in the liver. The similarities of response to neuroleptics in affective and schizophrenic disorders suggest that the primary deficit is not in the DA system for all schizophrenics. The effectiveness of neuroleptics in treating schizophrenia does suggest, however, that the primary alteration must either affect the DA system or be affected by it (Wyatt & Torgow, 1976).

D. *Environment*: Since schizophrenia cannot be accounted for entirely by genetic contribution, an environmental contribution must play a significant role. There are considerable data that some initial schizophrenic episodes begin during times of stress (Dohrenwend & Egri, 1981) and that subsequent exacerbations are also related to stress (Goldstein et al., 1978). Although the data are not conclusive, they suggest that any physiological phenomenon altered by stress might be related to schizophrenia. It has been demonstrated in a number of animal studies that frontal lobe dopaminergic activity is increased by stress (Reinhard, Bannon, & Roth, 1982).

E. *The Course of Schizophrenia Is Extremely Variable*: Some patients have one or several episodes and then return to normal function, while other patients have a gradual downhill course. Still other patients, even though they have been ill for many years, have what appears to be gradual recoveries. This variability must be considered as part of any explanatory hypothesis of schizophrenia.

F. *Neuroleptics Are Useful in the Treatment of Schizophrenia*. Any explanation of schizophrenia must deal with how neuroleptics produce their effects. As previously discussed, a number of scientists have demonstrated that the average daily dose of neuroleptics correlates with the drug's ability to inhibit DA receptors as measured by displacement of another neuroleptic, usually haloperidol. Clinicians glancing at some of the drugs used to derive these calculations may note discrepancies from their clinical experience. Promazine, for example, is often used in biochemical studies, yet a number of clinical studies have found promazine not to be as effective as chlorpromazine and others have found promazine no more effective than placebo. One of the displacement studies included trazodone, which is an antidepressant. The studies also contain drugs for which there is little or no experience in schizophrenic patients. Using equivalent clinical potencies of equally efficacious neuroleptics relative to chlorpromazine (Wyatt, 1976), I have recalculated the Pearson correlation (with log transformation) for 16 neuroleptics against their 3H-haloperidol IC_{50}. The 0.73 correlation found is not as high as that seen in previous calculations but, nonetheless, accounts for at least 50 percent of the variance. Once again this association suggests that at least part of the neuroleptics' mechanism of action can be accounted for by dopaminergic blockade.

Data Supporting an Increase of DA

A. *Stimulants, DA Precursors, and Agonists*: As discussed previously, one human model for schizophrenia is the amphetamine-induced paranoid psychosis. It should be pointed out, however, that while amphetamine does release DA, it also releases norepinephrine in at least equal quantities (Karoum et al., 1982). On occasion, L-dopa will produce a psychosis in patients taking it for Parkinson's disease, but again it is unclear if this result is related to the production of DA or norepinephrine. Perhaps more convincing are the number of case reports of DA agonists producing a psychosis.

B. *Brain DA and Its Metabolites*: Autopsy studies by Bacopoulos et al. (1979) and Bird, Langais, and Benes (1984) show increased homovanillic acid (HVA) in the frontal cortex, as well as increased DA and HVA in the nucleus accumbens and anterior perforated substance. Most studies of schizophrenic brains, however, do not show this phenomenon and Bacopoulos et al. theorize that the increase is a neuroleptic effect similar to that found in animals given neuroleptics (Matsumoto et al., 1983).

C. *Cerebrospinal Fluid (CSF)*: While there are few data indicating that there is an increase in DA or its metabolites in the CSF of schizophrenics compared with controls, there are two studies that show positive correlations between the quantity of HVA and productive symptoms (Rimon, Roos, & Rakkolainen, 1971; Kaufmann et al., submitted). This suggests that there might be increased DA turnover in those patients with active symptoms.

D. *Plasma*: There is one study indicating increased plasma HVA in schizophrenics compared with controls (Pickar et al., 1984). More striking, however, is the positive correlation between plasma HVA and symptoms (Davis et al., 1985). Neuroleptics produce a decrease in plasma HVA at a time when the patients improve.

Data Supporting a Decrease in DA

A. *Chronic Stimulant Use in Animals*: There is now considerable evidence that stimulants in high doses produce loss of dopaminergic terminals in the brain. One group (Seiden & Vosmer, 1984) has demonstrated that during the time of stimulant-induced DA release 6-hydroxy DA is produced, which in turn is taken into DA terminals and destroys them.

B. *Von Economo's Encephalitis or Encephalitis Lethargica*: During the world wide epidemic beginning during the winter of 1916–1917, Baron Constantine von Economo described a striking hypokinetic state he called "psychic torpor." Often reactions to encephalitis lethargica were mistaken for schizophrenia and at times it was even called epidemic schizophrenia. Even after patients apparently recovered, a number developed Parkinson's disease. While it is possible that the early symptoms were related to alternations in DA, it is equally likely that they were related to irritation of the brain by the encephalitis.

C. *Parkinson's Disease*: The major alteration in Parkinson's disease appears to involve destruction of DA containing neurons; primarily of the nigro-striatal system. The meso-cortico-limbic dopaminergic system is also involved. Since a number of the deficit symptoms (mild intellectual impairment, apathy or depression, lack of spontaneous speech, problems with concept formation) of Parkinson's disease are similar to those of schizophrenia, it is reasonable to contemplate a similar DA alteration in both disorders.

D. *Akinesia*: Akinesia is a well-known side effect of neuroleptic medications involving both motor and cognitive functions and is seen both in humans and animals. Akinesia is thought to be attributable to a blocking of DA by neuroleptic drugs. Neuroleptic induced akinesia is often indistinguishable from the deficit symptoms of schizophrenia.

E. *Brain DA and Its Metabolites*: While in general no statistically significant decreases of DA or its metabolites in the autopsied brains of schizophrenics have been found, in our study (Kleinman et al., 1979) of a limited number of subjects there were substantial (40% for dopylacetic acid (DOPAC) in the substantia nigra), but statistically nonsignificant decreases in DA, DOPAC, and HVA in the hypothalamus, nucleus accumbens, and substantia nigra.

F. *CSF*: There are several CSF studies indicating that DA or its metabolites are decreased in the CSF of some schizophrenic patients (Kaufman et al., submitted). In several of these studies there has been a negative correlation between HVA concentration and the deficit symptoms associated with schizophrenia. These include poor prognosis and length of illness, as well as negative symptoms ratings.

G. *Urine*: There are relatively few studies measuring DA and its metabolites in urine. One recent study (Karoum et al., 1985) found that when the molar sum of DA and its metabolites are expressed as a ratio over the sum of norepinephrine and its metabolites, medication-free schizophrenics had a lower mean sum DA/sum norepinephrine than a group of normal controls. The ratio increased to normal levels in the presence of neuroleptic drugs.

H. *Animal Models*: There are a number of animal models suggesting that decreased DA can produce symptoms consistent with those of schizophrenia. For example, Wise (1982) studying rats given neuroleptics, which consequently had decreased functional DA, found they had ". . . selective attenuation of motivational arousal which is (a) critical for goal-directed behavior, (b) normally induced by reinforcers and associated environmental stimuli, and (c) normally accompanied by the subjective experience of pleasure. . . ."

I. *Location of Changes*: There have now been well over 30 studies demonstrating that the brains of some schizophrenics, as seen on CT scans, are altered. The alterations include enlargements of the lateral and third ventricles and what appears to be cortical atrophy. One finding of considerable interest is an apparently high incidence of prefrontal cortical atrophy in chronic schizophrenia (Shelton et al., submitted). This is consistent with studies demonstrating decreased regional cerebral blood flow in the prefrontal cortex, particularly where the prefrontal cortex has been cognitively activated (Weinberger, Berman, & Zec, in press). As mentioned, there is reason to believe that prefrontal cortical function is dependent on DA. In animal studies it has been found that stress produces increased DA turnover in the frontal cortex (Thierry et al., 1977).

Variations on a Theme

Hypothesis 1: This variation suggests that schizophrenics have a vulnerable dopaminergic system (perhaps genetic) and that with repeated stress there is loss of dopaminergic terminals. The stress itself is responsible for increased DA turnover and the productive symptoms of schizophrenia. The loss of DA terminals is ultimately responsible for the burned out state of schizophrenia. This hypothesis is consistent with a retrospective course study of Pfohl and Winokur (1982) in which patients began their illness with predominantly productive symptoms but 35 years later had predominantly deficit symptoms. The hypothesis requires the progressive loss of dopaminergic terminals similar to what is seen in stimulant-induced release of DA.

Hypothesis 2: This variation suggests that there is decreased dopaminergic function in the prefrontal cortex of schizophrenics, and that this decrease is responsible for some of the progressive symptoms seen prior to the first acute phase of the disorder. The acute phase of schizophrenia might be caused by stress and a corresponding accompanying increase in DA turnover. Neuroleptics increase DA turnover in the prefrontal cortex without tolerance developing, as appears to occur in other parts of the brain. To speculate further, the increased DA turnover in the frontal lobes produced by neuroleptic administration might decrease the deficit symptoms. Thus, where there is a potentially active prefrontal dopaminergic system in schizophrenia, neuroleptics are capable of decreasing the deficit symptoms. But where the prefrontal DA system is not capable of activation, neuroleptics cannot effect these symptoms. The effects of neuroleptics in other parts of the brain decrease some of the productive or positive symptoms of schizophrenia. It is understood that these hypotheses are simplistic but are offered so that they might lead to further investigations.

References

Bacopoulos, N.C., Spokes, E.G., Bird, E.D., and Roth, R. H. Antipsychotic drug action in schizophrenic patients: Effect on cortical dopamine metabolism after long-term treatment. *Science*, 205:1405–1407, 1979.

Bird E.D., Langais, P.J., and Benes, F.M. Dopamine and homovanillic acid in postmortem schizophrenic brain. *Clin. Neuropharmacol.*, 7(Suppl 1):910–911, 1984.

Carlson, A., and Lindqvist, M. Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and norepinephrine in mouse brain. *Acta Pharmacol. Toxicol.*, 20:140–144, 1963.

Chouinard, G., and Jones, B.D. Evidence of brain dopamine deficiency in schizophrenia. *Can. J. Psychiat.*, 24:661–667, 1979.

Creese, I., Burt, D.R., and Snyder, S.N. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*, 192:481–483, 1976.

Crow, T.J. Positive and negative schizophrenic symptoms and the role of dopamine. *Br. J. Psychiat.*, 139:251–254, 1981.

Davis, K.L., Davidson, M., Mohs, R.C., et al. Plasma homovanillic acid concentration and the severity of schizophrenic illness. *Science*, 227:1601–1602, 1983.

Dohrenwend, B.P., and Egri, G. Recent stressful life events and episodes of schizophrenia. *Schizo. Bull.*, 7:12–23, 1981.

Goldstein, M., Rodnick, E., Evans, J., et al. Drug and family therapy in aftercare of acute schizophrenics. *Arch. Gen. Psychiat.*, 35:1169–1177, 1978.

Karoum F.K., Karson, C., Lawson, W.B., et al. Whole body turnover of catecholamine in chronic schizophrenia and depression: Evidence of low dopamine turnover in chronic schizophrenia. (Abstract, Vol. 11(2):819) Proceedings of 15th Annual Meeting of the Society of Neuroscience, Dallas, Texas, 1985.

Karoum, F., Speciale, S.G., Chaung, L-W., and Wyatt, R.J. Selective effects of phenylethylamine on central catecholamines: A comparative study of ampethamine. *J. Pharmacol. Exp. Ther.*, 223:432–439, 1982.

Kaufman, C.A., Weinberger, D.R., Linnoila, M., et al. Cerebrospinal fluid monoamines and metabolites in schizophrenic patients. Submitted, 1985.

Kleinman, J.E., Bridge, P., Karoum, F., and Speciale, S. Catecholamines and metabolities in the brains of psychotics and normals: Post-mortem studies. In: E. Usdin, I.J. Kopin, and J.S. Barchas (eds.), *Catecholamines: Basic and Clinical Frontiers*. New York: Pergamon Press, 1979, pp. 1845–1848.

Matsumoto, T., Uchimura, H., Hirano, M., et al. Differential effects of acute and chronic administration of haloperidol on homovanillic acid levels in discrete dopaminergic areas of rat brain. *Eur. J. Pharmacol.*, 89:27–33, 1983.

Mendelson, W.B., Gillin, J.C., and Wyatt, R.J. Sexual physiology and schizophrenia. *Acta Cientifica Venezolana*, 28:417–425, 1977.

Pfohl, B., and Winokur, G. The evolution of symptoms in institutionalized hebephrenic/catatonic schizophrenics. *Brit. J. Pyschiat.*, 141:567–572, 1982.

Pickar, D., Labarca, R., Linnoila, M., et al. Neuroleptic-induced decrease in plasma homovanillic acid and antipsychotic activity in schizophrenic patients. *Science*, 225:954–957, 1984.

Reinhard, J.R., Jr., Bannon, M.J., and Roth, R.H. Acceleration of stress of dopamine synthesis and metabolism in prefrontal cortex. *Naunyam-Schmiedeberg's Arch. Pharmacol.*, 318:374–377, 1982.

Rimon, R., Roos, B.E., and Rakkolainen, V. The content of 5-HIAA and HVA in the CSF of patients with acute schizophrenia. *J. Psychosom. Res.*, 15:375–378, 1971.

Seeman, M.V. Symposium: Gender and schizophrenia. *Canadian J. Psych.*, 30:311–312, 1985.

Seiden, L.S., and Vosmer, G. Formation of 6-hydroxydopamine in caudate nucleus of the rat brain after a single large dose of methylamphetamine. *Pharmacol. Biochem. Behav.*, 21:29–31, 1984.

Shelton, R.C., Doran, A.R., Pickar, D., and Weinberger, D.R. Cerebral structural pathology in schizophrenia: Evidence for a selective prefrontal cortical defect. Submitted, 1984.

Thierry, A.M., Tassin, J.P., Blanc, G., et al. Discovery of the mesocortical dopaminergic system: Some pharmacolgical and functional characteristics. *Adv. Biochem. Psychopharmacol.*, 16:5–12, 1977.

Weinberger, D.R., Berman, K.F., and Zec, R.F. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. I: Regional cerebral blood flow (rCBF) evidence. *Arch. Gen. Psychiat.* (In press)

Wise, R.A. Neuroleptics and operant behavior: The anhedonia hypothesis. *Behav. Brain. Sci.*, 5:39–87, 1982.

Woodrow, K.M., Reifman, A., and Wyatt, R.J. Amphetamine psychosis: A model for paranoid schizophrenia? In: B. Haber and M.H. Aprison (eds.), *Neuropharmacology and Behavior*. New York: Plenum Press, 1978, pp. 1–22.

Wyatt, R. The dopamine hypothesis: Variations on a theme. In: R. Cancro and S. R. Dean (eds.), *Research in the Schizophrenic Disorders: The Stanley R. Dean Award Lectures*. Vol. 2. Jamaica, NY: Spectrum Publications, 1985, pp. 225–247.

Wyatt, R.J., and Torgow, J.S. A comparison of equivalent clinical potencies of neuroleptics as used to treat schizophrenic and affective disorders. *J. Psychiat. Res.*, 13:91–98, 1976.

Wyatt, R.J., and Weinberger, D.R. Future directions for biological exploration of psychiatric disorders. In: J.L. Sullivan (ed.), *Principles of Psychiatric Medicine*. Boston: Butterworth, 1984, pp. 237–260.

Yakovlev, P., and LeCours, A-R. The myelogenetic cycles of regional maturation of the brain. In: A. Minkowski (ed.), *Regional Development of the Brain in Early Life*. Oxford: Blackwell Scientific Publications, 1964, pp. 3–70.

Young, D., and Scoville, W.B. Paranoid psychosis in narcolepsy and the possible danger of benzedrine treatment. *Med. Clin. North Am.*, 22:637–646, 1938.

The Combined Use of Neuroleptics and ECT in Drug Resistant Schizophrenic Patients

Robert O. Friedel, M.D.[1]

Introduction

The purposes of this paper are to review briefly the literature relevant to the efficacy and risks of using electroconvulsive therapy (ECT) combined with neuroleptics in the treatment of neuroleptic-resistant schizophrenic patients and to present the results of an open trial of ECT and neuroleptics in nine consecutive schizophrenic patients with drug-resistant psychotic symptoms. Because of the personal, social, and economic costs resulting from failures of existing pharmacological treatments of schizophrenic patients, a search for treatment alternatives seems indicated. A careful review of the literature (Roehrich & Friedel, unpublished data) covering the use of ECT combined with neuroleptics in the treatment of schizophrenic patients suggests that: 1) combined treatment may result in a more rapid onset of therapeutic response when typical and low doses of neuroleptics are used; 2) at low doses of neuroleptics, the addition of ECT may result in a synergistic therapeutic effect; 3) the ECT neuroleptic combination may be efficacious in some neuroleptic-resistant patients; and 4) there does not appear to be a clinically significant increase in the morbidity or mortality rate associated with the combined treatment, especially if high potency neuroleptics are used instead of chlorpromazine.

There are three studies which suggest an increased rate of therapeutic response by schizophrenics to ECT plus neuroleptics compared to the response rate to neuroleptics alone (Smith et al., 1967; Taylor & Fleminger, 1980; Janakiramaiah et al., 1982). In all of these studies, lower than normal neuroleptic doses were used and in one (Janakiramaiah et al., 1982), normal doses were also given. These findings suggest an increased rate of response to the ECT drug combination, with the possibility of enhanced peak effectiveness as a result of the combined treatment. Given increasing pressure to shorten hospital lengths of stay, improved response rate would be an important finding.

The results of four studies suggest that neuroleptics given at lower than normal doses combined with ECT are significantly more effective than comparable doses given alone (Smith et al., 1967; Taylor & Fleminger, 1980; Janakiramaiah et al., 1982; Ray, 1962). There are no controlled studies that do not show a significant advantage of low doses of neuroleptics combined with ECT compared to low doses of neuroleptics given alone. Because of growing and considerable concern about serious and permanent side effects to neuroleptics, some of which may be dose related (Gardos & Cole, 1976; Task Force Report No. 18, 1980; Marder et al., 1984), further study of the treatment of acute exacerbations of schizophrenic psychosis with low doses of neuroleptics and ECT seems indicated.

The often stated concern that the combination of ECT plus neuroleptics results in increased morbidity and mortality does not appear to be supported by the literature (Roehrich & Friedel, unpublished data). Although five reports of death and serious medical morbidity associated with ECT-neuroleptic treatment have been reported (Weiss, 1955; Kalinowsky, 1956; Gaitz et al., 1956; Lesse, 1959; Barker & Baker, 1959), a review of the controlled studies noted above and survey studies suggests that the death rate with combined ECT-neuroleptic treatment is no greater than that for ECT alone. In addition, the studies which report mortality as a result of combined treatment failed to provide contextual data to determine comparative mortality rates with neuroleptics and ECT alone in the same populations. Nonetheless, it may be concluded that the available evidence suggest the possibility of mortality and morbidity rates of chlorpromazine plus ECT greater than those with either chlorpromazine or ECT alone. There are some data that suggest this may not be true when high potency neuroleptics are used with ECT. In summary, the question of adverse treatment effects admonishes us to carefully evaluate the indications for the combined treatment in each patient for whom it is considered.

---

[1] Division of Psychiatric Medicine, Charter Medical Corporation, and Charter Westbrook Hospital, Richmond, VA 23227.

Finally, Childers and Therrien (1961) have reported that 11 of 23 schizophrenic patients who had been unresponsive to 5 weeks of treatment with either 1000 mg per day of chlorpromazine or 40 mg per day of trifluoperazine demonstrated a moderate to marked improvement when drug dose was reduced and a series of 15 ECT given. This is the only systematic study noted in the literature which evaluates the effect of the neuroleptic-ECT combination in patients unresponsive to a known and adequate trial on neuroleptics. The finding is weakened because there was no control group of drug-resistant patients continued on neuroleptics alone. To the best of my knowledge, no such controlled study exists in the literature in spite of this detailed report and similar findings in other uncontrolled studies which followed (Witton, 1962; Weinstein & Fischer, 1971; McNeill, 1977; Rahman, 1968). Because of the need for treatment alternatives for drug-resistant schizophrenic patients and the results of these older studies, an open trial of neuroleptics plus ECT was conducted on patients whose psychotic symptoms failed to respond to treatment with neuroleptics alone.

Methods

Twenty-one patients meeting DSM-III criteria for schizophrenia with moderate to severe psychotic symptoms were entered into the study. Treatment was initiated with thiothixene and dosages increased until a moderate to marked improvement was achieved, disabling and uncontrollable side effects intervened, or thiothixene plus desmethylthiothixene plasma levels exceeded 15 ng/ml. Thiothixene and desmethylthiothixene plasma levels were assayed using an HPLC technique (Narasimhachari et al., 1984). Nine of the 21 original patients achieved a moderate to marked improvement with medications. The thiothixene plus desmethylthiothixene plasma levels of these patients ranged from 6 ng/ml to 15 ng/ml.

Of the remaining 11 patients, who achieved either no (or slight) improvement with medications, all received dosage increases until drug plasma levels greater than 15 ng/ml were reached. These patients were considered to be medication nonresponders and nine of them were started on a course of either unilateral or bilateral ECT at the rate of three treatments per week. Patients were rated as either not improved or having mild, moderate, or complete remission of psychotic symptoms. In addition, global memory impairment was evaluated weekly and cardiovascular toxicity defined as any unusual alterations in blood pressure, pulse, or electrocardiogram observed during and after each ECT.

Results

Of the nine patients entering into treatment with thiothixene plus ECT, eight patients achieved a complete remission of psychotic symptoms and one patient continued to exhibit very mild symptoms at the completion of the course of ECT. In this open trial, a variable number of ECT were given depending on the individual patient's response. The range was from 8 to 25 treatments with a mean of 13.6 treatments. The dose of thiothixene varied from 30 mg to 60 mg per day during the course of ECT. Six of the patients received unilateral ECT and three received bilateral ECT. There did not appear to be any difference in the efficacy of these two electrode placements, but memory impairment was clearly greater using bilateral ECT with three patients experiencing either moderate or marked memory impairment with this electrode placement. Three of the patients receiving combined ECT plus neuroleptic treatment were lost to follow-up. Of the remaining six, the duration of remission appeared to be longer with bilateral ECT (6.5 months versus 4.6 months), but the number of patients treated is too small to draw firm conclusions.

Discussion

Based on the response of the nine patients treated with ECT plus thiothixene, the combined treatment appears to be effective in the treatment of psychotic symptoms of drug-resistant schizophrenic patients. The average patient in this study had been continously psychotic for over 3 years and had been treated with a number of neuroleptics and neuroleptics plus lithium with only mild to at best moderate success. After the combined treatment it was common for family members to report that the patient was "doing better than we have seen him in years." For example, one of the patients was able to return to outpatient care after more than 5 years of chronic continued hospitalization.

The lack of significant cardiovascular side effects in this population supports the contention that patients receiving ECT plus high potency neuroleptics are not at significant risk for serious cardiovascular complications.

In sum, these data suggest the need for a controlled trial of ECT combined with neuroleptics versus neuroleptics alone in a well-defined, drug-resistant population of psychotic schizophrenic patients. The results of this pilot study must be viewed with caution because patients were not evaluated during and after treatment with an operationalized rating scale by raters blind to treatment, and because a control group of patients continuing on medications alone was not employed. In addition, follow-up data need to be collected on patients for a significant period after treatment to determine the duration of remission in patients who respond to the combined treatment. Nonetheless, the data support the previous study by Childers and Therrien (1961) and the approach warrants further study.

References

Barker, J.C., and Baker, A.A. Deaths associated with electroplexy. *J. Ment. Sc.*, 105:339–348, 1959.

Childers, R.T., Jr., and Therrien, R. A comparison of the effectiveness of trifluoperazine and chlorpromazine in schizophrenia. *Am. J. Psychiatry*, 118:552–554, 1961.

Gaitz, C.M., Pokorny, A., and Mills, M. Death following electroconvulsive therapy. *Arch. Neurol. Psychiatry*, 75:493–499, 1956.

Gardos, G., and Cole, J.O. Maintenance antipsychotic therapy: Is the cure worse than the disease? *Am. J. Psychiatry*, 133:32–36, 1976.

Janakiramaiah, N., Channabasavanna, S.M., and Narasimha-Murthy, N.S. ECT-chlorpromazine combination versus chlorpromazine alone in acutely schizophrenic patients. *Acta Psychiatr. Scand.*, 66:464–470, 1982.

Kalinowsky, L.B. Premedication in convulsive therapy. *Am. J. Psychiatry*, 113:79–80, 1956.

Lesse, S. Electroshock therapy and tranquilizing drugs. *JAMA*, 170:1791–1795, 1959.

Marder, S.R., Van Putten, T., Mintz, J., et al. Costs and benefits of two doses of flupenazine. *Arch. Gen. Psychiatry*, 41:1025–1029, 1984.

McNeill, D.L. Phenothiazine resistance. *Br. Med. J.*, 2:127–128, 1977.

Narasimhachari, N., Dorey, R.C., Landa, B.L., and Friedel, R.O. Improved high-performance liquid chromatographic method for the quantitation of cis-thiothixene in plasma samples using trans-thiothixene as internal standard. *J. Chromatography*, 133:424–429, 1984.

Rahman, R. A review of treatment of 176 schizophrenic patients in the mental hospital, Pabna. *Br. J. Psychiatry*, 114:775–777, 1968.

Ray, S.D. Relative efficacy of electroconvulsive therapy and chlorpromazine in schizophrenia. *J. Indian Med. Assoc.*, 38:332–333, 1962.

Smith, K., Surphlis, W., Gynther, M., and Shimkunas, A. ECT-chlorpromazine and chlorpromazine compared in the treatment of schizophrenia. *J. Nerv. Ment. Dis.*, 144:284–290, 1967.

Task Force Report Number 18: *Tardive Dyskinesia.* Washington, DC, APA Press, 1980.

Taylor, P., and Fleminger, J. ECT for schizophrenia. *Lancet*, I:1380–1383, 1980.

Weinstein, M., and Fischer, A. Combined treatment with ECT and antipsychotic drugs in schizophrenia. *Dis. Nerv. System*, 32:801–808, 1971.

Weiss, D. changes in blood pressure with electroshock therapy in a patient receiving chlorpromazine hydrochloride. *Am. J. Psychiatry*, 111:617–619, 1955.

Witton, K. Efficacy of ECT following prolonged use of psychotropic drugs. *Am. J. Psychiatry*, 119:79–80, 1962.

Psychotropic Drug Receptors and Brain Function: Molecular Bases to Clinical Implications (CINP/ACNP)

Co-Chairs:

Giorgio Racagni, Ph.D.
University of Milan
Milan, Italy

Erminio Costa, M.D.
Saint Elizabeths Hospital
Washington, DC 20032

Lack of Serotonergic Modulation on ^{3}H-Imipramine Binding Sites in Basal Conditions and During Prolonged Treatment With Desmethylimipramine

Nicoletta Brunello, Ph.D.,[1] Alessandra Cecilia Rovescalli, Ph.D.,[1] Marco Riva, Ph.D.,[1] and Giorgio Racagni, Ph.D.[1]

Introduction

Typical antidepressants (ADs) display multiple neurochemical effects, generally consistent with the increase of monoamine synaptic availability, through inhibition of presynaptic uptake mechanisms (Korf, 1983).

However, while these effects occur after the acute administration of ADs, clinical studies reveal that prolonged treatments (7 to 15 days) are required to induce the symptomatic improvement of depressed patients. It is therefore apparent that the biochemical mechanisms underlying the therapeutic effects of ADs should be better investigated following repeated administration of these drugs. It is well known that a prolonged treatment with desmethylimipramine (DMI) decreases the activity of noradrenergic neurons in the central nervous system (CNS); in particular the following biochemical modifications have been observed: reduction of the concentration of cortical β-adrenergic receptors (Banerjee et al., 1977); reduced sensitivity of norepinephrine (NE)-dependent adenylate cyclase activity (Vetulani & Sulser, 1975); decrease of the central content of normetanephrine, the O-methylated metabolite of NE (Racagni et al., 1982). Previous studies indicate that an intact serotonergic function is required to enable chronic ADs to desensitize noradrenergic neurons (Brunello et al., 1982a; Janowsky et al., 1982). Moreover, the involvement of serotonergic system in the action of antidepressant drugs is further supported by the existence of high-affinity recognition sites for ^{3}H-imipramine (^{3}H-IMI) on serotonergic terminals (Raisman et al., 1979, 1980).

---

[1] Center of Neuropharmacology, Institute of Pharmacology and Pharmacognosy, University of Milan, via Balzaretti 9, 20133 Milan, Italy.

Correspondence should be addressed to: Prof. Giorgio Racagni, Institute of Pharmacology and Pharmacognosy, Center of Neuropharmacology, University of Milan, via Balzaretti 9, 20133 Milan, Italy.

Even if the precise physiological significance of ^{3}H-IMI binding sites is not yet known, they have been demonstrated allosterically coupled to the serotonin (5-HT)-uptake molecular complex (Langer et al., 1980). A chronic treatment with ADs induces opposite modifications in the kinetic properties of these two sites; in particular DMI-induced down-regulation of ^{3}H-IMI binding sites and increase of the V_{max} of *in vitro* 5-HT-uptake have been observed in brain (Barbaccia et al., 1983a; Racagni & Brunello, 1984).

The present paper reports studies on the involvement of 5-HT in the mediation of the effect of DMI on ^{3}H-IMI recognition sites. To this purpose kinetic properties of ^{3}H-IMI binding following repeated coadministration of DMI and para-chlorophenylalanine (pCPA), a selective inhibitor of 5-HT biosynthesis have been evaluated. Moreover, studies have been performed on the acute and chronic effects of tryptolines (THβCs: 5-methoxytryptoline, 5-MeOT; 5-hydroxytryptoline, 5-OHT; unsubstituted tryptoline, Tp), putative endogenous modulators of 5-HT-uptake molecular complex (Langer et al., 1984; Segonzac et al., 1985), on the kinetic properties of *in vitro* 5-HT-high affinity uptake and ^{3}H-IMI binding.

Materials and Methods

Adult male rats, Sprague-Dawley, 125 to 150 g (C.r.l. C.D. Charles River S.p.A., Calco, Italy) were employed in all the experiments. Rats were caged in air-conditioned light-dark controlled rooms (light from 6 a.m. to 8 p.m.) and fed with standard diet and water *ad libitum*.

In acute studies 25 mg/kg of 5-MeOT, 5-OHT, or Tp was intraperitoneally (i.p.) injected to rats, 20 minutes before the sacrifice.

In chronic studies, animals received 5-MeOT, DMI, and pCPA, according to the following schedule:

—pCPA, 300 mg/kg i.p., once daily for 3 days, followed by 100 mg/kg i.p. every other day for 13 days;

—5-MeOT, 25 mg/kg i.p. or DMI, 15 mg/kg i.p., once daily for 15 days, alone or together with pCPA when the dose of 100 mg/kg i.p. was administered.

All drugs were dissolved in water; control rats received daily injections of saline. Animals were killed 48 hours after the last injection of 5-MeOT or DMI, i.e., 24 hours after the last treatment with pCPA.

In vitro 5-HT-uptake was evaluated according to Baumann et al. (1977) with slight modifications. Briefly, cortical or hypothalamic slices were incubated for 15 minutes at 37°C in the presence of ^{3}H-5-HT, in a concentration range between 5×10^{-8}M and 4×10^{-6}M.

Blanks were obtained by adding 10^{-5}M fluoxetine.

^{3}H-IMI binding saturation curves were obtained in cortical membrane preparations, according to Raisman et al. (1980). The radioligand concentration ranged between 1.0 and 10.0 nM; nonspecific binding was determined in the presence of 10^{-4}M DMI. The incubation was performed at 0°C for 60 minutes. The kinetic properties of ^{3}H-IMI binding were calculated from the Scatchard analysis of at least three saturation curves.

Protein concentrations were determined according to Lowry et al. (1951) with slight modifications.

Results

Prolonged treatment with DMI induced a 30-percent decrease in the density of cortical ^{3}H-IMI binding sites, without significant changes in the K_d value; a similar reduction was detected also in animals treated with both pCPA and DMI. In animals treated only with pCPA the kinetic constants of ^{3}H-IMI binding sites did not differ from control values (Figure 1).

5-MeOT, 5-OHT, and Tp inhibited ^{3}H-IMI binding to rat cortical membranes (Figure 2). Scatchard analysis of saturation curves performed in the presence of a single concentration of THβCs indicate that the compounds behave as competitive inhibitors at the level of ^{3}H-IMI recognition sites, since they affect the K_d values without significant change in the B_{max}. The major decrease of K_d was observed in the presence of 100 nM 5-MeOT whereas 500 nM Tp induces the minor modification. IC$_{50}$ values calculated from displacement studies demonstrate that 5-MeOT possesses the higher affinity towards ^{3}H-IMI recognition sites, whereas Tp seems to

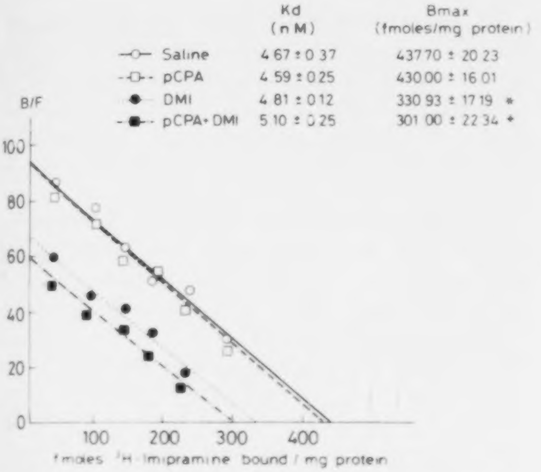


FIGURE 1. Scatchard analysis of ^{3}H-IMI binding to cortical membranes after chronic treatment with DMI, pCPA, pCPA + DMI or saline. Rats received repeated administration of pCPA, 300 mg/kg i.p. for 3 days followed by 100 mg/kg i.p. every other day for 15 days, DMI, 15 mg/kg i.p. daily for 15 days, pCPA + DMI or saline. Cortical 5-HT content (pmoles/mg protein) was reduced by chronic pCPA as much as 95% (saline: 7.5 ± 0.5; pCPA: 0.80 ± 0.04; DMI: 7.2 ± 0.3; pCPA + DMI: 0.60 ± 0.04). Data are the mean ± SEM of three separate experiments. [$^*p < 0.05$ vs. saline; $^+p < 0.05$ vs. pCPA (Dunnett's "t" test).]

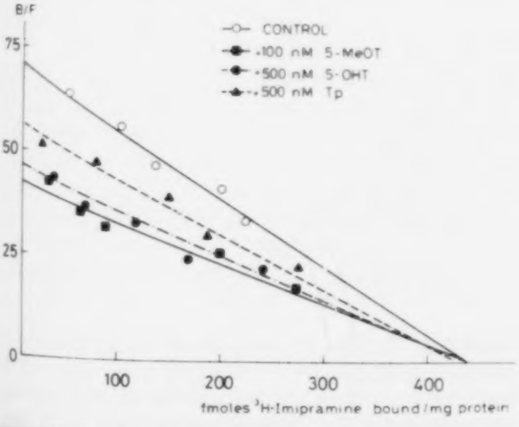


FIGURE 2. Scatchard analysis of ^{3}H-IMI binding to cortical membranes in the presence of 100 nM 5-MeOT, 500 nM 5-OHT or 500 nM Tp. IC_{50} values were calculated from displacement studies in which graded concentrations (from 10^{-8} to 5×10^{-5}M) of each THβC were tested on the binding of 5 nM ^{3}H-IMI to cortical membranes.

be the less potent compound (Figure 2). THβCs inhibited *in vitro* the ^{3}H-5-HT high affinity uptake by rat cortical slices with different potencies: IC_{50} values indicate that 5-MeOT and Tp are active at μM concentrations, whereas 5-OHT appears to be 10 times more potent (Figure 3).

The *in vivo* administration of 25 mg/kg i.p. of 5-MeOT, 5-OHT, or Tp resulted in a clear-cut decrease of the V_{max} of the *in vitro* ^{3}H-5-HT high affinity uptake both in the cortex and in the hypothalamus, Tp being the more potent compound (Table 1). In the same experimental conditions high affinity 5-HT uptake by platelets was completely blocked after the *in vivo* treatment with THβCs (data not shown). Repeated administration of 5-MeOT (25 mg/kg i.p. daily for 15 days) decreased the B_{max} value of ^{3}H-IMI binding to rat cortical membranes, without affecting the affinity of these recognition sites (Figure 4). As shown in Figure 4, the concomitant treatment with pCPA did not interfere with the 5-MeOT-induced decrease of the density of ^{3}H-IMI binding sites.

Discussion

It is generally accepted that ^{3}H-IMI recognition sites could be considered a target in

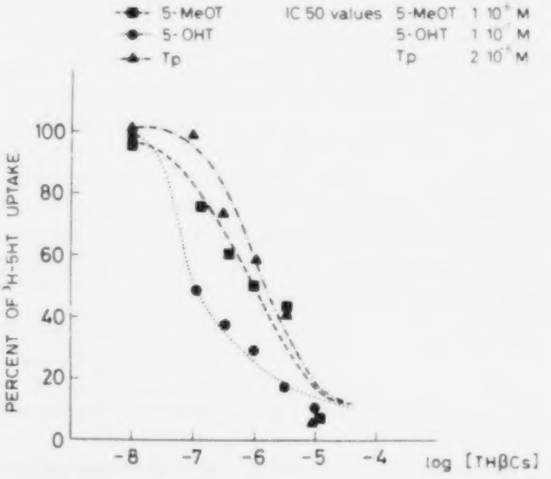


FIGURE 3. Inhibition of *in vitro* ^{3}H-5-HT uptake in cortical slices by 5-MeOT, 5-OHT, and Tp. Samples were incubated at 37°C for 15' in the presence of 10^{-7}M ^{3}H-5-HT and increasing concentration (10^{-8}M to 5×10^{-5}M) of THβCs. For blanks, 10^{-5}M fluoxetine was employed (for details, see Materials and Methods).

best copy available

TABLE 1. V_{max} values of *in vitro* ^{3}H-5HT high affinity uptake in cortical and hypothalamic slices after *in vivo* administration of 5-MeOT, 5-OHT, and Tp.

Treatments	V_{max} (pmoles/mg protein/min)	
	Cortex	Hypothalamus
Controls (saline)	29.58 ± 3.05	19.60 ± 0.65
5-MeOT (25 mg/kg i.p.)	16.10 ± 1.04*	13.80 ± 0.31*
5-OHT (25 mg/kg i.p.)	5.37 ± 0.47**	8.33 ± 0.17*
Tp (25 mg/kg i.p.)	1.00 ± 0.03**	6.40 ± 0.15**

Rats were killed by decapitation 20 minutes after the injection of each compound. Slices were immediately obtained and incubated at 37°C for 15 minutes in the presence of increasing concentrations of ^{3}H-5HT (see Materials and Methods for details). Each sample was assayed in triplicate.

Data are the mean ± S.E.M. of three separate experiments.

$^*p < 0.05$; $^{**}p < 0.01$ (Dunnett's *t* test).

the action of ADs, since a prolonged treatment with these drugs, especially the tricyclics, induces a marked reduction in the cerebral density of these sites (Raisman et al., 1980; Kinnier et al., 1981; Racagni et al., 1983). Moreover, recent reports from our laboratory indicate that not only typical, but also atypical ADs, such as fluvoxamine, citalopram, viloxazine, and dothiepin, are able to decrease the concentration of ^{3}H-IMI binding sites (Brunello et al., submitted).

The precise physiological role of ^{3}H-IMI recognition sites is still unknown; however, there is strong evidence indicating that these sites may act as modulators of the 5-HT-uptake molecular complex at the level of serotonergic terminals (Langer et al., 1980; Barbaccia et al., 1983b). In this line, concomitant, though opposite, modifications have been observed in the kinetic properties of ^{3}H-IMI binding and 5-HT-uptake, either in pharmacological conditions, i.e., chronic treatment with typical and atypical ADs, or in physiological situations, i.e., the aging processes (Brunello et al., 1985a).

In addition, clinical studies performed in human platelets indicate the coexistence of altered B_{max} of ^{3}H-IMI binding and V_{max} of 5-HT uptake in depressed patients (Briley et al., 1980; Suranyi-Cadotte et al., 1985).

Though ^{3}H-IMI recognition sites are mainly concentrated on central serotonergic terminals (Sette et al., 1981; Brunello et al., 1982b), it is unlikely that 5-HT itself can be considered as the endogenous ligand for these sites, since it displaces ^{3}H-IMI with low affinity (Raisman et al., 1979).

In agreement with these results, data reported in Figure 1 suggest the lack of a direct involvement of 5-HT in the modulation of ^{3}H-IMI recognition sites, since no modification in the kinetic properties of ^{3}H-IMI binding was observed after depletion of brain 5-HT content with pCPA.

Moreover, inhibition of 5-HT synthesis by pCPA does not counteract the reduction of the density of ^{3}H-IMI binding sites induced by prolonged DMI treatment (Figure 1). These data indicate that 5-HT is not involved in the adaptive mechanisms which lead to the desensitization of ^{3}H-IMI binding sites, whereas it has been shown to play a permissive role in the down-regulation of β-adrenoreceptors induced by chronic DMI (Brunello et al., 1982a; Janowsky et al., 1982; Brunello et al., 1985b).

The existence of endogenous ligands for the ^{3}H-IMI recognition site as physiological modulators of the 5-HT uptake molecular complex has been largely postulated (Barbaccia et al., 1983b; Langer et al., 1984; Rehavi et al., 1985). Among these, some putative derivatives (Buckholtz, 1980) of indoleamines, THβCs, have been shown to inhibit both ^{3}H-IMI binding and 5-HT uptake (Langer et al.,

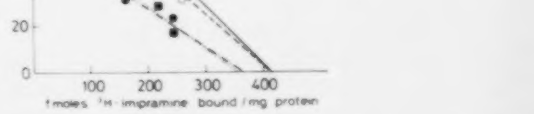


FIGURE 4. Scatchard analysis of ^{3}H-IMI binding to cortical membranes after prolonged treatment with 5-MeOT, pCPA, pCPA + 5-MeOT or vehicle (saline). Rats received pCPA, 300 mg/kg i.p. daily for 3 days followed by 100 mg/kg i.p. every other day for 15 days, 5-MeOT, 25 mg/kg i.p. for 15 days, pCPA + 5-MeOT, or saline. ^{3}H-IMI binding was performed as described in Materials and Methods. Data are the mean ± SEM of three separate experiments, each made in triplicate. $^*p < 0.05$ vs saline; $^+p < 0.05$ vs pCPA (Dunnett's "t" test).

1984; Segonzac et al., 1985). As shown in Figure 2, 5-MeOT, 5-OHT, and Tp inhibit competitively ^{3}H-IMI binding; in particular 5-MeOT is able to displace 50 percent of ^{3}H-IMI at high nanomolar concentration, being therefore as active as DMI.

In our experimental conditions THβCs are able to inhibit 5-HT uptake, both *in vitro* (Figure 3) and *in vivo* (Table 1). In agreement with data reported by Langer et al. (1984), 5-OHT is the more potent compound *in vitro*. In contrast it is now shown (Figure 3) that Tp, which inhibits 5-HT uptake in synaptosomes only at concentrations greater than 2000 μM, is as potent as 5-MeOT in cortical slices. Moreover, Tp when administered *in vivo* decreases the V_{max} of 5-HT uptake much more than 5-MeOT and 5-OHT (Table 1). These data could be explained by considering an *in vivo* metabolic conversion of Tp (Rommelspacher et al., 1978), which is partially preserved in slices and absent in synaptosomes.

Since 5-MeOT displays the higher affinity towards ^{3}H-IMI binding sites and inhibits also 5-HT uptake in a considerable manner, it was of interest to evaluate the effect of a prolonged treatment with 5-MeOT on ^{3}H-IMI binding. In particular 5-MeOT was daily administered at 25 mg/kg, a dose which has been demonstrated active in endocrine studies (Rovescalli et al., 1986).

As shown in Figure 4, the density of ^{3}H-IMI recognition sites is significantly reduced by chronic 5-MeOT. The magnitude of this decrease is about 25 to 30 percent and comparable to that obtained with DMI. Moreover, in line with data shown in Figure 1, the effect of 5-MeOT on ^{3}H-IMI binding does not seem to involve 5-HT directly, since it is maintained in pCPA + 5-MeOT-treated rats.

In conclusion, the present paper provides evidence that, unlike the effects of chronic ADs on adrenergic system which require a functional interaction with serotonergic neurons (Janowsky et al., 1982; Racagni & Brunello, 1984; Brunello et al., 1985b), ^{3}H-IMI binding sites seem to be poorly sensitive to 5-HT presence, both in basal condition and during pharmacological manipulations, thus emphasizing the likelihood of a precise endogenous ligand for this site. The continuance of this study will investigate whether THβCs, particularly 5-MeOT, may physiologically modulate the supramolecular complex of 5-HT uptake.

References

Banerjee, S.P., Kung, L.S., Riggi, S.J., and Chande, S.K. Development of β-adrenergic receptor subsensitivity by antidepressants. *Nature*, 268:455–456, 1977.

Barbaccia, M.L., Brunello, N., Chuang, D.M., and Costa, E. On the mode of action of imipramine: relationship between serotonergic axon terminal function and down regulation of beta adrenergic receptors. *Neuropharmacology*, 22:373–383, 1983a.

Barbaccia, M.L., Gandolfi, O., Chuang, D.M., and Costa, E. Modulation of neuronal serotonin uptake by a putative endogenous ligand of imipramine recognition sites. *Proc. Natl. Acad. Sci. U.S.A.*, 80:5134–5138, 1983b.

Baumann, P.A., and Maitre, L. Blockade of presynaptic alpha-receptors and of amine uptake in the rat brain by the antidepressant mianserin. *Naunyn Schmiedeberg's Arch. Pharmacol.*, 300:31–37, 1977.

Briley, M.S., Raisman, R., Sechter, D., et al. ^{3}H-imipramine binding in human platelets: a new biochemical parameter in depression. *Neuropharmacology*, 19:1209–1210, 1980.

Brunello, N., Barbaccia, M.L., Chuang, D.M., and Costa, E. Down-regulation of beta adrenergic receptors following repeated desipramine injections: Permissive role of serotonergic axons. *Neuropharmacology*, 21:1145–1149, 1982a.

Brunello, N., Chuang, D.M., and Costa, E. Different synaptic location of imipramine and mianserin binding sites. *Science*, 215:1112–1114, 1982b.

Brunello, N., Riva, M., Volterra, A., and Racagni, G. Age-related changes in 5-HT uptake and ^{3}H-imipramine binding sites in rat cerebral cortex. *Eur. J. Pharmacol.*, 110:393–394, 1985a.

Brunello, N., Volterra, A., Cagiano, R., et al. Biochemical and behavioral changes in rats after prolonged treatment with desipramine: Interaction with p-chlorophenylalanine. *Naunyn Schmiedeberg's Arch. Pharmacol.*, 331:20–22, 1985b.

Brunello, N., Riva, M., Volterra, A., and Racagni, G. Effects of some tricyclic and non tricyclic antidepressants on ^{3}H-imipramine binding and serotonin uptake in rat cerebral cortex after prolonged treatment. Submitted, 1986.

Buckholtz, N.S. Neurobiology of tetrahydro-β-carbolines. Minireview, *Life Sci.* 27:893–903, 1980.

Janowsky, A., Okada, F., Manier, D.H., et al. Role of serotonergic input in the regulation of beta adrenergic receptors-coupled adenylate cyclase system. *Science*, 218:900–901, 1982.

Kinnier, W.J., Chuang, D.M., Gwynn, G., and Costa, E. Characteristics and regulation of high affinity ^{3}H-imipramine binding to rat hippocampal membranes. *Neuropharmacolgy*, 20:411–419, 1981.

Korf, J. Central molecular aspects of tricyclic antidepressant drug action. Reviews in *Pure and Applied Pharmacological Sciences*, 4:139–212, 1983.

Langer, S.Z., Moret, C., Raisman, R., et al. High-affinity ^{3}H-imipramine binding in rat hypothalamus: Association with uptake of serotonin but not of norepinephrine. *Science*, 210:1133–1135, 1980.

Langer, S.Z., Raisman, R., Tahraoui, L., et al. Substituted tetrahydrobetacarbolines are possible candidates as endogenous ligands of the ^{3}H-imipramine recognition site. *Eur. J. Pharmacol.*, 98:153–154, 1984.

Lowry, D.H., Rosenbrough, N.J., Perr, A.L., and Randall, R.J. Protein measurement with phenol reagent. *J. Biol. Chem.*, 193:829–831, 1951.

Racagni, G., Mocchetti, I., Renna, G., and Cuomo, V. In vivo studies on central noradrenergic synaptic mechanisms after acute and chronic antidepressant drug treatment: Biochemical and behavioral comparison. *J. Pharm. Exp. Ther.*, 223:227–234, 1982.

Racagni, G., Mocchetti, I., Calderini, G., et al. Temporal sequence of changes in central noradrenergic system of rat after prolonged antidepressant treatment: Receptor desensitization and neurotransmitter interactions. *Neuropharmacology*, 22:415–424, 1983.

Racagni, G., and Brunello, N. Transynaptic mechanisms in the action of antidepressant drugs. *Trends Pharmacol. Sci.*, 5:527–531, 1984.

Raisman, R., Briley, M., and Langer, S.Z. Specific tricyclic antidepressant binding sites in rat brain. *Nature*, 281:148–150, 1979.

Raisman, R., Briley, M., and Langer, S.Z. Specific tricyclic antidepressant binding sites in rat brain characterized by high affinity ^{3}H-imipramine binding. *Eur. J. Pharmacol.*, 61:373–380, 1980.

Rehavi, M., Ventura, I., and Sarne, Y. Demonstration of endogenous "imipramine-like" material in rat brain. *Life Sci.*, 36:687–693, 1985.

Rommelspacher, H., Strauss, S., and Heyck Cohnitz, C. Inhibition of 5-hydroxytryptamine uptake by tetrahydronorharmane in vivo. *Naunyn Schmiedeberg's Arch. Pharmacol.*, 303:229–233, 1978.

Rovescalli, A.C., Brunello, N., Franzetti, C., and Racagni, G. Interaction of putative endogenous tryptolines with hypothalamic serotonergic system and prolactin secretion in adult male rats. *Neuroendocrinology* (in press).

Segonzac, A., Shoemaker, H., Tateishi, T., and Langer, S.Z. 5-Methoxytriptoline, a competitive endocoid acting at ^{3}H-imipramine recognition sites in human platelets. *J. Neurochem.* 45:249–256, 1985.

Sette, M., Briley, M.S., and Langer S.Z. Localization of tricyclic antidepressant binding sites on serotonin nerve terminals. *J. Neurochem.*, 37:40–42, 1981.

Suranyi-Cadotte, B.E., Quirion, E., Nair, N.P.V., et al., Imipramine treatment differentially affects platelet ^{3}H-imipramine binding and serotonin uptake in depressed patients. *Life Sci.*, 36:795–799, 1985.

Vetulani, J., and Sulser, F. Action of various antidepressant treatment reduced reactivity of noradrenergic cyclic AMP generating system in limbic forebrain. *Nature*, 257:495–496, 1975.

Drug Washout Effects on Clinical Studies in Depression and Schizophrenia

Chair:

Stephen H. Koslow, Ph.D.

National Institute of Mental Health
Rockville, MD 20857

Effects of Drug Washout on CSF Monoamine and Psychoendocrine Variables

Hans Ågren, M.D., Ph.D.,[1] and William Z. Potter, M.D., Ph.D.[2]

Introduction

Psychoactive drugs have been so successfully incorporated in psychiatric hospital practice that postponing drug treatment after a short initial period of evaluation at times is considered unethical. Issues like psychobiological research being dependent on reliable baseline conditions compete with a rational use of psychiatric beds. Research protocols in depression usually demand 8 to 14 days off antidepressants before tests, and the desirable period off neuroleptics in schizophrenia research is often 4 weeks. Few studies have focused on the minimum period of time before various biochemical effects of, for instance, antidepressants become insignificant. Rapid cessation of antidepressant medication has been shown to trigger increased concentrations of plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) (Charney et al., 1983). The same phenomenon has been observed during the abstinence phase of alcoholics (Hollister et al., 1980; Lubman et al., 1983). Alcoholic abstinence has also been clearly shown to trigger a transient elevation of CSF MHPG (Borg et al., 1981). We have analyzed the contribution of previous psychoactive medications in accounting for variance of several psychobiological variables in a large sample of affectively ill inpatients at the Department of Psychiatry at Uppsala University Hospital.

Methods

Patients

Currently or recently depressed patients ($n = 151$) were assessed using the Schedule for Affective Disorders and Schizophrenia (SADS) by Endicott and Spitzer (1979) and diagnosed as Research Diagnostic Criteria (RDC) major depressive disorders. Hamilton depression rating scale scores were extracted from selected SADS items following rules laid down by Endicott et al. (1981). Patients were subdivided into three groups (the "peak" va-

---

[1] Department of Psychiatry, University Hospital, S-751 85 Uppsala, Sweden.

[2] Section on Pharmacology, Laboratory of Clinical Science, National Institute of Mental Health, NIH, Bethesda, MD 20892

Address correspondence to Dr. Ågren.

TABLE 1. Composition of the Patient Sample, I.

	Males	Females
n	66	85
Age ± SD	42.7 ± 12.5	40.1 ± 12.7
HDRS ratings for Worst Week ± SD	25.5 ± 6.6	25.2 ± 6.8
HDRS ratings for Past Week ± SD	18.2 ± 9.0	18.8 ± 9.1
Time lapsed between Worst Week and Past Week:		
0: No time	34%	39%
1: 2–8 weeks	31%	23%
2: > 8 weeks	35%	38%

HDRS – Hamilton Depression Rating Scale extracted from the SADS (Endicott et al., 1981).

riable) according to time lapsed between period of peak severity of the depressive episode ("Worst Week") and the time of investigation ("Past Week") (*see* Table 1).

All patients were off antidepressant and neuroleptic medication for at least 8 days before lumbar punctures and 9 to 10 days before psychoendocrine tests. Almost half the males and one third of the females had received no antidepressants during the entire course of their current or recent depression, i.e., for several months (dichotomous variable "AD yes/no"). Close to 85 percent of both sexes were long-term free from neuroleptics, the rest having received low-dose drugs for anxiolytic purposes until recently (dichotomous variable "NL yes/no"). Patients were allowed continued medication with benzodiazepines throughout the investigation. About 40 percent had not taken any of this class of drugs for at least several months, about 35 percent had used these drugs at some time during the past week, and the rest were on a regular schedule (trichotomous variable "BDZ 0, 1, 2") (*see* Table 2).

TABLE 2. Composition of the Patient Sample, II.

	Males	Females
Patients long-term free from any antidepressant drugs	48%	35%
Patients long-term free from any neuroleptic drugs	84%	83%
Patients exposed to benzodiazepines:		
0: Long-term no BDZ	41%	37%
1: Some BDZ use past week	39%	32%
2: Daily regular medication	20%	31%

None of the sex differences is statistically significant.

Chemical and Hormonal Analyses

Monoamine metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) in lumbar CSF were assessed by gas chromatography—mass spectrometry by L. Svennerholm (Andersen et al., 1981). Analyses of plasma cortisol for 1 mg dexamethasone suppression tests and plasma thyroid-stimulating hormone (TSH) for thyroid-releasing hormone (TRH) stimulation tests were carried out using radioimmunological assays as described by Ågren and Wide (cortisol: 1982; TSH: 1986).

Statistics

Information concerning prior drug usage (yes/no for AD and NL; 0, 1, and 2 for BDZ) were in turns forced as a first independent variable in analyses of covariance (ANCOVA), "predicting," in turns, CSF MHPG, CSF HVA, CSF 5-HIAA, post-dexamethasone plasma cortisol at 8 a.m., 11 a.m., and 8 p.m., and δTSH. The cortisol and ΔTSH variables were log transformed before calculations. The General Linear Models (GLM) procedure in the Statistical Analysis System (SAS) package was used, with *F* values calculated on Type 1 Sums-of-Squares. Nine other independent variables were introduced as 2nd to 10th term in order to control for the influences of severity and stage of depression, sex, age, height, and weight as well as three interactional terms, thus allowing examination of a direct influence of the three drug treatment conditions on the biological variables. If a partial correlation coefficient (evaluated through *F* values) was significant at the 5 percent level, the direct univariate correlation was checked by calculating Spearman's r_s.

Results

Withdrawal From Antidepressants

The ANCOVAs demonstrated a significant influence of late cessation of antidepressant drugs on CSF MHPG. Table 3 shows this variable to be the only one reaching a signifi-

TABLE 3. CSF MHPG Predicted by Previous Antidepressant Medication Status and Nine Clinical Covariates by ANCOVA ($N = 133$).

Dependent variable: CSF MHPG Independent variables (Type I Sums-of-Squares):	F	r_s
AD Medication	3.98*	0.17*
HDRS Past Week	0.60	
Sex[b]	0.34	
Peak[c]	0.00	
AD × HDRS	0.49	
AD × Sex	0.28	
AD × Peak	0.04	
Age	4.32*	
Height	0.26	
Weight	0.68	

[a] Significant difference on Scheffé's test:

	CSF MHPG	n
	AD yes: 42.5 nmol/l	76
	AD no: 39.4 nmol/l	57

Minimum significant difference ($\alpha = 0.05$): 3.1 nmol/l

[b] Males: + 1; females: − 1.

[c] Values 0, 1 or 2; see text.

* $p < 0.05$.

cant partial correlation with CSF MHPG and also to show a significant direct univariate correlation. Scheffé's test demonstrates late withdrawal to increase CSF MHPG by a mean of 3.1 nmol/l, just reaching significance at the 5 percent level.

AD withdrawal did not significantly affect CSF HVA, CSF 5-HIAA, or any cortisol variable. However, Table 4 indicates a highly significant effect on ΔTSH: even when significant negative influences from depressive severity and male sex were accounted for, late AD withdrawal is associated with a less blunted ΔTSH (mean difference between the two groups is 2.8 mU/l).

Neuroleptic Withdrawal

No significant effect on any biological variable was detected.

TABLE 4. ΔTSH Predicted by Previous Antidepressant Medication Status and Nine Clinical Covariates by ANCOVA ($N = 139$).

Dependent variable: $\log_{10}$ ΔTSH Independent variables (Type I Sums-of-Squares):	F	r_s
AD Medication	12.89**	0.17*
HDRS Past Week	15.28****	−0.23**
Sex[b]	19.63****	−0.36****
Peak[c]	1.06	
AD × HDRS	0.22	
AD × Sex	0.10	
AD × Peak	0.06	
Age	3.17	−0.20*
Height	3.36	−0.24**
Weight	1.66	

[a] Significant difference on Scheffé's test:

	antilog$_{10}$ ΔTSH	n
	AD yes: 7.94 mU/l	78
	AD no: 5.13 mU/l	61

Minimum significant difference ($\alpha = 0.05$): 1.27 mU/l

[b] Males: + 1; females: − 1.

[c] Values 0, 1 or 2; see text.

* $p < 0.05$.

** $p < 0.01$.

**** $p < 0.0001$.

Benzodiazepine Usage

The extent of medication with benzodiazepines was not associated with any effects on CSF variables. However, Table 5 shows more regular usage to be associated with a more blunted ΔTSH, which obviously is not explained by severity of depression since the interaction term BDZ × Hamilton score is nonsignificant. A similar but weaker effect ($p = 0.05$) was seen as benzodiazepines' increasing post-dexamethasone plasma cortisol at 11 a.m. Since the univariate correlation was nonsignificant and there was no effect on plasma cortisol at either 8 a.m. or 8 p.m., the meaning of this finding is uncertain.

Discussion

The main finding of this study is moderately increased CSF MHPG concentrations in patients in whom antidepressants were withdrawn a short period before lumbar puncture when compared with patients long-term free from these drugs. It is possible that this MHPG elevation represents an abstinence reaction similar to what Charney et al. (1982) observed in human plasma. A parallel observation is that effects of desipramine persist after 3 weeks, at least on the growth hormone response to clonidine (Corn et al., 1984). Furthermore, in rats chronic treatment with antidepressants may increase the concentration of MHPG in whole brain (Przegalinski et al., 1981). Whatever the cause, the observed MHPG difference was in reality quite small (only 3.1 nmol/l) and by itself may not be sufficient to invalidate interpretations of CSF MHPG.

The only other drug effects detected were on TSH responses to TRH injections. Antidepressant withdrawal was associated with less blunted ΔTSH, and might then be regarded as a source of false negative tests. Current benzodiazepine medication, conversely, was related to reduced TSH response to TRH and might be a source of false positive tests.

No convincing drug withdrawal effects or drug effects were observed for CSF HVA and 5-HIAA concentrations and on plasma cortisol concentrations after dexamethasone administration.

Summary

The effects of cessation of antidepressant and neuroleptic medication and of degree of benzodiazepine usage upon CSF monoamine metabolite concentrations, post-dexamethasone plasma cortisol levels and TSH responses to TRH were investigated in 151 patients with RDC major depressive disorders. Late stopping antidepressants prior to lumbar puncture produced a minor but statistically significant increase in CSF MHPG as well as a less blunted ΔTSH, but no other effects. Usage of benzodiazepines was only

TABLE 5. ΔTSH Predicted by Operationally Defined Benzodiazepine Medication Status and Nine Clinical Covariates by ANCOVA ($N = 124$).

Dependent variable: $\log_{10}$ ΔTSH Independent variables (Type I Sums-of-Squares):	F	r_s
BDZ Medication[a]	7.26^{**}	-0.21^{*}
HDRS Past Week	10.14^{**}	-0.23^{**}
Sex[b]	28.02^{****}	-0.36^{****}
Peak[a]	2.18	
BDZ × HDRS	0.25	
BDZ × Sex	0.30	
BDZ × Peak	0.66	
Age	2.08	
Height	2.31	
Weight	0.17	

[a] Values 0, 1 or 2; see text.
[b] Males: +1; females: −1.
* $p < 0.05$.
** $p < 0.01$.
**** $p < 0.0001$.

associated with more blunted ΔTSH. These effects were unrelated to severity and phase of depression, sex, age, height, or weight.

Acknowledgments

Support from the National Institute of Mental Health, Bethesda, MD; the Swedish Medical Research Council (grant #6604); and the Fredrik and Ingrid Thuring Foundation is gratefully acknowledged.

References

Ågren, H., and Wide, L. Patterns of depression reflected in pituitary—thyroid and pituitary—adrenal endocrine changes. *Psychoneuroendocrinology*, 7:309–327, 1982.

Ågren, H., and Wide, L. TRH test with analyses of TSH, prolactin, and GH in subgroups of patients with major depressive disorders. *Acta Psychiat. Scand.* (1986, in press).

Andersen, O., Johansson, B., and Svennerholm, L. Monoamine metabolites in successive samples of spinal fluid. *Acta Neurol. Scand*, 63:247–254, 1981.

Borg, S., Czarnecka, A., Kvande, H., and Sedvall, G. Central noradrenaline metabolism and clinical conditions of alcoholic patients during withdrawal. In: Perris, C., Struwe, G., and Jansson, B. (eds.), *Biological Psychiatry*. Amsterdam: Elsevier/North-Holland Biomedical Press, 1981, pp. 924–928.

Charney, D.S., Heninger, G.R., Sternberg, D.E., and Landis, H. Abrupt discontinuation of tricyclic antidepressant drugs: evidence for noradrenergic hyperactivity. *Brit. J. Psychiat.*, 141:377–386, 1982.

Corn, T.H., Thompson, C., and Checkley, S.A. Effects of desipramine upon central adrenoceptor function in normal subjects. *Brit. J. Psychiat.*, 145:139–145, 1984.

Endicott, J., and Spitzer, R.L. Use of the Research Diagnostic Criteria and the Schedule for Affective Disorders and Schizophrenia to study affective disorders. *Am. J. Psychiat.*, 136:52–56, 1979.

Endicott, J., Cohen, J., Fleiss, J., and Sarantakos, S. Hamilton depression rating scale: extracted from regular and change versions of the Schedule for Affective Disorders and Schizophrenia. *Arch. Gen. Psychiat.*, 38:98–103, 1981.

Hollister, L.E., Prusmack, J.J., Knopes, K., and Kanaske, K. Asthma and alcohol withdrawal as sources of artefact in urinary excretion of 3-methoxy-4-methoxyphenylglycol (MHPG). *Communic. Psychopharmacol.*, 4:135–140, 1980.

Lubman, A., Emrick, C., Mosimann, W.F., and Freedman, R. Altered mood and norepinephrine metabolism following withdrawal from alcohol. *Drug Alcoh. Depend.*, 12:3–13, 1983.

Przegalinski, E., Kordecka-Magiera, A., Mogilnicka, E., and Maj, J. Chronic treatment with some atypical antidepressants increases the brain level of 3-methoxy-4-methoxyphenylglycol (MHPG) in rats. *Psychopharmacology*, 74:187–190, 1981.

Brain Norepinephrine and Stress: A Vertical Synthesis

Co-Chairs:

Barry L. Jacobs, Ph.D.
Princeton University
Princeton, NJ 08544

David S. Segal, Ph.D.
University of California, San Diego
La Jolla, CA 92093

Behavioral Depression Following Clonidine Withdrawal: A New Animal Model of Long-Lasting Depression?

Laura J. Hoffman, Ph.D.,[1] and Jay M. Weiss, Ph.D.[2,3]

In attempting to learn more about human clinical depression, numerous animal models of depression have been produced (Costa, Garattini & Valzelli, 1960; Nagayama, Hingtgen & Aprison, 1980; Hatotani, Nomura & Kitayama, 1982; McKinney, Soumi & Harlow, 1971; Seligman, 1974; Porsolt, Anton, Blavet & Jalfre, 1978; Katz, Roth & Carroll, 1979). These models vary in the extent to which they reproduce the behavioral symptoms of human depression. Among the symptoms seen in these models are psychomotor alterations, loss of appetite and weight, loss of normal grooming, play, and competitive behavior, and sleep changes. In some instances, modeling procedures generate sufficient symptoms to satisfy the criteria for a major depressive episode set forth in the Diagnostic and Statistical Manual of the American Psychiatric Association, 3rd edition (1980) (e.g., Weiss, Bailey, Goodman, Hoffman, Ambrose, Salman, & Charry, 1982). However, the duration of symptoms seen in models is of concern in that the DSM-III requires that symptoms persist for a minimum of 2 weeks. In contrast to this, many of the symptoms in the animal models described above are short-lived (*see* Maier, Drugan, Grau, Hyson, McLennan, Moye, Madden & Barchas, 1983; Overmier & Seligman, 1967; Weiss, Goodman, Losito, Corrigan, Charry & Bailey, 1981; Kaufman & Rosenblum, 1967).

We report here a procedure which, following treatment, generates depression of active behavior that endures without further treatment for at least 40 days. Also, this behavioral depression, once produced, can be reversed by the chronic, but not acute, treatment with the tricyclic antidepressant desmethylimipramine (DMI). In this animal model, behavioral depression is produced by administering clonidine to laboratory rats for a 2-week period and then removing the drug, after which the animals show reduced activity in a swim test. Reduction of motor activity is the most common symptom reproduced in animal models of depression (Costa et al.,

---

[1] Creedmoor Psychiatric Center, Elmhurst Community Service, Corona, NY 11427.
[2] Department of Psychiatry, Box 3829, Duke University Medical Center, Durham, NC 27710.
[3] To whom correspondence should be addressed.

1960; Katz et al., 1979; Kaufman & Rosenblum, 1967; Klinger, Barta, & Kemble, 1974; Porsolt, LePichon & Jalfre, 1977; Weiss & Glazer, 1975).

The pharmacological procedure introduced here was derived from previous reports of effects of clonidine. Numerous studies have reported that acute administration of clonidine depresses active behavior, reducing locomotor activity (Anden, Gabrowska, & Strombom, 1976; Maj, Sowinska, Baran, & Kapiurkiewicz, 1972; Maj, Baran, Sowinska, & Zielinski, 1975; Skolnick, Daly, & Segal, 1979; Tilson, Chamberlain, Gylys, & Boyniski, 1977), operant behavior (Harris, Snell, Loh, & Way, 1977; Meyer, El-Azhary, Bierer, Hanson, Robbins, & Sparber, 1977), active avoidance responding (Kostowski, Plaznik, Pucilowski, Bidzinski, & Hauptmann, 1981; Laverty & Taylor, 1969), exploratory behavior (Herman, Brus, Drybanki, Szkilnik, & Slominska, 1976; Strombom & Svensson, 1980), and reward/self-stimulation (Franklin & Herberg, 1977; Hunt, Atrens, Chesher, & Becker, 1976; Spencer & Revzin, 1976; Vetulani, Leith, Stawarz, & Sulser, 1977). However, a number of studies have also indicated that when clonidine is administered repeatedly, behavioral deficits that occur with acute administration of the drug are no longer seen (Meyer et al., 1977; Laverty & Taylor, 1969); thus, animals apparently habituate to the effects of the drug, at least with respect to certain of its behavioral consequences. However, and most important, one group of investigators additionally reported that subsequent removal of clonidine after the drug had been administered repeatedly resulted in reappearance of a deficit (suppression of operant performance) that had been seen when the drug was administered acutely. This behavioral suppression was observed to continue for at least 9 days after removal of the drug (Meyer et al., 1977).

On the basis of the foregoing, we surmised that repeatedly administering clonidine to rats and then withdrawing the drug might result in their showing reduced behavioral activity as normally shown after acute administration of the drug, and that this reduction in active behavior might persist for some time. Should this prove to be the case, the result would be drug-free animals (drug having been withdrawn) that showed long-lasting depression of active behavior, a potential animal model of clinical depression in which the symptom(s) was long-lasting.

In the experiments we carried out, depression of active behavior was assessed by placing animals (Holzman male albino rats obtained from Charles River breeding laboratories) in a tank of water and measuring the amount of activity they showed. This swim test measures the propensity of an animal to engage in, and the capacity for, active behavior in a situation that is threatening and therefore highly motivating. The test, which appears to be superior in certain respects to measuring spontaneous activity when modeling depression (Weiss, Simson, Hoffman, Ambrose, Cooper, & Webster, 1986) has been used to detect depression of active behavior that follows exposure to a strong uncontrollable stressor (Weiss et al., 1981). To quantify activity in this test, the amount of time that an animal struggles (struggling defined as vigorous activity in which the front paws break the surface of the water) and the amount of time that it floats (floating defined as no movement of any limb) are measured. The two behaviors quantified are shown in Figure 1. To obtain an overall index of activity for an animal, time spent floating is subtracted from time spent struggling, and the resulting value is an Activity Score (AS). This index has proved to be particularly convenient because an untreated, naive animal normally struggles for about as much time as it floats in a 15-minute swim test, thus achieving an Activity Score of approximately zero on the test. Consequently, negative Activity Scores (i.e., more floating than struggling) indicate depression of active behavior while positive Activity Scores (i.e., more struggling than floating) indicate stimulation of active behavior.

Figure 2 shows the results of the initial study. Performance of clonidine-treated groups (Clonidine A and B) is shown as the difference from the performance of a group of animals that was treated as were the clonidine-treated groups but did not receive any clonidine during the experiment; i.e., were given placebo (0.85 percent saline) injections and normal drinking water throughout (*see* below). On day 1, clonidine-treated

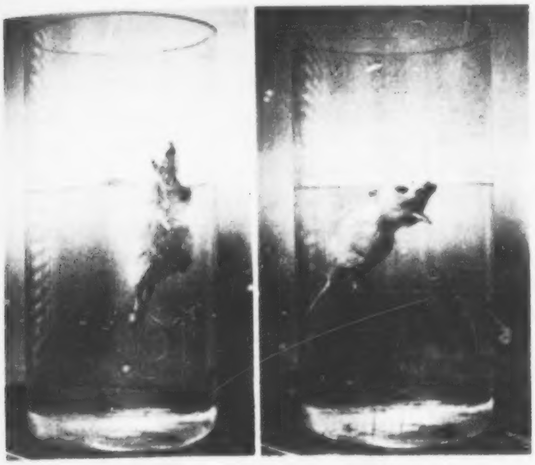


FIGURE 1. Shown above are the two types of behavior that were quantified (timed) in the swim test. At left is shown an animal engaged in struggling behavior in which the front paws break through the surface of the water in an apparent attempt to escape from the tank. At right is shown an animal engaged in floating behavior in which all four limbs are motionless in the water. Around the animal's midsection is visible a strip of tape which holds in place on its back a lightweight plastic bubble filled with air which prevents the animal from sinking if it ceases activity.

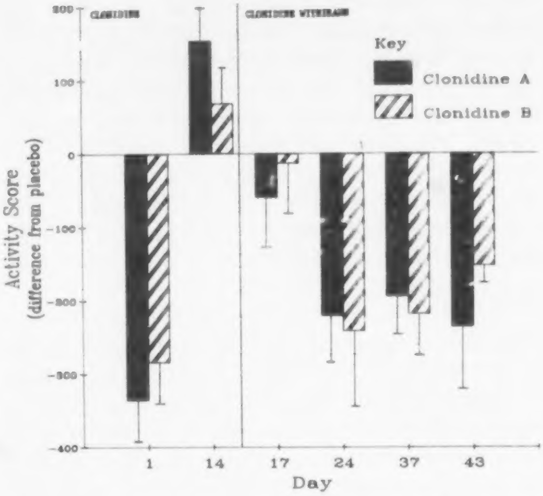


FIGURE 2. Mean (and standard error) Activity Scores in the swim test for two groups ($N = 6$ per group) treated with clonidine for 14 days after which the drug was then withdrawn. For details of clonidine treatment, *see* text. Mean Activity Scores for the clonidine-treated groups on each day are shown as the difference from the mean Activity Score of a group ($N = 6$) of untreated animals (i.e., placebo) tested on that day. When compared with the untreated group, mean Activity Scores of clonidine-treated groups were significantly different (at least $p = .05$) on the following days: Clonidine A—day 1, 24, 37, 43; Clonidine B—day 1, 24, 37.

animals were given an injection of clonidine (0.1 mg/kg) and tested in the swim tank 10 minutes later. As can be seen in Figure 1, the activity of these animals was quite low relative to placebo-injected animals, typical of what investigators have generally found when this drug is given. Following this initial test, these animals were treated with clonidine for 14 days, Clonidine A receiving clonidine by daily injection (0.1 mg/kg) together with drug in their drinking water (3 μg/ml) while Clonidine B received drug in drinking water only. On day 14, these animals were injected with clonidine again as on day 1, and all animals tested in the same manner a second time. It can be seen that clonidine no longer depressed activity in the swim test; in fact, the activity of the Clonidine A group approached (but did not reach) being significantly greater than that of the untreated animals at this time. The drug was then withdrawn; no further injections were given and normal tap water was now supplied to the animals. At varying intervals thereafter, the animals were returned for testing to the swim tank. When tested 3 days after clonidine was withdrawn, activity of clonidine-treated animals did not differ significantly from that of nontreated animals, but on subsequent tests beginning at day 10 after drug was withdrawn, they showed a marked depression of activity. The depression of activity was still present on the final test given in this study 29 days after the drug was withdrawn, although the effect had diminished in the Clonidine B group by this time.

The basic phemonena described above—initial depression of activity in the swim test in response to injection of 0.1 mg/kg clonidine, no depression of activity in response to this injection after 14 days (or in some cases 15 days) of clonidine treatment, and, most important, the development of prolonged behavioral depression following withdrawal of the drug—has now been repeated in three subsequent experiments. In one of these experiments, the depression of activity following withdrawal of clonidine was found to be present 3 days after drug withdrawal, so that post-clonidine depression of active behavior may in some cases present itself earlier than was seen in the first experiment. However, reduction of activity in the swim test following withdrawal of drug was seen in all experiments. In the longest experiment conducted thus far, behavioral depression has been found 60 days after the drug was withdrawn.

To summarize, experiments have shown that following administration of clonidine for 14 to 15 days, withdrawal of the drug results in a decrease in active behavior that is quite long-lasting (i.e., at least 30 to 60 days). The next question addressed was whether this behavioral depression would respond to treatment with an antidepressant. The response to desmethylimipramine (DMI) was therefore examined.

The results are shown in Figure 3. As in Figure 1, performance of clonidine-treated groups is shown as the difference from a group of animals tested at the same times but not given any drug (i.e., injected with placebo when drug injection is normally given and maintained on tap water throughout). In this experiment, procedures for clonidine treatment were the same as those used for the Clonidine A group in the previous experiments. Following 15 days of clonidine treatment, the drug was withdrawn, which resulted, as expected, in behavioral depression in the swim test 7 days later (day 22). These clonidine-withdrawn (i.e., behaviorally depressed) animals were then divided into two groups matched for behavioral depression seen in day 22. Beginning on day 27, one of these groups was then given daily injections of DMI (4 mg/kg) while the other was given vehicle. When tested on the first day of DMI treatment (swim tests given 2 hours after drug injection), DMI produced no significant change in the behavioral depression of clonidine-withdrawn animals. When tested after 8 days of DMI, however, the behavioral activity of the clonidine-withdrawn animals was found to have improved to the point where it no longer was different from that of normal untreated animals, whereas clonidine-withdrawn animals that had been given daily injections of saline vehicle rather than DMI

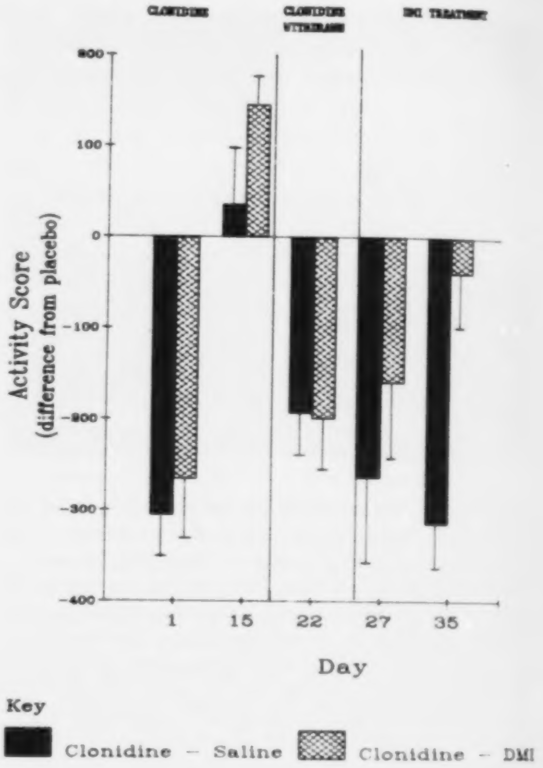


FIGURE 3. Mean (and standard error) Activity Scores in the swim test for two groups ($N = 9$ per group) treated with desmethylimipramine (DMI) (4 mg/kg) or saline vehicle after clonidine treatment for 15 days and withdrawal of clonidine. For details of clonidine treatment, *see* text. Mean Activity Scores for the clonidine-DMI and clonidine-saline groups on each day are shown as the difference from the mean Activity Score of a group ($N = 9$) of untreated animals (i.e., placebo) tested on that day. When compared with the untreated group, mean Activity Scores of clonidine-treated groups were significantly different (at least $p = .05$) on the following days: Clonidine-DMI—day 1, 22, 27; Clonidine-saline—day 1, 22, 27, 35. Also, clonidine-DMI differs significantly from clonidine-saline on day 35. (Note: in the results shown above, the clonidine-DMI group achieved somewhat higher activity scores [though not significantly higher] than the clonidine-saline animals on day 15. However, the ability of repeated DMI treatment to eliminate behavioral depression following clonidine withdrawal, as seen above, has been repeated in a second experiment. In this study, the activity scores of clonidine-saline and clonidine-DMI groups were essentially the same on day 15, so that the therapeutic effect of DMI seen above is not due to a difference in the populations selected for the two groups.)

remained behaviorally depressed. Thus, DMI eliminated the reduction in active behavior produced by withdrawal from clonidine, and did so when given repeatedly (for 8 days) but not when given only once.

In summary, the first attempt to evaluate how behavioral depression in the swim test following withdrawal of clonidine would respond to pharmacological treatment revealed that this behavioral depression was markedly reduced by 8 days of DMI administration but not by the first administration of DMI. In showing a therapeutic result from repeated but not acute treatment with a tricyclic antidepressant, this initial examination found the model to be consistent with what is seen in clinical depression. This experiment also demonstrates the potential usefulness of the model in that it permits the therapeutic efficacy of a treatment to be tested on animals that begin therapy when behaviorally depressed (i.e., following withdrawal from clonidine) and will remain so without further drug or other manipulation in the absense of therapeutic treatment.

In closing this report, some brief comments will be made about possible mechanisms underlying the behavioral depression that follows withdrawal from clonidine. Given the potency of clonidine in stimulating alpha-2 adrenergic receptors (Starke, Montel, Gayk, & Merker, 1974), the first possibility that warrants consideration as the potential mediator of behavioral depression following clonidine withdrawal is a change in alpha-2 receptors. In fact, the impetus for undertaking the procedures described above came in part from recent findings which suggested that withdrawing animals from clonidine was likely to affect certain alpha-2 receptors so as to produce behavioral depression. To be specific, our laboratory has recently found that behavioral depression which follows exposure of animals to uncontrollable shock appears to result from a "functional blockade" of alpha-2 receptors in the locus coeruleus (LC) due to large depletion of norepinephrine (NE) in this brain region brought about by the uncontrollable shock (e.g., Weiss et al., 1982; Weiss & Simson, 1985). If this hypothesized mechanism is correct, active behavior should also become depressed if alpha-2 receptors in the LC were made subsensitive. Several investigators (Engberg, Elam, & Svensson, 1982; Ishii, Yamamoto, & Kato, 1982) have demonstrated that prolonged administration of clonidine produces subsensitivity of presynaptic alpha-2 receptors in the LC region of the brain and, consequently, an increase in firing of LC cells (since alpha-2 receptors in the LC normally inhibit the firing of LC cells) after withdrawal of the clonidine. Thus, behavioral depression in the swim test following clonidine withdrawal may occur because alpha-2 receptors in the LC have become subsensitive, and thus this behavioral depression would share a similar mediation (i.e., disinhibition of LC cells) as behavioral depression produced by uncontrollable shock.

Another possibility focuses on beta receptors. Kistler and Davis (1980) have reported that, soon after animals were withdrawn from 6 days of clonidine treatment, an increase in the cyclic AMP response to the beta-adrenergic agonist isoproterenol is evident in brain stem tissue (but not in cortex). Thus, behavioral depression following withdrawal of clonidine might be related to an elevated responsiveness of beta adrenergic receptors in the brain stem. This possibility is attractive in that the brain stem contains loci which mediate clonidine's potent effects on the cardiovascular system (e.g., Schmitt, 1977; Kobinger, 1978; Zandberg, De Jong, & De Weid, 1979; Timmermans & Van Zwieten, 1981). This possibility also fits well with the fact that chronic, but not acute, treatment with DMI was found to eliminate behavioral depression following clonidine withdrawal in that the cyclic AMP response of brain tissue is reduced by chronic, but not acute, treatment with DMI (e.g., Vetulani, Stawarz, Dingell, & Sulser, 1976). It can be pointed out, however, that the therapeutic effect of chronic DMI (as well as its absence with acute DMI) is also consistent with the hypothesis advanced in the previous paragraph in that subsensitivity of alpha-2 inhibitory receptors in the LC will elevate norepinephrine release in the projection fields of the LC and consequently stimulate beta receptors in these regions at a higher-than-normal level; thus, down regulation of beta receptors should similarly counteract effects of this neural defect.

Turning to future analyses, numerous questions about this model remain to be answered before its value can be properly assessed. For example, it will be important to determine how many, if any, additional symptoms of clinical depression characterize the model in addition to the alteration in active behavior reported here. It similarly will be important to determine how specifically the behavioral depression responds to antidepressant treatment. Concerning mechanism, the time course of potential mediating changes (i.e., subsensitivity of alpha-2 receptors) needs to be measured in order to determine whether such changes present themselves at an appropriate time and are long-lasting. Through such studies, a useful animal model characterized by long-lasting behavioral depression may be developed.

Acknowledgments

Supported in part by grant BRSG SO7 RR05405 from the Public Health Service. The authors gratefully acknowledge the helpful comments of Dr. Prudence Simson in preparation of this manuscript.

References

Anden, N.E., and Grabowska, M. Pharmacological evidence for a stimulation of dopamine neurons by noradrenaline neurons in the brain. *Eur. J. Pharmacol.*, 39:275–282, 1976.

Costa, E., Garattini, S., and Valzelli, L. Interaction between reserpine, chlorpromazine, and imipramine. *Experientia*, 16:461–463, 1960.

Diagnostic and Statistical Manual of Mental Disorders (DSM-III). American Psychiatric Association, Washington, DC. 1980.

Engberg, G., Elam, M., and Svensson, T.H. Clonidine withdrawal activation of brain noradrenergic neurons with specifically reduced alpha-2 receptor sensitivity. *Life Sci.*, 30(3):235–243, 1982.

Franklin, K.B.M., and Herberg, L.J. Presynaptic adrenoceptors: The depression of self-stimulation by clonidine and its restoration by piperoxane but not by phentolamine or phenoxybenzamine. *Eur. J. Pharmacol.*, 43:33–38, 1977.

Harris, R.A., Snell, D., Loh, H.H., and Way, E.L. Behavioral interactions between naloxone and dopamine agonists. *Eur. J. Pharmacol.*, 43:243–246, 1977.

Hatotani, N., Nomura, J., and Kitayama, I. Changes of brain monoamines in the animal model for depression. In: Langer, S.Z., Takahashi, R., Segawa, T., and Briely, M. (eds.), *New Vistas in Depression*. Oxford: Pergamon Press, 1982, pp. 65–72.

Herman, Z.S., Brus, R., Drybanki, A., et al. Influence of 6-hydoxydopamine on the behavioral effects induced by apomorphine or clonidine in rats. *Psychopharmacol.*, 50:73–80, 1976.

Hunt, G.E., Atrens, D.M., Chesher, G.B., and Becker, G.T. Alpha-noradrenergic modulation of hypothalamic self-stimulation: Studies employing clonidine, L-phenylephrine, and alpha-methyl-p-tyrosine. *Eur. J. Pharmacol.*, 37:105–111, 1976.

Ishii, K., Yamamoto, S., and Kato, R. Development of clonidine tolerance in the rat vas deferens: Cross tolerance to other presynaptic inhibitory agents. *Life Sci.*, 30:285–292, 1982.

Katz, R.J., Roth, K.A., and Carroll, B.J. Acute and chronic stress effects on open field activity in the rat: Implications for a model of depression. *Neurosci. Biobehav. Rev.*, 5:247–251, 1981.

Kaufman, I.C., and Rosenblum, L.A. Depression in infant monkeys separated from their mothers. *Science*, 155:1030–1031, 1967.

Kistler, K., and Davis, J.N. Beta-adrenergic supersensitivity in rat brainstem during clonidine withdrawal. *Life Sci.*, 26:1053–1059, 1980.

Klinger, E., Barta, S.G., and Kemble, E.D. Cyclic activity changes during extinction in rats: A potential model of depression. *Anim. Learn. Behav.*, 2:313–316, 1974.

Kobinger, W. Central alpha-adrenergic systems as targets for hypotensive drugs. *Rev. Physiol. Biochem. Pharmacol.*, 81:39–100, 1978.

Kostowski, W., Plaznik, A., Pucilowski, O., et al. Lesion of serotonergic neurons antagonizes clonidine-induced suppression of avoidance behavior and locomotor activity in rats. *Psychopharmacol.*, 73:261–264, 1981.

Laverty, R., and Taylor, K.M. Behavioral and biochemical effects of 2-(2, 6-dichlorophenylamino)-2-imidazoline hydrochloride (St 155) on the central nervous system. *Br. J. Pharmacol.*, 35:253–264, 1969.

Maier, S.F., Drugan, R., Grau, J.W., et al. Learned helplessness, pain inhibition, and the endogenous opiates. In: Zeiter, M.D., and Harzem, P. (eds.), *Advances in Analysis of Behavior*, Vol. 3. New York: John Wiley and Sons Ltd., 1983, pp. 275–323.

Maj, J., Baran, L., Sowinska, H., and Zielinski, M. The influence of cholinolytics on clonidine action. *Pol. J. Pharmacol.*, 27:17–26, 1975.

Maj, J., Sowinska, H., Baran, L., and Kapiurkiewicz, Z. The effect of clonidine on locomotor activity in mice. *Life Sci.*, 11:483–491, 1972.

McKinney, W., Suomi, S., and Harlow, H. Depression in primates. *Am. J. Psychiatr.*, 127:1313–1320, 1971.

Meyer, D.R., El-Azhary, R., Bierer, D.W., et al. Tolerance and dependence after chronic administration of clonidine to the rat. *Pharmacol. Biochem. Behav.*, 7:227–231, 1977.

Nagayama, H., Hingtgen, J.N., and Aprison, M.H. Pre- and postsynaptic serotonergic manipulation in animal models of depression. *Pharmacol. Biochem. Behav.*, 13:575–579, 1980.

Overmier, J.B., and Seligman, M.E.P. Effects of inescapable shock on subsequent escape and avoidance learning. *J. Comp. Physiol. Psychol.*, 63:23–33, 1967.

Porsolt, R.D., Anton, G., Blavet, N., and Jalfre, M. Behavioral despair in rats: A new model sensitive to antidepressant treatments. *Eur. J. Pharmacol.*, 47:379–391, 1978.

Porsolt, R.D., LePichon, M., and Jalfre, M. Depression: A new animal model sensitive to antidepressant treatments. *Nature*, 266:730–732, 1977.

Schmitt, H. The pharmacology of clonidine and related products. In: Gross, F. (ed.), *Antihypertensive Agents*. Berlin: Springer-Verlag, 1977, pp. 299–396.

Seligman, M.E.P. Depression and learned helplessness. In: Friedman, R.J., and Katz, M.M. (eds.), *The Psychology of Depression: Contemporary Theory and Research*. Washington, DC: V.H. Winston, 1974, pp. 83–125.

Skolnick, P., Daly, J.W., and Segal, D.S. Neurochemical and behavioral effects of clonidine and related imidazolines: interaction with alpha-adrenoceptors. *Eur. J. Pharmacol.*, 47:451–455, 1978.

Spencer, J., and Revzin, A. Amphetamine, chlorpromazine, and clonidine effects on self-stimulation in caudate or hypothalamus of the squirrel monkey. *Pharmacol. Biochem. Behav.*, 5:149–156, 1976.

Starke, K., Montel, H., Gayk, W., and Merker, R. Comparison of the effects of clonidine: An action on pre- and postsynaptic adrenoceptors in rabbit pulmonary artery. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 285:133–150, 1974.

Stone, E. Subsensitivity to norepinephrine as a link between adaptation to stress and antidepressant therapy: An hypothesis. *Res. Commun. in Psychol., Psychiatr., Behav.*, 4(3):241–255, 1979.

Strombom, U., and Svensson, T.H. Clonidine: Attenuation of sedative action by facilitated central noradrenergic neurotransmission. *J. Neurol. Trans.*, 47:29–39, 1980.

Tilson, H.A., Chamberlain, J.H., Gylys, J.A., and Buyniski, J.P. Behavioral suppressant effects of clonidine in strains of normotensive and hypertensive rats. *Eur. J. Pharmacol.*, 43(2):99–105, 1977.

Timmermans, P.B.M.W.M., and Van Zwieten, P.A. The postsynaptic alpha 2-adrenoceptor. *J. Auton. Pharmacol.*, 1:171–183, 1981.

Vetulani, J., Leith, N.J., Stawarz, R.J., and Sulser, F. Effects of clonidine on the noradrenergic cyclic AMP generating system in the limbic forebrain and on medial forebrain bundle self-stimulation behavior. *Experientia*, 33:1490–1491, 1977.

Vetulani, J., Stawarz, R., Dingell, J., and Sulser, F.A. A possible common mechanism of action of antidepressant treatments—reduction in the sensitivity of the noradrenergic cyclic AMP generating system in the rat limbic forebrain. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 293:109–114, 1976.

Weiss, J.M., and Glazer, H.I. Effects of acute exposure to stressors on subsequent avoidance-escape behavior. *Psychosom. Med.*, 37:499–521, 1975.

Weiss, J.M., Bailey, W.H., Goodman, P.A., et al. A model for neurochemical study of depression. In: Spiegelstein, M.Y. and Levy, A. (eds.), *Behavioral Models and Analysis of Drug Action*. Amsterdam: Elsevier Scientific, 1982, pp. 195–223.

Weiss, J.M., Goodman, P.A., Losito, B.G., Corrigan, S., Charry, J.M., and Bailey, W.H. Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain. *Brain Res. Rev.*, 3:167–205, 1981.

Weiss, J.M., and Simson, P.G. Neurochemical mechanisms underlying stress-induced depression. In: Field, T., McCabe, P., and Schneiderman, N. (eds.), *Stress and Coping*, vol. 1. Hillsdale, N.J.: Lawrence-Erlbaum Associates, 1985, pp. 93–116.

Weiss, J.M., Simson, P.G., Hoffman, L.J., et al. Infusion of adrenergic receptor agonists and antagonists into the locus coeruleus and ventricular system of the brain: Effects on swim-motivated and spontaneous motor activity. *Neuropharmacology*, 25; 1986 (In press.)

Zandberg, P., De Jong, W., and De Wied, D. Effect of catecholamine receptor stimulating agents on blood pressure after local application in the nucleus tractus solitarii of the medulla oblongata. *Eur. J. Pharmacol.*, 55:43, 1979.

Mechanisms of Action of Indole and Phenylalkylamine Hallucinogens

Chair:

Richard H. Rech, Ph.D.

Michigan State University
East Lansing, MI 48824

Introduction

Richard H. Rech, Ph.D.

Although the effects of hallucinogenic drugs have been recognized throughout the ages, extensive scientific investigation was prompted only in recent times by the synthesis and characterization of lysergic acid diethylamide (LSD) by Hofmann in 1943 (Hofmann, 1970). Important recent studies in this area are listed in Table 1. The suggestion that LSD may act via brain serotonin (5-HT) functions was made independently by Gaddum (1953) and Woolley and Shaw (1954), based on smooth muscle interactions. Prominent effects on animal operant behavioral models were described by Appel, Freedman, and colleagues (Appel, 1968) several decades ago.

The use of electrophysiological techniques by Aghajanian and co-workers (1975) supported the concept that LSD acted as a 5-HT agonist to suppress discharge of brainstem raphe neurons by acting at neurosomal autoreceptors. Jacobs and colleagues (1978), and later work by Aghajanian's group (1975), demonstrated that the autoreceptor effect of LSD was not sufficient to explain the hallucinogenic activity. Only a few laboratories have dealt more broadly with investigation of various classes of hallucinogenic agents. Domino's group (1964) is one of these. He has demonstrated the more generalized behavioral disruption of deliriant hallucinogens such as atropine and PCP when compared to the psychedelics. The literature on clinical research with hallucinogens is derived mainly from studies done from 1950 to 1970 by Hollister (1984) and a few others. Due to later restrictions, carefully controlled human research on hallucinogenic mechanisms has been rare in the last decade.

TABLE 1. Milestones in Hallucinogenic Drug Research.*

1. Synthesis, description of human effects of LSD by Albert Hofmann in 1943.
2. Gaddum; Woolley and Shaw: LSD induces CNS effects by antagonizing 5-HT neurotransmitter function, 1953, 1954.
3. Appel, Freedman and colleagues: Operant behavior of rats disrupted in a distinctive pattern by indolealkylamine and phenalkylamine hallucinogens, 1960's.
4. Aghajanian and coworkers: LSD was a potent suppressor of 5-HT raphe cell discharge by agonistic action at autoreceptors, early 1970's.
5. Jacobs and colleagues: Autoreceptor activity of LSD was not sufficient to explain hallucinogenic action, late 1970's.
6. Domino and others: Contrasted effects of deliriant hallucinogens (atropine-type, PCP) with those of the psychedelics, 1960's, 1970's.
7. Hollister and others: Clinical research on hallucinogens performed in the 1950's, 1960's.
8. Recent experimental research (Appel; Glennon; Jacobs; Rech): Psychedelics act at a certain subset(s) of 5-HT receptors in forebrain (as well as hindbrain?) to alter CNS functions.

*See selected references below.

Current animal research with the psychedelics has led to a consensus that these agents act at a certain type (or types) of brain 5-HT receptors to disturb a balance in the functioning of these systems that is necessary for normal sensory and other cognitive processings.

References

Aghajanian, G.K., Haigler, H.J., and Bennett, J.L. Amine receptors in the CNS. III. 5-Hydroxytryptamine in brain. In: Iversen, L.L., Iversen, S.D., and Snyder, S.H. *Handbook of Psychopharmacology*, Vol. 6, New York: Plenum Press, 1975, pp. 63–96.

Appel, J.B. The effects of "psychotominetic" drugs on animal behavior. In: Efron, D.E. (ed.), *Psychopharmacology: A Review of Progress*, 1957–1967. Washington, D.C.: U.S. Government Printing Office, 1968, pp. 1211–1230.

Appel, J.B., White, F.J., and Holohean, A.M. Analyzing mechanism(s) of hallucinogenic drug action with drug discrimination procedures. *Neurosci. Biobehav. Rev.*, 6:529–536, 1982.

Domino, E.F. Neurobiology of phencyclidine (Sernyl), a drug with an unusual spectrum of pharmacological activity. *Int. Rev. Neurobiol.*, 6:383, 1964.

Gaddum, J.H. Antagonism between LSD and 5-hydroxytryptamine. *J. Physiol.*, (Lond.), 121:15P, 1953.

Glennon, R.A., Young, R., and Rosecrans, J.A. Antagonism of the effects of the hallucinogen DOM and the purported 5HT agonist quipazine by $5HT_2$ antagonists. *Eur. J. Pharmacol.* 91:189–196, 1983.

Hofmann, A. The discovery of LSD and subsequent investigations on naturally occurring hallucinogens. In: Ayd, F.J., Jr., and Blackwell, B. *Discoveries in Biological Psychiatry*. Philadelphia: J.B. Lippincott, 1970, pp. 93–94.

Hollister, L.E. Effects of hallucinogens in humans. In: Jacobs, B.L. (ed.), *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives*. New York: Raven Press, 1984, pp. 19–33.

Jacobs, B.L. Dreams and hallucinations: A common neurochemical mechanism mediating their phenomenological similarities. *Neurosci. Biobehav. Rev.*, 2:59–69, 1978.

McCall, R.B. Neurophysiological effects of hallucinogens on serotonergic neuronal systems. *Neurosci. Biobehav. Rev.*, 6:509–514, 1982.

Rech, R.H., and Commissaris, R.L. Neurotransmitter basis of the behavioral effects of hallucinogens. *Neurosci. Biobehav. Rev.*, 6:521–527, 1982.

Woolley, D.W., and Shaw, E. A biochemical and pharmacological suggestion about certain mental disorders. *Science*, 119:587–588, 1954.

Structure-Activity Relationships and Mechanism of Action of Hallucinogenic Agents Based on Drug Discrimination and Radioligand Binding Studies

Richard A. Glennon, Ph.D.,[1] Milt Titeler, Ph.D.,[2] and Richard Young, Ph.D.[1]

The classical hallucinogens can be divided into several structural classes: phenalkylamine (PAA) derivatives and indolealkylamine (IAA) derivatives (Figure 1). Lysergic acid diethylamide (LSD) and related analogs have been classified as indolealkylamines, but might just as readily be classified as phenalkylamines based on their structural resemblance to these agents; as shown in Figure 1, they are accorded their own separate designation, i.e., lysergamides. Certain phenalkylamines [e.g., 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM)] are hallucinogenic whereas others (e.g., amphetamine) are not. The same may be said of indolealkylamine derivatives. One of the early goals of our work was to to determine if a representative member of each of these three classes of hallucinogens was capable of producing a common behavioral (i.e., discriminative stimulus) effect in animals. After we had shown that this was indeed possible (Glennon et al., 1979; Young et al., 1981), our next goal was to determine which members within each of these classes of agents could produce similar behavioral effects. Once accomplished, attention could then be focused on (a) formulation of structure-activity relationships (SAR), (b) investigation of mechanism(s) of action, and (c) determination of a possible relationship between animal data and human hallucinogenic activity/potency.

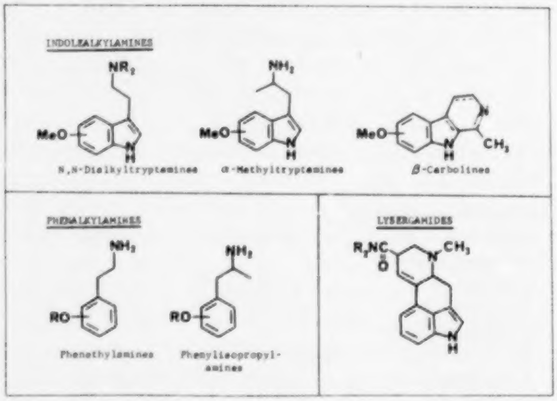


FIGURE 1. Structural classes of hallucinogenic agents.

Behavioral Studies

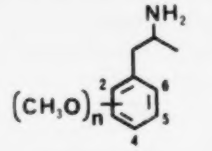
To accomplish the first goal, groups of rats were trained to discriminate either 1.0 mg/kg of racemic DOM hydrochloride or (+)−amphetamine sulfate from saline using a standard two-lever operant procedure. These animals, once trained, were then administered various doses of PAA and IAA derivatives in tests of stimulus generalization (i.e., transfer, substitution). In this way, it was possible to classify these agents as producing either DOM-like or amphetamine-like discriminative stimulus effects. Certain agents produced neither effect; that is, with some agents stimulus generalization did not occur with either the DOM- or the amphetamine-stimulus. Agents not resulting in stimulus generalization were of two types; some agents [e.g., 3,5-dimethoxyphenyl-2–aminopropane (3,5-DMA)] produced saline-appropriate responding (in both groups of animals) at the highest dose evaluated, whereas others (e.g., 2,6-DMA) resulted in partial generalization (in at least one of the two groups of animals) followed, at a slightly higher dose, by disruption of behavior. The present discussion will deal primarily with those agents that resulted in complete stimulus generalization (i.e., greater than 80 percent DOM-appropriate responding) in the DOM-trained animals. Table 1 presents qualitative results on selected

---

[1] Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298.

[2] Department of Pharmacology, School of Medicine, Albany Medical College, Albany, NY.

TABLE 1. Representative Results of Stimulus Generalization Studies Using Racemic DOM or (+)-Amphetamine as Training Drug.



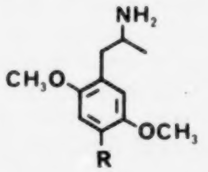
Monomethoxy Analogs:		
OMA = A	MMA = A	PMA = A
Dimethoxy Analogs:		
2,3-DMA = *	2,4-DMA = D	2,5-DMA = D
2,6-DMA = *	3,4-DMA = *	3,5-DMA = *
Trimethoxy Analogs:		
2,3,4-TMA = D	2,3,5-TMA = D	2,3,6-TMA = #
2,4,5-TMA = D	2,4,6-TMA = D	3,4,5-TMA = D
Other Analogs:		
AMPH = A	(+)AMPH = A	(−)AMPH = A
DOM = D	DOET = D	MDA = A/D
(−)DOM = D	DOPR = D	(−)MDA = D
(+)DOM = D	DOBU = D	(+)MDA = A
DOB = D	(−)DOB = D	(+)DOB = D
DOI = D	(−)DOI = D	(+)DOI = D

Racemic mixtures were used unless otherwise noted. OMA, MMA, and PMA are the 2-, 3- and 4-monomethoxy derivatives, respectively. AMPH = amphetamine. D = DOM-stimulus generalization. A = amphetamine-stimulus generalization. Agents not resulting in complete stimulus generalization (in either group of animals) are indicated with (*); a (#) denotes agent not tested. Data from Glennon et al., 1983; Young and Glennon, 1986.

PAA derivatives that were evaluated both in DOM-trained and amphetamine-trained animals. It can be seen that none of the monomethoxy analogs, two of the six dimethoxy analogs (DMAs), and five of the five trimethoxy analogs (TMAs) resulted in DOM-stimulus generalization. In like manner, various other derivatives also resulted in either DOM- or amphetamine-stimulus generalization. With one exception, there were no examples of agents that were recognized by both groups of animals; this one exception is 3,4-methylenedioxyphenylisopropylamine (3,4-MDA, MDA). [The DOM-stimulus generalized to racemic and R(−)-MDA but not to S(+)-MDA, whereas the amphetamine-stimulus generalized to racemic and S(+)-MDA but not to R(−)-MDA. It appears that each of the component optical isomers produces a different stimulus effect.] Quantitative data for a small number of agents that produced DOM-like effects are shown in Table 2. Substitution at the 4-position of 2,5-DMA results in some of the more potent DOM-like analogs. With respect to the alkyl substituted derivatives, potency increases as the length of the alkyl chain increases from methyl to ethyl (DOET) to *n*-propyl (DOPR). DOPR is the most potent of the alkyl series and a further increase in chain length to *n*-butyl (DOBU) results in a decrease in potency. 4-Halogenated analogs, such as the bromo analog (DOB) are also among the most potent agents (Table 2). Where optical isomers were evaluated (e.g., DOM, DOET, DOB), the R(−)-isomers were generally twice as potent as the racemates and 5- to 10-times more potent than their corresponding S(+)-enantiomers. Data such as these have allowed for the formulation of *in vivo* SAR for the phenalkylamines.

Various indolealkylamines were also evaluated in the DOM-trained animals (Glennon et al., 1983). IAA derivatives with a primary amine function (e.g., tryptamine, 5-methoxy tryptamine) did not produce DOM-like effects unless there was an alkyl group alpha to the amine. With respect to these alpha-alkyl tryptamines, alpha-methyl derivatives were more potent than their corresponding alpha-ethyl derivatives. Alpha-methyltryptamines,

TABLE 2. Potencies of Selected Phenalkylamine Derivatives in DOM-Trained Animals.



Agent		R	ED50 (μmoles/kg)
2,5-DMA		H	23.75
2,4,5-TMA		OCH_3	13.70
DOM	(±)	CH_3	1.79
	(−)		0.85
	(+)		6.91
DOET	(±)	C_2H_5	0.88
	(−)		0.36
	(+)		3.27
DOPR		nC_3H_7	0.62
DOBU		nC_4H_9	3.14
DOB	(±)	Br	0.64
	(−)		0.32
	(+)		2.60
DON[a]	(±)	NO_2	2.75
	(−)		2.02

Rats were trained to discriminate 1.0 mg/kg racemic DOM HCl from saline. Racemic mixtures were employed unless otherwise noted.

[a] 1,(2,5-dimethoxy-4-nitrophenyl)-2-amino propane.

like the phenylisopropylamines mentioned above, also exist as optical isomers; S(+)-alpha-methyltryptamine was approximately twice as potent as racemic alpha-methyltryptamine whereas the R(−)-isomer did not produce DOM-like effects. Both isomers of 5-methoxy alpha-methyltryptamine produced DOM-like effects; the (+)-isomer was about twice as potent as its racemate and 5-times as potent as its (−)-enantiomer. *N,N*-Dimethyltryptamine (DMT) was half as potent as racemic alpha-methyltryptamine; both the 5- and 4-methoxy derivatives (i.e., 5-OMe DMT and 4-OMe DMT) were more potent than DMT whereas 6-OMe DMT was less potent than DMT. A variety of other tryptamine derivatives were examined. With respect to beta carbolines, several (e.g., harmaline, 6-methoxyharmalan) produced DOM-like effects, but none was more potent than DMT. As with the phenalkylamines, SAR were formulated for the IAA.

Mechanistic Studies

It has already been fairly well documented that serotonin (5-HT) plays an important role in the mechanism of action of hallucinogenic agents. With respect to our studies, several different approaches were taken. Using animals trained to discriminate DOM from saline, tests of stimulus generalization and stimulus antagonism were undertaken using known 5-HT agonists and antagonists. In the second approach, animals were trained to discriminate other 5-HT agonists from saline; DOM and several related analogs were then examined in tests of stimulus generalization. Finally, radioligand binding studies were conducted using rat brain homogenates.

(1) *DOM-Trained Animals.* Fenfluramine is known to release endogenous stores of 5-HT; administration of fenfluramine to DOM-trained animals resulted in stimulus generalization supporting the contention that 5-HT may play a mechanistic role in the stimulus effects produced by DOM. However, there is considerable evidence for the existence of multiple populations of central 5-HT binding sites. Peroutka and Snyder (1979) have demonstrated the existence of 5-HT$_1$ and 5-HT$_2$ sites, and Pedigo et al. (1981) have shown that the 5-HT$_1$ sites are heterogeneous and consist of several different subpopulations of sites. Currently, three sub-populations of 5-HT$_1$ sites have been identified: 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1C}$ (for a review, *see* Glennon, 1986). Although there are no 5-HT$_{1C}$-selective agonists, there is evidence that 8-hydroxy-*N,N*-(di-*n*-propylamino) tetralin (8-OH DPAT) is selective for 5-HT$_{1A}$ sites whereas agents such as 1-(3-trifluoromethylphenyl)piperazine (TFMPP) and RU-24969 are selective for 5-HT$_{1B}$ sites. Quipazine is a 5-HT agonist that appears to bind both to 5-HT$_1$ and 5-HT$_2$ sites. The DOM-stimulus generalized to quipazine, but not to 8-OH DPAT, TFMPP, or RU-24969. These results suggest that the DOM-stimulus might involve a 5-HT mechanism that is probably not 5-HT$_{1A}$ or 5-HT$_{1B}$ mediated.

Silverman and Ho (1980) demonstrated that the DOM-stimulus could be attenuated by pretreatment of the animals with the 5-HT antagonists cinanserin and methysergide; we later found that pizotyline (pizotifen, BC-105) was also an effective antagonist (Young et al., 1981). Shortly thereafter, Leysen et al. (1981) reported that agents such as cinanserin, methysergide, and pizotyline were 5-HT$_2$ antagonists; they also reported the development of two new agents, ketanserin and pirenperone, that were highly potent and selective 5-HT$_2$ antagonists. Subsequently, we demonstrated that ketanserin and pirenperone were very effective in blocking the stimulus effects of DOM, and DOM-stimulus generalization to mescaline, 5-OMe DMT, LSD, and quipazine. A 5-HT$_2$ mechanism had now been implicated, for the first time, as possibly being involved in the stimulus properties of DOM and agents to which the DOM-stimulus generalized.

One of the problems associated with ketanserin and pirenperone (and a number of other 5-HT$_2$ antagonists) is that although they are selective for 5-HT$_2$ vs 5-HT$_1$ sites, they are not necessarily selective for 5-HT; some of these agents display a high affinity for dopaminergic, histaminergic, and/or adrenergic binding sites. In order to determine if these other neurotransmitters might be playing a mechanistic role, antagonism studies were conducted with a variety of antagonists; none of these agents effectively antagonized or attenuated the DOM response. By this time, several new 5-HT antagonists had become available; although these agents (e.g., tetrahydrotrazodone, LY-53857, dihydroflutroline, ritanserin) are not necessarily specific for 5-HT sites, they possess different binding profiles and have in common the ability to bind at 5-HT_2 sites. Each of these agents was an antagonist of the DOM-stimulus (Glennon & Hauck, 1985). Thus, evidence was mounting for 5-HT_2 involvement.

(2) *Site-Selective Serotonin Agonists.* In the next phase of our study, groups of animals were trained to discriminate the 5-HT_{1A} agonist 8-OH DPAT and the 5-HT_{1B} agonist TFMPP from saline. If DOM and related agents produce their stimulus effects via a 5-HT_2 agonist effect, stimulus generalization should not occur when these agents are administered to the 8-OH DPAT-trained or TFMPP-trained animals. Also, it should not be possible to block the stimulus effects of these two training drugs with 5-HT_2 antagonists. In rather limited tests of stimulus antagonism, it was found that ketanserin, pirenperone, pizotyline, and/or tetrahydrotrazodone were unable to antagonize the stimulus effects of 8-OH DPAT or TFMPP. In tests of stimulus generalization (Table 3), the 8-OH DPAT stimulus generalized to 8-methoxy DPAT, but not to the 5-HT_{1B} agonists TFMPP, 1-(3-chlorophenyl) piperazine (mCPP), or RU-24969, or to the (putative) 5-HT_2 agonists DOM or 1(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). The TFMPP-stimulus generalized to the 5-HT_{1B} agonists mCPP and RU-24969 but not to the 5-HT_{1A} agonist 8-OH DPAT, or to DOM, DOB, or DOI. The DOM-stimulus generalized to LSD and quipazine; however, neither agent resulted in generalization in the 8-OH DPAT- or TFMPP-trained animals. Interestingly, both of these agents did result in partial generalization in each group of animals, supporting the finding that LSD and quipazine bind both at 5-HT_1 and 5-HT_2 sites.

TABLE 3. Results of Stimulus Generalization Studies Using Site-Selective Serotonin Agonists as Training Drugs.

	Training Drug		
Generalization to	8-OH DPAT (5-HT_{1A})	TFMPP (5-HT_{1B})	DOM (5-HT_2)
Fenfluramine	—	Yes	Yes
5-HT_{1A} Agonists			
8-OH DPAT	Yes	No	No
8-OMe DPAT	Yes	—	No
5-HT_{1B} Agonists			
TFMPP	No	Yes	No
RU-24969	No	Yes	No
mCPP	—	Yes	No
5-HT_2 Agonists			
DOM	No	No	Yes
DOB	—	No	Yes
DOI	No	No	Yes
Other Agents			
LSD	No (P)	No (P)	Yes
Quipazine	—	No (P)	Yes

Data from Glennon and McKenney, 1985.

TABLE 4. Representative 5-HT Binding Data for Phenalkylamine Analogs.

	K_i (nM)	
Agent	5-HT_1	5-HT_2
Amphetamine	7,660	43,000
OMA	3,500	8,130
MMA	2,660	7,850
PMA	79,400	33,600
3,4-DMA	64,600	43,300
2,5-DMA	1,020	5,200
3,4,5-TMA	12,800	16,500
2,4,5-TMA	46,800	1,650
DOF[a]	3,470	1,100
N-Me DOM	4,300	415
DON	14,100	300
DOM	2,890	100
DOM(−)	3,550	60
DOET	4,570	100
DOPR	3,170	69
DOBU	2,660	210
DOB	3,340	63
DOB(−)	4,200	60
DOB(+)	5,000	120
DOI	2,240	19
DOI(−)	2,290	10
DOI(+)	1,670	35

Binding data are for racemates unless otherwise stated. Data from Shannon et al., 1984; Glennon et al., 1984; Glennon et al., 1986.

[a] 1(2,5-dimethoxy-4-fluorophenyl)-2-aminopropane.

(3) *Radioligand Binding Studies.* If DOM and related agents act as 5-HT_2 agonists, it should be possible to demonstrate binding of these agents at 5-HT_2 sites. Using rat cortical membranes, 5-HT_1 and 5-HT_2 binding data were obtained for a series of PAAs (Table 4) and a representative number of IAAs. Only data for the PAA analogs will be discussed at this time. In general, PAAs display micromolar affinities (i.e., K_i values) for 5-HT_1 sites; binding at 5-HT_2 sites seems to be very sensi-

tive to the presence and position of various substituents, and a number of agents possess nanomolar affinities. The 2,5-dimethoxy pattern appears to be an important feature for binding at 5-HT_2 sites; further substitution at the 4-position of 2,5-DMA can result in a further increase in affinity and selectivity for 5-HT_2 sites. With respect to 4-alkyl substituents, the *n*-propyl analog DOPR is more potent than either the methyl, ethyl, or butyl analogs. The 4-halogenated derivatives such as DOB and DOI are among the most potent agents in terms of potency/selectivity for 5-HT_2 sites. In the few instances where optical isomers were examined, the R(−)-isomers are several-fold more potent than their S(+)-enantiomers at 5-HT_2 sites, whereas stereoselective binding is less evident at 5-HT_1 sites.

Conclusions

It is difficult to separate mechanistic studies involving large numbers of compounds from studies of SAR in that both provide similar types of information. We have previously demonstrated that a significant correlation ($r = \geq 0.9$) exists between the human hallucinogenic potencies of a series of PAA and IAA derivatives and their ED_{50} values as determined in stimulus generalization studies using DOM as the training drug. We have also found significant correlations ($r = \geq 0.9$) between the affinities of a series of these agents for 5-HT_2 sites and both these ED_{50} values and hallucinogenic potencies (Glennon et al., 1984). Structure-activity relationships derived from all three types of studies afford similar results. The results of these studies also suggest that certain of these hallucinogenic agents may be producing their stimulus effects via a 5-HT_2-mediated mechanism, and, further, that they may be acting as 5-HT_2 agonists. It might be noted that certain agents to which the DOM-stimulus generalizes (e.g., fenfluramine, quipazine, lisuride) and/or that possess an affinity for 5-HT_2 sites (e.g., quipazine, lisuride) are not necessarily hallucinogenic in humans. A satisfactory explanation cannot yet be provided although several can be offered: these agents may not be sufficiently selective for 5-HT_2 sites, may be partial agonists, may possess a still higher affinity for some other binding sites, may produce other effects that mask their anticipated behavioral effects, and/or may be differently distributed or metabolized in humans vs rats.

A dividend of our work with hallucinogenic agents was the identification of the first examples of a series of 5-HT_2-selective agonists. This prompted us to conduct several additional studies. A detailed SAR study on DOB has recently been completed. Substituent groups were removed or transposed in a systematic manner and each of the resulting agents was evaluated with respect to its stimulus properties and binding characteristics. Most structural alterations served only to reduce potency in the discrimination studies, or reduce affinity/selectivity for 5-HT_2 sites (Glennon et al., 1986). Subsequently, [^{3}H]DOB was synthesized and evaluated as an agonist radioligand for 5-HT_2 sites (Titeler et al., 1985). Also, animals have now been trained to discriminate the more 5-HT_2-selective agent DOI from saline; with a training dose of 0.5 mg/kg, an ED50 value of 0.16 mg/kg (0.44 micromoles/kg) was obtained (Glennon and McKenney, 1985). The DOI-stimulus did not generalize with 8-OH DPAT or TFMPP, although generalization did occur with DOM (ED_{50} = 0.45 mg/kg; 1.83 micromoles/kg). Stimulus generalization also occurred with the optical isomers of DOI, with R(−)-DOI being about three times more potent than S(+)-DOI. The DOI-stimulus was blocked by pretreatment of the animals with the 5-HT_2 antagonist ketanserin (ID50 = 0.03 mg/kg).

The overall results of our work lead us to suggest that PAA and IAA hallucinogens may act primarily via a 5-HT_2 agonist mechanism.

Acknowledgments

This work was supported, in part, by U.S. Public Health Service grant DA-01642. We would also like to express our appreciation to R. A. Lyon, J. D. McKenney, and A. E. Hauck for their contributions to various aspects of this project.

References

Glennon, R.A. Serotonin receptor agonists and antagonists. In: Williams, M., Glennon, R. A., and Timmermans, P. (eds.), *Receptor Function and Pharmacology*. New York: Marcel Dekker, 1986.

Glennon, R.A., and Hauck, A.E. Mechanistic Studies on DOM. *Pharmacol. Biochem. Behav.*, 23:937–941, 1985.

Glennon, R.A., and McKenney, J.D. Site-selective 5-HT agonists as discriminative stimuli. *Pharmacologist*, 27:194, 1985.

Glennon, R.A., Rosecrans, J.A., and Young, R. Drug-induced discrimination: A description of the paradigm and a review of its application in the study of hallucinogenic agents. *Med. Res. Rev.*, 3:289–340, 1983.

Glennon, R.A., Titeler, M., and McKenney, J.D. Evidence for 5-HT$_2$ involvement in the mechanism of action of hallucinogenic agents. *Life Sci.*, 35:2505–2511, 1984.

Glennon, R.A., McKenney, J.D., Titeler, M., and Lyon, R. 5-HT$_1$ and 5-HT$_2$ binding characteristics of DOB analogues. *J. Med. Chem.*, 29:194–199, 1986.

Glennon, R.A., Rosecrans, J.A., Young, R., and Gaines, J. Hallucinogens as discriminative stimuli. *Life Sci.*, 24:993–998, 1979.

Leysen, J.E., Niemegeers, C.J.E., Van Nueten, J.M., and Laduron, P.M. [^{3}H]Ketanserin (R41468), A selective ^{3}H-ligand for serotonin$_2$ receptor binding sites. *Mol. Pharmacol.*, 21:301–314, 1982.

Pedigo, N.W., Yamamura, H.I., and Nelson, D.L. Discrimination of multiple [^{3}H]5-hydroxytryptamine binding sites by the neuroleptic spiperone in rat brain. *J. Neurochem.*, 36:220–226, 1981.

Peroutka, S.J., and Snyder, S.H. Multiple serotonin receptors: Differential binding of [^{3}H]5-hydroxytryptamine, [^{3}H]lysergic acid diethylamide and [^{3}H]spiroperidol. *Mol. Pharmacol.*, 16:687–699, 1979.

Shannon, M., Battaglia, G., Glennon, R.A., Titeler, M. 5-HT$_1$ and 5-HT$_2$ binding properties of derivatives of the hallucinogen 1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-DMA). *Eur. J. Pharmacol.*, 102:23–29, 1984.

Silverman, P.B., and Ho, B.T. The discriminative stimulus properties of 2,5-dimethoxy-4-methylamphetamine (DOM): Differentiation from amphetamine. *Psychopharmacology*, 69:209–215, 1980.

Titeler, M., Herrick, K., Lyon, R.A., et al. [^{3}H]DOB: A specific radioligand for 5-HT$_2$ sites. *Eur. J. Pharmacol.*, 117:145–147, 1985.

Young, R., and Glennon, R.A. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. *Med. Res. Rev.*, 1986 (In press).

Young, R., Glennon, R.A., and Rosecrans, J.A. The hallucinogen DOM as a discriminative stimulus. *Commun. Psychopharm.*, 4:501–504, 1981.

The Use of Drug Discrimination Procedures to Characterize Hallucinogenic Drug Actions[1]

James B. Appel, Ph.D.,[2] and Kathryn A. Cunningham Ph.D.[2,3]

Drug discrimination (DD) is a behavioral procedure in which animals are trained through differential reinforcement to detect the internal or "subjective" effects of psychoactive drugs. It has been useful in analyzing the neuronal mechanisms underlying the effects of diverse classes of compounds because of its reliability, sensitivity and, particularly, specificity (Appel et al., 1982).

Like most other assays, DD suggests that indolealkylamine and phenylalkylamine hallucinogens act primarily, if not exclusively, at postsynaptic 5-HT receptors, probably of the 5-HT$_2$ subtype. The evidence in support of this conclusion includes (but is not limited to) the following:

1) Antagonists with a high affinity for 5-HT$_2$ receptors (ketanserin, pirenperone, ritanserin) are the most effective antagonists of the discriminative stimulus properties of lysergic acid diethylamide (LSD) (Colpaert et al., 1982, 1985; Cunningham, 1985; Nielsen et al., 1985).

2) The stimulus effects of 2,5-dimethoxyphenyl-4-methylphenyl isopropylamine (DOM) and quipazine, both of which mimic LSD in rats (Kuhn et al., 1977), are blocked by pirenperone (Friedman et al., 1984; Glennon et al., 1983).

3) The 5-HT$_2$ binding affinities (K_i values) of various phenylisopropylamine derivatives correlate significantly with both DD-derived ED$_{50}$ values and hallucinogenic potencies (Glennon et al., 1982; Glennon, 1985).

4) The relative abilities of various 5-HT antagonists to block the quipazine cue correlate highly with their abilities to inhibit 5-HT$_2$, but not 5-HT$_1$, binding (Friedman et al., 1984).

Nevertheless, the possibility that indolealkylamine and phenylalkylamine hallucinogens act at 5-HT$_1$ as well as 5-HT$_2$ "receptors" cannot yet be dismissed, primarily because some of these agents (e.g., LSD) displace both 5-HT$_1$ and 5-HT$_2$ ligands *in vitro* (Peroutka & Snyder, 1979). We therefore reexamined the stimulus properties of the "prototype" hallucinogen, LSD, and compared them systematically to those of the 5-HT$_{1B}$ agonist, 1-(*m*-trifluoromethylphenyl piperazine) (TFMPP). In the present paper, we review the results of two such experiments.

Experiment 1: LSD-Saline Discrimination

Methods: The methods were similar to those we have been using for some time and are described in detail elsewhere (e.g., Appel et al., 1982).

Rats ($N = 23$) were trained (in commercially available, two lever chambers) to discriminate intraperitoneal injections of LSD (0.08 mg/kg) from saline (0.9% NaCl). A fixed-ratio (FR) 20 schedule of water reinforcement for "correct" (intraperitoneally, drug-appropriate) responding was used.

Once animals demonstrated mean individual accuracies of at least 85 percent correct over a period of 10 consecutive sessions, testing began. In *substitution* (cross-transfer, generalization) tests, a wide range of doses of novel serotonergic compounds (putative 5-HT agonists) were given (interperitoneally, in a volume of 1.0 ml/kg) in place of the training drug (LSD); these were: 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OHDPAT; 0.02 to 0.64 mg/kg), Ru 24969 (0.2 to 3.2 mg/kg), *m*-chlorophenylpiperazine (mCPP; 0.1 to 1.6 mg/kg), 1-(*m*-trifluoromethylphenyl) piperazine (TFMPP; 0.1 to 1.6 mg/kg), and quipazine (0.2 to 3.2 mg/kg). In *combination*

---

[1] Supported by USPHS Research Grant 2R01 DA02543, from the National Institute on Drug Abuse.

[2] Behavioral Pharmacology Laboratory, Department of Psychology, University of South Carolina, Columbia, SC 29208.

[3] Present Address: Department of Pharmacology and Toxicology, The University of Texasx Medical Branch, Galveston, TX 77550.

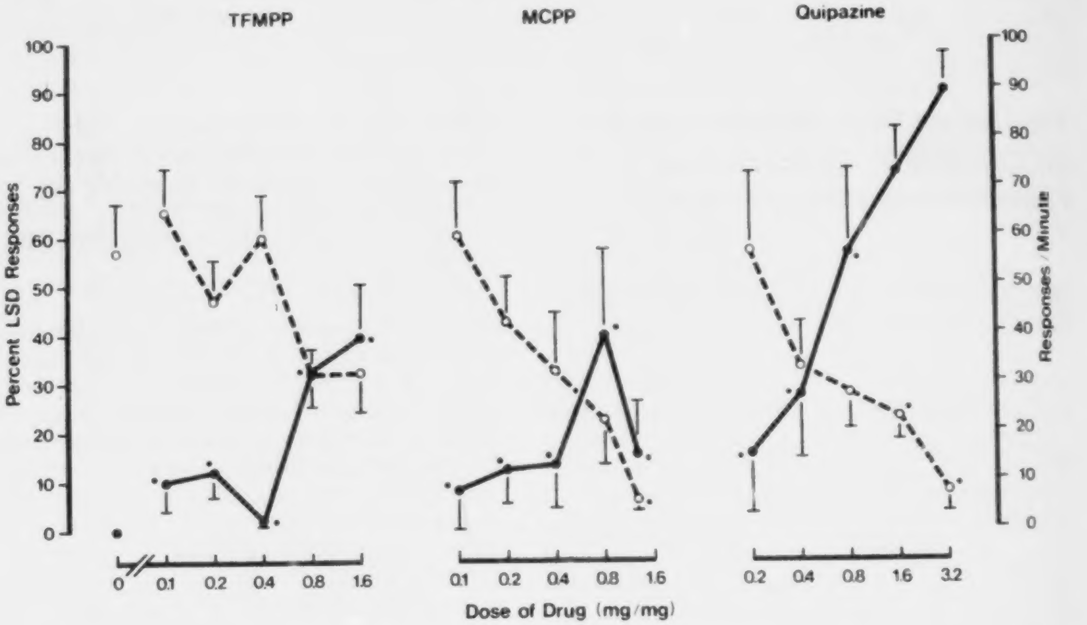


FIGURE 1. Results of substitution tests with TFMPP, MCPP, and quipazine in rats trained to discriminate LSD (0.08 mg/kg) from saline. Closed circles (connected by solid lines) denote the mean percentage of drug-appropriate responses (± S.E.M.) (left ordinate) and open circles (connected by broken lines) denote the mean response rate before completion of the first FR 20 on either lever (± S.E.M.) (right ordinate). Asterisks represent performances during test sessions which were significantly different from previous drug training sessions ($p < 0.05$). Control points, included for comparison, show the degree of stimulus control (± S.E.M.) (closed circle) and the response rate (± S.E.M.) (open circle) produced by saline when administered under test (extinction) conditions.

(antagonism) tests, the following 5-HT antagonists were injected 60 min prior to the training drug (0.08 mg/kg of LSD): pizotyline (BC 105) (0.2 to 3.2 mg/kg), 2-bromolysergic acid diethylamide (BOL; 0.1 to 1.6 mg/kg), Ly 53857 (0.4 to 3.2 mg/kg), metergoline (0.05 to 0.8 mg/kg), ketanserin (0.2 to 3.2 mg/kg), pirenperone (0.0025 to 0.08 mg/kg), and spiperone (0.02 to 0.32 mg/kg).

Results: Of the novel compounds tested, the only substance that mimicked the training drug was quipazine (1.6 and 3.2 mg/kg), the stimulus properties of which appear to be mediated by 5-HT$_2$ receptors (above). No dose of any 5-HT$_1$ agonist (5-HT$_{1A}$ or 5-HT$_{1B}$) induced more than 50 percent LSD-appropriate responding (higher doses disrupted choice behavior and could not be tested). The effects of quipazine as well as those of the putative 5-HT$_{1B}$ agonists TFMPP and mCPP on discrimination accuracy and response rate are shown in Figure 1.

While hampered by an absence of available 5-HT$_1$ antagonists, combination testing also produced consistent results; both relatively selective 5-HT$_2$ (e.g., pirenperone and ketanserin) and less selective (e.g., BC 105, Ly 53857, and metergoline) antagonists blocked the training drug cue; indeed the only 5-HT antagonist which did *not* alter the amount of LSD-appropriate responding was spiperone. Some of these data are illustrated in Figure 2.

Experiment 2: TFMPP-Saline Discrimination

Methods: Rats ($N = 24$) were trained to discriminate TFMPP (0.8 mg/kg) from saline using the same behavioral methods as those of Experiment 1.

After attaining criterion (85 percent correct for 10 consecutive sessions), testing began. Compounds given in substitution tests included LSD (0.01 to 0.16 mg/kg) as well as the following 5-HT agonists: fenfluramine

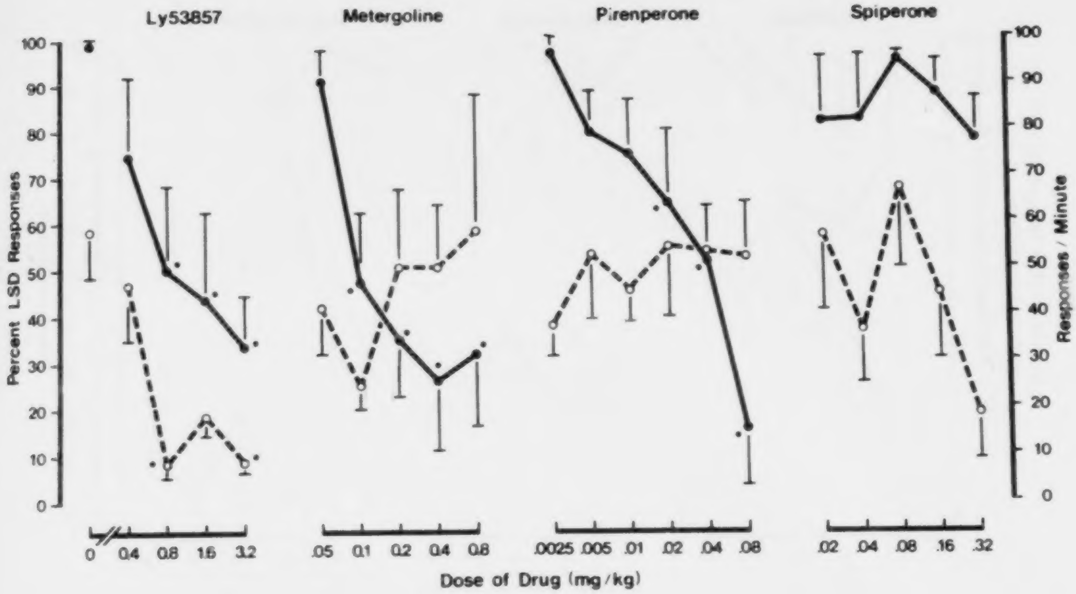


FIGURE 2. Results of combination tests with Ly-53857, metergoline, pirenperone, and spiperone in rats trained to discriminate LSD (0.08 mg/kg) from saline. Closed circles (connected by solid lines) denote the mean percentage of drug-appropriate responses (± S.E.M.) (left ordinate) and open circles (connected by broken lines) denote the mean response rate before completion of the first FR 20 on either lever (± S.E.M.) (right ordinate). Asterisks represent performances during test sessions which were significantly different from previous LSD training sessions ($p < 0.05$). Control points, included for comparison, show degree of stimulus control (± S.E.M.) (closed circle) and response rate (± S.E.M.) (open circle) produced by saline plus LSD administered under test (extinction) conditions.

(0.8 mg/kg to 1.6 mg/kg), mCPP (0.1 to 1.6 mg/kg), Ru 24969 (0.1 to 1.6 mg/kg), 8-OHDPAT (0.02 to 0.32 mg/kg), and quipazine (0.2 to 3.2 mg/kg). Compounds tested in combination with TFMPP were: BC 105 (1.6 to 12.8 mg/kg), BOL (0.8 to 1.28 mg/kg), ketanserin (0.8 to 6.4 mg/kg), Ly 53857 (0.2 to 1.6 mg/kg), metergoline (0.4 to 6.4 mg/kg), pirenperone (0.08 to 0.64 mg/kg), and spiperone (0.08 to 1.28 mg/kg).

Results: In marked contrast to the first experiment, mCPP and Ru 24969 (as well as TFMPP), each of which supposedly acts at 5-HT_{1B} sites, mimicked the training drug as did the 5-HT releasing agent fenfluramine; 8-OHDPAT (a 5-HT_{1A} agonist) and quipazine elicited saline lever responding. While the results with LSD were difficult to interpret, because all doses tested (0.01 to 0.16 mg/kg) elicited at least some (20 to 50 percent) responding on the drug-appropriate lever, this hallucinogen cannot be said to substitute for TFMPP. The effects of Ru 24969, 8-OHDPAT, and LSD on animals trained to discriminate TFMPP from saline are shown in Figure 3.

The results of combination tests also contrast markedly with those of the first experiment. No dose of any 5-HT_2 antagonist had any effect on the TFMPP cue; typical data are shown in Figure 4. While spiperone and metergoline did reduce drug appropriate responding somewhat (40 to 50 percent), even relatively high doses of these compounds did not antagonize the TFMPP stimulus completely (data not shown).

General Discussion

Since 5-HT_1 agonists (of either the 5-HT_{1A} or 5-HT_{1B} subtype) do not mimic and 5-HT_2 antagonists effectively block the LSD cue while 5-HT_{1B} agonists mimic and 5-HT_2 antagonists do not block the TFMPP cue, it is probably safe to conclude that LSD and

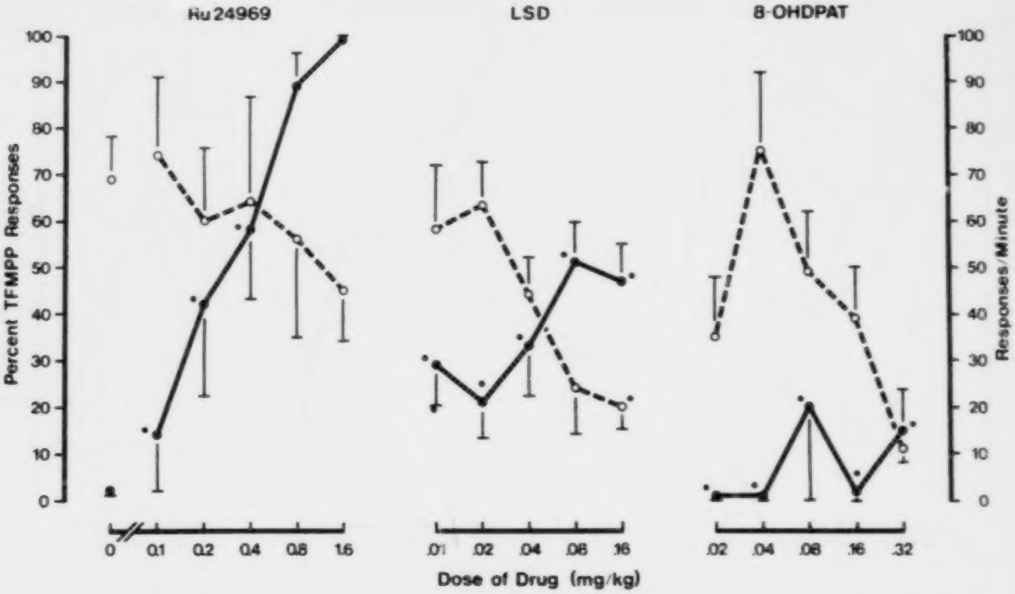


FIGURE 3. Results of substitution tests with Ru 24969, LSD, and 8-OHDPAT in rats trained to discriminate TFMPP (0.8 mg/kg) from saline. The symbols are the same as those of Figure 1. Reprinted from: Cunningham, K.A. & Appel, J.B. Possible 5-hydroxytryptamine-1 (5-HT_2) receptor involvement in the stimulus properties of 1-(*m*-trifluoromethylphenyl) piperazine (TFMPP). *J. Pharmacol. Exp. Ther.* (In Press) with the permission of the Am. Soc. for Pharmacol. and Exp. Ther. and Williams & Wilkins, Inc.

TFMPP have discriminably different properties (induce different "subjective" states) which are mediated by different neuronal mechanisms. The present results thus support those appearing elsewhere in this volume; converging biochemical, electrophysiological and behavioral evidence indicate that, in general, long-chain phenylpiperazines (e.g., TVX 07821), as well as 8-OHDPAT, act at 5-HT_{1A} while short-chain phenylpiperazines (e.g., TFMPP) act at 5-HT_{1B} receptor sites (Aghajanian, 1985; Fuller, 1985). The mechanisms underlying the effects of quipazine are difficult to characterize but appear to differ from those of structurally similar phenylpiperazines (e.g., Martin & Sanders-Bush, 1982).

The results of DD experiments in which LSD was investigated are summarized in Tables 1 and 2; since only one reference is cited for each finding (in the interest of space) these tables are meant to be illustrative rather than exhaustive. The data indicate that, out of the many, diverse psychoactive compounds that have now been examined: 1) The only agents that are similar to LSD (substitute completely) are other indolealkylamine and phenylalkylamine hallucinogens, putatively hallucinogenic beta-carbolines, structural congeners of LSD (most of which are not known to be hallucinogenic), and 5-HT agonists which have at least some affinity for 5-HT_2 receptors (Table 1a). Certain agents appear to substitute "partially" for LSD and therefore require further study (Table 1b). 2) The only compounds that block the LSD cue completely are 5-HT_2 and non-selective 5-HT antagonists (Table 2a). Thus, these results support the idea that, like other indolealkylamine and phenylalkylamine hallucinogens, the *in vivo* actions of LSD are mediated by 5-HT_2 receptors.

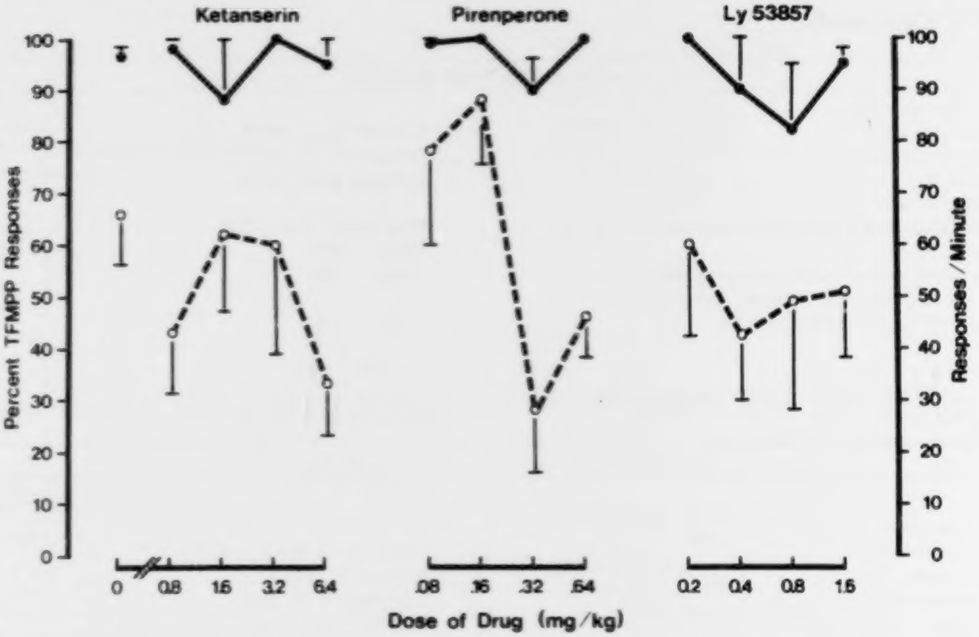


FIGURE 4. Results of combination tests with Ketanserin, pirenperone, and Ly-53857 in rats trained to discriminate TFMPP (0.8 mg/kg) from saline. The symbols are the same as those of Figure 2.

TABLE 1. Results of Substitution (Generalization) Tests in Rats Trained to Discriminate LSD From Saline.

a. Complete Substitution (≥ 80 %)	
Hallucinogens:	
DOB (2,5-Dimethoxy-4-bromophenyl)-2-aminopropane)	(Silverman & Ho, 1979)
DOM (2,5-Dimethoxy-4-methylphenyl)-2-aminopropane)	(Silverman & Ho, 1979)
Mescaline	(Cameron & Appel, 1973)
MDA (2,5-Dimethoxyphenyl)-2-aminopropane	(Shannon et al., 1984)
5-MeODMT (5-Methoxy-N,N-dimethyl tryptamine)	(Rosecrans & Glennon, 1979)
2,5-Dimethoxy-4-ethoxyphenyl isopropylamine	(Oberlender et al., 1984)
2,4-Dimethoxy-5-ethoxyphenyl isopropylamine	(Oberlender et al., 1984)
4,5-Dimethoxy-2-ethoxyphenyl isopropylamine	(Oberlender et al., 1984)
Psilocybin	(Schechter & Rosecrans, 1972)
2,4,5-Trimethoxyamphetamine	(Silverman & Ho, 1979)
Beta-Carbolines:	
6-MeO-THBC (6-Methoxy-tetra hydro-B-carboline)	(Nielsen et al., 1982)
THBC	(Nielsen et al., 1982)
Structural Congeners (Ergolines):	
Lisuride	(White & Appel, 1982)
N(6)-ethyl norlysergic acid-N,N-diethylamide	(Hoffman & Nichols, 1985)
N(6)-allyl norlysergic acid-N,N-diethylamide	(Hoffman & Nichols, 1985)
N(6)-propyl norlysergic acid-N,N-diethylamide	(Hoffman & Nichols, 1985)
Serotonin (5-HT$_2$?) Agonists:	
BL-3912 (2,5-dimethoxy-4-methyl-alpha-ethyl-phenethylamine)	(Winter, 1980)
MK-212 [6-chloro-2-(1-piperizinyl)-pyrazine]	(White & Appel, 1982)
Quipazine	(Colpaert et al., 1979)
Others:	
Yohimbine	(Colpaert, 1984)

TABLE 1. (Continued)

b. Partial Substitution (60–79 %)	
Serotonin Antagonists:	
Cyproheptadine	(Colpaert et al., 1979)
Methysergide (UML)	(Colpaert et al., 1979)
Mianserin	(Colpaert et al., 1979)
Phenylethylamines:	
1-[2,5-Dimethoxy-4-(2-butyl)phenyl-2-aminopropane]	(Oberlender et al., 1984)
Fenfluramine	(Winter, 1980)
PMA (alpha-methyl-4-methoxyphenyl ethylamine)	(Winter, 1984)
Sch 12679 (N-Methyl-1-phenyl-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine)	(Winter, 1980)
Others:	
Clonidine	(Colpaert, 1984)
DPI [(3,4-Dihydroxyphenyl amino)-2-imidazoline]	(Appel et al., 1980)
Scopolamine	(Cameron & Appel, 1973)
THC (delta-9-tetrahydrocannabinol)	(Hirschhorn & Rosecrans, 1976)
Xylazine	(Colpaert, 1984)
c. No Substitution (≤ 59%)	
Dopamine Agonists:	
Amphetamine	(Schechter & Rosecrans, 1972)
Apomorphine	(Kuhn et al., 1978)
Bromocriptine	(Holohean et al., 1982)
Lergotrile	(Holohean et al., 1982)
Serotonin (5-HT$_1$) Agonists:	
mCPP (*m*-chlorophenylpiperazine)	(Cunningham, 1985)
8-OHDPAT [8-hydroxy-2-(di-*n*-propylamino) tetralin]	(Cunningham, 1985)
Ru 24969 [5-methoxy-3-(1,2,3, 6-tetrahydro-pyridin-4-yl) succinate]	(Cunningham, 1985)
TFMPP [1-(*m*-trifluoromethylphenyl) piperazine]	(Cunningham, 1985)
Serotonin Precursors and Uptake Inhibitors:	
Chlorimipramine	(Kuhn et al., 1978)
Fluoxetine	(Kuhn et al., 1978)
5-HTP (L-5-hydroxytryptophan)	(Cunningham et al., 1985)
L-Tryptophan	(Kuhn et al., 1978)
Structural Congeners (Ergolines):	
BOL (2-bromo-lysergic acid diethylamide)	(Colpaert et al., 1982)
1-LSD	(Cameron & Appel, 1973)
Ly-53857 [6-methyl-1-(1-methylethyl) ergoline-8-carboxylic acid, 2-hydroxy-1-methylpropyl ester (z)-2-butenedioate) (1:1)]	(Cunningham, 1985)
Neurotransmitter Antagonists:	
BC 105 (Pizotyline)	(Colpaert et al., 1982)
Chlorpromazine	(Cameron & Appel, 1972)
Cinanserin	(Colpaert et al., 1982)
Haloperidol	(White & Appel, 1982)
Ketanserin	(Nielsen et al., 1985)
Metergoline	(Colpaert et al., 1982)
Methiothepin	(Colpaert et al., 1982)
Ritanserin	(Colpaert et al., 1985)
Spiperone	(Colpaert et al., 1982)
Trazodone	(Cunningham, 1985)
Opiates:	
Meperidine	(Hirschhorn & Rosecrans, 1974)
Methadone	(Hirschhorn & Rosecrans, 1976)
Morphine	(Hirschhorn & Rosecrans, 1976)
Nalorphine	(Hirschhorn & Rosecrans, 1976)
Pentazocine	(Hirschhorn & Rosecrans, 1976)

Others:	
Barbital	(Hirschhorn & Winter, 1975)
Ditran	(Kuhn et al., 1977)
Harmaline	(Nielsen et al., 1982)
Harmane	(Nielsen et al., 1982)
5-MeOT (5-methoxytryptamine)	(White & Appel, 1982)
PCP (Phencyclidine)	(Kuhn et al., 1977)

TABLE 2. Results of Combination (Antagonism) Tests in Rats Trained to Discriminate LSD From Saline.

a. Drugs That Antagonize LSD (≤ 30% Drug-Appropriate Responding)	
$5\text{-}HT_2$ Antagonists:	
Ketanserin	(Nielsen et al., 1985)
LY-53857	(Cunningham, 1985)
Pirenperone	(Colpaert & Janssen, 1983)
Ritanserin	(Colpaert et al., 1985)
Trazodone	(Cunningham, 1985)
Non-Selective 5-HT Antagonists:	
BC 105	(Holohean et al., 1982)
BOL	(Colpaert et al., 1982)
Metergoline	(Cunningham, 1985)
b. Partial (Incomplete) Antagonism (31 ≤ 60% Drug-Appropriate Responding)	
Non-Selective 5-HT Antagonists:	
Cinanserin	(Colpaert et al., 1982)
Cyproheptadine	(Colpaert et al., 1982)
Methiothepin	(Colpaert et al., 1982)
Methysergide	(Colpaert et al., 1982)
Mianserin	(Colpaert et al., 1982)
c. Drugs That Do Not Antagonize LSD (≥ 61% Drug-Appropriate Responding)	
DA Antagonists:	
Butaclamol	(Kuhn et al., 1978)
Chlorpromazine	(Kuhn et al., 1978)
Fluphenazine	(Kuhn et al., 1978)
Haloperidol	(Kuhn et al., 1978)
Sulpiride	(Appel et al., 1980)
Trifluoperazine	(Kuhn et al., 1978)
Spiperone	(Colpaert et al., 1982)
NE Antagonists:	
Phentolamine (Alpha)	(Kuhn et al., 1978)
Propranalol (Beta)	(Kuhn et al., 1978)
Serotonin Uptake Inhibitors:	
Chlorimipramine	(Kuhn et al., 1978)
Citalopram	(Kuhn et al., 1978)
Fluoxetine	(Kuhn et al., 1978)
Others:	
Atropine	(Kuhn et al., 1978)
8-OHDPAT	(Cunningham, 1985)
Naloxone	(Kuhn et al., 1978)
Promethazine	(Kuhn et al., 1978)
Xylamidine	(Kuhn et al., 1978)

References

Aghajanian, G.K. Electrophysiological responses to 5-HT$_{1A}$ and 5-HT$_{1B}$ ligands at pre- and postsynaptic sites in rat brain. Paper presented at meeting of the American College of Neuropsychopharmacology, Maui, Hawaii, 1985.

Appel, J.B., Holohean, A.M., and White, F.J. Generalization of LSD and apomorphine cues to ergot alkaloids: 5-HT and DA mechanisms. Paper presented at meeting of the Committee on Problems of Drug Dependence (Satellite Session of the Society for the Stimulus Properties of Drugs), Hyannis, MA 1980.

Appel, J.B., White, F.J., and Holohean, A.M. Analyzing mechanism(s) of hallucinogenic drug action with drug discrimination procedures. *Neurosci. Biobehav. Rev.*, 6:529–536, 1982.

Cameron, O.G., and Appel, J.B. A behavioral and pharmacological analysis of some discriminable properties of d-LSD in rats. *Psychopharmacologia*, 33:117–134, 1973.

Colpaert, F.C. Cross generalization with LSD and yohimbine in the rat. *Eur. J. Pharmacol.*, 102:541–544, 1984.

Colpaert, F.C., and Janssen, P.A.J. A characterization of LSD-antagonist effects of pirenperone in the rat. *Neuropharmacology*, 22:1001–1005, 1983.

Colpaert, F.C., Meert, T.F., Niemegeers, C.J.E., and Janssen, P.A.J. Behavioral and 5-HT antagonist effects of ritanserin: A pure and selective antagonist of LSD discrimination in rat. *Psychopharmacology*, 86:45–54, 1985.

Colpaert, F.C., Niemegeers, C.J.E., and Janssen, P.A.J. In vivo evidence of partial agonist activity exerted by purported 5-HT antagonists. *Eur. J. Pharmacol.*, 58:505–509, 1979.

Colpaert, F.C., Niemegeers, C.J.E., and Janssen, P.A.J. A drug discrimination analysis of LSD (LSD): In vivo agonist and antagonist effects of purported 5-HT antagonists and of pirenperone, an LSD-antagonist. *J. Pharmacol. Exp. Ther.*, 221:206–214, 1982.

Cunningham, K.A. Multiple serotonin receptors: Behavioral and neurochemical correlates. Unpublished Ph.D. Dissertation. University of South Carolina, 1985.

Cunningham, K.A., Callahan, P.M., and Appel, J.B. Differentiation between the stimulus effects of 1-5-hydroxytryptophan and LSD. *Eur. J. Pharmacol.*, 108:179–186, 1985.

Friedman, R.L., Barrett, R.J., Sanders-Bush, E. Discriminative stimulus properties of quipazine: Mediation by serotonin-2 binding sites. *J. Pharmacol. Exp. Ther.*, 228:628–635, 1984.

Fuller, R.W. Substituted phenylpiperazines as serotonin agonists: Structural determinants of potency and interaction with receptor subtypes. Paper presented at meeting of the American College of Neuropsychopharmacology, Maui, Hawaii, 1985.

Glennon, R.A. Structure-activity relationships of hallucinogenic agents based on drug discrimination and binding data. Paper presented at meeting of the American College of Neuropsychopharmacology, Maui, Hawaii, 1985.

Glennon, R.A., Young, R., Benington, F., and Morin, R.D. Behavioral and serotonin receptor properties of 4-substituted derivatives of the hallucinogen 1-(2,5-dimethoxyphenyl)-2-aminopropane. *J. Med. Chem.*, 25:1163–1168, 1982.

Glennon, R.A., Young, R., Rosecrans, J.A. Antagonism of the effects of the hallucinogen DOM and the purported serotonin agonist quipazine by 5-HT$_2$ antagonists. *Eur. J. Pharmacol.*, 91:189–196, 1983.

Hirschhorn, I.D., and Rosecrans, J.A. A comparison of the stimulus effects of morphine and lysergic acid diethylamide (LSD). *Pharmacol. Biochem. Behav.*, 2:361–366, 1974.

Hirschhorn, I.D., and Rosecrans, J.A. Generalization of morphine and lysergic acid diethylamide (LSD) to narcotic analgesics. *Psychopharmacology*, 47:65–69, 1976.

Hirschhorn, I.D., and Winter, J.C. Differences in the stimulus properties of barbital and hallucinogens. *Pharmacol. Biochem. Behav.*, 3:343–347, 1975.

Hoffman, A.J., and Nichols, D.E. Synthesis and LSD-like discriminative stimulus properties in a series of N(6)-alkyl norlysergic acid N, N-diethylamide derivatives. *J. Med. Chem.*, 28:1252–1255, 1985.

Holohean, A.M., White, F.J., and Appel, J.B. Dopaminergic and serotonergic mediation of the discriminable effects of ergot alkaloids. *Eur. J. Pharmacol.*, 81:595–602, 1982.

Kuhn, D.M., White, F.J., and Appel, J.B. Discriminative stimulus properties of hallucinogens: Behavioral assay of drug action. In: Lal, H. (ed.), *Discriminative Stimulus Properties of Drugs*. New York: Plenum Press, 1977, pp. 137–155.

Kuhn, D.M., White, F.J., and Appel, J.B. The discriminative stimulus properties of LSD: Mechanism of action. *Neuropharmacology*, 17:257–263, 1978.

Martin, L.L., Sanders-Bush, E. The serotonin autoreceptor: Antagonism by quipazine. *Neuropharmacology*, 21:445–450, 1982.

Nielsen, E.B., Ginn, S.R., Cunningham, K.A., and Appel, J.B. Antagonism of the LSD cue by putative serotonin antagonists: Relationship to inhibition of *in vivo* ^{3}H-spiroperidol binding. *Behav. Brain Res.*, 16:171–176, 1985.

Nielsen, E.B., White, F.J., Holohean, A.M., et al. Behavioral and biochemical evidence for serotonergic actions of tetrahydro-B-carbolines. *Life Sci.*, 31:2433–2439, 1982.

Oberlender, R.A., Kothari, P.J., Nichols, D.E., and Zabik, J.E. Substituent branching in phenethylamine-type hallucinogens: A comparison of 1-(2,5-

dimethoxy-4-(2-butyl)phenyl)-2-aminopropane and 1-(2,5-dimethoxy-4-(methylpropyl))-2-aminopropane. *J. Med. Chem.*, 27:788–792, 1984.

Peroutka, S.J., and Snyder, S.H. Multiple serotonin receptors: Differential binding of ^{3}H-5-hydroxytryptamine, ^{3}H-lysergic acid diethylamide and ^{3}H-spiroperidol. *Mol. Pharmacol.*, 16:687–699, 1979.

Rosecrans, J.A., and Glennon, R.A. Drug induced cues in studying mechanisms of drug action. *Neuropharmacology*, 18:981–989, 1979.

Schechter, M.D., and Rosecrans, J.A. Lysergic acid diethylamide (LSD) as a discriminative cue: Drugs with similar stimulus properties. *Psychopharmacologia*, 26:313–316, 1972.

Shannon, M., Battaglia, G., Glennon, R.A., and Titeler, M. 5-HT$_1$ and 5-HT$_2$ binding properties of derivatives of the hallucinogen 1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-DMA). *Eur. J. Pharmacol.*, 102:23–29, 1984.

Silverman, P.B., and Ho, B.T. Effect of some amphetamine analogues in rats trained to discriminate LSD. *Soc. Neurosci. Abstr.*, 5:662, 1979.

White, F.J., and Appel, J.B. Training dose as a factor in LSD-Saline discrimination. *Psychopharmacology*, 76:20–25, 1982.

Winter, J.C. Effects of phenylethylamine derivatives, BL-3912, fenfluramine and Sch-12679 in rats trained with LSD as a discriminative stimulus. *Psychopharmacology*, 68:159–162, 1980.

Winter, J.C. The stimulus properties of paramethoxyamphetamine: A nonessential serotonergic component. *Pharmacol. Biochem. Behav.*, 20:201–203, 1984.

Disruption of Operant Behavior by Hallucinogenic Drugs[1]

Richard H. Rech, Ph.D.,[2] and David J. Mokler, Ph.D.[3]

Introduction

The use of animal models to study the effects of hallucinogenic drugs has never been very satisfying. This is true whether the test systems are based on analogous patterns of biological functions or presumed behavioral homologs. Nevertheless, various animal neurophysiological and behavioral models have been helpful in describing neuro–pharmacological and psychopharmacological aspects of the activity of these drug classes (Aghajanian et al., 1970; Appel & Rosecrans, 1984; Jacobs, 1976; McCall & Aghajanian, 1980; Rech & Commissaris, 1982; Sloviter et al., 1980). The test object that we employ is the pattern of the fixed ratio-40 (FR-40) schedule of operant responding in rats, originally observed by Freedman, Appel, and coworkers (1964) to be disrupted by hallucinogenic drugs. However, we have incorporated a counter to register number of interresponse times greater than 10 sec ("pauses"), since the hallucinogenic profile is to induce these abrupt pauses rather than a reduced rate of responding based on increased interresponse times of less than 10 seconds.

Results

Results of previous studies from our laboratory already reviewed (Rech & Commissaris, 1982) generally support the conclusions that the pattern of disruption of FR-40 behavior by hallucinogens relates to serotonin (5HT) agonistic activity at multiple sites in the brain, but not critically to dopaminergic activity or to specific patterns of altered turnover of brain dopamine or 5HT.

Interactions of lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (DOM), quipazine, and lisuride with the three 5HT antagonists metergoline, pizotifen (BC–105), and cinanserin were examined (Mokler et al., 1983; Table 1). LSD was found to be most effectively antagonized by pretreatment with pizotifen, while metergoline and cinanserin were about equal in shifting the ED_{50}'s of LSD. Dimethyltryptamine (DMT) (not shown in Table 1) interacted with the antagonists in a pattern very similar to that of LSD. The effects of DOM were most dramatically antagonized by metergoline, with pizotifen being considerably less active and cinanserin being least effective. Interactions with mescaline resembled those for DOM (data not included in Table 1). Quipazine interacted with the 5HT antagonists with a pattern more like that of DOM and mescaline. The ED_{50}'s of lisuride were shifted to about the same extent by pretreating with metergoline and pizotifen (more like LSD). However, cinanserin pretreatment failed to increase the ED_{50}'s of lisuride, and this antagonist actually reduced the ED_{50} of lisuride to decrease the reinforcers earned.

The above 5HT antagonists are considered to act at both $5HT_1$ and $5HT_2$ type receptors (Martin & Sanders-Bush, 1982). Pirenperone appears to be selective as a $5HT_2$ antagonist (Leysen et al., 1981). Table 2 shows the extent of shift in the ED_{50}'s for pause intervals comparing agonists alone with agonists plus various doses of pirenperone (Mokler et al., 1985). Even the lowest dose of pirenperone (20 μg/kg) shifted the LSD ED_{50} by almost 3 times and all of the hallucinogens showed significant shifts in the dose-response curves from 3.45 to 15.1 times. As with metergoline, pirenperone was more effective in antagonizing DOM and mescaline than in blocking LSD and DMT. The quipazine dose for disrupting FR-40 was shifted by 7.98 times after

---

[1] These studies were supported by Grant DA–01836 from NIDA and by NIH Training Grant GM07392.

[2] Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824.

[3] Department of Pharmacology and Toxicology, Virginia Commonwealth Univ., Medical College of Virginia, Box 613, MCV Station, Richmond, VA 23298.

TABLE 1. ED_{50}'s for Hallucinogens and 5HT Agonists Alone and in Combination With 5HT Antagonists.

	Reinforcers			
	LSD (µg/kg)	DOM (mg/kg)	QUIP (mg/kg)	LIS (µg/kg)
Alone	85	0.6	1.6	30
	[52–122][a]	[0.3–2.9]	[0.9–5.4]	[25–36]
+1.0 Metergoline	141 (1.7)[b]	26.5 (44.2)	>8.0[c]	58 (1.9)
(180 min pretreatment)	[6–236]	[6.7–7.0E24]		[44–102]
+1.0 Pizotifen	334 (3.9)	3.2 (5.3)	>8.0[c]	57 (1.9)
(40 min pretreatment)	[220–3931]	[1.1–16.4]		[47–72]
+20 Cinanserin	181 (2.1)	1.8 (3.0)	3.7 (2.3)	16 (0.5)
(80 min pretreatment)	[119–369]	[1.2–3.6]	[1.6–13.7]	[11–24]
	Pause Intervals			
Alone	81	0.6	1.6	31
	[68–98]	[0.3–1.7]	[1.0–3.1]	[25–39]
+ Metergoline	195 (2.4)	>8.0[c]	12.3 (7.7)	59 (1.9)
	[132–281]		[5.2–2.1E9]	[44–105]
+1.0 Pizotifen	305 (3.8)	5.0 (8.3)	7.0 (4.4)	64 (2.1)
	[219–493]	[2.9–14.2]	[3.7–19.9]	[54–80]
+20 Cinanserin	196 (2.4)	2.8 (4.7)	5.0 (3.1)	35 (1.1)
	[144–305]	[1.7–8.2]	[2.5–15.2]	[29–44]

ED_{50}'s for reinforcers and pause intervals determined by orobit analysis of data from LSD, DOM, quipazine (QUIP), and lisuride (LIS) analyses.

[a] 95 percent confidence limits.

[b] Ratio of [ED_{50} (agonist + antagonist)]/ED_{50} (agonist).

[c] Estimation; probit analysis of dose-response curve indicates non-significant slope.

160 µg/kg pirenperone. However, the FR-40 effects of lisuride were not significantly antagonized even by the highest dose of pirenperone.

Domino and colleagues published several reports demonstrating a naloxone potentiation of disruption of fixed-ratio operant behavior by indole-type hallucinogens (Ruffing et al., 1979). Moreover, morphine and synthetic metenkephalins attenuated the behavioral effects of these hallucinogens (Ruffing & Domino, 1981, 1983). We verified that naloxone pretreatment potentiates indole hallucinogens and extended the interaction to phenalkylamine hallucinogens (Commissaris et al., 1980; Mokler et al., 1984). However, the effects of quipazine to disrupt FR–40 were antagonized by pretreatment with naloxone. Other opioid-hallucinogenic drug interactions in the FR–40 are summarized in Table 3 (*see* Henck et al., 1983, and Rech et al., 1983).

In an effort to identify areas of the brain most involved in the FR–40 behavioral ef-

TABLE 2. ED_{50}'s for Change in Pause Intervals for Agonists Alone and Combinations With Pirenperone.

	Alone	+ 20 µg/kg PIR	+ 40 µg/kg	+ 80 µg/kg	+ 160 µg/kg
LSD	103	307 (2.98)[a]	266 (2.58)	374 (3.63)	368 (3.57)
(µg/kg)	(61–184)[b]	(213–443)	(216–354)	(290–552)	(299–452)
DMT	4.35	6.95 (1.60)	7.69 (1.77)	15.0 (3.45)	—
(mg/kg)	(3.6–5.43)	(5.18–10.7)	(5.98–10.7)	(9.9–78.5)	—
DOM	0.84	3.93 (4.68)	3.11 (3.70)	4.59 (5.46)	4.94 (5.88)
(mg/kg)	(0.63–1.15)	(2.84–6.79)	(2.40–4.23)	(3.63–5.87)	(3.68–9.22)
Mescaline	10.4	48.9 (4.70)	82.5 (7.93)	157 (15.10)	—
(mg/kg)	(7.8–17)	(34–28201)	(41–9458)	(69–2614)	—
Quipazine	1.68	3.93 (2.34)	3.88 (2.31)	8.07 (4.80)	13.4 (7.98)
(mg/kg)	(1.38–5.88)	(2.84–6.79)	(3.04–5.11)	(6.03–12.21)	(4.8–923040)
Lisuride	27	56 (2.07)	37 (1.37)	46 (1.70)	37 (1.37)
(µg/kg)	(20–40)	(34–85)	(31–46)	(39–55)	(27–53)

ED_{50}'s were determined by probit analysis.

[a] Dose ratio = (ED_{50}:agonist plus pirenperone)/ED_{50}:agonist alone.

[b] 95 percent confidence interval.

fects of LSD and DOM, we administered these agents directly into various brain regions in rats with chronically prepared cannulae. The potency of the agent infused intracranially (IC) was compared with that established by infusion into the lateral cerebral ventricle (ICV; Mokler & Rech, 1984). LSD was only slightly more effective (1.3 times) by the ICV route than by i.p. injection, while lisuride showed no dose differential by the two routes. ICV DOM was about 2.7 times more potent than i.p. DOM. Only for mescaline was the ICV route much more potent than i.p. injection (30 times). When LSD was infused IC into the dorsal raphe, the potency to disrupt FR–40 was slightly greater than for ICV administration (Table 4). On the contrary, when LSD was infused in the lateral habenula, potency by this intracranial (IC) route was less than by ICV infusion. LSD administered into other IC sites yielded intermediate potency values. The values for potencies of DOM administered IC into the various brain sites compared to that by ICV infusion are also listed in Table 4. In contrast to LSD, DOM was not more potent by IC infusion into any brain region, relative to ICV potency. The effects of DOM placed into the lateral habenula were complex; the overall ED$_{50}$ was 103 μg, but the dose-response pattern was multiphasic. The initial disruption of behavior (20 to 120 μg) demonstrated an ED$_{50}$ of 69 μg. Above 120 μg, the behavior appeared to be reinstated, and then to show a secondary disruption at doses of 160 to 240 μg, with an ED$_{50}$ of 176 μg.

TABLE 3. Summary of Opioid-Hallucinogen Interactions.

1. NAL (naloxone) potentiated FR–40 disruption by hallucinogens (blocking of modulating endorphin systems?).
2. CYCL (cyclazocine) disrupted FR–40 with the hallucinogenic pattern, but NAL antagonized CYCL; MTG (metergoline) also antagonized CYCL (kappa and sigma vs. delta and 5HT receptor activities?).
3. QUIP (quipazine) disruption of FR–40 is slightly antagonized by pretreating with NAL or CYCL (5HT-opioid interactions on appetite?).
4. EKC (ethylketocyclazocine) disruption of FR–40 is potentiated by NAL and MTG at low doses of EKC but blocked at high doses of EKC (kappa and 5HT receptor interactions?).
5. SKF–10,047 disruption of FR–40 is little affected by NAL and only slightly antagonized by MTG (direct sigma activity resistant to NAL and only slightly affected by 5HT systems?).

TABLE 4. ED$_{50}$'s for Change in Pause Intervals ICV vs. IC Administration.

Route	LSD (μg)	DOM (μg)
ICV	15 (10–19)	58 (13–83)
IC		
Dorsal Raphe	9 (2–20)	77 (60–117)
Median Raphe	25 (21–28)	47 (0–95)
Lateral Habenula	54 (29–249)	103 (29–208)
Dorsal Hippocampus	23 (14–37)	114 (74–187)
Prefrontal Cortex	13 (0–47)	92 (17–298)

Values are ED$_{50}$'s for increases in pause intervals using probit analysis. Values in parenthesis are 95 percent confidence limits.

Discussion

Comparing the 5HT antagonists with presumed 5HT$_1$ and 5HT$_2$ receptor activity for blocking the 5HT agonistic effects on FR–40, LSD and lisuride were antagonized best by pizotifen. However, lisuride was not blocked significantly by the 5HT$_2$-selective antagonist pirenperone, suggesting that lisuride exerts more 5HT$_1$ receptor effects to interfere with FR–40 behavior, and pizotifen then would have relatively more prominent antagonistic activity via 5HT$_1$ receptors. By inference, the indole hallucinogens appear to exert disruptive effects by a balance of 5HT$_1$ and 5HT$_2$ activity. Since cinanserin actually potentiated FR–40 effects of lisuride, cinanserin may be more of a partial agonist at 5HT$_1$ receptors. The fact that cinanserin administered alone causes a significant decrease in reinforcers earned also suggests a partial agonistic action at 5HT$_1$ receptors. Since the phenalkylamine hallucinogens were very effectively antagonized by metergoline and pirenperone and less effectively antagonized by pizotifen and cinanserin, these agonists may influence behavior to a greater extent via 5HT$_2$ receptor activity. Quipazine was well antagonized by metergoline, pizotifen, and pirenperone, although the actions of quipazine on behavior appear to be mediated primarily via 5HT$_2$ receptors (*see* Friedman et al., 1984).

An important finding is that the lisuride dose-response curve was not shifted significantly by even the largest doses of pirenperone. Therefore, lisuride may not exert a strong enough action at 5HT$_2$ receptors to alter brain functioning as do the hallucinogens. Quipazine, though having many behavioral effects in rats similar to the hallucinogens, does not appear to be hallucinogenic in man. Quipazine must affect FR–40 behavior in a somewhat different manner than do the hallucinogens, since naloxone pretreatment antagonized the disruption rather than potentiating it. Perhaps quipazine lacks efficacy as a 5HT$_1$ agonist at relevant brain sites to alter central functions to bring about the same imbalance as occurs with hallucinogenic drugs.

Intracranial administration of LSD into various brain sites indicated that activity at the dorsal raphe and prefrontal cortex may be important for the lowest dose effects on FR–40 responding. Nevertheless, the small dose differential between the various brain sites suggests that LSD activity at multiple brain sites generally contributes to the behavioral disruption. This conclusion could be extended to the activity of DOM since doses at various brain sites to disturb the operant behavior were not significantly different. Furthermore, these findings are consistent with previous results from our laboratory regarding enhanced potency of hallucinogens in rats pretreated ICV with 5,7-DHT. When this 5HT neurotoxin was administered IC into various forebrain sites, the potency of the i.p.-injected hallucinogens to disrupt FR–40 was not increased in any systematic manner (Rech & Commissaris, 1982).

References

Aghajanian, G.K., Foote, W.E., and Sheard, M.H. Action of psychotogenic drugs on single midbrain raphe neurons. *J. Pharmacol. Exp. Ther.*, 171:178–187, 1970.

Appel, J.B., and Rosecrans, J.A. The behavioral pharmacology of hallucinogens and its relation to serotonergic neuronal mechanisms. In: Jacobs, B.L. (ed.), *Hallucinogens: Neurochemical, Behavioral and Clinical Perspectives*. New York: Raven Press, 1984, pp. 77–94.

Commissaris, R.L., Moore, K.E., and Rech, R.H. Naloxone potentiates the disruptive effects of mescaline on operant responding in the rat. *Pharmacol. Biochem. Behav.*, 13:601–603, 1980.

Freedman, D.X., Appel, J.D., Hartman, F.R., and Molliver, M.D. Tolerance to behavioral effects of LSD-25 in rats. *J. Pharmacol. Exp. Ther.*, 143:309–313, 1964.

Friedman, R.L., Barrett, R.J., and Sanders-Bush, E. Discriminative stimulus properties of quipazine: Mediation by serotonin$_2$ binding sites. *J. Pharmacol. Exp. Ther.*, 228:628–635, 1984.

Henck, J.W., Mokler, D.J., Commissaris, R.L., and Rech, R.H. Cyclazocine disruption of operant behavior is antagonized by naloxone and metergoline. *Pharmacol. Biochem. Behav.*, 18:41–45, 1983.

Jacobs, B.L. Minireview: An animal behavior model for studying central serotonergic synapses. *Life Sci.*, 19:777–786, 1976.

Leysen, J.E., Awouters, F., et al. Receptor binding profile of R41468, a novel antagonist at 5-HT$_2$ receptors. *Life Sci.*, 28:1015–1022, 1981.

Martin, L.L., and Sanders-Bush. E. Comparison of the pharmacological characteristics of 5HT$_1$ and 5HT$_2$ binding sites with those of serotonin autoreceptors which modulate serotonin release. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 321:165–170, 1982.

McCall, R.B., and Aghajanian, G.K. Hallucinogens potentiate response to serotonin and norepinephrine in the facial motor nucleus. *Life Sci.*, 26:1149–1156, 1980.

Mokler, D.J., Commissaris, R.L., Henck, J.W., and Rech, R.H. Naloxone alters the effects of LSD, DOM and quipazine on operant behavior of rats. *Pharmacol. Biochem. Behav.*, 21:333–337, 1984.

Mokler, D.J., Commissaris, R.L., Warner, M.R., and Rech, R.H. Blockade of the behavioral effects of LSD, DOM, quipazine and lisuride by 5-hydroxytryptamine antagonists. *J. Pharmacol. Exp. Ther.*, 227:557–562, 1983.

Mokler, D.J., and Rech, R.H. Behavioral effects of intracerebroventricular administration of LSD, DOM, mescaline or lisuride. *Pharmacol. Biochem. Behav.*, 21:281–287, 1984.

Mokler, D.J., Stoudt, K.W., and Rech, R.H. The 5HT$_2$ antagonist pirenperone reverses disruption of FR–40 by hallucinogenic drugs. *Pharmacol. Biochem. Behav.*, 22:677–682, 1985.

Rech, R.H., and Commissaris, R.L. Neurotransmitter basis of the behavioral effects of hallucinogens. *Neurosci. Biobehav. Rev.*, 6:521–527, 1982.

Rech, R.H., Mokler, D.J., Commissaris, R.L., and Henck, J.W. Behavioral interactions of opioid agonists and antagonists with serotonergic systems. NIDA Research Monograph Series 49, pp. 179–184, Dept. of Health and Human Services, PHS, March, 1984.

Ruffing, D.M., and Domino, E.F. Effects of selected opioid agonists and antagonists on DMT- and LSD-25-induced disruption of food-rewarded bar pressing behavior in the rat. *Psychopharmacology (Berlin)*, 75:226–230, 1981.

Ruffing, D.M., and Domino, E.F. Interaction of synthetic opioid metenkephalin peptide analogs, Lilly 127623 and FK33–824 with indole hallucinogens: Antagonism of *N,N*-dimethyltryptamine and LSD-induced disruption of food-rewarded bar pressing behavior in the rat. *Psychopharmacology (Berlin)*, 80:315–318, 1983.

Ruffing, D., Kovacic, B., Demetrious, S., and Domino, E. Naloxone enhancement of DMT and LSD-25 induced suppression of food-rewarded bar pressing behavior in the rat. *Psychopharmacology (Berlin)*, 62:207–210, 1979.

Sloviter, R.S., Drust, E.G., Damiano, B.P., and Connor, J.D. A common mechanism for LSD, indolealkylamine and phenethylamine hallucinogens: Serotonergic mediation of behavioral effects in rats. *J. Pharmacol. Exp. Ther.*, 214:231–238, 1980.

Comparison of Phencyclidine and Related Substances With Various Indole, Phenethylamine, and Other Psychotomimetics[1,2]

Edward F. Domino, M.D.[3]

Introduction

Psychotomimetics are logically classified on the basis of chemical structure. They include: 1) Indolealkylamines such as tryptamine, dimethyltryptamine (DMT), 5-methoxydimethyltryptamine (5-MeODMT), psilocin, etc. 2) Lysergic acid amides (also called lysergimides) such as lysergic acid diethylamide-25 (LSD-25) or LSD for short. LSD contains an indole structure and is frequently classified as an indole hallucinogen. However, its more complex chemical structure warrants a separate classification. Furthermore, it is much more difficult to synthesize and therefore to obtain illicitly. 3) Some of the phenethylamines, including amphetamine-like compounds (amphetamine, *p*-methoxyamphetamine, methamphetamine), and mescaline-like compounds [mescaline, 2, 5-dimethoxy-4-methylamphetamine (DOM), methylenedioxyamphetamine (MDA)]. 4) Infrequently abused are the M-cholinergic antagonists such as atropine and 3-quinuclidinyl benzilate (QNB). The latter is also known as BZ and at one time was proposed as a chemical warfare agent to induce a psychotomimetic state. 5) Still another class of psychotomimetic agents is the arylcyclohexylamines such as phencyclidine (PCP). At least five chemical subtypes include PCP-like compounds, dioxalanes, benzomorphans, and unbridged and bridged benz(f)isoquinolines, all of which have been called "phencyclinoids" and/or "*sigma*" opioids (for SKF 10,047). Substances with other heterocyclic structures also produce psychotomimetic effects including 6) cannabinoids like Δ^9-THC, the active ingredient in marijuana, 7) β-carbolines like harmine and harmaline, 8) some of the constituents of nutmeg including myristicin and elemicin, and 9) catatonic producing agents such as bulbocapnine.

Prototypic Chemical Structures of Various Substances Showing PCP-Like Activity

As mentioned above, a number of chemicals with different molecular structures have PCP-like effects. All of these have been tested in animals. Only some of these have been verified to be similar in man. The compounds with prototypic structures include those shown in Figure 1. An important chemical problem is to establish the absolute configuration of all of these substances to determine the common elements shared with PCP itself. To make matters even more complex, PCP exists in four different conformations as shown in Figure 2.

This has prompted Kamenka (1983) to use the term "chameleon" in describing the PCP molecule and its four different conformations. Which is the active conformation in the PCP receptor complex?

Mechanism of Action of Psychotomimetic Agents

An important book which summarizes some of our knowledge on the neurochemical, behavioral, and clinical perspectives of hallucinogens is that edited by Jacobs (1984). With so many diverse chemical classes of psychotomimetics, there is no simple unifying theory as to how they act. Most investigators feel that the major chemical messengers in the brain including norepinephrine (NE), dopamine (DA), serotonin (5-HT), acetylcholine

---

[1] Supported in part by NIDA grant DA 01531.

[2] Presented as part of the Panel on Mechanisms of Action of Indole and Phenalkylamine Hallucinogens, December 13, 1985, ACNP Meetings, Maui, HI.

[3] Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109–0010.

Address all correspondence concerning this manuscript to: Dr. E.F. Domino, Department of Pharmacology, M6414 Medical Science Bldg. I, Ann Arbor, MI 48109–0010.

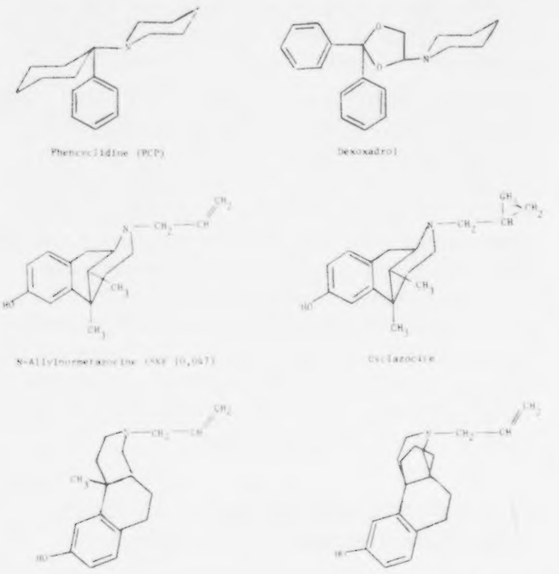

Phencyclidine (PCP)
Dexoxadrol
N-Allylnormetazocine (SKF 10,047)
Cyclazocine
Benz(f)isoquinolines
Bridged Benz(f)isoquinolines

FIGURE 1. Chemical structures of various compounds that have phencyclidine-like activity.

(ACh), and some excitatory amino acids like glutamate, in particular, N-methylaspartate (NMA), are involved. The two catecholamines, DA and NE, along with the trace brain amines phenethylamine and phenethanolamine, appear to be most implicated with stimulant-induced psychoses such as those produced by amphetamine, methamphetamine, etc.

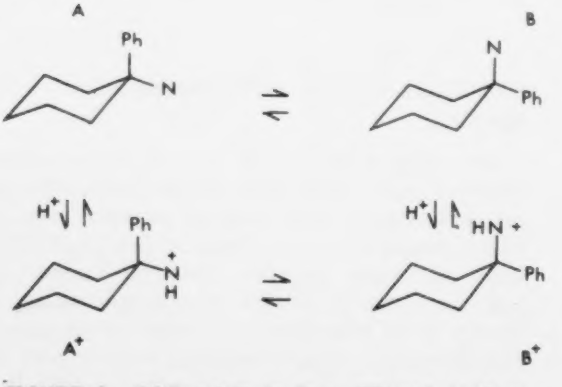


FIGURE 2. PCP exists in four different conformations.

On the other hand, other phenethylamines such as mescaline, DOM, and various indolealkylamine and lysergic acid amides, appear to involve the chemical messenger 5-HT. The newer developments in this field relate to the subtypes of 5-HT receptors. Ligand binding assays using *in vitro* brain membrane fractions from animals are now widely used by neuroscientists. LSD-25 binds to both 5-HT_1 and 5-HT_2 receptors as do some nonhallucinogenic ergot analogs like lisuride. However, almost all of these two classes of hallucinogens seem to interact more on 5-HT_2 sites (Peroutka & Snyder, 1983; Shannon et al., 1984). Shannon et al. (1984) used radiolabeled ^{3}H-5-HT and ^{3}H-ketanserin to label 5-HT_1 and 5-HT_2 sites, respectively. They found that among the various hallucinogens studied (especially phenethylamine derivatives which can be further subclassified as phenisopropylamines) that radioactive binding was more stereoselective to 5-HT_2 than 5-HT_1 sites. Furthermore, the 5-HT_2 binding affinities (called K_i values) of those hallucinogens correlated with rat behavioral discriminative data (effective dose 50 percent or ED50s). In turn, these correlated with the potencies of some of these compounds as hallucinogens in man.

About 20 years ago, it was discovered that animals, when properly trained, discriminate the effects of drugs. Ho et al. (1978), Colpaert and Rosecrans (1978), and Colpaert and Slangen (1982) organized symposia that have summarized much of our knowledge in this field. A given class of drugs such as LSD has discrete stimulus properties that can be distinguished from another unrelated class (Δ^9-THC, etc). Furthermore, animals such as rats can be trained to distinguish morphine from 0.9 percent NaCl placebo from LSD-25, etc. Appel et al. (1982) and Appel and Rosecrans (1984) have reviewed the behavioral pharmacology of hallucinogens in animals on respondent (pavlovian) conditioning and operant (instrumental) conditioning. They point out that the most highly specific operant paradigm to distinguish hallucinogens is drug discrimination. They reviewed the evidence for a common 5-HT_2 and/or hallucinogen receptor mode of action for a variety of compounds. Rech and Commissaris (1982) additionally have provided evidence that a particular spectrum of activity at 5-HT$_2$ relative to 5-HT$_1$ receptor sites is characteristic of a large variety of hallucinogens.

Jacobs (1984) summarized the evidence that hallucinogens such as DMT, DOM, LSD-25, mescaline, and psilocybin act on postsynaptic 5-HT receptors. All of these compounds elicit a so-called "5-HT behavioral syndrome" in rats which consists of head weaving, tremor, rigidity, Straub tail, splayed hindlegs, and forepaw treading. Tolerance and cross-tolerance to these effects are observed which correlate with decreases (down-regulation) of 5-HT binding sites. Jacobs (1984) has provided evidence that the behavioral effects of such 5-HT acting hallucinogens can be dissociated from their presynaptic actions on 5-HT neurons.

Can the actions of LSD-25 and related indole and phenethylamine hallucinogens on the 5-HT system be related to the actions of arylcyclohexylamines such as PCP or to psychomotor stimulants like amphetamine? Probably not, but there are some interesting relationships and contrasts. Most psychotomimetics, when given chronically, induce tolerance. On the other hand, in rodents chronic amphetamine effects are potentiated. In other words, chronic use produces supersensitivity. Nabeshima and his colleagues in Japan (1985) have shown that PCP given chronically to rats produces a mixed picture. The PCP-induced "5-HT like syndrome" is attenuated with chronic PCP administration and shows cross-tolerance to 5-MeODMT, while DA mediated behavioral effects such as sniffing, rearing, or licking are enhanced in chronic PCP treated rats given PCP or DA agonists such as apomorphine and methamphetamine. Thus, tolerance is observed in the 5-HT mediated but not the DA mediated effects of PCP. The conclusions by Nabeshima and colleagues are only partially in agreement with those of Greenberg and Segal (1985). The latter found that the acute co-administration of amphetamine and PCP increased only stereotypy, a classic DA mediated behavior. On the other hand, although chronic administration of both drugs separately produced enhanced locomotor stimulation, the chronic PCP treated rats showed a decreased response to amphetamine, indicating different mechanisms underlie the effects of acute and chronic administration of both drugs.

Perhaps the most important new development in the mechanisms of action of PCP involves its effects on excitatory amino acid neurotransmitter systems. It has long been known that PCP in receptor, binding assays acts on the muscarinic cholinergic receptor, on the *delta* subunit of the ion channel of the nicotinic receptor, and on various Ca^{++} and K^{+} ion channels (*see* Domino, 1981; Kamenka et al., 1983). Lodge et al. (1982, 1983) and Anis et al. (1983) were the first to show that arylcyclohexylamines including ketamine, PCP, tiletamine, and etoxadrol selectively reduced excitation of mammalian neurons by NMA, but not by quisqualate and kainate. Subsequently, Snell and Johnson (1985, 1986) reported that several substances with PCP-like behavioral effects inhibited the release of two chemical messengers, ACh and DA, evoked by NMA from rat striatal slices *in vitro*. They also showed that these effects were similar to the classic NMA antagonist, 2-amino-5-phosphonovalerate, except that the latter produced a parallel shift to the right in the concentration effect curve, while PCP produced a non-parallel shift to the right, suggesting a noncompetitive interaction between PCP and NMA. Koek et al. (1986) have used a behavioral analysis in animals regarding PCP and its interaction with NMA. They suggest that this might be important in the mechanisms of anesthesia induced by arylcyclohexylamines and related substances.

Conclusions

PCP-like compounds appear to possess a unique wide spectrum of pharmacological effects. Their mechanisms of action are as yet unknown, but clearly appear to be different from other major classes of psychotomimetic agents.

References

Anis, N.A., Berry, S.C., Burton, N.Y., and Lodge, D. The dissociative anaesthetics, ketamine and phencyclidine selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *Br. J. Pharmacol.*, 79:565–575, 1983.

Appel, J.B., White, F.J., and Holohean, A.M. Analyzing mechanism(s) of hallucinogenic drug action with drug discrimination procedures. *Neuroscience and Behavioral Reviews*, 6:529–536, 1982.

Appel, J.B., and Rosecrans, J.A. Behavioral pharmacology of hallucinogens of animals: Conditioning studies. In: Jacobs, B.L., (ed.), *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives*. New York: Raven Press, 1984, pp. 77–94.

Colpaert, F.C., and Rosecrans, J.A., eds. *Stimulus Properties of Drugs: Ten Years of Progress*. Amsterdam: Elsevier, 1978, 572 pp.

Colpaert, F.C., and Slaugen, J.F., eds. *Drug Discrimination: Application in CNS Pharmacology*. Amsterdam: Elsevier, 1982, pp. 1–447.

Domino, E.F., ed. *PCP (Phencyclidine): Historical and Current Perspectives*. Ann Arbor, MI: NPP Books, 1981, 537 pp.

Greenberg, B.D., and Segal, D.S. Acute and chronic behavioral interactions between phencyclidine (PCP) and amphetamine: Evidence for a dopaminergic role in some PCP-induced behaviors. *Pharmacol. Biochem. Behavior*, 23:99–105, 1985.

Ho, B.T., Richards, D.W., and Chute, D.L. *Drug Discrimination and State Dependent Learning*. New York: Academic Press, 1978, pp. 1–392.

Jacobs, B.L., ed. *Hallucinogens: Neurochemical, Behavioral and Clinical Perspectives*. New York: Raven Press, 1984. 233 pp.

Kamenka, J.M., Domino, E.F., and Geneste, P., eds. *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*. Ann Arbor, MI: NPP Books, 1983, 660 pp.

Koek, W., Kleer, E., Mudar, P.J., and Woods, J.H. Phencyclidine-like catalepsy induced by the excitatory amino acid antagonist DL-2-amino-5-phosphonovalerate. *Behav. Brain Res.* (In press, 1986.)

Lodge, D., Anis, N.A., and Burton, N.R. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurons by amino acids and acetylcholine. *Neurosci. Lett.*, 29:282–286, 1982.

Lodge, D., Anis, N.A., Berry, S.C., and Burton, N.R. Arylcyclohexylamines selectively reduce excitation of mammalian neurons by aspartate-like amino acids. In: J.M. Kamenka, E.F. Domino, and P. Geneste (eds.), *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*. Ann Arbor, MI: NPP Books, 1983, pp. 595–616.

Nabeshima, T., Yamaguichi, K., Hiramatsu, M., et al. Development of tolerance and supersensitivity in rats treated with phencyclidine (PCP) chronically. *Personal Communication to E.F. Domino*, December, 1985.

Peroutka, S.J. and Snyder, S.H. Multiple serotonin receptors and their physiological significance. *Federation Proc.*, 42:213–217, 1983.

Rech, R.H., and Commissaris, R.L. Neurotransmitter basis of the behavioral effects of hallucinogens. *Neurosci. Biobehav. Rev.*, 6:521–527, 1982.

Shannon, M., Battaglia, G., Glennon, R.A., and Titeler, M. 5-HT_1 and 5-HT_2 binding properties of derivatives of the hallucinogen 1-(2,5-dimethoxy-phenyl)-2-aminopropane (2,5-DMA). *Eur. J. Pharmacol.*, 102:23–29, 1984.

Snell, L.D., and Johnson, K.M. Antagonism of N-methyl-D-aspartate induced transmitter release in the rat striatum by phencyclidine like drugs and its relationship to turning behavior. *J. Pharmacol. Exp. Ther.*, 235:50–58, 1985.

Snell, L.D., and Johnson, K.M. Characterization of the inhibition of excitatory amino acid induced neurotransmitter release in the rat striatum by phencyclidine-like drugs. *J. Pharmacol. Exp. Ther.* (In press, 1986.)

Clinical Aspects of Use of Phenylalkylamine and Indolealkylamine Hallucinogens

Leo E. Hollister, M.D.[1]

Scarcely any clinical studies of hallucinogens have been reported since 1968. A variety of reasons account for this diminution of interest. Much of the information about clinical effects, potential therapeutic uses, and adverse effects must be gleaned from older work (Hollister, 1968).

Mescaline is the prototypic phenylalkyl amine hallucinogen. Others include 2,5-dimethoxy-4-methyl amphetamine ("STP") and methylene-dioxymethamphetamine (MDMA). Lysergic acid diethylamide (LSD) and psilocybin are the prototypic indolealkylamine hallucinogens, which also include N,N-dimethyltryptamine and bufotenin. Aside from great differences in potency (1 μg LSD equals 225 μg psilocybin equals 5 mg mescaline), the clinical syndromes produced by these three drugs are virtually identical. Somatic symptoms include dizziness, weakness, tremors, nausea, drowsiness, paresthesia, and blurred vision. Perceptual changes include altered shapes and colors, difficulty in focusing on objects, sharpened sense of hearing and, rarely, synesthesias. Psychic manifestations include alterations in mood, tension and, rarely, hallucinations. The usual doses, in terms of LSD, to produce such effects range from 50 to 200 μg. No fatal overdoses have been recorded. The usual duration of drug effect is about 6 to 8 hours, or longer with higher doses.

Various claims have been made for therapeutic utility of these drugs in alcoholism, depression, schizophrenia, neuroses, and psychopathy. The drugs have been averred to facilitate insight psychotherapy, to provide a "mock death," to create religious experiences, and to promote better interaction in group psychotherapy. None of these claims has ever been validated experimentally. That claim most often studied, beneficial effect of LSD for treating alcoholics, has never been confirmed.

Acute panic reactions are the most common adverse effect, but are of limited duration. Depression and psychosis may be precipitated by the drug but are not created de novo. Thus, these drugs have failed to produce a valid model psychosis. "Flashbacks" are still of uncertain cause. Injury to self, and occasionally a homicide, are related to lack of judgment and/or disinhibition.

The major current concern is about the fad drug, methylene-dioxymethamphetamine (MDMA). This phenethylamine derivative was first synthetized many years ago but is not as well known or as well studied as methylene-dioxyamphetamine (MDA). The latter drug was one of many phenethylamine hallucinogens of interest to the U.S. Army as part of its studies of "incapacitating agents." A study of this drug at a major medical center during the early 1950s came to an abrupt halt with the death of one of the subjects. He had been given a dose of around 30 mg without much effect. Other subjects had received higher doses of related compounds. When he received the second dose of about 460 mg (6 mg/kg), he experienced muscle spasms, seizures, and cardiovascular collapse. The dose of 6 mg/kg had been predicted as potentially lethal based on toxicological studies.

In the late 1950s, Gordon Alles ran a series of clinical trials in which MDA was compared with amphetamine at doses ranging from 60 to 120 mg. At the highest doses, distinct visual and other sensory changes (increased auditory sensitivity and alterations in peripheral vision) were noted, but no hallucinogenic effects (Alles, 1959). In 1967 Alex Shulgin and collaborators reported on 8 subjects who received doses up to 150 mg. These subjects, who were well experienced with other LSD-type hallucinogens, reported no hallucinations, perceptual distortions, or eye-closed

---

[1] Veterans Administration Medical Center (151H), 3801 Miranda Avenue, Palo Alto, CA 94304.

imagery, all of which are very common reactions to LSD-type drugs. Similarities between MDA and LSD-type drugs were intensification of feelings, increased perceptions of insight, and heightened empathy with others. Most subjects also reported increased esthetic enjoyment. Effects appeared within 40 to 60 minutes of ingestion, peaked in about 90 minutes and had largely dissipated by 8 hours, a time course comparable to that of LSD-type drugs. It was concluded that MDA was not classifiable as a hallucinogen but rather was unique in producing an "inward, talky experience" (Naranjo et al., 1967).

Shulgin's group reported a few years later on 3-methoxy-4-,5-methylene-dioxyphenyl–isopropylamine (MMDA), a related compound. Clinical effects were similar to those from MDA, without true hallucinogenic effects. It, too, was deemed useful for psychotherapy. Rather low toxicity was found in rats, with a therapeutic index (LD_{50} rats/MED_{50} humans) to be 85, rather high. Striking hypotension was noted in dogs, however, indicating species differences in response (Shulgin et al., 1973).

A 1970 report on MDA confirmed the time course of the drug's effects. Subjects experienced a mild sense of physical well-being, increased taste sensation, decreased awareness of bodily sensations, and increased need for interpersonal relationships. Several short visual hallucinations were experienced by one subject. Physical exhaustion and free-floating anxiety which lasted up to 2 days were the usual sequelae (Jackson & Reed, 1970).

The potential lethality of MDA in overdose was again confirmed by a 1983 report. A subject who had taken a dose of about 500 mg experienced a tonic seizure followed by coma some 15 minutes after ingestion. Tachycardia, rapid respirations, and slight hypertension were noted. The pupils became dilated and fixed, sweating and piloerection were observed, the extremities became rigid along with trismus, and respiratory depression followed. The subject eventually recovered. Two other users of the drug had similar, though milder reactions (Richards & Borgstedt, 1971).

Another disconcerting aspect of the MDA story is that a recent study in animals suggests that it is a neurotoxin specific for serotonergic pathways in the brain (Ricuarte et al., 1985). The full implications of this observation are not at all clear. A similar observation has suggested that fenfluramine is also a serotonin neurotoxin, yet this drug has been widely used in clinical practice without any evident adverse neurological consequences.

It is conceivable that MDA is not truly a hallucinogen. Substitution of the aromatic portion of the molecule at the 3 and 4-positions is usually not adequate for producing hallucinogenic effects. Thus, the contention that MDA is not truly a hallucinogen but more closely related to amphetamine may be correct. The story with MDMA as reported by those therapists who use it sounds much the same. They report the same sort of empathetic experiences in their patients without major hallucinogenic actions. It would be surprising if MDMA were to be markedly different from MDA. Usual doses used in therapeutic sessions are around 200 mg, about 50% of the potential lethal dose. In contrast, a lethal dose of LSD has not yet been determined.

We should be hearing much more about MDMA, for some entrepreneur is funding studies of the drug directed towards a New Drug Application. He envisions a chain of clinics in which this drug would be used to facilitate psychotherapy. Specially trained "therapists," not necessarily physicians, would monitor the therapy. If MDMA is commercialized it would be the first such instance for a hallucinogen.

The 4-bromo homolog of 4-methyl,2,5-dimethoxyamphetamine (DOM, STP) has appeared in some countries as a street hallucinogen under several names including DOB or bromo-DMA (Delliou & Bromo, 1980). Shulgin had reported that in doses of 2 mg it resembled MDA. Even doses of 3 mg have been associated with convulsions, attesting to its much greater potency than DOM. Further, the Br substituent delays metabolism, so effects of this drug are prolonged.

Two young persons were poisoned by DOB. A young woman who had ingested what was believed to be 30 to 35 mg died after seizures and cardiovascular collapse. Postmortem finding included evidence of increased intracranial pressure and acute pulmonary congestion. Her companion, a young man poisoned with an unknown amount of this drug, experienced repeated convulsions and prolonged coma with permanent brain damage (Winek et al., 1981).

An unusual effect of DOB is the production of marked, diffuse, and progressive peripheral arterial vasospasm. A 33-year old man had taken an unknown amount of DOB several hours before the onset of cold extremities. Pulses were absent and spasm was demonstrated on subclavian angiograms. Vasodilators were used with reversal of the vasospasm in 24 hours. An earlier instance of vasospasm after a putative dose of 75 mg of DOB resulted in bilateral above-the-knee amputations. It is possible that the cerebral effects of overdoses of this drug are also associated with vasospasm (Bowen et al., 1983).

These two new phenethylamines have serious potential side effects, including death. Although no deaths have been directly attributed to MDMA, experience with MDA strongly suggests this possibility. Some trismus and muscle spasms have been noted even in subjects who received 200 mg "therapeutic" doses of MDMA. Thus, doses usually used in therapeutic sessions with this drug are perilously close to those that have been lethal. As it is not always certain that doses of street drugs can be accurately determined, a relatively minor error in dose could have serious consequences.

Whether MDMA will, despite its evident hazards, prove to be the panacea for psychotherapy claimed by its adherents remains to be seen. The present claims are exactly the same as those made by many of the same persons about LSD 20 years ago. The difference is that LSD has a remarkable margin of safety, something lacking in the newer agents.

References

Alles, G.A. Some relations between chemical structure and physiological action of mescaline and related compounds. In: Abramson, H.A. (ed.), *Neuropharmacology, Transactions of the Fourth Conference.* New York: Josiah Macy, Jr. Foundation, 1959.

Bowen, J.S., Davis, G.B., Kearney, T.E., and Bardin, J. Diffuse vascular spasm associated with 4-bromo-2,5-dimethoxyamphetamine ingestion. *JAMA*, 249:1477, 1479, 1983.

Delliou, D., and Bromo, D.M.A. New hallucinogenic drug. *Med. J. Aust.*, 1:83, 1980.

Hollister, L.E. *Chemical Psychoses. LSD and Related Drugs.* Springfield, Ill.: Charles C Thomas, 1968, p. 190.

Jackson, B., and Reed, A., Jr. Another abusable amphetamine. *JAMA*, 211:830, 1970.

Naranjo, C., Shulgin, A.T., and Sargent, T. Evaluation of 3,4-methylenedioxyamphetamine (MDA) as an adjunct to psychotherapy. *Med. Pharmacol. Exptl.*, 17:359–366, 1967.

Richards, K.C., and Borgstedt, N.N. Near fatal reaction to ingestion of the hallucinogenic drug MDA. *JAMA*, 218:1826–1827, 1971.

Ricuarte, G., Bryan, G., Strauss, L., et al. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. *Science*, 229:986–988, 1985.

Shulgin, A.T., Sargent, T., and Naranjo, C. Animal pharmacology and human psychopharmacology of 3-methoxy-4,5-methylenedioxyphenylisopropylamine (MMDA). *Pharmacology*, 10:12–18, 1973.

Winek, C.L., Collom, W.D., and Bricker, J.D. A death due to 4-bromo-2,5-dimethoxyamphetamine. *Clin. Toxicol.*, 18:261–266, 1981.

The "Pros" and "Cons" of Anticholinergic Prophylaxis

Chair:

C. Raymond Lake

Uniformed Services University
of the Health Sciences
Bethesda, MD 20814-4799

Anticholinergic Prophylaxis in Young Adults Treated With Neuroleptic Drugs

C. Raymond Lake, M.D., Ph.D.,[1,*] Daniel E. Casey, M.D.,[2] Joseph P. McEvoy, M.D.,[3] Samuel G. Siris, M.D.,[4] William F. Boyer, M.D.,[5] and George Simpson, M.D.[6,*]

Although substantial literature supports prophylactic anticholinergic medication during neuroleptic treatment for reducing the incidence and severity of extrapyramidal side effects (EPS), arguments against this practice have been raised (McEvoy, 1983). Opponents contend that anticholinergic drugs have serious side effects of their own. These side effects consist of reversible increases in dyskinesia and dysphoria (Gardos et al., 1984), and various other anticholinergic effects, including new memory deficits (Tune et al., 1982) and the common peripheral effects (dry mouth, blurred vision, constipation, urinary retention, etc.). The severe effects of delirium and toxic psychosis have been observed in a small percentage of patients on combined medication (Simpson, 1983). These numerous side effects, which are particularly dangerous in the elderly (McEvoy, 1983), are produced not only by the prophylactic anticholinergic drugs themselves but also by their additive effects with the antipsychotic agents. Another argument is that the high doses of potent neuroleptics now commonly used are excessive and cause an unnecessarily high incidence of EPS. Opponents, who are usually proponents of low-dose neuroleptics, argue that if smaller doses were used, prophylaxis with the anticholinergics may be obviated. Little evidence exists to support prophylaxis with neuroleptics other than haloperidol, because few drugs, excluding haloperidol, have been tested in prophylactic studies (Simpson, 1983).

The first appearance of mild neuroleptic side effects, especially hypokinesia and rigidity, may signify the achievement of therapeutic neuroleptic doses (Simpson et al., 1970); identification of such a marker is impossible if prophylactic anticholinergic drug treat-

---

[1] Professor of Psychiatry and Pharmacology, Uniformed Services University of the Health Sciences, F. Edward Hebert School of Medicine, B 3049, 4301 Jones Bridge Road, Bethesda, MD 20814-4799.

[2] Chief, Psychiatric Research (116A), Veterans Administration Medical Center, Portland, OR 97207.

[3] Assistant Professor of Psychiatry, Medical Director of the Inpatient Schizophrenic Unit, Western Psychiatric Institute and Clinic, Pittsburgh, PA 15213.

[4] Director, Division of Clinical Psychopharmacology Research, Mount Sinai School of Medicine, New York, NY 10029.

[5] Chief of Psychiatry, U.S. Naval Hospital, Guantanamo Bay, Cuba, FBPO Norfolk, VA 23593.

[6] Professor of Psychiatry, Director of Clinical Psychopharmacology, Medical College of Pennsylvania Eastern Pennsylvania, Psychiatric Institute, Philadelphia, PA 19129.

[*] Address all correspondence to Dr. Lake.

ment has been initiated. Opponents of prophylactic anticholinergic drug use contend that institution of medication from this class can be reasonably delayed until after neuroleptic-induced side effects are exhibited. These side effects, apart from acute dystonic reactions, develop progressively and gradually, are usually neither severe nor intolerable, and can be treated as required rather than prophylactically.

Nevertheless, high-dose neuroleptic treatment for acute episodes of schizophrenia and mania remains in fashion, despite the lack of evidence supporting such an approach (Ericksen et al., 1978). If high doses (greater than 10 mg haloperidol daily) are used, then arguments for using prophylactic anticholinergics are more convincing. The common and disturbing neuroleptic-induced side effects antagonize therapeutic rapport and medication compliance, which are critical in the treatment of schizophrenic patients. Under the best of circumstances and with minimal side effects, follow-up treatment and attention are frequently less than ideal for a considerable percentage of schizophrenic patients, partly because of the nature of the illness (disordered thinking with frequent paranoid ideations).

Although quite distressing, common neuroleptic side effects are often subtle and easily overlooked, and sometimes even misdiagnosed as worsening psychopathology (Van Putten, 1974; Rifkin et al., 1978; Siris, 1985). Akinesia, a syndrome of reduced spontaneity on a neuroleptic-induced extrapyramidal basis, may also arise insidiously and, while not dramatic, may be devastating to the patient's subjective and psychosocial progress (Rifkin et al., 1975; Rifkin et al., 1978; Van Putten, 1974). In contrast, one of the most dramatic and frightening side effects of the more potent neuroleptics is the acute dystonic reaction. Prophylactic use of anticholinergics to prevent or reduce subtle, but distressing akinesia and painful, startling dystonic reactions is likely to enhance patient compliance. An earlier contention that such prophylactic use may predispose to tardive dyskinesia no longer appears valid (Gardos and Cole, 1983).

Withdrawal studies in which the anticholinergic drugs were discontinued apparently support the use of anticholinergic drugs (Manos et al., 1981a,b; Jellinek et al., 1981). In a pair of studies, a large majority of schizophrenic patients chronically medicated with neuroleptic and anticholinergic drugs developed worsening EPS upon acute or gradual (over 3 weeks) withdrawal of the latter drug (Manos et al., 1981a,b). However, the withdrawal studies did not address the question of whether the anticholinergic agents were actually required initially. Additionally, in more than 30 studies examining drug discontinuation, only Stratas et al. (1963) intervened by decreasing neuroleptic drug dosage when EPS occurred: These side effects disappeared in 13 of the 16 patients without deterioration in psychiatric status.

Prophylaxis is justified to a greater degree if patients likely to develop EPS can be identified. Data indicate that youth, male sex, and high potency neuroleptics are associated with a high incidence of EPS. For example, one study reported that 29 of 30 males between ages 19 and 30, treated with haloperidol, experienced EPS (Neborsky et al., 1981), and similarly, another study found that 100 percent of their adolescent patients who were given high-potency neuroleptics suffered from these reactions (Chiles, 1978). In addition, Keepers et al. (1983) found 90 percent of their patients between 10 and 19 years old and 80 percent of 20 to 29 year olds treated with various neuroleptics experienced EPS. The popularity of prescribing more potent neuroleptics in higher doses has apparently increased the prevalence of EPS (Prien and Cole, 1968; Ericksen et al., 1978).

Several types of neuroleptic-induced EPS vary in severity and in times of onset. The most striking and acutely debilitating of these EPS is the acute dystonic reaction, which consists of intense muscle cramps primarily in the head and neck. This reaction is considered a form of EPS, which, like akinesia and the other symptoms of neuroleptic-induced parkinsonism, is both effectively treated and prevented with centrally acting anticholinergic drugs (Keepers et al., 1983; Stern and Anderson, 1979). Neuroleptic-induced dystonia differs in some respects from other EPS and may have a different pathophysiology. For example, dystonic reactions occur sooner after neuroleptics are administered (hours to days) than the other EPS (days to years). These reactions are more painful, frightening, acute in onset, develop without warning signs, and, if the respiratory muscles are affected, they are potentially fatal.

Data on the incidence of dystonic reactions implicate the same risk factors as for EPS in general. Moleman et al. (1982) found dystonic reactions especially common in neuroleptic-treated males under age 34. Chiles (1978) reported a 64 percent incidence of dystonia in 11 adolescents between ages 13 and 18 who were treated with potent neuroleptics. Dystonic reactions occurred in 33 percent of 40 neuroleptic-treated patients, some of whom also received benztropine (Stern & Anderson, 1979). In addition, Keepers et al. (1983) noted a 45 percent incidence of acute dystonia in 20 to 29 year olds and a 65 percent occurrence in 10 to 19 year olds treated with both high- and low-potency antipsychotics. Boyer et al. (in press) found an extremely high incidence of dystonia (94 percent) among young patients given haloperidol.

Several studies support the contention that anticholinergics are effective in preventing dystonic reactions in these populations. Keepers et al. (1983) observed that prophylaxis produced a significant decrease in dystonic reactions among those 10 to 39 years old, but not among older patients. Stern and Anderson (1979) reported an 11-fold increase in dystonia among patients given high-potency antipsychotics without prophylaxis. DiMascio and Demirgian (1970) noted incidences of dystonia of 18 and 10 percent, respectively, in "non-prophylactic" vs. prophylactic groups. In contrast, Sramek et al. (in press) found no significant difference in the incidence of dystonia between the prophylactic and "non-prophylactic" groups (12 and 20.6 percent, respectively); however, the difference between the groups reached significance (11.5 and 38.2 percent) when patients given only haloperidol were examined. Boyer et al. (in press) observed no dystonic reactions in their small group of seven patients who received benztropine prophylaxis, while 94 percent of 16 patients who received no prophylaxis incurred dystonia. The majority of these data imply that many young patients given high potency neuroleptics will incur dystonic reactions and, furthermore, that prophylactic use of an anticholinergic drug will substantially deter this side effect.

Opponents note that the incidence of dystonic reactions has increased from 2.3 percent in 1961 (Ayd, 1961) to 50 percent in 1979 (Stern et al., 1979) and believe that this increase relates to the unwarranted prescription of higher dosages of the potent neuroleptics (Sramek et al., in press). In this study by Sramek et al. (in press), no dystonic reactions developed in those patients given only low-potency neuroleptics ($N = 33$).

Some of the studies reviewed above reported that almost all dystonic reactions appeared shortly after beginning and maintaining patients on neuroleptic drugs (hours to a few days) (Keepers et al., 1983; Ericksen et al., 1978; Sramek et al., in press; Boyer et al., in press). In the study by Keepers et al. (1983), 85 percent of dystonic reactions occurred within the first 4 days of neuroleptic treatment. By day five and afterward, the incidence of dystonia in "non-prophylactic" patients was similar to that in patients who had received anticholinergic prophylaxis. Almost 90 percent of all dystonic reactions happened by day three in the study by Sramek et al. (in press). In the study by Boyer et al. (in press), all dystonic reactions occurred within 60 hours; 12 of the 14 patients experienced this side effect within 48 hours. From these data, it is conceivable that tolerance to the dystonic effects of the neuroleptic drugs develops over several days to a week.

Because it is the acute dystonic reaction that carries the greatest potential for detrimental effects in our patients, a compromise strategy may be forthcoming for initial and temporary prophylaxis with the centrally acting anticholinergic drugs aimed at specifically preventing these reactions. Such a strategy, particularly significant for young patients, especially males, given high potency neuroleptic drugs, proposes prophylaxis for a week followed by tapering of the anticholinergic drug over several days to a week. Then, if EPS subsequently occur, neuroleptic dosage can be decreased and/or an anticholinergic drug reinstated. Further definitive studies must determine if significant EPS emerge upon gentle tapering of the anticholinergic medication after only brief (1 week) prophylactic use. The data from the withdrawal studies may not apply here considering that those patients were on chronic prophylaxis for months to years (Manos et al., 1981a, b). Clearly, the strategy of using lower doses and less potent neuroleptics will decrease the incidence of EPS and lessen the need for prophylactic anticholinergics. Further research is warranted to determine the role of anti cholinergic prophylaxis in all EPS, particularly drug-induced parkinsonism and akathisia.

References

Baker, L.A., Cheng, L.Y., and Amara, I.B. The withdrawal of benztropine mesylate in chronic schizophrenic patients. *Brit. J. Psychiatry*, 143:584–590, 1983.

Boyer, W.F., Bakalar, N.H., and Lake, C.R. Anticholinergic prophylaxis of acute haloperidol-induced dystonic reactions. *J. Clin. Psychopharmacology*. (In Press).

Chiles, J.A. Extrapyramidal reactions in adolescents treated with high potency antipsychotics. *Am. J. Psychiatry*, 135:239–240, 1978.

DiMascio, A., and Demirgian, E. Antiparkinson drug overuse. *Psychosomatics*, 11:596–601, 1970.

Ericksen, S.E., Hurt, S.W., Chang, S., et al. Haloperidol dose, plasma levels and clinical response: A double blind study. *Psychopharmacology Bull.*, 14:15–16, 1978.

Gardos, G., and Cole, J.O. Tardive dyskinesia and anticholinergic drugs. *Am. J. Psychiatry*, 140:200–202, 1983.

Gardos, G., Cole, J.O., Rapkin, R.M., et al. Anticholinergic challenge and neuroleptic withdrawal. *Arch. Gen. Psychiatry*, 41:1030–1035, 1984.

Jellinek, T., Gardos, G., and Cole, J.O. Adverse effects of antiparkinson drug withdrawal. *Am. J. Psychiatry*, 138:1567–1571, 1981.

Keepers, G.A., Clappison, V.J., and Casey, D.E. Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. *Arch. Gen. Psychiatry*, 40:1113–1117, 1983.

Manos, N., Gkiouzepas, J., and Logothetis, J. The need for continuous use of antiparkinsonian medication with chronic schizophrenic patients receiving long-term neuroleptic therapy. *Am. J. Psychiatry*, 138:184–188, 1981a.

Manos, N., Gkiouzepas, J., Tzotzoras, T., and Tzanetoglou, A. Gradual withdrawal of antiparkinson medication in chronic schizophrenics: Any better than the abrupt? *J. Nerv. Ment. Dis.*, 169:659–661, 1981b.

McEvoy, J.P. The clinical use of anticholinergic drugs as treatment for extrapyramidal side effects of neuroleptic drugs. *J. Clin. Psychopharmacology*, 3:288–302, 1983.

Moleman, P., Schmitz, P.J.M., and Ladee, G.A. Extrapyramidal side effects and oral haloperidol: An analysis of explanatory patient and treatment characteristics. *J. Clin. Psychiatry*, 43:492–496, 1982.

Neborsky, R., Janowsky, D., Munson, E., and Depry, D. Rapid treatment of acute psychotic symptoms with high- and low-dose haloperidol: Behavioral considerations. *Arch. Gen. Psychiatry*, 38:195–199, 1981.

Prien, R.F., and Cole, J.O. High dose chlorpromazine therapy in chronic schizophrenia. *Arch. Gen. Psychiatry*, 18:482–485, 1968.

Rifkin, A., Quitkin, F., and Klein, O.F. Akinesia. A poorly recognized, drug-induced extrapyramidal behavioral disorder. *Arch. Gen. Psychiatry*, 32:672–674, 1975.

Rifkin, A., Quitkin, F., Kane, J., et al. Are prophylactic antiparkinson drugs necessary? *Arch. Gen. Psychiatry*, 35:483–489, 1978.

Simpson, G.M. (ed.). Identification and treatment of neuroleptic-induced extrapyramidal reactions. *Clinical Neuropharmacology*, 6:S1–S83, 1983.

Simpson, G.M., Brakor, B.L., Matke, D., and St. Chard, G. A controlled comparison of the treatment of schizophrenic patients when treated according to the neuroleptic threshold or by clinical judgment. *Acta Psychiat. Scand*. (Suppl.), 212:38–43, 1970.

Siris, S.G., Akathisia and "acting out." *J. Clin. Psychiatry*, 46:395–397, 1985.

Sramek, J., Simpson, G.M., Morrison, R.L., and Heiser, J.F. Anticholinergic agents for prophylaxis of neuroleptic-induced dystonic reactions. *J. Clin. Psychiatry*. (In press, 1986.)

Stern, T.A., and Anderson, W.H. Benztropine prophylaxis of dystonic reactions. *Psychopharmacology*, 61:261–262, 1979.

Stratas, N.E., Phillips, R.D., Walker, P.A., and Sandifer, M.D. A study of drug-induced parkinsonism. *Dis. Nerv. Syst.*, 24:180, 1963.

Tune, L.E., Strauss, M.E., Lew, M.F., et al. Serum levels of anticholinergic drugs and impaired recent memory in chronic schizophrenic patients. *Am. J. Psychiatry*, 139:1460–1462, 1982.

Van Putten, T.O. Why do schizophrenic patients refuse to take their drugs? *Arch. Gen. Psychiatry*, 31:67–72, 1974.

Van Putten, T., May, P.R.A., and Marder, S.R. Response to antipsychotic medication: The doctor's and consumer's view. *Am. J. Psychiatry*, 141:16–19, 1984.

Poster Sessions—Editors' Choice—

The Inventory of Depressive Symptomatology (IDS): Preliminary Findings[1]

A. John Rush, M.D.,[2] Donna E. Giles, Ph.D.,[2] Michael A. Schlesser, M.D.,[2] Carl L. Fulton, M.D.,[2] Jan Weissenburger, M.A.,[2] and Cheryl Burns, M.S.[2]

The Hamilton Rating Scale for Depression (HRS-D) (Hamilton, 1960, 1967) is the most frequently used clinical rating. However, several difficulties are apparent upon inspection. First, only the 17-item version has undergone thorough psychometric assessment. The 17-item form gives differential weight to different symptoms (e.g., sad mood or work and interest are rated 0 to 4, while each of the three types of insomnia are rated 0 to 2), which is an arbitrary judgment. Second, some symptoms often found with depressed patients are not rated at all (e.g., hypersomnia; weight or appetite increase). Third, some endogenous symptoms are not rated (e.g., quality of mood; reactivity of mood). Furthermore, some items are confounded (e.g., the somatic energy item rates both specific pains and overall bodily energy/fatigability). In addition, some symptoms are rated under two or more items (e.g., headaches contribute to both the somatic energy and somatic anxiety items). Finally, the anchor points for some items are difficult to judge.

This is a preliminary report of findings with a new scale — the Inventory of Depressive Symptomatology (IDS) (Rush et al., in press), which is being developed both as a self-report (IDS-SR) and clinician rating (IDS-C).

Methods

Scale Development

The Inventory for Depressive Symptomatology (IDS) was designed to measure specific signs and symptoms of depression in both in- and outpatients. Items were developed from inspection of several existing inventories, diagnostic criteria, and clinical judgment. The present item wording and selection was achieved through an iterative process that incorporated feedback from both clinicians and patients.

The scale contains 28 items; each is rated from 0 to 3 with increasing severity represented as a higher item rating. Twenty-six of the 28 items contribute to the final score, since either appetite increase *or* decrease, and weight increase *or* decrease are rated. Total scores range from 0 to 78. The initial intent in developing items was to tap the following symptom dimensions: vegetative, cognitive, mood disturbance, endogenous, and anxiety/panic.

All items are equally weighted. Items were clinically selected to (a) include all symptoms required by DSM-III (Diagnostic and Statistical Manual — 3rd ed., 1980); (b) diagnose major depression and melancholic features;

---

[1] This study was supported in part by grant No. MH-35370 from the National Institute of Mental Health and by a grant from the Biohumanics Foundation.

[2] Affective Disorders Unit and Department of Psychiatry, University of Texas Health Science Center at Dallas, Dallas, TX 75235.

Reprint requests: A. John Rush, M.D., Department of Psychiatry, Affective Disorders Unit, 5323 Harry Hines Blvd., Dallas, TX 75235.

(c) include all symptoms to define endogenous depression by Research Diagnostic Criteria (RDC) (Spitzer et al., 1978); and (d) include items used to differentiate atypical (weight gaining, hypersomnic), endogenous, and anxious (anxious/irritable mood, sympathetic arousal, panic/phobic) depressions.

Part I: Self-Report IDS (IDS-SR)

Subjects and Procedure. The patient sample consisted of consecutive referrals to the Outpatient Clinic of the Affective Disorders Unit (ADU) between August 1982 and December 1983 and four inpatients. All patients completed the self-report form of the IDS (IDS-SR), the 21-item Beck Depression Inventory (BDI) (Beck et al., 1961) and were interviewed by the Schedule for Affective Disorders and Schizophrenia Life-Time Version (SADS-L) (Endicott & Spitzer, 1978). The 17-item HRS-D was completed by the interviewing clinician who was unaware of the IDS-SR and BDI responses. Table 1 shows the diagnostic breakdown of the group according to RDC.

Patients averaged 38.2 (SD 12.1) years of age and 14.3 (SD 2.9) years of education. Sixty-four percent were female and almost all (97.2 percent) were Caucasian.

Normal controls (N = 23) included those who had negative personal and first-degree family histories of depression, alcoholism, schizophrenia, or other psychopathology. All normals were free of significant medical problems and were taking no medication of any type. Normals averaged 40.4 (SD 15.8) years of age, 15.2 years of education (SD 3.4) and 65.0 percent were female. Caucasians (95.7 percent) predominated.

Results

Reliability

Coefficient alpha (Cronbach, 1951) for the IDS-SR was 0.85 (high internal consistency). By comparison, coefficient alpha for this patient sample was 0.90 for the BDI and 0.80 for the HRS-D. Item total correlations were also satisfactory except for distinct quality to mood, which has been reworded in the present form.

Concurrent Validity

Of the 289 patients who completed the IDS-SR, 274 had concurrent BDI and 280 had concurrent HRS-D ratings. Mean IDS-SR score for the total sample was 32.0 (SD 12.3). The mean BDI score was 21.9 (SD 11.2) and the mean HRS-D score was 15.5 (SD 7.1). The IDS-SR positively correlated with both the BDI (r = 0.78) and the HRS-D (r = 0.67).

Since the HRS-D and BDI are highly intercorrelated, the relationship between the IDS-SR and these scales, independent of the other, was assessed with partial correlations. The partial correlation between IDS-SR and HRS-D (BDI covaried out) was 0.34 (p <.001). The partial correlation between IDS-SR and BDI (HRS-D covaried out) was 0.68 (p <.001). HRS-D and BDI scores corre-

TABLE 1. Diagnostic Description of the Sample (IDS-SR).

Diagnosis	*n*	Diagnosis	*n*	Diagnosis	*n*
Unipolar MDD	174	Bipolar I	22	Other Diagnoses	38
Primary	138	Depressed	18	Remitted	33
Secondary	35	Manic	3	Unipolar	27
(Unknown)	1	Mixed	1	Bipolar I	5
Endogenous	65	Bipolar II	22	Bipolar II	1
Nonendogenous	106	Depressed	19		
(Unknown)	3	Hypomanic	3		
Psychotic	5				
Nonpsychotic	166				
(Unknown)	3				

lated with each other (IDS-SR covaried out) ($r = 0.25, p <.001$). Thus, the IDS-SR was as highly correlated with the HRS-D (BDI covaried out) as the BDI was with the HRS-D (IDS-SR covaried out) ($Z = 1.06, p >.20$). These findings suggest that the IDS-SR has concurrent validity with other depressive symptom measures.

Construct Validity

IDS-SR scores for patients with unipolar major depression and bipolar, depressed phase disorder ($n = 211$) were significantly higher than for those with other diagnoses ($n = 38$) ($t = 8.42, df = 247, p <.001$) and for normals ($t = 16.9, df = 232, p < .001$). The mean IDS-SR score for depressed patients was 36.5 (SD 9.7) compared to 21.8 (SD 11.3) for other diagnoses. For controls, the mean score was 2.1 (SD 2.2).

The mean BDI score for depressed patients was 26.0 (SD 9.3), while other diagnoses averaged 11.3 (SD 7.6), which was significantly different ($t = 9.2, df = 238, p <.001$). The normals averaged 1.2 (SD 2.0) on the BDI which significantly differed from depressed patients ($t = 12.7, df = 223, p <.001$) and other diagnoses ($t = 6.23, df = 59, p <.001$).

A stepwise discriminant analysis (Jennrich & Sampson, 1983) was used to determine which IDS-SR items discriminated RDC endogenous and nonendogenous depressed patients, and to identify which combination of IDS-SR items maximally discriminated these two groups. The analysis contrasted unipolar endogenous (E) ($n = 52$) with unipolar nonendogenous (NE) ($n = 76$) patients. Results of these analyses are presented in Table 2.

All three ratings yielded satisfactory, but not spectacular classifications of E and NE patients. The IDS-SR was equivalent to the BDI and the HRS-D in correctly classifying endogenous ($\chi^2 = 2.46, df = 2, p = .29$) and nonendogenous ($\chi^2 = 2.00, df = 2, p = .37$) patients. Discriminating symptoms fit predictions from the literature.

A principal components factor analysis was conducted. We expected four factors: a general factor measuring mood and cognition, a vegetative (endogenous) factor, an atypical symptom factor (weight gain, hypersomnia, appetite increase), and an anxious depression factor.

The factor pattern following varimax rotation revealed four factors that accounted for

TABLE 2. Summary of Discriminant Analyses Using Rating Scale Items to Classify Endogenous and Nonendogenous Depressed.

Scale	Step	Variable Entered	Wilks' Lambda	F	Mean Score	
					E ($n = 52$)	NE ($n = 76$)
IDS-SR	1	19. Involvement	.94	7.9^a	2.2	1.7
	2	3. Morning Insomnia	.90	7.0^a	1.3	0.7
	3	27. Panic/Phobic	.89	6.3	1.2	1.4
	4	24. Psychomotor Agitation	.84	6.0	1.0	0.7
% Correct Classification					57.5%	69.7%
					E ($n = 56$)	NE ($n = 90$)
BDI	1	16. Morning Sleep	.93	10.0^a	1.5	1.0
	2	17. Tiredness	.90	7.8	2.0	1.5
% Correct Classification					51.8%	68.9%
					E ($n = 49$)	NE ($n = 101$)
HRS-D	1	12. Decreased Appetite	.91	14.7	0.9	0.5
	2	9. Psychomotor Agitation	.86	12.4	0.8	0.5
	3	4. Initial Insomnia	.81	12.1	1.6	1.2
	4	2. Guilt	.79	10.4	0.9	1.1
% Correct Classification					66.1%	77.2%

All p's <.001 except where noted.

$^a p <.01$.

a cumulative variance of 45.1 percent, with a final commonality estimate of 12.6. Factor 1 was interpreted as a mood/cognition factor. Items with high positive loadings on factor 1 included sad, irritable, and anxious mood; mood reactivity; concentration; self and future outlook; suicidal ideation; involvement; energy; pleasure and sexual interest. Factor 2 was labeled anxious/hypochondriacal, with high positive loadings on sleep onset insomnia, psychomotor changes, somatic and gastrointestinal complaints, sympathetic arousal, and panic and phobic symptoms. Factor 3 was identified as an endogenous symptom factor loading on items measuring decreases in weight and appetite, middle and terminal insomnia, and diurnal mood variation. Factor 4 showed high positive loadings on increases in appetite and a moderate loading on hypersomnia, and was labeled an atypical feature factor.

Part II: Clinician-Rated IDS (IDS-C)

Subjects and Procedures. Eighty-two outpatients were evaluated at initial interview with the clinician-rated Inventory of Depressive Symptoms (IDS-C) and the 17-item HRS-D. Clinicians conducted SADS-L diagnostic interviews on these patients and rendered RDC diagnoses. Table 3 shows the diagnostic composition of the sample. The sample averaged 36.9 (SD 3.1) years of age; 65 percent were female; most patients were Caucasian (89 percent).

Results

Reliability

The IDS-C had high reliability as revealed by item-total correlations and a coefficient alpha (Cronbach, 1951) of 0.88. The HRS-D and BDI demonstrated similar alphas of 0.89 and 0.91, respectively.

TABLE 3. Diagnostic Description of the Sample (IDS-C).

Diagnosis	*n*	Diagnosis	*n*
Unipolar MDD	68	Bipolar I	2
Primary	57	Depressed	2
Secondary	11	Bipolar II	5
Endogenous	37	Depressed	4
Nonendogenous	31	Mixed	1
Psychotic	0	Other Diagnoses	5
Nonpsychotic	68	Remitted Unipolar	2

Items most highly related to total score were: decreased pleasure, reactivity of mood, decreased appetite, lack of involvement, decreased energy, and sad mood. Hypersomnia, irritable mood, panic/phobic symptoms, increased appetite, and increased weight were least correlated with IDS-C total score as might be expected in a population with endogenous, nonendogenous, and atypical major depressions.

Concurrent Validity

All 82 patients also had HRS-D ratings, and 71 completed the BDI. The mean IDS-C score was 35.5 (SD 13.7), while the 17-item HRS-D was 22.6 (SD 8.9) for the total sample. The mean BDI score was 27.4 (SD 11.5). The IDS-C correlated with the BDI (r = 0.61, p <.001) and very highly with the HRS-D (r = 0.92, p <.001). Figure 1 shows the relationships between the IDS-C and HRS-D.

Partial correlations examined the relationship between the IDS-C, BDI, and HRS-D independent of the other. The partial correlation between the IDS-C and the HRS-D (BDI covaried out) was 0.83 (p <.001). The partial correlation between the IDS-C and the BDI (HRS-D covaried out) was 0.13 (p <.05). The partial correlation between the HRS-D and BDI (IDS-C score covaried out) was 0.24 (p <.05). Thus, the IDS-C was *not*

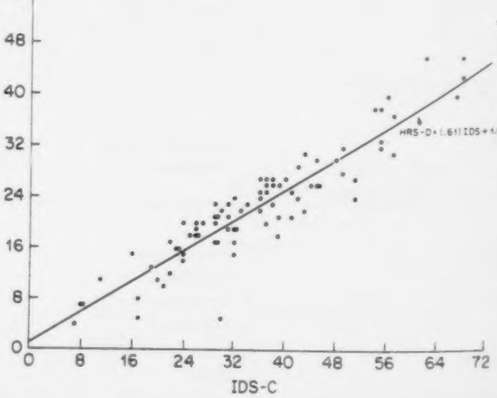


FIGURE 1. Total scores on the IDS-C and 17-item HRS-D for all patients (n = 82).

highly correlated with that portion of the BDI that is independent of the HRS-D. The IDS-C was *highly* correlated with the HRS-D (BDI covaried out) — even more so than the BDI was correlated with the HRS-D (IDS-C covaried out).

Construct Validity

Construct validity was evaluated by a stepwise discriminant analysis to determine which IDS-C items discriminated RDC endogenous from nonendogenous depressions and to identify which combination of IDS-C items maximally discriminated the two groups. Unipolar endogenous (E) ($n = 37$) were contrasted with unipolar nonendogenous (NE) ($n = 31$) patients. Table 4 summarizes these results.

Of the 3 ratings, the IDS-C most powerfully differentiated endogenous from nonendogenous depressions.

Discussion

The IDS-SR has good internal consistency by Cronbach's alpha and item-total correlation. However, the quality to mood item weakly related to total score, and has been reworded. Strong evidence for concurrent validity was obtained. A better partial correlation between the IDS-SR and the HRS-D was found than with the BDI and HRS-D.

Given the various scale ranges (BDI = 0 to 63; HRS-D = 0 to 52; IDS-SR = 0 to 78), a higher mean IDS-SR score (36.5) than BDI (26.0) and HRS-D score (18.0) was expected. No normal scored over 9 on the IDS-SR. One might expect the IDS-SR to be more sensitive than the HRS-D in detecting minor depressive symptomatology as more scale points are available between the upper end of normal (9) and the mean depressive level (36.5) for the IDS-SR.

It is not suprising that both self-reports (the IDS-SR and BDI) were somewhat less useful in differentiating E from NE depressions than was the HRS-D, as clinician judgment is employed with the HRS-D. What is reassuring is that the IDS-SR items that contributed to this discrimination were among those predicted by the literature.

Finally, the factor structure of the IDS-SR fit our *a priori* decisions with a robust commonality. This structure fits the notion that major depressions may include classical endogenous depressions, anxious phobic, atypical depressions, and nonendogenous depressions. These notions have been argued by Sargant and Dally (1962), Kiloh and Garside (1963), and Klein (1974) over several years. A recent study (Liebowitz et al., 1984) suggested that atypical depressions respond better to

TABLE 4. Summary of Discriminant Analyses Using Rating Scale Items to Classify Endogenous and Nonendogenous Depressed ($n = 65$).

Scale	Step	Variable Entered	Wilks' Lambda	F^a	Mean Score	
					E($n = 36$)	NE ($n = 29$)
IDS-C	1	21. Pleasure	.66	32.3	2.3	1.2
	2	11. Decreased Appetite	.59	21.9	1.4	0.3
	3	22. Sexual Interest	.53	18.0	2.4	1.1
% Correct Classification					77.8%	89.7%
					E ($n = 26$)	NEΔ($n = 26$)
BDI	1	21. Sexual Interest	.78	14.0	2.1	1.0
	2	18. Decreased Appetite	.70	10.4	1.5	0.8
	3	20. Somatic Concern	.63	9.5	0.8	0.9
% Correct Classification					69.2%	69.2%
					E ($n = 35$)	NE ($n = 28$)
HRS-D	1	14. Libido	.70	25.6	1.7	0.8
	2	2. Guilt	.62	18.3	2.0	1.2
% Correct Classification					77.1%	75.0%

[a] All p's $<.001$.

MAOI's than to tricyclics, which argues for the validity of the concept of atypical depression. None of the commonly used symptom rating scales, however, will detect certain symptom changes that can be expected in this group (e.g., hypersomnia, increased appetite/weight) except for the IDS.

The IDS-C also had high internal consistency. Concurrent validity was strongly supported by the correlations between the HRS-D, and IDS-C.

Several IDS-C items contributed to a very robust differentiation of endogenous from nonendogenous depression. In fact, a *better* differentiation was obtained with the IDS-C than with the BDI, HRS-D, or IDS-SR. Importantly, capacity for pleasure, appetite, and libido were discriminating as predicted by Klein (1974), who suggested that the capacity for pleasure was core to endogenomorphic depression. Apparently, the clinician's judgment about capacity for pleasure is better than the patient's self-report, as this item on the IDS-C but *not* the IDS-SR contributed to the discrimination.

In summary, an optimal measure of depressive symptomatology should weigh each symptom equally, include endogenous symptoms, be available as a self-report and as a clinician rating, keep the demand for abstract judgment to a minimum, and be easily applied in a clinical setting. Finally, reliability, internal consistency, construct, and concurrent validity are required. Both the IDS-SR and IDS-C appear to meet these requirements. Further studies to develop item kappas and to determine whether the IDS-SR and IDS-C reflect symptomatic change with treatment are ongoing.

Acknowledgments

The authors express their appreciation to David Savage for his secretarial support, and to Kenneth Z. Altshuler, M.D., Professor and Chairman, for his administrative support. In addition, we appreciate the review of initial items provided by Donald F. Klein, M.D., Michael R. Liebowitz, M.D., Bernard J. Carroll, M.D., Ph.D., and Aaron T. Beck, M.D.

References

Beck, A.T., Ward, C.H., Mendelson, M., et al. An inventory for measuring depression. *Arch. Gen. Psychiatry*, 4:561–571, 1961.

Cronbach, L.J. Coefficient alpha and the internal structure of tests. *Psychometrika*, 16:297–334, 1951.

Endicott, J., and Spitzer, R.L. A diagnostic interview: The schedule for affective disorders and schizophrenia-life-time version. *Arch. Gen. Psychiatry*, 35:837–844, 1978.

Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry*, 12:56–62, 1960.

Hamilton, M. Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychology*, 6:278–296, 1967.

Jennrich, R., and Sampson, P. P7M: Stepwise discriminant analysis. In: Dixon, W.J., and Brown, M.B. (eds.), *BMDP-83*. Berkeley, CA: University of California Press, 1983.

Kiloh, L.G., and Garside, R.F. The independence of neurotic depression and endogenous depression. *Br. J. Psychiatry*, 109:451–463, 1963.

Klein, D.F. Endogenomorphic depression. *Arch. Gen. Psychiatry*, 31:447–454, 1974.

Liebowitz, M.R., Quitkin, E.M., Stewart, J.W., et al. Phenelzine versus imipramine in atypical depression. *Arch. Gen. Psychiatry*, 41:669–677, 1984.

Rush, A.J., Giles, D.E., Schlesser, M.A., et al. The inventory of depressive symptomatology (IDS): Preliminary findings. *Psychiatry Res.* (In press.)

Sargant, W., and Dally, P. Treatment of anxiety states by antidepressant drugs. *Br. Med. J.*, 4:6–9, 1962.

Spitzer, R.L., Endicott, J., and Robins, E. Research diagnostic criteria: Rationale and reliability. *Arch. Gen. Psychiatry*, 36:773–782, 1978.

Chronic Lithium and Desmethylimipramine Modulation of Locomotor Response to Growth Hormone Releasing Factor

Cindy L. Ehlers, Ph.D.,[1] Alfred Lopez,[1]
and R. Ian Chaplin, B.S.[1]

Electroencephalographic (EEG) studies of the sleep patterns of patients with affective disorder have clearly demonstrated that a cluster of abnormalities in sleep accompany the acute phase of the illness (Kupfer & Reynolds, 1983). In addition to these EEG findings, recent studies have also established that the sleep associated release of growth hormone is disturbed in depressed subjects (Jarrett et al., 1986).

The discovery and characterization of a growth hormone releasing factor (GRF) (Guillemin et al., 1984) has opened new avenues for exploration of the hypothalamic-pituitary axis in affective disorder. This 44 amino acid peptide was first isolated from a pancreatic tumor found in a patient with acromegaly (Guillemin et al., 1982) and has since been sequenced and synthesized using solid phase methodology. It has been demonstrated that in addition to its ability to release physiologically relevant amounts of growth hormone (Wehrenberg et al., 1982) GRF may have direct effects on central nervous system functioning. Recent studies have reported that intracerebroventricular (i.c.v.) administration of GRF can have potent consequences on measures of electrophysiology and behavior in rats; for instance, i.c.v.-GRF in doses of 2 nMols has been found to produce significant reductions in locomotor activity as well as significant increases in time spent in slow wave sleep (Ehlers et al., 1986; Wehrenberg et al., 1986).

The present study attempted to test whether chronic administration of two drugs commonly used to treat affective disorder, lithium (LI) and desmethylimipramine (DMI), could modify locomotor response to i.c.v.-GRF.

Method

Thirty-two male Wistar rats weighing between 300 to 450 g were used in the study. They were group housed, maintained in a normal light cycle (12:12 light:dark) and given diet and water ad libitum. For implantation of i.c.v. cannulae rats were anesthetized with nembutal [50 mg/kg given intraperitoneally (i.p.)] and secured in a Kopf stereotaxic instrument. Guided by the Atlas of Konig and Klippel a 23-gauge stainless steel guide cannula and stylet (Plastic Products) was lowered into the lateral ventricle (PO. 8, L2.0, V3.2, toothbar 5 mm above the interaural line) and cemented to the skull with dental acrylic. The animals were allowed 7 to 10 days to recover from the surgical procedures and were then assigned to one of four treatment groups: 1) chronic LI diet (Teklad Mills TD 79092, 30 mM/kg LI) $n = 8$; 2) control diet $n = 8$; 3) daily DMI injections (10 mg/kg dissolved in bacteriostatic water and given i.p. $n = 8$; 4) daily bacteriostatic water injections given i.p. $n = 8$.

After 21 days of exposure to LI or control diet or 18 days of DMI or water injections, behavioral response to GRF was tested. For locomotor measurements, rats were placed singly in wire-mesh cages equipped with two infrared photocell beams aimed across the long axis 2 cm above the cage floor. Rats were habituated to these cages for 90 minutes prior to (i.c.v.) injections. Each rat received a single i.c.v. dose of GRF (2.0 nmol), on one test day, and an i.c.v. injection of saline 5 to 7 days later. The order of the injections was randomized so that half of the rats in each group received saline first and half received GRF as a first injection. I.c.v. injections were accomplished by removing a dummy stylet and inserting an 8 mm 30-gauge stainless

---

[1] Division of Preclinical Neuroscience and Endocrinology, Scripps Clinic and Research Foundation, La Jolla, CA 92037.

steel cannula with 50 cm of Tygon microbase tubing through the guide previously implanted in the skull. Five μl of saline or saline plus GRF was then injected over a one minute period using a 50-μl Hamilton syringe. Only those rats in which no impedance to flow was noted were used in the experiment. An i.c.v. route of administration was not used to simulate a physiological event, as rates of transport into the brain of these peptides from cerebrospinal fluid (CSF) are not known. Rather, this method was used in order to gain access to several potential sites of action following a single injection. Ten minutes following i.c.v. injections locomotor measurements were begun. Activity was quantified by totaling photocell beam interruptions recorded on computer automated electromechanical counters, for 10 minute epochs, over a 3-hour test session. The tests were carried out between 1300 and 1600 hours. Statistical comparison of locomotor activity between saline sessions and GRF sessions between the 4 groups (LI diet, control diet, DMI injections, water injection) was determined using a two factor analysis of variance with repeated measure on one factor (time).

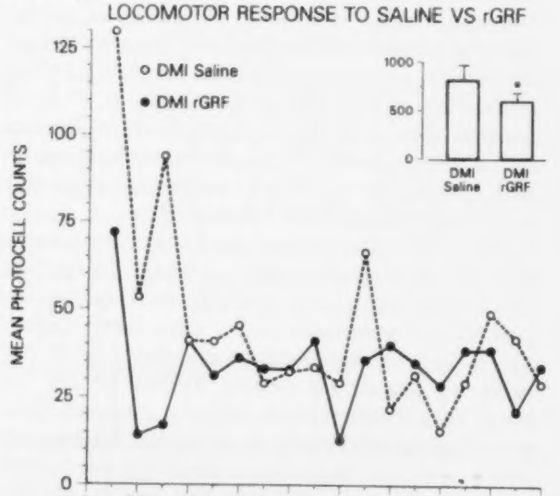


FIGURE 1. Locomotor response to an ICV injection of saline or rat growth hormone releasing factor (rGRF, 2 nMols) in rats given daily injections of DMI (10 mg/kg IP, 18 days). DMI significantly enhanced locomotor response to rGRF (ANOVA g×t, F = 1.6, df = 1,15, $p <$ .05).

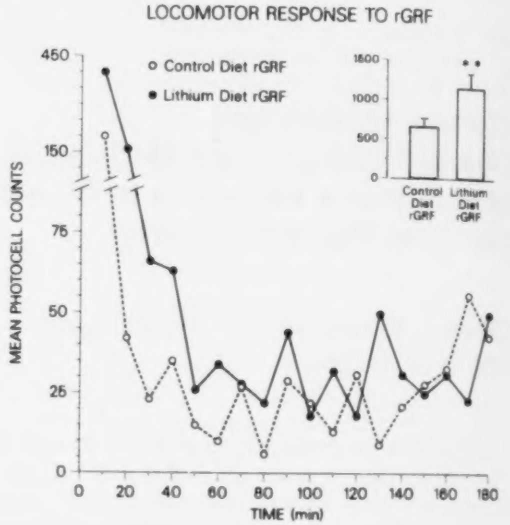


FIGURE 2. Locomotor response to an ICV injection of rat growth hormone releasing factor (rGRF, 2 nMols) in rats fed LI (30 nM/kg × 21 days) or control diet. Lithium significantly attenuated the locomotor response to rGRF (ANOVA Group effect, F = 5.9, df = 1,15, $p < .03$, g×t =2.06, df = 1,15, $p < .01$).

Results

Growth hormone releasing factor, when injected intracerebroventricularly, produced some decreases in locomotor activity in all four treatment groups. As seen in Figure 1, however, the pattern of locomotor response to GRF vs saline was significantly modified in rats given daily DMI injections (ANOVA gXt, $p < .05$), with DMI producing an enhanced response to GRF. In contrast chronic LI treatment in the diet produced a different response to i.c.v. administered GRF. As seen in Figure 2, rats receiving LI as compared to control diet were found to be significantly less responsive to GRF over the 3-hour test period (ANOVA g, $p < .03$, gXt, $p < .01$).

Discussion

These studies have demonstrated that chronic administration of the antimanic drug LI and the antidepressant DMI can significantly modify the locomotor response to i.c.v. administration of GRF in rats. DMI treatment was found to enhance the depression of locomotion seen following GRF; whereas, LI significantly attenuated the reductions in locomotor activity produced by i.c.v.-GRF.

The results of this investigation are consistent with previous studies where decreases in locomotion and increases in slow wave sleep were found following i.c.v. administration of GRF in the same dose range in rats (Ehlers et al., 1986). How these behavioral effects of GRF are mediated, however, still remains speculative. The anatomic distribution of GRF in the central nervous system (CNS) appears, from early studies, to be limited to hypothalamic sites. This severely restricts the possibility of GRF having direct neurotransmitter effects on the biogenic amine neurons suggested previously to play a major role in the actions of antidepressants (Snyder & Peroutka, 1984) and lithium (Emrich et al., 1982). Since it is not known whether GRF may be released into the ventricles, it is possible that it may influence biogenic amine neurons through diffusion from the CSF or it may act by reducing the activity or release of a behaviorally activating hypothalamic peptide such as corticotropin releasing factor (CRF).

The findings of an enhanced response to GRF following DMI treatment are interesting in light of previous studies which have reported enhanced responses to i.c.v. administration of CRF following identical chronic DMI treatment procedures in rats (Ehlers et al., 1985). Thus DMI may be acting to "sensitize" the system to the actions of these hypothalamic peptides. Conversely, depression may represent a state where the CNS is "desensitized" and thus cannot respond normally to peptide input. This notion is supported by clinical data demonstrating a blunted response of adrenocorticotrophic hormone to an i.v. infusion of CRF (Gold et al., 1984). In the case of LI, the attenuation of response to GRF is also consistent with previous studies in rats which have demonstrated that chronic dietary LI tends to reduce the variance of locomotion (Ehlers et al., 1983). Although the mechanisms underlying the actions of GRF are unknown, these studies suggest that the clinical effectiveness of DMI and LI may be partially enacted through systems responsive to GRF.

Acknowledgments

The authors would like to thank Trisha Reed for help in the statistical analysis and Nancy Callahan for editing and typing the manuscript. These studies were supported by a grant from NIAAA, AA-06059 to Cindy L. Ehlers, Ph.D., and the MacArthur Foundation.

References

Ehlers, C.L., Russo, P.V., Mandell, A.J., and Bloom, F.E. Architecture of rat nocturnal locomotion: A predictive descriptor of the effect of antidepressant and antimanic treatments. *Psychopharm. Bull.*, 19(2):692–695, 1983.

Ehlers, C.L., Chaplin, R.I., and Koob, G.F. Chronic desmethyimipramine but not lithium modifies locomotor response to corticotropin releasing factor. *Neurosci. Abst.*, 15:619, 1985.

Ehlers, C.L., Reed, T.K., and Henriksen, S.J. Effects of corticotropin releasing factor on sleep and activity in rats. *Neuroendocrinology*, 42:467–474, 1986.

Emrich, H.M., Aldenhoff, J.B., and Lux, H.D. Basic mechanisms in the action of lithium. *Excerpta Medica*, Amsterdam, 1982.

Gold, P.W., Chrovsos, G., Kellner, C., et al. Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am. J. Psychiatry*, 141(5):619–627, 1984.

Guillemin, R., Brazeau, P., Bohlen, P., et al. Growth hormone-releasing factor from a human pancreatic tumor that caused acromegaly. *Science*, 218:585–587, 1982.

Guillemin, R., Zeytin, F., Ling, N., et al. Growth hormone releasing factor chemistry and physiology. *Proc. Soc. Exp. Biol. Med.*, 175:407–413, 1984.

Jarrett, D.B., Greenhouse, J.B., Thompson, S.T., et al. Growth hormone secretion during sleep: A comparison between patients and healthy control subjects. (Submitted 1986.)

Kupfer, D.J., and Reynolds, C.F. Neurophysiological studies of depression: State of the art. In: Angst, J. (ed.), *The Origins of Depression: Current Concepts and Approaches* (Dahlem Konfereze). Berlin: Springer-Verlag, 1983, pp. 235–252.

Snyder, S.H., and Peroutka, S.S. Antidepressants and neurotransmitter receptors. In: Post, R.M., and Ballenger, J.C. (eds.), *Neurobiology of Mood Disorders.* Baltimore: Williams and Wilkins, 1984, pp. 686–697.

Wehrenberg, W.B., Ling, N., Bohlen, P., et al. Physiological roles of somatocrinin and somatostatin in the regulation of growth hormone secretion. *Biochem. and Biophys. Res. Commun.*, 109(2):562–567, 1982.

Wehrenberg, W., Ling, N., and Ehlers, C.L. Effects of growth hormone-releasing factor in the brain. *Science*, 232:1271–1272, 1986.

Postmarketing Surveillance of Long-Term Amitriptyline Side Effects

Stephen G. Bryant, Pharm.D.,[1] Seymour Fisher, Ph.D.,[2] and Ronica M. Kluge, M.D.[3]

Information obtained by both clinical trial and experience have demonstrated that adverse reactions caused by tricyclic antidepressants (TCA's) interfere with patients' tolerance of drug therapy and may result in an inadequate trial because of poor compliance. Anticholinergic and sedative side effects of TCA's have been widely described as being most bothersome early on in the course of drug treatment with patients' subjective complaints becoming diminished with continued use (Schoonover, 1983; Klerman, 1978). The purpose of this report is to characterize the adverse drug reactions reported by amitriptyline-treated patients who have started the drug quite recently compared to those reported by patients who have taken amitriptyline over a much longer period using a novel method for drug safety surveillance.

Methods

Study Design. The investigators have recently undertaken a large-scale study aimed at developing new methods for collecting postmarketing data on prescription drug experiences in ambulatory patients (Fisher et al.,1986; Fisher et al., unpublished). The new monitoring method is designed to complement rather than replace existing voluntary prescriber-initiated reporting systems for detecting adverse drug reactions (ADR's).

At the time that a targeted prescription drug is being dispensed at our outpatient pharmacies, cooperation is randomly solicited from half of the patients (experimental sample) via a printed notice attached to the outside of their medication bag; this patient package "outsert" provides a brief, concise statement of what the patient is being asked to do, the reason for the request, and a removable sticker that gives a toll-free phone number along with a summary of details about how to report "*any* new or unusual symptoms" experienced during the next 2 weeks. The other half of the patients (validation sample) do not receive any outsert, but approximately 2 weeks later are interviewed by a cadre of experienced personnel via telephone using a computer-directed, standardized method of collecting accurate reports of new or unusual "adverse clinical events" (ACE's) during or following a drug's use. An ACE may or may not be an ADR, depending upon information that permits inferences about causality; but all ADR's must first be valid ACE's. A "valid" ACE is defined as any untoward reaction that began only after the patient started our target drug and within the specific allowable 14-day reporting period.

The interview used to identify, describe, and quantify ACE's was developed from modifications of the SAFTEE, The National Institute of Mental Health's Systematic Assessment for Treatment Emergent Events, and has four sections: a general inquiry for spontaneously reported ACE's, a systematic ACE inquiry, a post-spontaneous ACE inquiry, and a medication inquiry.

For each symptom mentioned by the patient, the interviewer records its onset, duration, frequency, and pattern. In addition, the subject is asked to rate the subjective severity of each symptom by answering the questions "How bad is/was it at its worst?," choosing a rating from 1 to 5 (1 = minimal; 5 = very severe). The medication inquiry portion of the interview determines what medicines the patient is currently taking, when the patient most recently started the target medicine, whether it is still being taken and with any

---

[1] Assistant Professor, Department of Psychiatry and Behavioral Sciences, the University of Texas Medical Branch, Galveston, TX 77550.

[2] Professor, Department of Psychiatry and Behavioral Sciences, the University of Texas Medical Branch, Galveston, TX 77550.

[3] Professor, Department of Internal Medicine, the University of TX Medical Branch, Galveston, TX 77550.

significant dosage changes (whether and when it had been used previously), and—if one or more ACE's were reported—whether starting the target drug unequivocally preceded each ACE onset.

In the present study, because there is general agreement on a core set of expected side effects of our TCA target drugs, the investigators can single out those valid ACE's matching one or more of our assumed "true ADR's." Consisting mainly of sedative, anticholinergic, neurologic, and cardiovascular symptoms, tricyclic ADR's defined prior to the start of our study and obtained from recognized sources (Long, 1977; USP, 1983) were as follows: dry mouth, blurred vision, constipation, difficult urination, headache, fainting, dizziness or lightheadedness, rapid or irregular heartbeat, tremor, numbness or tingling of the extremities, excessive sleeping or drowsiness during the day, increased thirst, eye pain, and craving for sweets. *Any one of these predefined ADR's reported by a tricyclic patient was recorded as an* ACE_{tca}.

Subjects. Through the use of our staff-initiated telephone interviews with our validation sample, the investigators have completed analysis of side effect assessments for 85 control patients receiving amitriptyline who clearly fell into two groups on the basis of when they started their most recent course of continuous TCA treatment: 45 had started within 2 weeks preceding our telephone interview, while 40 had started more than 2 weeks before. These two groups of amitriptyline users did not significantly differ with regard to the number of days elapsed since starting the TCA, age, sex, race, number of current medications, and number of valid ACE's reported. The two groups had remarkably similar obvious characteristics, with the exception of time elapsed since starting amitriptyline (short-term = 10.1 ± 1.6 days; long-term = 227 ± 135 days).

Table 1 shows that almost two-thirds of the patients had at least one valid ACE (i.e., a new complaint) during the reporting period, with a somewhat higher but nonsignificant proportion occurring in those patients who had started the amitriptyline during the past 2 weeks. However, if only ACE_{tca}'s are considered, then the incidence estimate for patients with a potentially true amitriptyline side effect drops to 44 percent for the short-term patients and 35 percent for the long-term patients, a nonsignificant difference.

TABLE 1. Number and Percentage of Patients With at Least One Valid ACE and at Least One Valid ACE_{tca}.

	Short	Long	All
Total number of interviews	45	40	85
Number of patients with at least one valid ACE	32	22	54
Complaint percent	71.1	55.0	63.5
Number of patients with at least one valid ACE_{tca}	20	14	34
Predefined side effect percent	44.4	35.0	40.0

Table 2 presents frequency, incidence, and subjective severity data on the individual ACE_{tca}'s for the 20 "short" patients and the 14 "long" patients and demonstrated that the mean number of ACE_{tca}'s per patient was not appreciably different for the two groups. It may not be surprising that 16 percent and 9 percent of the short-term patients reported sedative effects and tremor or tingling, respectively, compared to 0 percent of those who had been on amitriptyline more than 2 weeks; or that heart rate symptoms, headaches, and lightheadedness or dizziness seem to appear less frequently with long-term use. More unexpected, however, is the likelihood that there may be other side effects that appear even with long-term use: 12.5 percent reported dry mouth as a new symptom occurring within the immediately preceding 2 weeks, 7.5 percent experienced blurred vision, 5 percent reported difficulty with urination, and 5 percent complained of new bouts of constipation; these incidences of anticholinergic ADR's are similar to those seen in the short-term patients. Table 2 further shows that the mean subjective severity of these ACE's was nonsignificantly higher for the short-term users (2.7) than for the long-term patients (2.2).

Amitriptyline daily dosage data (on all those patients for whom such data could be obtained) for those patients with a least one valid ACE as well as for patients with at least one valid ACE_{tca} showed no significant differences. Mean doses were remarkably low for all groups, probably indicating that some of these patients were not prescribed amitriptyline for the treatment of depression

TABLE 2. Individual Pre-Defined Side Effects Reported by Short-Term and Long-Term Usage Patients.

	Short (N = 45)			Long (N = 40)		
	f	%	Mean Subjective Severity	*f*	%	Mean Subjective Severity
Anticholinergic:						
Dry mouth	8	17.8	2.9	5	12.5	1.8
Constipation	2	4.4	3.0	2	5.0	1.5
Blurred vision	1	2.2	3.0	3	7.5	1.7
Difficult urination	1	2.2	1.0	2	5.0	3.5
Neurological:						
Excessive sleeping or drowsiness during the day	7	15.6	2.3	0	0.0	
Shakiness or tremor	0	0.0		1	2.5	2.0
Numbness or tingling (extremity)	4	8.9	2.8	0	0.0	
Other:						
Rapid or irregular heartbeat	2	4.4	2.0	1	2.5	1.0
Headache, dizziness or lightheadedness	6	13.3	3.2	3	7.5	3.3
Total ACE_{tca}'s	31			17		
Total patients	20			14		
ACE_{tca}'s per patient	1.6			1.2		
Mean subjective severity			2.7*			2.2*

*Weighted means, nonsignificant.

(most of these prescriptions were prescribed by nonpsychiatrists), and that less than expected therapeutic doses were prescribed for some patients who were depressed. Alternatively, the similar daily dosages prescribed for both short- and long-term patients may reflect that short-term patients were started at lower initial doses to be eventually titrated upward, while long-term patients' daily doses were stable maintenance therapy.

Discussion

A recent FDA study by Rossi et al. (1983) has shown that none of the existing formal postmarketing monitoring systems fare very well in detecting ADR's: manufacturer-initiated surveillance studies of three drugs requiring FDA-mandated labeling changes failed to identify any new ADR's, and all labeling changes for two of the drugs were added as a result of voluntary, spontaneous reports by practitioners. Yet there is widespread agreement that the system suffers from serious underreporting (Wardell et al., 1979), and it seems that reliance solely on a desultory system of voluntary reporting by physicians to manufacturers, journals, and governmental agencies is less than ideal.

The investigators' finding that approximately two-thirds of amitriptyline patients reported at least one adverse clinical event (irrespective of causality) within the 2 weeks after starting a prescription for the drug is comparable in magnitude to what others have labeled as "side effect incidence" (Newton, 1981). Obviously, patients asked to report "*any* new or unusual symptoms" will describe changes in physical state that may or may not be side effects of their medication. One of the clearest findings emerging from this study is that approximately 40 percent of patients reported at least one "true" tricyclic ADR (ACE_{tca}) at some point in the interview. If this global ACE_{tca} incidence is 40 percent, then the true incidence of ADR's must be less because patients could still be reporting any of the authors' pre-defined ADR's for reasons other than a true amitriptyline side effect: from the natural course or complication of current medical disorders, from the onset of a new illness, from environmental causes, from placebo effects, or from other concomitant medications.

The analysis of ACE_{tca}'s reported by patients just starting amitriptyline therapy compared to patients who have taken the drug for a much longer period at very similar doses challenges the common clinical impression that TCA side effects, in general, abate with continued treatment. These reports of new ADR's by long-term amitriptyline users may reflect the fact that such symptoms fluctuate in their occurrence and may not be recognized as potentially drug-induced until some threshold for patient tolerance is exceeded. The similar mean subjective severity ratings for all ACE$_{tca}$'s reported by either short- or long-term patients further qualify the perception held that patients accommodate to all of these ADR's. It is striking that many of the ACE$_{tca}$'s reported by the study subjects may well be anticholinergic side effects (blurred vision, difficult urination, constipation). It warrants emphasis that these are *new* symptoms reported by patients who have taken amitriptyline at a steady dosage for an average of over 7 months.

Acknowledgments

This study is currently funded by MH–39661 from the National Institute of Mental Health.

The following individuals have all been instrumental in conducting the project: Sherri Beck, Denise Byrd, Lisbeth Carlson, Antoinette Jensen, Becky Koonce, Bruce Mansbridge, Claudia Mansbridge, Delva Siemsen, and Jodi Ziontz. The study would not have been possible without the continued support of Eustacio Galvan and Charles Blair from the Department of Pharmaceutical Services.

References

Fisher, S., Bryant, S.G., and Kluge, R.M. "Detecting adverse drug reactions in a postmarketing surveillance system: Validity of a standardized interview." (Unpublished, 1986).

Fisher, S., Bryant, S.G., and Kluge, R.M. Measuring adverse drug reactions in a postmarketing surveillance system. *Psychopharmacology Bull.*, 22:272–277, 1986.

Klerman, G.L. Pharmacologic treatment of depression. In: Bernstein, J.G. (ed.), *Clinical Psychopharmacology*. Littleton: PSG Publishing Company, Inc., 1978, p.74.

Long, J.W. *The Essential Guide to Prescription Drugs*. New York: Harper and Row, 1977.

Newton, R. The side effect profile of trazodone in comparison to an active control and placebo. *J. Clin. Psychopharmacol.*, 1(Supp.):89S–93S, 1981.

Rossi, A.C., Knapp, D.E., and Anello, C., et al. Discovery of adverse drug reactions: A comparison of selected Phase IV studies with spontaneous reporting methods. *JAMA*, 249:2226–2228, 1983.

Schoonover, S.C. Depression. In: Bassuk, E.L., Schoonover, S.C., Gelenberg, A.J. (eds.), *The Practitioner's Guide to Psychoactive Drugs*. New York: Plenum Medical Book Co., 1983, pp. 48–50.

USP. *USPDI: II. Advice for the Patient*. Rockville, MD.: U.S. Pharmacopeial Convention, 1983.

Wardell, W.M., Tsianco, M.C., Anavekar, S.N., et al. Postmarketing surveillance of new drugs: II. Case studies. *J. Clin. Pharmacol.*, 19:169–184, 1979.

The Patient, the Family, and Compliance With Posthospital Treatment for Affective Disorders

Gretchen L. Haas, Ph.D.,[1] Ira D. Glick, M.D.,[1] James H. Spencer, M.D.,[1] John F. Clarkin, Ph.D.,[1] Alfred B. Lewis, M.D.,[1] Marcie Good-Ellis, M.S., O.T.R.,[1] Joanne Peyser, M.S.W.,[1] Nancy DeMane, M.S.W.,[1] Elizabeth Harris, R.N., M.A.,[1] and Veronica Lestelle, M.S.W.[1]

The efficacy of pharmacotherapy in the treatment of the affective disorders has been amply demonstrated in multiple controlled clinical trials. However, the bulk of these studies have focused on treatment during the acute phase of the illness wherein control of the acute symptoms is the primary goal (Prien, 1983). Few studies have investigated the efficacy of continuation and maintenance pharmacotherapy—delivered over an extended period—beyond the acute phase of illness. Moreover, recent research has shown that the benefits of medication for depressive disorders may be limited in several respects: pharmacotherapy may have only minimal impact on impaired social functioning (DiMascio et al., 1979; Friedman, 1975; Weissman et al., 1975; Klerman, 1983); psychosocial stress may provoke relapse—even among patients adherent to a prophylactic drug regimen. Finally, noncompliance with prophylactic medication is a serious problem in a high percentage of cases (Jamison & Akiskal, 1983; Shaw et al., unpublished). When medication is discontinued prematurely, the patient may relapse and the likelihood of multiple episodes is greatly increased (Prien, 1983).

Controlled outcome research indicates that psychosocial treatments may be helpful in dealing with each of these problems (DiMascio et al., 1979; Friedman, 1975; Weissman et al., 1979; Klerman, 1983; Jamison & Akiskal, 1983; Shaw et al., unpublished). In fact, several controlled studies suggest that optimal treatment for some types of depressive disorders is a combination of an antidepressant and psychotherapy which, together, are more potent than either alone. For example, controlled-clinical studies on unipolar depression have demonstrated that outpatient psychotherapy—when used in conjunction with pharmacologic treatments—can enhance patient functioning in the areas of social, family, and primary (work) role adjustment (DiMascio et al., 1979; Friedman, 1975; Weissman et al., 1979; Klerman et al., 1974). Relatively less is known about the effectiveness of psychosocial interventions for patients with bipolar disorders. What data there are suggest that long-term psychosocial treatments may enhance drug compliance (Fitzgerald, 1972; Cochran, 1984; Davenport et al., 1977) and minimize impairment of social, family, and work functioning among bipolar patients (Fitzgerald, 1972; Cochran, 1984; Davenport et al., 1977; Shakir et al., 1979; Volkmar et al., 1980). In view of the lack of controlled studies in this area, this study was designed to investigate the efficacy of a particular psychosocial intervention—Inpatient Family Intervention (IFI)—delivered in combination with pharmacotherapy and oriented toward enhancing compliance with the recommended posthospital continuation treatment program (including both pharmacotherapy and psychosocial interventions).

The specific aim was to test the incremental efficacy of a brief, crisis-oriented psychoeducational inpatient family treatment (added to a standard, multimodal hospital treatment) for DSM-III Major Affective Disorders recently admitted to hospital. One of the central questions addressed in this study was whether the addition of family intervention would enhance patient outcome. Two subsidiary questions were whether treatment with IFI would result in: 1) better patient

---

[1] Payne Whitney Clinic, Cornell University Medical College, 525 East 68th Street, New York, NY 10021.

Supported, in part, by an NIMH Grant (MH-34466), an NIMH Biomedical Research Support Grant to Cornell University Medical College (507-RR05396), and grant from the Norman and Rosita Winston Foundation.

compliance with posthospital treatments; and 2) more positive family attitudes toward the patient and toward the prescribed treatment.

Methods

Subjects

Subjects were 60 Major Affective Disorder patients consecutively admitted to the hospital and screened for admission to the study by the unit treatment team. The following criteria were used for selection:

a) recent admission (within 2 working days of admission to the unit);

b) a DSM-III diagnosis of Major Affective Disorder; and

c) age 18 to 45.

Patients without available family or significant others or for whom a full course (a minimum of six sessions) of Inpatient Family Intervention was not feasible due to anticipated short stay (3 weeks or less), were excluded from the study.

Treatment Assignment

Within the first 2 days of admission to hospital all patients (and families) who satisfied the selection criteria and consented to participate in the study were assigned to one of two treatment conditions—multimodal hospital treatment with IFI or multimodal hospital treatment without IFI (the "comparison treatment" condition).

Six (five IFI and one comparison treatment) cases of the original 60 failed to complete the minimum amount of treatment to meet study criteria. For this report, data on the full sample of patients who met study criteria ($N = 54$) will be reported.

Comparison of Treatment Groups at Baseline

IFI and the comparison treatment groups were essentially equivalent in terms of demographics with the exception of marital status. There were proportionately more patients married (or previously married) in the comparison treatment than in IFI ($p < .006$). On baseline clinical ratings patients in IFI tended to show less severe overall symptomatology on the Psychiatric Evaluation Form (PEF) ($p < .05$). IFI family members tended to give higher ratings of patients' work functioning than did family of comparison patients at admission ($p < .05$).

Treatment

Treatment setting and procedures for random assignment have been described in a previous report (Glick et al., 1985). The average length of hospital stay was 51.0 (SD = 30.0) days.

The treatment programs for the two groups in this study have been described in a prior report (Glick et al., 1985). Both programs included the standard multimodal regimen of hospital treatments (pharmacotherapy, individual supportive, group, and activities therapies). A partially fixed drug regimen was implemented for all patients in an effort to balance the level of medication used across the two treatment conditions (Glick et al., 1975). This effort was successful in that there were no statistically significant differences in the amount of medication received.

The goals of the IFI treatment included the following: 1) helping patient and family to accept the reality of the illness and to develop an understanding of the current episode; 2) identification of possible precipitating stresses relevant to the current episode; 3) identification of likely future stresses both within and outside of the family; 4) elucidation of the family interaction sequences that produce stress on the identified patient; 5) planning strategies to manage or minimize future stresses; and 6) educating the patient and family regarding the nature of the treatment and the need for continued treatment following discharge from the hospital.

Assessment Procedures

Because hospital treatment of the major affective disorders is concerned primarily with ameliorating symptoms and improving functioning in the hospitalized patient, the traditional focus of assessment is on individual outcome. Therefore, the majority of outcome measures in this study are individual patient measures. However, because it was hypothesized that IFI would result in adaptive change in the family's attitudes toward the patient and posthospital treatments, measures of family attitudes were also included in this study. Patients and families were assessed at four times: admission, discharge and at 6- and 18-month follow-up.

Patient Measures. The areas of patient outcome that we have targeted for study include: global functioning, as assessed on both the Global Assessment Scale (GAS) (Endicott et al., 1976) and the Psychiatric Evaluation Form (PEF) (Endicott & Spitzer, 1972); symptom severity, as assessed on the PEF; and role functioning, as assessed on the Role Performance Treatment Scale (RPTS) (Good-Ellis et al., in press). Treatment compliance was assessed using the Treatment Compliance Scale of the RPTS.

Family Measures. Family attitudes were assessed using the *Family Attitude Scale (FAS)* (Levitt, 1982), a 53-item, structured interview, self-rating instrument for family members. The FAS includes a modified version of Kreisman's (1979) Patient Rejection Scale, items from the Family Evaluation Form (Herz et al., 1977) which assesses the family's sense of burden, and items which tap the family's willingness to seek help from professionals.

Data Analysis

All results were analyzed using three general statistical procedures: 1) analysis of covariance techniques were used where appropriate (i.e., where homogeneity of variance and a moderate size (.50) correlation between the independent and dependent variables existed); 2) in cases in which analysis of covariance could not be used, a repeated measures analysis of variance was performed to assess change over two or more assessment times; and 3) patient outcome measures were transformed into standardized residual scores via regression of the outcome scores against the admission scores, in order to control for possible pretreatment differences.

In addition to the above univariate analyses we have performed multivariate analyses on our data. A multivariate approach to data reduction was used to control for the increased likelihood of a Type I error with multiple outcome measures and univariate analyses. A principal components analysis was performed on the transformed (standardized residualized scores) data, yielding four orthogonal factors. The first rotated factor, comprised of the GAS, the PEF-OS, the symptom subscales of the PEF, and the role functioning scales of the RPTS (at follow-up only) represented a global outcome measure that was used as the dependent variable in subsequent analyses. Finally, a hierarchical multiple regression procedure was used to test the relative contributions of: 1) pre-treatment functioning and demography; 2) treatment assignment and treatment parameters; 3) posthospital compliance; and 4) two-way and higher order interactions on the global outcome variable.

Results

Patient Outcome

At Discharge. Patients treated with IFI showed better global outcome (than their comparison patient counterparts) as measured on the GAS ($F = 4.38$, $p < .04$, $df = 1,51$) and less symptomatology as measured on the grandiosity scale of the PEF ($F = 4.75$, $p < .03$, $df = 1,51$).

Independent analyses by gender revealed that this treatment effect was restricted to females, for whom treatment with IFI was associated with better global outcome, as measured on the GAS ($F = 6.16$, $p < .02$, $df = 1,32$). In fact, for males, treatment with IFI was associated with worse symptomatology at discharge ($F = 5.11$, $p < .04$, $df = 1,17$).

At 6 Months. For all patients combined, IFI treatment effects were attenuated at time of 6-month follow-up. However, independent analyses by gender revealed that for females, treatment with IFI was associated with better global functioning, as measured on the GAS ($F = 4.58$, $p < .05$, $df = 1,32$).

Indices of Clinically Significant Change. In addition to the more traditional statistical analyses of outcome using aggregate data as discussed above, we have chosen to describe patient outcomes in terms of criteria for clinically significant change, as suggested by

Kazdin and Wilson (1978) and more recently by Jacobson, Follette, and Revenstorf (1984).

Using the Jacobson et al. (1984) criterion of clinically significant improvement, i.e., exceeding the critical margin (mean score at admission + 2SD + 2.Se) for significant change, we found that at discharge a higher percentage of patients treated with IFI (84.6 percent) had achieved "significant improvement" as compared with patients given the comparison treatment (60 percent). The difference between these two proportions was significant ($z = 1.96$, one-tailed, $p < .03$). This contrast was maintained at 6 months, at which time 80.0 percent of the major affective disorder patients treated with IFI had achieved, and sustained, significant improvement, whereas only 57.1 percent of the patients given the comparison treatment had met this criterion. This difference was statistically significant ($z = 1.76$, one-tailed, $p < .04$).

Family Outcome

On measures of family outcome, there was a significant treatment effect favoring IFI on the family's willingness to accept professional help both at discharge ($F = 5.43, p < .01, df = 1,51$) and at 6 months ($F = 5.38, p < .03, df = 1,50$).

Multivariate Analyses

A hierarchical multiple regression analysis was conducted to assess the relative influence of demographic, pretreatment, and treatment variables on a composite global patient outcome factor. Results indicated that only the treatment/sex interaction was significantly related to outcome ($p < .003$), accounting for 16.2 percent of the total variance at discharge. These results confirm the importance of the striking contrast in treatment effects (reported above) for males and females at discharge. At 6 months the treatment/sex interaction effect on global patient outcome was not significant.

Results of the hierarchical multiple regression analyses are important in that they rule out the possible confounding influence of such covariates as severity of illness, chronicity, and age; demographic variables such as marital status, race, and living situation; and finally, such variables as subdiagnosis (unipolar versus bipolar disorder) and history of treatment compliance.

Second, the sex by treatment interaction effect at discharge (found in many of the univariate analyses) is confirmed by these multivariate results. The fact that neither treatment assignment nor the sex by treatment interaction factors proved significant in contributing to global outcome at 6 months is consistent with results of the univariate analyses which show a "weakening" of the treatment effect at 6 months. One explanation for this finding is that 6-month outcome is markedly influenced by a factor not present at discharge—posthospital treatment compliance. Support for this explanation comes from the finding that global patient outcome at 6 months (as measured on the GAS) is correlated with posthospital treatment compliance, $R(47) = .63, p < .0001$. These results suggest that posthospital treatment compliance may be a significant mediating variable linking hospital treatment with posthospital outcome.

Effects of Hospital Treatment and Prehospital Treatment Compliance on Outcome. Results of a series of multivariate analyses provide evidence for a model describing the relationship among prehospital treatment compliance, treatment, posthospital compliance, and outcome as follows:

> [Prehospital Compliance + Hospital Treatment→Posthospital Treatment Compliance → Patient Outcome]

Prehospital treatment compliance predicted global patient outcome ($F=18.40, p<.0001, 1,51$)—as revealed in a two-way analysis of variance, which tested the effects of treatment and prehospital compliance on global patient outcome at discharge. Second, hospital treatment exerted a significant main effect on global patient outcome at discharge, as measured on the GAS ($F = 4.55, p<.04, df=1,51$). Finally, there was a trend suggesting an interaction of treatment and prehospital compliance on global outcome ($F=2.443, p<.13, df=2,50$). This trend suggested that the treatment effect was confined to people who had either no history of previous treatment, or were adequately compliant with treatment prior to their hospitalization.

Patients with a history of adequate to good treatment compliance were likely to show better global patient outcome if assigned to IFI than if assigned to the comparison treatment.

The relative contribution of posthospital compliance to prediction of global outcome at 6 months was tested using a hierarchical multiple regression procedure. Results revealed that length of hospital stay and posthospital compliance accounted for 48.8 percent of the total variance in global outcome at follow-up. Posthospital treatment compliance was found to account for 24.4 percent of the total variance in outcome at 6 months.

Effects of Hospital Treatment on Compliance With Outpatient Treatments. Hospital Treatment Assignment (IFI vs. Comparison Treatment) was associated with posthospital treatment compliance, as revealed in results of an analysis of covariance, controlling for prehospital treatment compliance ($F = 4.15$, $p < .05$, $df = 1,50$). Patients who had relatively good prehospital compliance (or no history of previous treatment) showed equivalent or improved treatment compliance if treated with IFI. For these patients, treatment with IFI was associated with better posthospital compliance than was found for patients treated with Comparison ($F = 3.12$, $p < .09$, $df = 1,46$). For patients who showed poor prehospital compliance, there was no significant influence of treatment on posthospital compliance.

Discussion

Results of this study suggest that the addition of a brief, crisis-oriented family intervention to standard multimodal hospital treatment for major affective disorder contributes to improved global patient outcome and greater willingness on the part of the family to accept professional help during the posthospital phase of continuation treatment. Prehospital treatment compliance is a strong predictor of both posthospital treatment compliance and global patient outcome. The addition of an inpatient family intervention appears to enhance posthospital compliance, though only in those patients who have a history of good compliance or no previous treatment.

Another interesting finding is that the effects of IFI are largely restricted to females. The differential treatment effect for males and females was not anticipated; however, it is not wholly inconsistent with findings from controlled studies of psychosocial interventions for patients with other acute psychotic disorders. For example, in the area of psychosocial treatments for schizophrenia, there are some reports of males tending to do relatively poorly with family, as compared with individual, intervention (Goldstein et al., 1978; Hogarty, 1985). Speculating that what we have discovered for a sample of major affective disorder patients is more generally characteristic of males with major psychiatric disorders, one possible explanation for this differential outcome is that these males are biologically vulnerable to psychosocial stressors and thus less able to effectively respond to psychosocial, and specifically, multiple person interventions such as family, interventions. An alternate explanation is that because males, more often than females, are responsible for financial support of the family, the family may place greater stress on the male patient to resume functioning after hospital.

The family outcome data suggest that involvement of family members in the inpatient treatment program may enhance the family's willingness to turn to professional help during the posthospital treatment phase. In a prior analysis it was found that the family's willingness to rely on help from professionals is correlated with global patient outcome ($p < .05$). The implications of these findings are not clear. However, they suggest the possibility that the family's support of treatment compliance may have some functional relationship to patient outcome—either as a *causal link* initiating or sustaining patient compliance with treatment or as an *indirect outcome of successful treatment*, secondary to the patient's improvement during the posthospital recovery phase.

As would be expected, prehospital treatment compliance is a strong predictor of posthospital treatment compliance. The finding that IFI appears to enhance posthospital compliance in those patients who have a history of relatively good compliance or no previous treatment, is relevant to determining which patients are likely to benefit most from Inpatient Family Intervention. Future studies should address the prehospital noncompliance patients directly in order to determine their clinical characteristics and whether modifications in IFI might result in more impact on this refractory group.

The effect of IFI on posthospital treatment compliance has important implications. As noted earlier, noncompliance with prescribed treatment during the continuation and maintenance phases of treatment for affective disorder is a serious problem. The most severe episodes of affective disorder often result in hospitalization. Treatment of the acute phase with pharmacotherapy is not difficult, but noncompliance after discharge may result in relapse or recurrence. IFI is a psychosocial intervention which can be used while the patient is in the hospital and the family is often available and interested in obtaining help. If this treatment can significantly increase compliance with subsequent treatment during the posthospital continuation and maintenance phases, it can make an important contribution to the treatment of major affective disorders.

References

Cochran, D.S. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. *J. of Consulting and Clinical Psychology*, 52:873–878, 1984.

Davenport, Y.B., Ebert, M.H., Adland, M.L., Goodwin, F.K. Couples group therapy as an adjunct to lithium maintenance in the manic patient. *Am. J. Orthopsychiatry*, 47:495–502, 1977.

DiMascio, A., Weissman, M.M., Prusoff, B.A., et al. Differential symptom reduction by drugs and psychotherapy in acute depression. *Arch. Gen. Psychiatry*, 36:1450–1456, 1979.

Endicott, J., Spitzer, R.L. What! Another rating scale? The Psychiatric Evaluation Form. *J. Nerv. Ment. Dis.*, 154:88–104, 1972.

Endicott, J., Spitzer, R., Fleiss, J., and Cohen, J. The global assessment scale. *Arch. Gen. Psychiatry*, 33:766–771, 1976.

Fitzgerald, R.G. Mania as a message: Treatment with family therapy and lithium carbonate. *Am. J. Psychother.*, 26:547–555, 1972.

Friedman, A.S. Interaction of drug therapy with marital therapy in depressive patients. *Arch. Gen. Psychiatry*, 32:619–637, 1975.

Glick, I.D., Clarkin, J.F., Spencer, J.H., et al. A controlled evaluation of inpatient family intervention. *Arch. Gen. Psychiatry*, 42:882–886, 1985.

Glick, I.D., Hargreaves, W.A., Raskin, M., and Kutner, S.J. Short versus long hospitalization: A prospective controlled study: II. Results for schizophrenic inpatients. *Am. J. Psychiatry*, 132:385–390, 1975.

Goldstein, M.J., Rodnick, E.H., Evans, J.R., et al. Drug and family therapy in the aftercare of acute schizophrenics. *Arch. Gen. Psychiatry*, 35:1169–1177, 1978.

Good-Ellis, M., Fine, S.B., and Spencer, J.H. Development of an instrument to rate role performance. *J. Amer. Occupational Therapy Assoc.* (In Press).

Herz, M.I., Endicott, J., and Spitzer, R.L. Brief hospitalization: A two-year follow-up. *Am. J. Psychiatry*, 134:502–507, 1977.

Hogarty, G. Paper presented at the Annual Meeting of the American College of Neuropsychopharmacology, Maui, Hawaii, December, 1985.

Jacobson, N.S., Follette, W.C., and Revenstorf, D. Psychotherapy outcome research: Methods for reporting variability and evaluating clinical significance. *Behavior Therapy*, 15:336–352, 1984.

Jamison, K.R., and Akiskal, H.S. Medication compliance in patients with bipolar disorder. *Psychiatric Clinics of North America*, 6:175–192, 1983.

Kazdin, A.E., and Wilson, G.T. Criteria for evaluating psychotherapy. *Arch. Gen. Psychiatry*, 35:407–416, 1978.

Klerman, G.L. Psychotherapies and somatic therapies in affective disorders. *Psychiatr. Clin. North Am.*, 6:85–103, 1983.

Klerman, G.L., DiMascio, A., Weissman, M.M., et al. Treatment of depression by drugs and psychotherapy. *Am. J. Psychiatry*, 131:186–191, 1974.

Kreisman, D.E., Simmens, S.J., and Joy, V.D. Rejecting the patient: Preliminary validation of a self-report scale. *Schizophr. Bull.*, 5:220–222, 1979.

Levitt, M. *The impact of family intervention on the attitudes of key relatives of psychiatric inpatients.* Unpublished doctoral dissertation, Columbia University, 1982.

Prien, R.F., Long-term maintenance therapy in affective disorders. In Rifkin, A. (ed): *Schizophrenia and Affective Disorders: Biology and Treatment.* Boston: John Wright, 1983, pp. 95–115.

Shakir, S.A., Volkmar, F.R., Bacon, S., et al. Group psychotherapy as an adjunct to lithium maintenance. *Am. J. Psychiatry*, 136:455–456, 1979.

Shaw, E.D., Weiden, P., Mann, J.J. A new look at why patients stop their lithium treatment. Unpublished manuscript.

Volkmar, F.R., Shakir, S.A., Bacon, S., et al. Group therapy as an adjunct to lithium maintenance. Paper presented at Annual Meeting of the American Psychiatric Association, San Francisco, 1980.

Weissman, M.M., Prusoff, B.A., DiMascio, A., et al. The efficacy of drugs and psychotherapy in treatment of acute depressive episodes. *Am. J. Psychiatry*, 136:555–558, 1979.

The Antipsychotic Drug Haloperidol Decreases Basal Ganglia Substance P, Substance K, and Preprotachykinin mRNAs

Michael J. Bannon, Ph.D.,[1] Jin-Moo Lee, B.S.,[1] Pierre Giraud, M.D.,[2,3] Alice Young, B.S.,[2] Hans-Urs Affolter, Ph.D.,[2] and Tom I. Bonner, Ph.D.[2]

The tachykinin neuropeptide substance P (SP) is present throughout the brain and peripheral tissues. The prominent SP projection from the striatum to the substantia nigra is thought to play an important role in the regulation of basal ganglia function and the response to dopaminergic and other pharmacological agents (Bannon et al., 1986). However, the physiological and pharmacological significance of this striatonigral SP system has been difficult to assess, since no useful measures of SP turnover have been available. Previous studies have shown that the repeated administration of dopamine antagonist (antipsychotic) drugs decreases the concentration of SP in the substantia nigra (Hong et al., 1978; Hanson et al., 1981; LeDourin et al., 1983; Oblin et al., 1984). Although the relationship between SP concentration and SP turnover remains obscure, the antipsychotic drug-induced decrease in SP has generally been thought to result from an imbalance between increased SP biosynthesis and an even greater acceleration of SP release (Hong et al., 1978; Hanson et al., 1981).

It has recently been demonstrated (Nawa et al., 1983, 1984) that two messenger ribonucleic acids (mRNA) derived from one preprotachykinin (PPT) gene by alternate RNA splicing encode for either SP alone or for both SP and the newly discovered tachykinin (Maggio et al., 1983; Kimura et al., 1983) substance K (SK): these are termed α and β PPT mRNA, respectively. Thus the biosynthesis of SP and SK could be differentially regulated in response to dopamine antagonists or other stimuli. We have quantitated the acute and chronic effects of the antipsychotic drug haloperidol on the levels of striatonigral PPT mRNAs (as well as SP and SK peptide levels) in single rat brain striata as a dynamic index of tachykinin turnover. The concentrations of both tachykinin mRNAs and peptides were decreased in parallel after haloperidol, suggesting that antipsychotic drugs may, in fact, decrease striatonigral tachykinin biosynthesis.

Methods

Adult male Sprague-Dawley rats (Charles River; 225 to 250 g) were killed by decapitation either 2 to 4 h after haloperidol or 24 h after 1 to 10 days of haloperidol treatment (1 mg/kg, i.p.; McNeil). Brains were blocked in a chilled aluminum brain mold (Activational Systems), dissected using previously described procedures for the striatum and substantia nigra (Deutch et al., 1985), quickly frozen on dry ice, then stored at −70°C until further use.

Tissues were extracted and SP-like immunoractivity and SK-like immunoreactivity were assayed by radioimmunoassay (RIA) as previously described (McLean et al., 1985; Lee et al., 1986). SK showed approximately 1 percent cross-reactivity compared to SP in the SP RIA; conversely SP cross-reacted to approximately 1 percent in the SK RIA. High performance liquid chromatographic analysis coupled to the tachykinin RIAs established that all detected striatal and nigral SP immunoreactivity was authentic SP, while authentic SK accounted for at least 86 percent of striatal and 94 percent of nigral SK immunoreactivity (Lee et al., 1986). Therefore, SP- and SK-immunoreactivity are hereafter referred to simply as SP and SK, respectively. Protein concentrations were determined by the method of Lowry et al. (1951).

---

[1] Departments of Psychiatry and Pharmacology, Yale University School of Medicine and the Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT 06508

[2] Laboratory of Cell Biology, National Institute of Mental Health, Bethesda, MD 20205.

[3] Current address: Laboratorie d'Endocrinologie, Faculte de Medicine, Secteur Nord, Boulevard P. Dramert, 13326 Marseille Cedex 15, France

One or two striata (~30 mg tissue each) previously stored at −70°C were rapidly Dounce homogenized in 3 ml of SET buffer (1 percent sodium dodecyl sulfate/5 mM EDTA/10 mM Tris pH 8) containing 100 μg/ml proteinase K (Rowe et al., 1978). After a 1.5 h incubation at 42°C, 100 μg of tRNA was added as a carrier, and the samples extracted 2 to 3 times with 2 volumes of 1:1 Tris-saturated phenol/chloroform. Following a further extraction with 2 volumes of 1:1 chloroform/butanol, total nucleic acids in the aqueous phase were precipitated overnight at −20°C with 0.4M sodium acetate/ 2.5 volumes of ethanol.

The construction, isolation and characterization of plasmids containing rat preprotachykinin genomic sequences is described elsewhere (Affolter et al., 1985). Plasmids RSP p23, RSP p18, and RSP p13 were purified from HB101 lysates using a DEAE high performance liquid chromatography column (Alltech). Restriction endonuclease digestion yielded DNA probes containing exon 7 (~460bp), exon 6 (~300bp), and intron 6 (~600bp), respectively. Restriction fragments were isolated by gel electrophoresis, purified on Nensorb columns (New England Nuclear) and labeled by nick-translation (Rigby et al., 1977) using [α-^{32}P] dATP (3000 Ci/mmol, Amersham) to a specific activity of 2×10^7 to 5×10^8 cpm/μg DNA.

Nucleic acids were denatured in 50 percent formamide/6 percent formaldehyde at 65°C for 5 to 10 min and electrophoresed in 1 percent agarose (formaldehyde-containing) gels (Lehrach et al., 1977). Gels were stained with ethidium bromide, destained, and photographed over a UV source. Photographic negatives were densitometrically scanned to quantitate the amount of 28S RNA/sample (Mocchetti et al., 1985). Only those samples where the 28S values differed by more than one standard deviation from the mean of the experiment (4/48 samples in total) were corrected for differences in extraction recovery. Nucleic acids were then transferred by the electroblot procedure (Thomas, 1980) to nylon-based membranes (Gene Screen; New England Nuclear), which were then baked at 80°C for several hours.

Northern blots were prehybridized for 6 to 18 h at 37°C with several milliliters of hybridization solution (50 percent deionized formamide, 0.1 percent polyvinylpyrrolidone, 0.1 percent bovine serum albumin, 0.14 percent ficol, 50 m*M* sodium pyrophosphate, 1 percent sodium dodecylsulfate, 0.75 M sodium chloride, 0.075 M sodium citrate, 250 μg/ml tRNA and 250 μg/ml herring sperm DNA) and 50 percent dextran sulfate in a 4:1 ratio. This solution was replaced with an identical solution containing 1×10^6 cpm/ml of various nick-translated, ^{32}P-labelled PPT genomic subclones. After a further 16 to 24 h incubation at 37°C, membranes were washed several times for 15 to 30 min at 37°C with 0.2 × SSC/0.1 percent sodium dodecylsulfate, then placed in a cassette with an intensifying screen and Kodak XAR-5 film for several hours at −70°C. Autoradiograms were scanned with an EC densitometer to quantitate probe hybridization to rat PPT mRNA. Each blot was autoradiographed for several different exposure lengths in order to obtain autoradiograms within the linear scanning range, which was established using serial dilutions of striatal nucleic acids.

Results and Discussion

As previously reported (Hong et al., 1978; Oblin et al., 1984; Bannon and Goedert, 1984), administration of the antipsychotic drug haloperidol did not alter either striatal or nigral SP concentrations within 2 to 4 h (with the exception of a possible decrease in striatal SP 4 h post-haloperidol; Figure 1). Likewise, SK concentrations were unaltered 2 to 4 h after haloperidol (Figure 1). Twenty-four hours after a single dose of haloperidol, striatal SP and SK concentrations were decreased (Figure 1). After 3 to 10 days of treatment, both striatal and nigral SP and SK levels were decreased (Figure 1). Thus, changes in SK concentrations after acute and chronic haloperidol administration parallel the previously reported changes in its cotransmitter, SP.

Total (α and β) PPT mRNA from single rat striata was quantitated using a genomic clone derived from the final PPT exon (exon 7), common to both mRNA species, as described

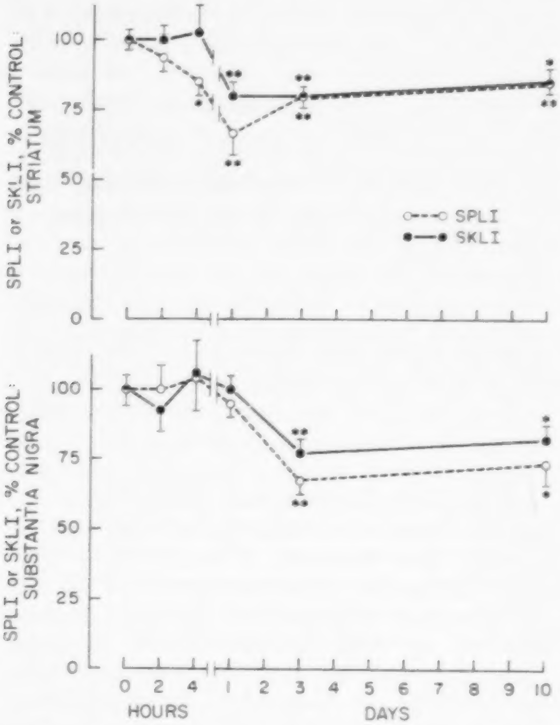


FIGURE 1. Effect of the antipsychotic drug haloperidol on striatal and nigral content of substance P and substance K. Tissue handling and radioimmunoassay procedures are described under Methods. The bars on the circles indicate the standard error of the mean. Values are expressed as a percentage of control striatal or nigral SP or SK values pooled from three separate experiments (striatal SP: 0.819 ± 0.036 fm/mg protein, $n = 23$; striatal SK: 0.861 ± 0.037 fm/mg protein, $n = 23$; nigral SP: 4.673 ± 0.306 fm/mg protein, $n = 21$; nigral SK: 4.030 ± 0.244 fm/mg protein, $n = 21$). Except for the 4 h group ($n = 5$), all experimental groups were comprised of 10 to 11 animals. $^{*}p < 0.05$, $^{**}p < 0.005$ when compared by a 1-tailed Student's *t*-test with vehicle injected rats.

in Methods. Twenty-four hours after a single dose of haloperidol, PPT mRNA levels were significantly decreased (Figure 2). Further decreases in PPT mRNA were seen after 3 to 10 days of haloperidol (Figure 2). Similar results were obtained by dot blot hybridization quantitated by either densitometry or liquid scintillation counting (data not shown). When β PPT mRNA was specifically quantitated using an exon 6 containing (SK encoding) probe, parallel changes of a similar magnitude were seen (data not shown). Thus, both α PPT (SP encoding) mRNA levels and β PPT (SP/SK encoding) mRNA levels decrease in parallel with SP and SK peptides (compare Figures 1 and 2).

Following hybridization, the prominent band visualized corresponds in migrational position (~1 kilobase) to the size of the bovine PPT mRNAs previously reported (Nawa et al., 1983, 1984). Since α PPT and β PPT mRNA differ by only ~50 nucleotides, these two bands are unresolved under the conditions employed. Upon longer exposure of blots, a higher molecular weight band (>6 kilobases) was also visualized. Since this band was also visualized using an intron probe derived from the PPT gene (data not shown), it is conceivable that this band corresponds to an unprocessed or partially processed precursor of mature PPT mRNA. Further experiments will be required to clarify the nature of this higher molecular weight band. The intensity of this higher molecular weight band apparently decreased after haloperidol in parallel with the mature (~1 kilobase) PPT mRNAs (data not shown). Although an effect on mRNA stability cannot be ruled out at present, the parallel changes in the tachykinin peptides, PPT mRNAs and the higher molecular weight band suggest that

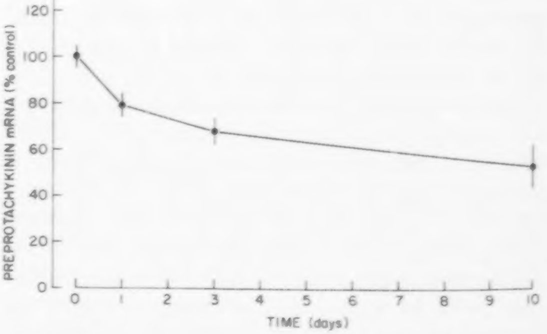


FIGURE 2. The effect of the antipsychotic drug haloperidol on striatal preprotachykinin mRNA levels. Rats were treated with haloperidol and the levels of PPT mRNA in single rat striata determined as described under Methods. Values are signal densities/unit 28S rRNA (arbitrary units), expressed as a percentage of control levels pooled from two separate experiments ($n = 10$ to 12 in each group). The bars on the circles indicate the standard error of the mean. All time points differ significantly ($p < 0.02$, 2-tailed *t*-test) from vehicle treated rats.

decreased PPT mRNA levels after haloperidol are reflective of decreased PPT gene transcription.

The present findings may offer some insight into the effects of acute and chronic antipsychotic drug administration on basal ganglia function. Dopamine is thought to normally provide a tonic inhibitory influence in the striatum (Bunney, 1983). Antipsychotic drugs like haloperidol, by blocking striatal dopamine receptors, may cause a disinhibition of many striatal cells, including γ-aminobutyric acid- and/or enkephalin-containing inhibitory neurons. For example, striatal enkephalin mRNA and peptide levels increase after haloperidol (Tang et al., 1983; Blanc et al., 1984; Hong et al., 1985). Thus, disinhibition of striatal inhibitory cells could account for the subsequent inhibition of SP/SK-containing neurons. SP, SK, and PPT mRNAs decrease after haloperidol with a time course that apparently parallels the period of maximal risk for the development of certain antipsychotic drug-induced extrapyramidal (Parkinsonian) side effects in man (Baldessarini, 1980). Thus, it is conceivable that decreased striatonigral SP/SK output is somehow related to the production of these adverse neurological symptoms. In support of this suggestion, the loss of basal ganglia dopamine cells in Parkinson's disease is also accompanied by a decrease in basal ganglia SP content (Mauborgne et al., 1983). The data presented suggest that, despite brain tissue heterogeneity, neuropeptide-encoding mRNAs from discrete brain regions of individual animals can be quantitated as a dynamic index of peptide biosynthesis.

Acknowledgments

We thank Drs. J.E. Maggio and R.L. Eskay for their gifts of SK and SP antisera, respectively. We gratefully acknowledge the expert technical assistance of Mr. Rolf Hanson and the excellent secretarial assistance of Mrs. Angelika Mayes and Mr. Rich Clement.

References

Affolter, H.-U., Young, A.C., and Bonner, T.I. Structural organization of the human and rat tachykinin genes. *Soc. Neurosci. Abstr.*, 11:1115, 1985.

Baldessarini, R.J. Drugs and the treatment of psychiatric disorders. In: Gilman, S.G., Goodman, L.S., Rall, T.W., and Murad, F. (eds.), *The Pharmacological Basis of Therapeutics*. New York: Macmillan Publishing Co., 1985, pp. 387-445.

Bannon, M.J., Freeman, A.S., Chiodo, L.A., et al. The biochemical and electrophysiological pharmacology of mesocortical and mesolimbic dopamine neurons. In: Iversen, L.L., Iversen, S.D., and Snyder, S.H. (eds.), *Handbook of Psychopharmacology: Behavioral Pharmacology*, Vol. 19. New York, NY: Plenum Press, in press, 1986.

Bannon, M.J., and Goedert, M. Changes in substance P concentrations after synthesis inhibition provide an index of substance P utilization. *Brain Res.*, 301:184–186, 1984.

Blanc, D., Cupo, A., Castanas, E., et al. Influence of acute subchronic and chronic treatment with neuroleptic (haloperidol) on enkephalins and their precursors in the striatum of rat brain. *Neuropeptides*, 5:567–570, 1985.

Bunney, B.S. The electrophysiological pharmacology of midbrain dopaminergic systems. In: Horn, A.S., Korf, J., and Westerink, B.H.C. (eds.), *The Neurobiology of Dopamine*. New York: Academic Press, 1983, pp. 417–450.

Deutch, A.Y., Tam, S.-Y., and Roth, R.H. Footshock and conditioned stress increase 3,4-dihydroxyphenylacetic acid (DOPAC) in the ventral tegmental area but not substantia nigra. *Brain Res.*, 333:143–146, 1985.

Hanson, G.R., Alphs, L., Wolf, W., et al. Haloperidol-induced reduction of nigral substance P-like immunoreactivity: A probe for the interactions between dopamine and substance P neuronal systems. *J. Pharmacol. Ther.*, 218:568–574, 1981.

Hong, J.S., Yang, H.-Y.T., and Costa, E. Substance P content of substantia nigra after chronic treatment with antischizophrenic drugs. *Neuropharmacol.*, 17:83–85, 1978.

Hong, J.S., Yoshikawa, K., Kanamatsu, T., and Sabol, S.L. Modulation of striatal enkephalinergic neurons by antipsychotic drugs. *Fed. Proc.*, 44:2535–2539, 1985.

Kimura, S., Okada, M., Sugita, Y., et al. Novel neuropeptides, neurokinin α and β, isolated from porcine· spinal cord. *Proc. Jpn. Acad.*, 59 (Ser. B.):101–104, 1983.

LeDouarin, C., Oblin, A., Fage, D., and Scatton, B. Influence of lithium on biochemical manifestations of striatal dopamine target cell supersensitivity induced by prolonged haloperidol treatment. *Eur. J. Pharmacol.*, 93:55–62, 1983.

Lee, J.-M., McLean, S., Maggio, J.E., et al. The localization and characterization of substance P and substance K in striatonigral neurons. *Brain Res.*, 371:152–154, 1986.

Lehrach, H., Diamond, D., Wozney, J.M., and Boedtker, H. RNA molecular weight determinations by gel electrophoresis under denaturing conditions, a critical reexamination. *Biochem.*, 16:4743–4751, 1977.

Lowry, O.H., Rosenbrough, N.J., Farr, A.L., and Randall, R.J. Protein measurement with folin phenol reagent. *J. Biol. Chem.*, 193:265–275, 1951.

Maggio, J.E., Sandberg, B.E.B., Bradley, C.V., et al. Substance K: A novel tachykinin in mammalian spinal cord. *Irish J. Med. Sci.*, 152(Suppl. 1):20–21, 1983.

Mauborgne, A., Javoy-Agid, F., Legrand, J.C., et al. Decrease of substance P-like immunoreactivity in the substantia nigra and pallidum of parkinsonian brains. *Brain Res.*, 268:167–170, 1983.

McLean, S., Bannon, M.J., Zamir, N., and Pert, C.B. Comparisons of the projections of substance P and dynorphin to the rat substantia nigra: A radioimmunocychemical and biochemical study. *Brain Res.*, 361:185–192, 1985.

Mocchetti, I., Schwartz, J.P., and Costa, E. Use of mRNA hybridization and radioimmunoassay to study mechanisms of drug-induced accumulation of enkephalins in rat brain structures. *Mol. Pharmacol.*, 28:86–91, 1985.

Nawa, H., Hirose, T., Takeshima, H., et al. Nucleotide sequences of cloned cDNAs for two types of bovine brain substance P precursor. *Nature*, 306:32–36, 1983.

Oblin, A., Zivkovic, B., and Bartholini, G. Involvement of the D_2-dopamine receptor in the neuroleptic-induced decrease in nigral substance P. *Eur. J. Pharmacol.*, 105:175–177, 1984.

Rigby, P.W.J., Dieckmann, M., Rhodes, C., and Berg, P. Labeling deoxyribonucleic acid to high specific activity in vitro by nick-translation with DNA polymerase K. *J. Mol. Biol.*, 113:237–251, 1977.

Rowe, D.W., Moen, R.C., Davidson, J.M., et al. Correlation of procollagen mRNA levels in normal and transformed chick embryo fibroblasts with different rates of procollagen synthesis. *Biochem.*, 17:1581–1590, 1978.

Tang, F., Costa, E. and Schwartz, J.P. Increase of proenkephalin mRNA and enkephalin condition of rat striatum after daily injection of haloperidol for 2 to 3 weeks. *Proc. Natl. Acad. Sci. USA*, 80:3841–3844, 1983.

Thomas, P.S. Hybridization of denatured RNA and small DNA fragments transferred to nitrocellulose. *Proc. Natl. Acad. Sci. USA*, 77:5201–5205, 1980.

Alpha-2 Adrenergic Agonist Binding in Schizophrenic Brains

Grant N. Ko, M.D.,[1] James R. Unnerstall, Ph.D.,[2] Michael J. Kuhar, Ph.D.,[2] Richard J. Wyatt, M.D.,[3] and Joel E. Kleinman, M.D., Ph.D.[3]

Quantitative *in vitro* autoradiography is applied to postmortem brain tissue from schizophrenic and control brains in the pursuit of a neurochemical hypothesis. This technique allows for the quantification of possible group differences between patients and controls. Preliminary delineation of group differences between schizophrenic and controls is presented.

Introduction

That the schizophrenia syndrome is a group of disorders is not a new concept (Bleuler, 1911). Recent biological advances, however, have introduced the possibility that patients with the syndrome can be subtyped according to such structural and neurochemical variables as brain atrophy and dopamine (DA) hyperactivity (Crow, 1980; Wyatt et al., 1981). The paranoid subtype of schizophrenia is recognized phenomenologically (American Psychiatric Association, 1980) and may have genetic determinants distinct from other subtypes of schizophrenia (Kendler, 1981). One neurochemical hypothesis suggests that increased noradrenergic activity may identify and even account for some of the psychopathology in paranoid schizophrenia (Hornykiewiez, 1982). Increased norepinephrine (NE) seen postmortem in a number of primarily limbic structures, as well as increased cerebrospinal fluid (CSF) NE in primarily paranoid schizophrenic subjects, support this hypothesis (Farley et al., 1978; Lake et al., 1980; Gomes et al., 1980; Kleinman et al., 1979).

One possible explanation for increased NE in paranoid schizophrenia is a defect in the constant inhibitory control exerted on NE-synthesizing neurons. There could exist fewer inhibitory α_2 receptors on NE-producing cells. The inhibitory receptors on these cells respond to NE or the antihypertensive drug, clonidine, decreasing the number of discharges per unit time and the amount of NE released into the synapse with each impulse (Svenssen, 1975; Cederbaum & Aghajanian, 1976, 1977). Thus, NE in the synapse constantly regulates its own production. The antihypertensive action of clonidine is thought to occur, in part, through this mechanism.

In support of the possibility that faulty α_2-inhibitory control of NE-synthesizing neurons occurs, Sternberg and colleagues (1982) found that the plasma MHPG response of schizophrenic patients to a clonidine challenge was less robust than that of normal individuals. More recently, Rice and colleagues (1984), using platelets as a model for central nervous system (CNS) tissue, found decreased α_2-receptor ligand binding in schizophrenics compared with controls. [^{3}H]para-aminoclonidine (PAC) has been shown to label α_2 receptors in human and animal CNS (Unnerstall, 1984). In order to examine CNS α_2 receptors directly, we applied the technique of *in vitro* receptor autoradiography to postmortem samples from patients with paranoid schizophrenia and age-matched controls using PAC as the α_2 ligand. Since almost half of NE-synthesizing neurons are concentrated in the locus coeruleus (Swanson, 1975), thin coronal sections through the pons will include some of these cells. The technique of *in vitro* quantitative receptor autoradiography (Kuhar, 1978a and 1978b; Unnerstall, 1982) can be applied to these tissue sections. This technique circumvents the technical problem posed by small tissue quantities, such as the collection of NE cell bodies in the locus coeruleus. The results of this preliminary study will be presented.

---

[1] Please address all correspondence to: Grant Norman Ko, M.D., Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, and the Veterans Administration Medical Center, 1660 South Columbian Way (116A), Seattle, WA 98107.

[2] Neuroscience, Johns Hopkins University, Baltimore, MD 21205.

[3] Neuropsychiatry, NIMH, Rockville, MD 20852.

Methods

Unfixed pontine material was obtained from the Medical Examiner's Office, cut and mounted on brass microtome chucks with brain paste, and, in the cryostat, coronal sections of 16 μ thickness were thaw mounted on subbed microscope slides and allowed to air dry at room temperature before being stored. [^{3}H]para-aminoclonidine (PAC, 40 Ci/mmol) was used to label α_2-adrenergic binding sites in the mounted tissue sections (Unnerstall et al., 1984). Briefly, sections were preincubated for 30 minutes at room temperature in Krebs-phosphate buffer (pH 7.4 at 25°C) containing 100 uM Na^+-GTP. Adjacent sections were then washed for 10 minutes at room temperature in the incubation buffer alone (0.17 M Tris HCl, pH 7.6 at 25°C plus 10 mM $MgCl_2$). Sections were then incubated for 60 minutes at room temperature in buffer containing 0.25 nM [^{3}H]PAC and 25 nM [^{3}H]PAC, in order to assess both the high and low affinity α^2 sites. Nonspecific binding was assessed utilizing the above ligand in the presence of 10^{-5} M phentolamine. After a 10 minute wash at 4°C in incubation buffer and a rinse in cold deionized water, the sections were dried under a stream of cool dry air. Standard curves were constructed from 16 μ sections of brain paste containing varying concentrations of [^{3}H]ornithine so as to allow for conversion of optical density measurements to receptor concentrations. Labeled tissue was then apposed to tritium sensitive film which after exposure and development was scanned by an automated densitometric system allowing each to be digitized and stored (Goochee et al., 1980).

Eighteen brains were examined. The identities of the sample donors were concealed from the tissue handlers, so as to preserve unbiased sampling, until after the final densitometric readings from [^{3}H] Ultrofilm (LKB Industries, Rockville, MD) were obtained. Schizophrenic specimens were compared with both non-psychiatric normals and suicide victims as control groups. One sample from each of the three groups was prepared for incubation in PAC simultaneously so as to minimize interassay variability. Exposure time for the films was about 2.5 months.

Conversion of optical density readings to femtomoles of ligand bound per unit of tissue protein (fmoles/mg protein) was made by constructing the standard curve from the ornithine-brain paste standards. Receptor concentrations for the group of schizophrenic samples were compared with control groups by analysis of variance (Winer, 1971). The formula for conversion is

$$\text{mmoles/mg protein} = \text{OD} \times \frac{\text{DPM/mg protein}}{\text{OD}} \times \frac{\text{mmole}}{\text{Ci}} \times \frac{\text{ICi}}{2.22 \times 10^{12}\text{DPM}} \qquad \text{(Unnerstall, 1982).}$$

Results

A review of the records available at the Medical Examiner's Office yielded the antemortem demographic features shown in Table 1. Blanks in the table indicate that data were not available. When possible, we attempted to match the postmortem interval and age of sample donors in each group.

Figures 1 and 2 are photographs of tritium sensitive film which has been exposed to pontine tissue from a normal control brain labeled with [^{3}H]PAC, which labels the α_2 receptors in each tissue section. The first film illustrates PAC binding to the locus coeruleus and surrounding tissue. The greatest exposure occurs over the locus coeruleus where α_2 receptors exist on NE-synthesizing neurons. The second film was placed next to an adjacent tissue section illustrating the result of displacement of PAC binding by an excess of phentolamine. Notice that optical density generated by this adjacent tissue section is obliterated.

We could not differentiate between high- and low-affinity binding sites given our single-exposure time of 10 weeks. The optical density of film was similar for both concentrations of PAC used. For the high-affinity binding site (low-PAC concentration), the mean concentration of ligand bound was lower for schizophrenic locus coeruleus than either the age-matched normal controls or the

TABLE 1. Demographic Data, Arranged by Diagnostic Group, From the 18 Patients Studied, Using *in vitro* Receptor Autoradiography.

Patient Group	Age (years)	Post-Mortem Delay (hours)	Sex	Race	Drug History	Drugs on Board	Cause of Death
CPS*	23	18.25	M	B	Haldol	Chlordiazepoxide	Suicide strangling
CPS	36	7.25	M	B	Haldol	Constrictive Coronary Arteriosclerosis	Cardiac arrest
CPS	51	11.25	F	W	Thorazine, Haldol, Cogentin	CPZ, 1.5 mg%	Hypertensive, Cardiov. disease
CPS	44	15.75	F	B	Haldol, Syntroid	Phenothiazine, 16 mg%	Hypertensive, Cardiov. disease
CPS	49	22.50	F	W			
Suicide	30	18.00	M	B	PCP	Negative	Gun shot wound to the head
Suicide	57	26.50	M	W	Meds for seizures, no seizure since 1979	Alcohol: 2.6%, Phenobarb: 0.4 mg%	Gun shot wound to the head
Suicide	59	24.50	F	W	Amytriptyline, Imipramine	Amitriptyline, Imipramine	Jumped
Suicide	65	22.25	M	W	Nifedipine, Digoxin, Seconal, Hydrazaline	Secobarbital, Acetaminophen, Quinidine, Alcohol	Overdose Seconal
Suicide	70	12.00	M	W		Not done	Gun shot wound to the abdomen
Suicide	58	24.00	M	W	Alcohol	Negative, Alcohol negative	Jumped
Suicide	31	18.25	M	B		Morphine, Blood: 0.10 mg%	Hanging
Normal	59	17.00	F	B		Negative	Cardiac arrest
Normal	57	28.50	F	O	Hospitalized 2 weeks post MVA	Not done	Motor vehicle accident (MVA)
Normal	39	41.50	F	B		Negative	Cardiac arrest
Normal	26	6.50	F	B		Negative	Carcinoma
Normal	39	25.00	M	B		.09% Alcohol	Homicide, stabbed
Normal	51	8.50	M	O		Negative	MVA

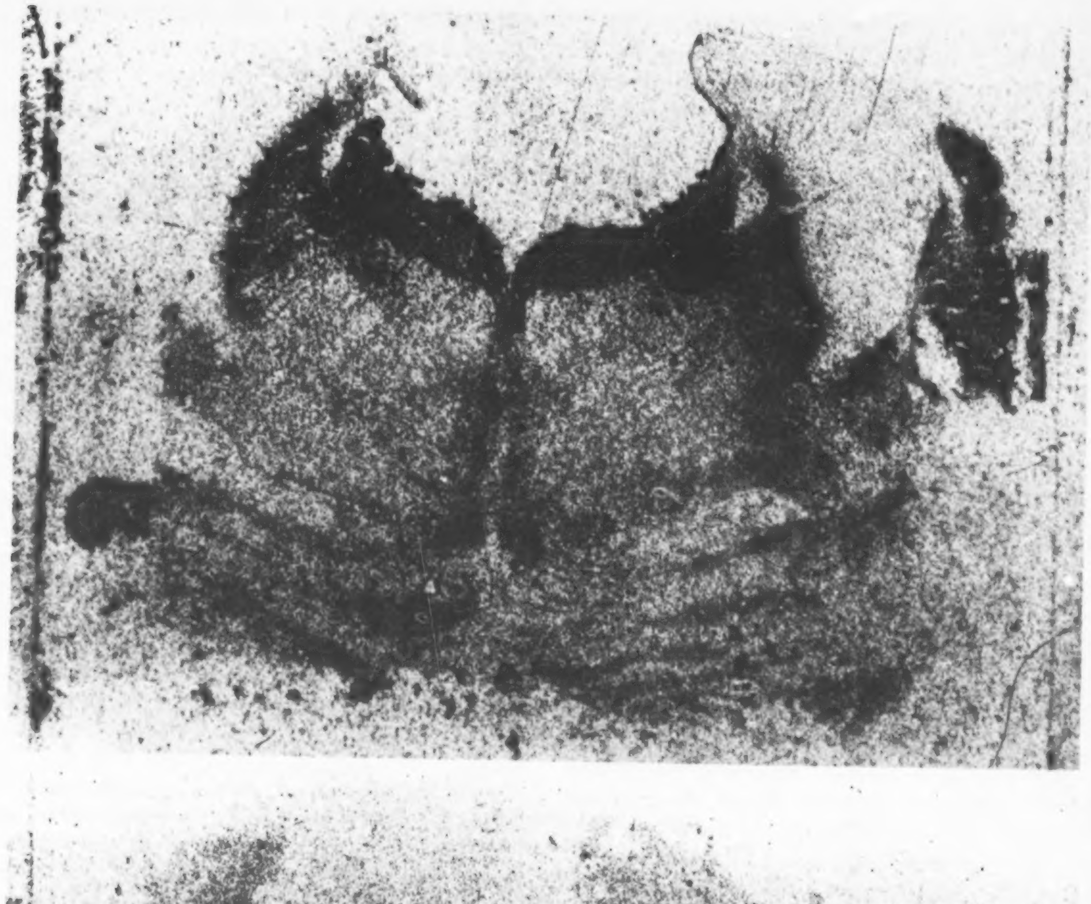
*Chronic paranoid schizophrenia.

suicide victims, although this was not statistically significant ($P = 0.08$, ANOVA; Figure 3).

Discussion

This study demonstrates the application of *in vitro* receptor autoradiography to the investigation of the neurobiologic substrate for schizophrenia. It demonstrates that the application of *in vitro* quantitative receptor autoradiography (Unnerstall et al., 1982) to schizophrenia, as well as other neuropsychiatric disorders, is feasible and has the potential to substantiate current neurochemical and receptor change hypotheses generated from clinical observations and studies of CSF, blood, and urinary metabolites. The preliminary data suggest lower numbers of α_2 receptors at the locus coeruleus of schizophrenic patients, although the results were not statistically significant and the number of samples studied was small. We are continuing to pursue this question as more postmortem samples become available.

A quantitative decrease in the number of α_2 receptors on NE neurons in the schizophrenic condition represents only one explanation for the possibility of dysfunction of NE regulation in schizophrenia. These data by themselves cannot differentiate whether the changes seen in α_2 binding in the locus coeruleus are the cause of the increased NE turnover seen in schizophrenics or the result



of desensitization of α_2 receptors due to excess NE in the synaptic space. Further, while these data suggest that the number of α_2 receptors has changed in the locus coeruleus of schizophrenic patients, the possibility still exists that changes in receptor-effector coupling mechanisms may underlie the differences in NE function reported between schizophrenic patients and normal controls. Given the limited number of samples in this preliminary study, it was not possible to differentiate the high- and low-affinity components of the [^{3}H] PAC binding. In order to determine whether alterations in the molecular events involved in the coupling of receptors to second messengers may underlie the pathology, more extensive analyses of the binding characteristics and biochemical nature of the system are required.

Further extension of knowledge from animal studies to the human brain is possible utilizing this technique. For instance, Arnsten and Goldman-Rakic (1985) have reported that stimulation of α_2 receptors in prefrontal cortex of nonhuman primates is associated with improvement in performance of memory tasks. An application of receptor autoradiography to the study of postmortem Alzheimer's disease frontal cortex might lend valuable human relevance to emerging nonhuman primate data.

The following deficiencies in the present study can be alleviated in the future. We would like to construct a map of α_2-adrenergic receptors in the rostral to caudal dimension. We would also be happier with not one but rather a full spectrum of PAC concentrations to allow comparison of mean B_{max} and K_D for subject groups. Also, shortening the film exposure time should help to distinguish a high- and low-affinity binding site, if they exist distinct from one another.

FIGURES 1 and 2. (Opposite) These black and white prints were made directly from Ultrofilm which has been apposed to tritium-labeled NE cells in adjacent tissue sections from the same brain. Note darkened area (encircled) in Figure 1 (top). The degree of exposure is the data which yield an indirect measure of receptor numbers. Under constant experimental conditions, the degree of exposure will vary from individual to individual. Figure 2 (bottom) is an exposure from an adjacent tissue section which has been prepared with an excess of a competitive displacer, illustrating that binding in Figure 1 is specific. The tissue studied is pons from a normal control brain at autopsy.

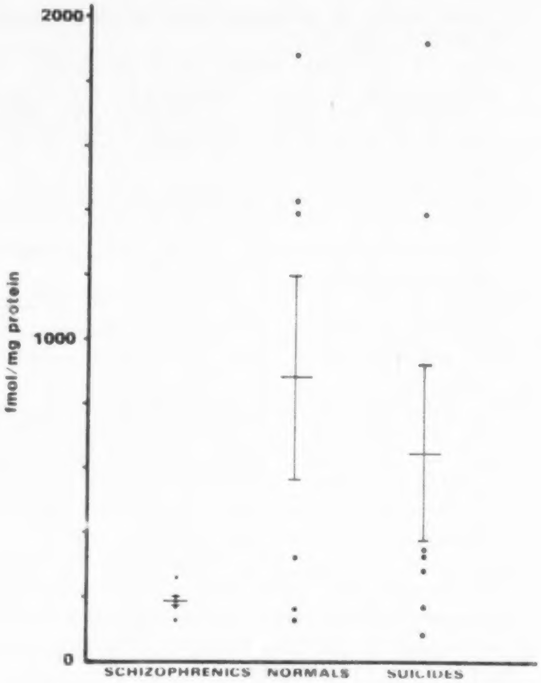


FIGURE 3. Illustration of the data from 18 postmortem brain specimens, with means and standard error bars. The mean and standard error for PAC binding to LC, expressed as femtomoles/mg protein, in normal controls was 887 ± 315 ($n = 6$), in suicide victims was 647 ± 270 ($n = 7$), and in schizophrenic patients was 190 ± 19 ($n = 5$). Schizophrenic brains had a lower mean α_2-receptor number than both control groups, but this did not reach statistical significance ($P = 0.08$, ANOVA).

Acknowledgments

The authors would like to thank Sheila Day for preparing this manuscript and Lynn Guthrie for editorial assistance. This research was supported in part by USPHS Grants MH-25951 and NS-15080.

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, third edition. Washington, DC: American Psychiatric Association, 1980.

Arnsten, A.F., and Goldman-Rakic, P.S. α_2 Adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science*, 230:1273, 1985.

Bleuler, E. *Dementia Praecox oder die Gruppe der Schizophrenien*. Leipzig: Deuticke, 1911. Translated by J. Zinkin. *Dementia Praecox or the Group of Schizophrenias*. New York: International University Press, 1950.

Cedarbaum, J.M., and Aghajanian, G.K. Noradrenergic neurons of the locus coeruleus: Inhibition by epinephrine and activation by the alpha-antagonist piperoxane. *Brain Res.*, 112:413, 1976.

Cedarbaum, J.M., and Aghajanian, G.K. Catecholamine receptors on locus coeruleus neurons: Pharmacological characterization. *Eur. J. Pharmacol.*, 44:375, 1977.

Crow, T.J. Molecular pathology in schizophrenia: more than one disease process? *Br. Med. J.*, 280:66, 1980.

Farley, I.J., Price, K.S., McCullough, E., et al. Norepinephrine in chronic paranoid schizophrenia: Above-normal levels in limbic forebrain. *Science*, 200:456, 1978.

Gomes, U.C., Shanley, B.C., Potgieter, L., and Roux, J.T. Noradrenergic overactivity in chronic schizophrenia: Evidence based on cerebrospinal fluid noradrenaline and cyclic nucleotide concentrations. *Brit. J. Psychiatry*, 137:346, 1980.

Goochee, C., Rasband, W., and Sokoloff, L. Computerized densitometry and color coding of [^{14}C] deoxyglucose autoradiographs. *Ann. Neurol.*, 7:359, 1980.

Hornykiewicz, O. Brain catecholamines in schizophrenia: A good case for noradrenaline. *Nature*, 299:484, 1982.

Kendler, K.S., and Davis, K.L. The genetics and biochemistry of paranoid schizophrenia and other paranoid psychoses. *Schizophr. Bull.*, 7:689, 1981.

Kleinman, J.E., Bridge, P., Karoum, F., et al. Catecholamines and metabolites in the brains of psychotics and normals: Postmortem studies. In: Usdin, E., Kopin, I.J., and Barchas, J.D. (eds.), *Biological Markers in Psychiatry and Neurology*. New York: Pergamon Press, 1979, pp. 1845–1847.

Kuhar, M.J. Autoradiographic localization of receptor sites in the CNS in vivo. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978a, pp. 371–376.

Kuhar, M.J. Histochemical localization of neurotransmitter receptors. In: Yamamura, H.I., Enna, S.J., and Kuhar, M.J. (eds.), *Neurotransmitter Receptor Binding*. New York: Raven Press, 1978b, pp. 113–126.

Lake, C.R., Sternberg, D.E., van Kammen, D.P., et al. Schizophrenia: Elevated cerebrospinal fluid norepinephrine. *Science*, 207:331, 1980.

Rice, H.E., Smith, C.B., Silk, K.R., and Rosen, J. Platelet alpha$_2$-adrenergic receptors in schizophrenic patients before and after phenothiazine treatment. *Psychiatry Res.*, 12:69, 1984.

Sternberg, D.E., Charney, D.S., Heninger, G.R., et al. Impaired presynaptic regulation of norepinephrine in schizophrenia. Effects of clonidine in schizophrenic patients and normal controls. *Arch. Gen. Psychiatry*, 39:285, 1982.

Svensson, T.H., Bunney, B.S., and Aghajanian, G.K. Inhibition of both noradrenergic and serotonergic neurons in brain by the α-adrenergic agonist clonidine. *Brain Res.*, 92:291, 1975.

Swanson, L.W., and Hartman, B.K. The central adrenergic system, an immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-β-hydroxylase as a marker. *J. Comp. Neurol.*, 163:467, 1975.

Unnerstall, J.R., Niehoff, D.L., Kuhar, M.J., and Palacios, J.M. Quantitative receptor autoradiography using [^{3}H]Ultrofilm: application to multiple benzodiazepine receptors. *J. Neurosci. Methods*, 6:59, 1982.

Unnerstall, J.R., Kopajtic, T.A., and Kuhar, M.J. Distribution of a$_2$ agonist binding sites in the rat and human central nervous system: Analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. *Brain Res. Rev.*, 319:69, 1984.

Winer, B.J. *Statistical Principles in Experimental Design*, second edition. New York: McGraw-Hill, 1971.

Wyatt, R.J., Potkin, S.G., Kleinman, J.E., et al. The schizophrenia syndrome: Examples of biological tools in subclassification. *J. Nerv. Ment. Dis.*, 169:100, 1981.

Dose-Dependent Increases in Rat Spontaneous Chewing Rates During Long-Term Administration of Haloperidol but Not Clozapine

Per Johansson, Ph.D.,[1] Daniel E. Casey, M.D.,[2] and Lars M. Gunne, M.D.[1]

Rats can be observed displaying fairly regular chewing movements even in the absence of food. Though the frequency of such vacuous or spontaneous chewing movements (SCM) is to some extent modifiable by environmental changes (e.g., stress seems to increase it), SCM counts are markedly elevated by chronic neuroleptic drug administration. For that reason SCM measurements have been suggested as a rodent model of tardive dyskinesia (Gunne et al., 1982; Gunne & Häggström, 1983; Waddington et al., 1983; Sant & Ellison, 1984), a condition often characterized by involuntary oral movements. When various antipsychotic drugs were compared using this model, clozapine and sulpiride were found to produce low SCM rates while thioridazine, chlorpromazine, fluphenazine, and haloperidol all yielded high chewing rates (Gunne et al., 1986). In those experiments doses of each drug were chosen to correspond to the therapeutic doses used in the control of schizophrenia. However, a fair comparison between antipsychotics must involve a range of doses to elucidate whether the absence of SCM rise seen with some drugs is actually drug-related, or if it can merely be ascribed to an unfortunate choice of dose. Whenever a drug produces elevation of SCM rates the possibility of a dose dependency should also be explored.

The present study reports on a comparison between clozapine and haloperidol employing three different doses of each drug during chronic administration for 13 months. It is concluded that haloperidol produced dose-related increases in SCM rates, while clozapine in a range of doses was without effect.

Methods

Fifty-six Sprague-Dawley rats (28 male, 28 female) weighing approximately 200 to 250 g at the beginning of the experiment were randomly assigned to seven groups of 8 rats (4 male, 4 female) and housed under standard conditions of lighting, food, and temperature.

Three groups were given clozapine with the drinking water (0.2, 0.4, 0.5 mg/ml) and another three groups got haloperidol (1.0, 2.0, 4.0 μg/ml). In a pilot experiment 0.6 mg/ml of clozapine had been shown to be toxic. One group served as untreated controls. Drugs were given continuously for 13 months. Table 1 shows that the addition of drugs changed the intake of water to varying degrees. The table also shows the mean daily doses obtained in the various groups.

Observations of individual rats were made in a plexiglas cage (2×3×4 dm) with a mirror to improve visibility. SCM rates were assessed during 2 min sessions as described earlier (Gunne et al., 1982). These assessments were carried out at time point 0 and then monthly in all animals until the end of month 13.

Behavioral data were analyzed by a mixed design ANOVA. The between subject factor

TABLE 1. Relative Water Consumption and Mean Dose Levels Obtained During 13 Months in Rats Given Various Concentrations of Clozapine or Haloperidol With Their Drinking Water.

Drug	Drug Conc. (mg/ml)	Water Intake (% of untreated)	Dose (mg/kg/d)
None	—	100	—
Clozapine	0.2	76	11
Clozapine	0.4	65	19
Clozapine	0.5	60	50
Haloperidol	0.001	122	0.07
Haloperidol	0.002	98	0.14
Haloperidol	0.004	85	0.24

---

[1] Psychiatric Research Center, S-750 17 Uppsala, Sweden.

[2] VA Medical Center, Oregon Health Sciences University, Portland, OR 97207.

was drug and drug dose. The within subject factor was time of drug treatment. Planned comparisons of the untreated controls vs. the drug-treated groups were made for each drug and dose. The dose-effect function was examined by making the orthogonal comparison of the highest vs. the lower doses and the lower doses vs. each other for both drugs.

Results

In the untreated control group (Figures 1 and 2, broken lines) there was a gradual increase in SCM rate during the 13 months of experiment [$F(1,42) = 11.68$, $p < 0.002$]. This seems to indicate a rise in chewing rate with increasing age. ANOVA yielded no significant differences between controls and any clozapine group (Figure 1).

After 2 months of treatment all three haloperidol groups showed a significant increase in SCMs (Figure 2). Following the initial rise the SCM frequencies stayed up throughout the treatment period. ANOVA for the lowest dose level yielded [$F(1,42) = 9.77$, $p < 0.004$], the medium dose gave [$F(1,42) = 24.60$, $p < 0.0001$], and the highest dose [$F(1,42) = 55.03$, $p < 0.0001$] compared to controls. Furthermore, this long-term effect was dose-dependent, the highest dose (0.24 mg/kg/d) differed significantly from the medium (0.14 mg/kg/d) [$F(1,42) = 6.04$, $p < 0.02$] and lowest dose (0.07 mg/kg/d) [$F(1,42) = 18.42$, $p < 0.0003$]. The medium dose did not differ significantly from the lowest dose.

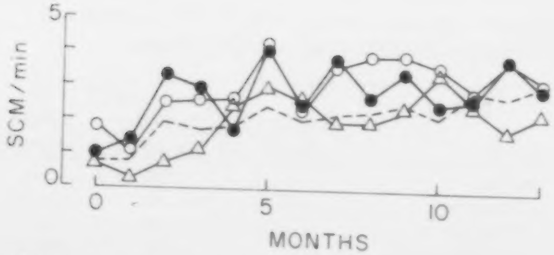


FIGURE 1. Long-term effects of clozapine 11 mg/kg/d (○), 19 mg/kg/d(●) and 50 mg/kg/d (Δ) on SCM rates. Broken line: untreated control rats.

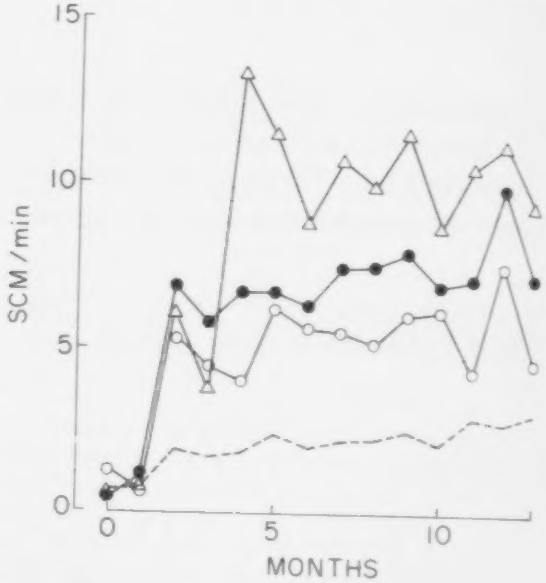


FIGURE 2. Long-term effects of haloperidol 0.07 mg/kg/d (○), 0.14 mg/kg/d (●), and 0.24 mg/kg/d (Δ) on SCM rates. Broken line: untreated control rats.

Discussion

The present study has shown that during long-term administration of haloperidol and clozapine in rats there are important differences in SCM response between the two drugs. Haloperidol in a dose range between 0.07 to 0.24 mg/kg/d produced various degrees of increased SCM rates, which were more pronounced at the higher dose levels, while clozapine-treated animals in a dose range between 11 to 50 mg/kg/d did not differ from untreated controls.

In an attempt to compare various antipsychotics with regard to their SCM-producing properties clozapine, sulpiride, thioridazine, chlorpromazine, fluphenazine, and haloperidol have been administered to rats for 10 months (Gunne et al., 1986). In those experiments clozapine gave no effects on SCMs, sulpiride was marginally higher than the controls, while the other drugs caused clearcut elevations in SCM rates. The doses employed were in ratio to the doses used in the clinic for the control of schizophrenia. However, due to species differences regarding drug metabolism and excretion the doses must be regarded as arbitrary. To eliminate the possibility that low or absent SCM responses may be due to inadequate dosing, a range of chronically administered doses should be employed for each drug.

The present findings show that the differences noticed between clozapine and haloperidol are most likely due to fundamental differences between the two drugs, and can hardly be ascribed to an inappropriate choice of doses. Major differences in action between clozapine and classical neuroleptics have been demonstrated both on dopamine systems in limbic and striatal brain areas (Andén & Stock 1973; Zivkovic et al., 1975) and on nigral GABA turn-over (Costa et al., 1978; Mao & Costa, 1978). Since haloperidol is known to produce TD both in the clinic (Jacobson et al., 1974; Jus et al., 1976) and in a nonhuman primate model (Gunne & Barany, 1976) whereas clozapine seems devoid of this long-term side effect (Ackenheil & Hippius, 1977; Simpson & Lee, 1978) the present findings appear to validate this rodent model of TD and support its usefulness for monitoring the inherent risk of TD in individual drugs.

Acknowledgments

This study was supported by a Swedish MRC grant 4546 and by grants from The Grass Foundation and The Swedish Institute.

References

Andén, N-E., and Stock, G. Effect of clozapine on the turnover of dopamine in the corpus striatum and in the limbic system. *J. Pharm. Pharmacol.*, 25:346–348, 1973.

Costa, E., Cheney, D.L., Mao, C.C., and Moroni, F. Action of antischizophrenic drugs on the metabolism of gamma-aminobutyric acid and acetylcholine in globus pallidus, striatum and n. accumbens. *Fed. Proc.* 37:2408–2414, 1978.

Gunne, L.M., Andersson, U., Bondesson, U., and Johansson, P. Spontaneous chewing movements in rats during acute and chronic antipsychotic drug administration. (In press.)

Gunne, L.M., and Barany, S. Haloperidol-induced tardive dyskinesia in monkeys. *Psychopharmacology*, 50:237–240, 1976.

Gunne, L.M., Growdon, J., and Glaeser, B. Oral dyskinesia in rats following brain lesions and neuroleptic drug administration. *Psychopharmacology*, 77:134–139, 1982.

Gunne, L.M., and Häggström, J.E. Reduction of nigral glutamic acid decarboxylase in rats with neuroleptic-induced oral dyskinesia. *Psychopharmacology*, 81:191–194, 1983.

Jacobson, G., Baldessarini, R.J., and Manschreck, T. Tardive and withdrawal dyskinesia associated with haloperidol. *Am. J. Psychiat.*, 131:910–913, 1974.

Jus, A., Pineau, R., Lachance, R., et al. Epidemiology of tardive dyskinesia. Part II. *Dis. Nerv. Syst.*, 37:257–261, 1976.

Mao, C.C., and Costa, E. Biochemical pharmacology of GABA transmission. In: Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978, pp. 307–318.

Sant, W.W., and Ellison, G. Drug holidays alter onset of movements in rats following chronic haloperidol. *Biol. Psychiat.* 19:95–99, 1984.

Simpson, G.M., and Lee, J.H. A ten year review of antipsychotics. In: Lipton, M.A., DiMascio, A., and Killam, K.F., (eds.), *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978, pp. 1131–1137.

Waddington, J.L., Cross, A.J., Gamble, S.J., and Bourne, R.D. Spontaneous orofacial dyskinesia and dopaminergic function in rats after 6 months of neuroleptic treatment. *Science*, 220:530–532, 1984.

Zivkovic, B., Guidotti, A., Revuelta, A., and Costa, E. Effect of thioridazine, clozapine and other antipsychotics on the kinetic state of tyrosine hydroxylase and on the turnover rate of dopamine in striatum and n. accumbens. *J. Pharm. Exp. Ther.*, 194:37–46, 1975.

Identification and Testing of New Drugs for Modulating Alcohol Consumption

Mary O. Lawrin, M.Sc.,[1] Claudio A. Naranjo, M.D.,[1] and Edward M. Sellers, M.D., Ph.D.[1]

Introduction

The identification of new drugs for decreasing alcohol consumption has been based mostly on serendipitous observations. The most commonly prescribed agents still are the alcohol sensitizing drugs (i.e., disulfiram). However, their clinical efficacy remains unproven and their use is limited by toxicity and other contraindications (Naranjo et al., 1981; Peachey & Naranjo, 1983). While the incidence of problems related to alcohol abuse continues to increase, research efforts have not yielded new effective pharmacotherapies. Until recently no systematic program had been designed to specifically identify and test new drugs to decrease alcohol consumption (Naranjo et al., 1981). Such a research program was developed in the Clinical Pharmacology Program, Addiction Research Foundation, Clinical Institute, Toronto, Canada (Naranjo et al., 1981).

The search for new pharmacologic treatments was based on the assumption that biologic factors play an important role in the regulation of ethanol consumption. The selection of probe drugs required a critical analysis of the available evidence, as well as the conduct of the appropriate studies in animals and humans (Naranjo et al., 1986b). Previous experiments indicated that ethanol intake is regulated by a complex interaction between neurobiological and systemic factors possibly involving several neurotransmitters (monoamines and neuropeptides), and/or hormones (Naranjo et al., 1986a). Studies suggested that the central serotonergic (5-HT, 5-hydroxytryptamine) system may be involved in the regulation of ethanol intake. Pharmacologic manipulations of central 5-HT neurotransmission had been reported to alter ethanol consumption and preference in experimental animals (Rockman et al., 1979, 1982; Amit et al., 1984; Naranjo et al., 1985, 1986a). The most consistent findings were obtained with treatments which directly or indirectly activate central serotonin activity (Naranjo et al., 1986a). Thus, the present research focused on drugs which enhance central serotonergic function. An additional factor in the selection of such drugs was their availability for animal and human experiments.

This paper will illustrate a strategy for identifying and testing drugs to decrease alcohol consumption by reviewing some experiments conducted with serotonergic drugs. A detailed review is presented elsewhere (Naranjo & Sellers, 1985; Naranjo et al., 1986a,b). The effects of several 5-HT uptake inhibitors and a 5-HT_2 agonist on ethanol consumption were tested in Wistar rats using a free-choice drinking paradigm between water and ethanol (6 or 7 percent v/v). The effects of two 5-HT uptake inhibitors, zimelidine and citalopram, on alcohol intake were also assessed in nondepressed alcohol abusers (Naranjo et al., 1984; 1986c).

Animal Studies

Methods

Animals: Male Wistar rats (Canadian Breeding Farm and Lab., Ltd., Charles River, Canada), originally weighing 200 to 220 g, were individually housed in stainless steel cages in a room regulated for constant temperature

---

[1] Clinical Pharmacology Program, Addiction Research Foundation Clinical Institute and Departments of Pharmacology and Medicine, University of Toronto, Toronto, Canada.

Reprint requests to: Dr. Claudio A. Naranjo, Clinical Pharmacology Program, Addiction Research Foundation, 33 Russell Street, Toronto, Ontario M5S 2S1, Canada.

The views expressed in this publication are those of the authors and do not necessarily reflect those of the Addiction Research Foundation.

(22 to 24°C), humidity (55 percent), and a 12-hour day–night cycle (7:00 p.m.–7:00 a.m. darkness). Each cage was equipped with two 100 ml calibrated Richter tubes to deliver fluid (ethanol solution and/or water) and a food dispenser. The position of the Richter tubes was randomly reversed to avoid position preference. Purina Rat Chow was available ad libitum throughout.

Drugs: The following specific serotonin uptake inhibitors (Fuller, 1980) were tested: zimelidine (Astra Lakemedel AB, Sweden); citalopram (Lundbeck, Denmark); fluvoxamine (Duphar BV Laboratory, Weesp, Netherlands); and viqualine (Pharmuka Laboratories, France). The selective 5-HT$_2$ postsynaptic receptor agonist tested was MK-212 (Merck Sharpe & Dohme, U.S.A.) (Fuller, 1980).

MK-212 (2.5, 10, 30, 40 mg/kg) and fluvoxamine (10, 25, 30, 40, 90 mg/kg) were made up to a concentration of 10 mg/ml by dissolving them in distilled water. Half of their doses were administered intraperitoneally (i.p.) twice daily at 1900 h and 0000 h. Zimelidine (10, 20, 30 mg/kg), citalopram (10, 20, 30 mg/kg), and viqualine (5, 10, 20 mg/kg) were dissolved in Ringer's solution in a concentration of 10 mg/ml. Zimelidine and citalopram were delivered via the Alzet® osmotic mini-pump (Alza Corp., U.S.A.) implanted subcutaneously under pentobarbital anesthesia. Viqualine was injected i.p. once daily at 1700 h. Ringer's solution served as the control for both the i.p. and Alzet® mini-pump administration.

Experimental Design: After a 5-day adaptation period, the rats were screened for their ethanol intake by presenting them with a free-choice drinking schedule between water and an ethanol solution. The concentration of ethanol (95 percent ethyl alcohol) was increased every 3 days from 2 percent to 4 percent up to 6 percent v/v (for fluvoxamine, viqualine, and MK-212) and up to 7 percent v/v (for zimelidine and citalopram). During the consecutive baseline, treatment, and post-treatment periods (each consisting of 7 days, except for 14 days with citalopram), the free-choice drinking presentation between water and the ethanol solution was continued. Body weight, fluid consumption (water, ethanol, total fluid intake), and food intake were also measured daily at the same time. Only those rats consuming more than 50 percent of their total fluid intake as the final ethanol solution (6 or 7 percent v/v) during baseline were used in the experiment. During the treatment period, the test drugs (zimelidine, citalopram, fluvoxamine, viqualine, and MK-212) were administered daily either IP or via the Alzet® mini-pump as previously described. The data were analyzed using the Duncan's Multiple Range test comparing ethanol consumption (g/kg/day) and ethanol preference (percent ethanol consumed/total fluid intake) of each dose level of drug with Ringer's control at $p < 0.05$ level.

In a separate experiment the effect of 5-HT uptake inhibitors (zimelidine, fluvoxamine) and a 5-HT agonist (MK-212) was assessed on water consumption alone to rule out a generalized effect on fluid intake. The experiment consisted of four periods each lasting for 5 days: adaptation, baseline, treatment, and post-treatment. Throughout these periods Wistar rats were allowed to consume water and food ad lib. During treatment, half of the respective doses of MK-212 (10, 20, 40 mg/kg), fluvoxamine (10, 20, 40 mg/kg) or Ringer's solution (4 ml/kg) were injected IP twice daily at 1900 h and 2300 h. Zimelidine (10, 30 mg/kg) was injected once daily at 1900 h. The data were analyzed using Duncan's Multiple Range test comparing water intake of each dose level of drug with every other group including Ringer's control at $p < 0.05$ level.

Results

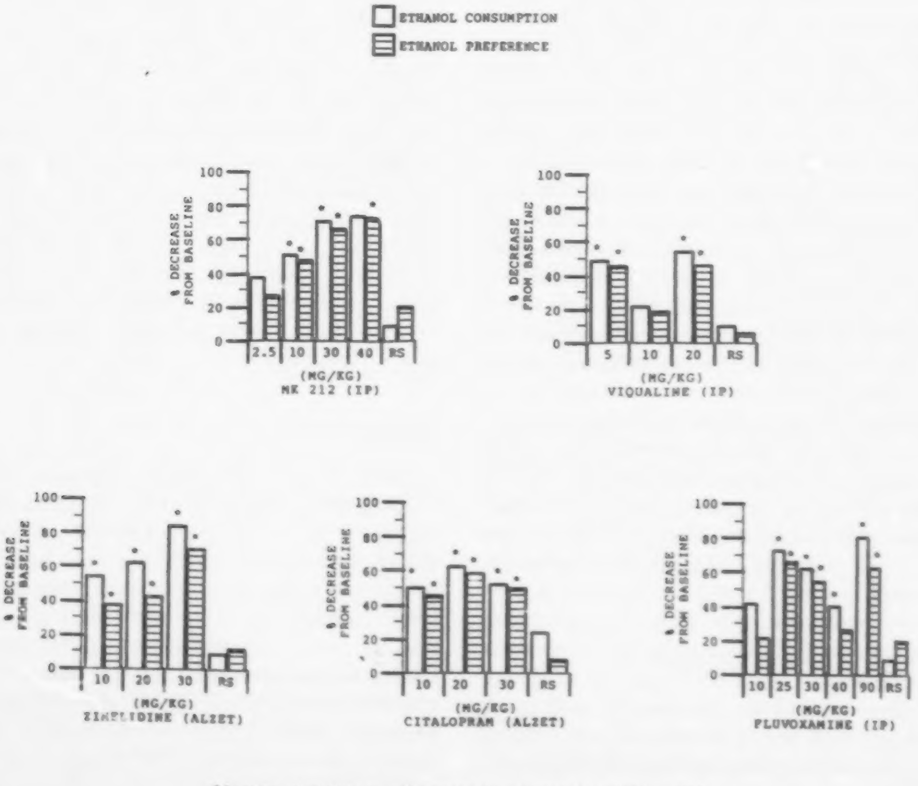
The effect of 5-HT uptake inhibitors (zimelidine, citalopram, fluvoxamine, viqualine) and a 5-HT$_2$ agonist (MK-212) on ethanol consumption (g/kg/day) and ethanol preference (percent ethanol consumed/total fluid intake) are presented in Figure 1. The results are expressed as percentage DECREASE in ethanol consumption and preference from BASELINE. All drugs significantly reduced both ethanol consumption and preference ($p < 0.05$). The ranges of decrease were 18 to 84 percent for ethanol consumption and 3 to 77 percent for ethanol preference. The effect was dose-related with zimelidine and MK-212. All decreases in ethanol intake reversed during the post-treatment period (i.e., returned to baseline levels) except for zimelidine 40 mg/kg, fluvoxamine 90 mg/kg, and MK-212 40 mg/kg. Only the highest doses of the drugs (i.e., 20 mg/kg viqualine, 30 mg/kg citalopram, 40 mg/kg MK-212, and 90 mg/kg fluvoxamine) decreased food intake.

In terms of their effects on water intake alone, MK-212 (10 and 20 mg/kg), fluvoxamine (10 and 20 mg/kg) and zimelidine (10 and 30 mg/kg) did not significantly alter water consumption when compared to Ringer's control ($p > 0.05$). The highest doses of MK-212 (40 mg/kg) and fluvoxamine (40 mg/kg) did significantly reduce water intake with respect to all other treatment groups including Ringer's. However, these effects are reflective of such toxic dose levels.

Human Studies

Methods

The effects of zimelidine (200 mg/day p.o.) were tested in 16 nondepressed, socially stable, physically, and emotionally healthy men (Naranjo et al., 1984). This double-blind, randomized, cross-over experiment consisted of five 2-week experimental periods: baseline, placebo 1 and 2, and zimelidine 1 and 2. Subjects were not instructed to modify their alcohol consumption. During the first 2 weeks (baseline), subjects recorded their alcohol consumption on a self-monitoring form and mailed in daily urine samples. Subjects who complied with these procedures and who consumed approximately 28 drinks per week were randomly allocated to initially



*denotes significant difference from Ringer's solution (RS) at P<0.05 level.

FIGURE 1. Effects of a 5-HT$_2$ agonist (MK-212) and serotonin uptake inhibitors (viqualine, zimelidine, citalopram, fluvoxamine) on ethanol consumption and preference in Wistar rats.

receive either 200 mg of zimelidine or placebo daily for 2 weeks. Every 2 weeks thereafter they received the alternate treatment. At the end of each day they recorded the total number of standard drinks consumed. They were reassessed biweekly. Changes in alcohol intake during each treatment period were assessed in terms of the number of drinks consumed and the percentage of abstinent days.

Results

Subjects took their experimental drugs and reported their alcohol consumption accurately. Three of the 16 subjects developed symptoms of drug-induced hepatitis, 2 subjects dropped out during the second zimelidine period, and a sixth did not comply with protocol during the last 2 experimental periods. Thus, the results for the first 2 experimental periods include the 13 subjects who did not have hepatitis, and the results for the 4 experimental drug periods include the remaining 10 subjects (Naranjo et al., 1984). In the 13 subjects, zimelidine decreased the number of drinks consumed ($F_{1,12} = 5.77$, $p < 0.05$) and increased the percentage of days of abstinence ($F_{1,12} = 14.14$, $p < 0.005$). In the 10 subjects the days of abstinence also increased ($F_{1,8} = 5.34$, $p < 0.05$), but the decrease in the number of drinks consumed was not significant ($F_{1,8} = 4.10$, $p < 0.10$). Zimelidine's effect on ethanol intake occurred in less than 2 weeks, indicating a rapid onset and offset of effect, in contrast to the usual 2- to 3-week delay required to observe the clinical effects of most antidepressant drugs. The pattern of response varied considerably among individuals, but the increase in the days of abstinence was a consistent and robust finding. Approximately half of the subjects were responders to zimelidine, 35 percent were partial responders, and 15 percent were nonresponders (Naranjo et al., 1986a). Our findings have been confirmed by another group (Amit et al., 1985).

In another recently completed randomized, double-blind, cross-over trial in nondepressed, healthy heavy drinkers, citalopram (40 mg/day p.o.) significantly decreased the number of drinks consumed and increased the number of days of abstinence (Naranjo et al., 1986c).

Discussion

This paper describes results obtained from a research program specifically designed to identify and test new drugs to decrease alcohol consumption. Because previous reports suggested a link between the central serotonergic system and ethanol consumption, the effectiveness of drugs, which enhance central serotonergic activity, to decrease alcohol intake was systematically evaluated. These drugs included specific 5-HT uptake inhibitors (zimelidine, citalopram, fluvoxamine, and viqualine) and a selective 5-HT$_2$ agonist (MK-212). Initially, they were investigated in an appropriate animal model consuming ethanol preferentially under free-choice conditions. Subsequently, the effects were assessed in alcohol abusers. Using such an approach provided a better insight into the neurochemical mechanism(s) which may regulate ethanol intake. More importantly, it also proved to be a valuable strategy with which to develop a new possibly effective treatment for alcohol abusers.

All serotonin uptake inhibitors tested (zimelidine, citalopram, fluvoxamine, viqualine) significantly and consistently decreased ethanol consumption and preference in Wistar rats, when offered a free choice between water and ethanol (6 to 7 percent v/v). These findings confirm and extend to previous studies showing that these and other 5-HT uptake inhibitors (norzimelidine, alaproclate, fluoxetine, indalpine) also reduce ethanol consumption in rats (Rockman et al., 1979, 1982; Le Bourhis, 1981; Amit et al., 1984). Serotonin uptake inhibitors have also been reported to decrease ethanol intake in ethanol-preferring genetically inbred animals. Fluoxetine decreased ethanol intake in P rats (Murphy et al., 1985) while other 5-HT uptake inhibitors, such as zimelidine, citalopram, and fluvoxamine, reduced ethanol intake and preference in UChB rats.*

The fact that all specific 5-HT uptake blockers consistently and repeatedly decrease alcohol intake in different animal models strongly supports the notion that enhancing central serotonergic function decreases ethanol intake. Further convincing evidence for such a notion comes from the other finding of this study, namely, that the alternative mechanism of increasing central 5-HT activity, i.e., stimulation of post-synaptic 5-HT_2 receptors with the specific 5-HT agonist, MK-212, also reduces ethanol intake in a dose-related manner. Additional evidence suggesting a role of central serotonin systems in the regulation of alcohol intake comes from reports showing that ethanol intake decreases following the administration of 5-HT itself (Hill, 1974) or its precursors, such as tryptophan (Zabik et al., 1985) and 5-hydroxytryptophan (Myers & Veale, 1972; Geller, 1973; Walters, 1977; Zabik et al., 1978, 1985).

---

*Mardones et al., personal communication.

The mechanism of this effect is not fully elucidated. However, several hypotheses have been suggested. For example, the effect has been attributed to an inhibition of the positive reinforcing properties of ethanol (Rockman et al., 1979). Since serotonin also plays a role in the regulation of food consumption (Blundell, 1984; Wurtman & Wurtman, 1984), it is also conceivable that enhanced central serotonergic activity produces its effects on alcohol intake by modulating critical synapses involved in the regulation of consummatory behaviors.

The clinical importance of serotonin-altering drugs becomes apparent with the findings that serotonin uptake inhibitors, zimelidine and citalopram, also attenuate ethanol intake in humans. Since these agents acted rapidly and subjects were not clinically depressed, this action is distinct from their antidepressant effects and most likely represents an interference with the neurobiological mechanisms regulating ethanol intake. The human findings provide cross-validation for the results obtained in animals, therefore indicating that the simple free-choice drinking paradigm in rats is a valid test for screening new pharmacological interventions. These findings also suggest an innovative approach for moderating ethanol consumption in problem drinkers.

In summary, the strategy described in this paper suggests an effective approach for the identification and testing of new pharmacotherapies for reducing ethanol intake. The findings also illustrate the progress being made by combining both animal and human experiments in a research program specifically designed to identify and test new drugs to decrease alcohol consumption. A similar strategy can be used for testing neuropharmacological agents affecting other neurotransmitter systems.

Acknowledgments

The authors gratefully acknowledge the help of Dr. J. Sullivan, Dr. V. Khouw, Dr. S.L. Lee, Ms. D. Woodley, Ms. K. Kadlec, Ms. M. Harrison, Ms. K. Kaplan, Ms. K. Sykora, and Mr. W. Juzytsch in the conduct of the human and animal studies. We also thank Ms. C. Van Der Giessen for typing the manuscript.

References

Amit, Z., Sutherland, E.A., Gill, K., and Ogren, S.O. Zimelidine: A review of its effects on ethanol consumption. *Neurosci. Biobehav. Rev.*, 8:35–54, 1984.

Amit, Z., Brown, Z., Sutherland, A., et al., Reduction in alcohol intake in humans as a function of treatment with zimelidine: Implications for treatment. In: Naranjo, C.A., and Sellers, E.M. (eds.), *Research Advances in New Psychopharmacological Treatments for Alcoholism*. Amsterdam: Elsevier Science Publishers B.V., 1985, pp. 189–198.

Blundell, J.E. Serotonin and appetite. *Neuropharmacology*, 23:1537–1551, 1984.

Fuller, R.W. Pharmacology of central serotonin neurons. *Ann. Rev. Pharmacol. Toxicol.*, 20:111–127, 1980.

Geller, I. Effects of para-chlorophenyl alanine and 5-hydroxytryptophan on alcohol intake in the rat. *Pharmacol. Biochem. Behav.*, 1:361–365, 1973.

Hill, S.Y. Intraventricular injection of 5-hydroxytryptamine and alcohol consumption in rats. *Biol. Psychiat.*, 8:151–158, 1974.

Le Bourhis, B., Uzan, A., and Aufrere, G. Effects de l'indalpine, inhibiteur specifique de la recapture de la serotonine sur la dependance comportementale a l'ethanol et sur la prise volontaire d'alcool chez le rat. *Ann. Pharm. Fr.*, 39:11–20, 1981.

Murphy, J.M., Waller, M.B., Gatto, G.J., et al. Monoamine uptake inhibitors attenuate ethanol intake in alcohol-preferring (P) rats. *Alcohol*, 2:349–352, 1985.

Myers, R.D., and Veale, W.L. The determinants of alcohol preference in animals, Chapter 6. In: Begleiter, H., and Kissin, B. (eds.), *Biology of Alcohol-*

ism, Volume II. New York: Plenum Press, 1972, pp. 131–168.

Naranjo, C.A., Cappell, H., and Sellers, E.M. Pharmacological control of alcohol consumption: Tactics for the identification and testing of new drugs. *Addict. Behav.*, 6:261–269, 1981.

Naranjo, C.A., Sellers, E.M., Roach, C.A., et al. Zimelidine-induced variations in alcohol intake by non-depressed heavy drinkers. *Clin. Pharmacol. Ther.*, 35:374–381, 1984.

Naranjo, C.A., and Sellers, E.M. (eds.), *Research Advances in New Psychopharmacological Treatments for Alcoholism*. Amsterdam: Elsevier Sciences Publishers B.V., 1985.

Naranjo, C.A., Sellers, E.M., Wu, P.H., and Lawrin, M.O. Moderating ethanol drinking: Role of enhanced serotonergic neurotransmission. In: Naranjo, C.A., and Sellers, E.M. (eds.), *Research Advances in New Psychopharmacological Treatments for Alcoholism*. Amsterdam: Elsevier Science Publishers B.V., 1985, pp. 171–186.

Naranjo, C.A., Sellers, E.M., and Lawrin, M.O. Modulation of ethanol intake by serotonin uptake inhibitors. *J. Clin. Psychiatry*, 47(4, Suppl.):16–, 1986a.

Naranjo, C.A., Sullivan, J.T., Lawrin, M.O., and Sellers, E.M. Strategies for the identification and testing of new pharmacological modulators of ethanol consumption. In: Engel, J., and Oreland, L. (eds.), *Brain Reward Systems and Abuse*. New York: Raven Press, 1986b (in press).

Naranjo, C.A., Sellers, E.M., Sullivan, J.T., et al. Serotonin uptake inhibitors (SUI) consistently moderate ethanol intake (EI) in humans: Citalopram (C) effects. *Clin. Pharmacol. Ther.* (Abstract), 39(2):228, 1986c.

Peachey, J.E., and Naranjo, C.A. The use of disulfiram and other alcohol-sensitizing drugs in the treatment of alcoholism. In: Israel, Y., Glaser, F.B., Kalant, H., et al. (eds.), *Research Advances in Alcohol and Drug Problems, Volume 7*. New York: Plenum Publishing Corporation, 1983, pp. 397–431.

Rockman, G.E., Amit. Z., Carr, G., et al. Attenuation of ethanol intake by 5-hydroxytryptamine uptake blockade in laboratory rats. I. Involvement of brain 5-hydroxytryptamine in the mediation of the positive reinforcing properties of ethanol. *Arch. Int. Pharmacodyn. Ther.*, 241:245–259, 1979.

Rockman, G.E., Amit, Z., Brown, W., et al. An investigation of the mechanisms of action of 5-hydroxytryptamine in the suppression of ethanol intake. *Neuropharmacol.*, 21:341–347, 1982.

Walters, J.K. Effects of PCPA on the consumption of alcohol, water and other solutions. *Pharmacol. Biochem. Behav.*, 6:377–383, 1977.

Wurtman, R.J., and Wurtman, J.J. Nutrients, neurotransmitter synthesis and the control of food intake. In: Stunkard, A.J., and Stellar, E. (eds.), *Eating and Its Disorders*. New York: Raven Press, 1984, pp. 77–86.

Zabik, J.E., Liao, S.-S., Jeffreys, M., and Maickel, R.P. The effects of DL-5-hydroxytryptophan on ethanol consumption by rats. *Res. Commun. Chem. Pathol. Pharmacol.*, 20:69–78, 1978.

Zabik, J.E., Binkerd, K., and Roache, J.D. Serotonin and ethanol aversion in the rat. In: Naranjo, C.A., and Sellers, E.M. (eds.), *Research Advances in New Psychopharmacological Treatments for Alcoholism*. Amsterdam: Elsevier Science Publishers B.V., 1985, pp. 87–101.

Effects of Noon Meals Varying in Nutrient Composition on Plasma Amino Acids, Glucose, Insulin, and Behavior[1]

Bonnie Spring, Ph.D.,[2] June Chiodo, Ph.D.,[2] Margarette Harden, Ph.D.,[3] Michael Bourgeois, M.D.,[4] Lorenz Lutherer, M.D.,[4] Debra Harner, B.A.,[2] Sherry Crowell, M.A.,[2] and Geoffrey Swope, B.A.[2]

A widely held popular belief is that the ingestion of carbohydrates, especially sugar, induces a temporary mood involving a sensation of high energy. On the contrary, our research findings to date reveal an opposite effect. Spring, Maller, Wurtman, Digman and Cozolino (1983) compared the responses of 184 normal adults 2 hours after they ate carbohydrate or protein meals. The carbohydrate meal used in this study was primarily high in sucrose. Mood was less tense and more drowsy, and concentration was poorer after the carbohydrate than the protein meal, especially among female subjects and older individuals. In a followup study Lieberman, Spring and Garfield (in press; *see also* Spring, Lieberman, Swope & Garfield, in press) compared the mood and performance of 40 young male subjects who ate carbohydrate and protein lunches on 2 different days in counterbalanced order. The carbohydrate meals in the second study contained primarily wheat starch, a complex carbohydrate. As compared to their responses to protein, subjects displayed slowed response speed and impaired concentration from 1 to 3.5 hours after the carbohydrate meal. Most recently, Conners, Caldwell, Caldwell, et al. (in press) randomly assigned normal and hyperactive children to a high-carbohydrate or high-protein breakfast or to fasting. From .5 to 3.75 hours after eating, the carbohydrate meal induced greater vigilance impairments than did the protein meal or fasting.

At least three candidate mechanisms have been proposed to explain the behavioral effects of carbohydrate foods. First, unlike protein-rich foods, many snacks rich in carbohydrate are sweet, dessert-type foods. Consequently, differences in taste or hedonic qualities might be at least partially responsible for the behavioral differences observed after meals varying in nutrient composition. Second, some popular accounts hold that reactive hypoglycemia underlies the low energy mood observed after carbohydrate intake. Since insulin given *exogenously*, as in the treatment of diabetes, can induce hypoglycemia, it has been suggested that *endogenous* insulin, triggered by carbohydrate intake, can also induce hypoglycemia and its associated symptoms.

A third explanation is based on the demonstration that certain food constituents are neurotransmitter precursors that can alter the synthesis and release of brain neurotransmitters (Fernstrom & Wurtman, 1971, 1972). Consequently, foods might produce changes in behavior by altering the levels of brain neurotransmitters that are associated with various psychological functions.

The brain synthesizes the monoamine neurotransmitter serotonin from its amino acid precursor, tryptophan. Although the body's nutritional supply of tryptophan is obtained from protein, a high-protein meal does not elevate brain tryptophan or serotonin. In fact the opposite occurs: brain tryptophan declines, as does serotonin synthesis. This paradox arises because tryptophan is scarce in protein (1 to 1.6 percent) in comparison with the other large neutral amino acids (LNAA): leucine, isoleucine, valine, tyrosine, and phenylalanine (25 percent). These LNAA's compete with tryptophan for access to the same carrier molecules for

---

[1] Supported in part by grants from the Institute for Nutritional Sciences and the Graduate School, Texas Tech University.

[2] Department of Psychology, Texas Tech University, Box 4100, Lubbock, TX 79409.

[3] Department of Nutrition, Texas Tech University.

[4] Texas Tech University Health Sciences Center.

transport across the blood-brain barrier. In addition, tryptophan is metabolized in its passage through the liver, whereas leucine, isoleucine, and valine are not. Hence these branched chain amino acids can represent as much as 90 percent of *all* the amino acids to enter systemic circulation from the liver and portal circulation after a high-protein meal. In sum, a high-protein meal decreases the ratio of plasma tryptophan to the competing LNAA, lowers tryptophan's influx into the brain and reduces brain serotonin synthesis and release.

In contrast, a carbohydrate-rich, protein-poor meal increases brain tryptophan and serotonin synthesis even though such a meal lacks tryptophan. In animals that have fasted overnight, the insulin secretion triggered by a carbohydrate meal causes a 40 to 60 percent fall in plasma leucine, isoleucine and valine and a 15 to 30 percent fall in plasma tyrosine. Plasma tryptophan levels do not decline because tryptophan binds to albumin molecules as insulin strips away the free fatty acids that are usually albumin-bound. Consequently, a meal that is poor in protein but rich in carbohydrate increases the plasma tryptophan/LNAA ratio. In humans, this ratio is significantly elevated from 1.5 to 4 hours after a carbohydrate meal containing either sugar or starch (Lieberman, Spring, & Garfield, in press). The rise in the tryptophan/LNAA ratio causes increased brain influx of tryptophan and increased release of serotonin from brain neurons, insofar as the latter can be assessed by CSF levels of serotonin's metabolite, 5-HIAA. To bring about an increase in brain serotonin release, a test meal must be not only carbohydrate-rich but also protein-poor. A balanced meal containing a substantial amount of protein directly contributes sufficient LNAA to the bloodstream to compensate for the insulin-mediated fall in LNAA that is triggered by carbohydrate.

Much of the brain's serotonin is localized in the midbrain raphe nuclei that play a role in the onset of sleep. Therefore, an elevation of brain serotonin induced by carbohydrates could simulate in the brain a state of readiness to fall asleep, and might account for the fatigue and concentration impairments observed after carbohydrate intake.

The purpose of this study was to test which of the three mechanisms—hedonic properties, fluctuations in plasma glucose, or changes in the plasma tryptophan/LNAA ratio—could best account for the behavioral effects of a carbohydrate meal.

In a within-subjects design in counterbalanced order, subjects fasted or consumed a lunch rich in carbohydrate and poor in protein, a lunch rich in protein and poor in carbohydrate, or a balanced lunch rich in both nutrients. The carbohydrate and balanced lunches were both sweet-tasting, cookie-like lunch bars. Consequently, they were expected to be similar in hedonic properties and in their effects on plasma glucose and insulin, but different in their effects on the tryptophan ratio. The inclusion of a fasting control condition permitted an assessment of whether any lunch, regardless of nutrient composition, would induce behavioral changes when compared to no lunch.

The subjects were seven normal females between the ages of 18 to 29. Subjects were screened to rule out a history of diabetes, hypoglycemia, eating disorders, obesity, substance abuse, or psychiatric hospitalization. Screening procedures also excluded any subject who had, in the past 6 months, met Research Diagnostic Criteria for mania, hypomania, or major depression. Selection criteria also specified that subjects could not be taking appetite suppressants, birth control pills, or any medication that could cause drowsiness (e.g., antihistamines, cold medication) or activation (e.g., stimulants). Prior to entering the protocol, all subjects were examined by a physician to ensure that they were in good physical health and not at risk from study procedures.

On 4 different days, 1 week apart, subjects fasted from 8:00 p.m. on the evening prior to the test day, until 7:30 a.m. the following morning. At 7:30 a.m. subjects reported to the laboratory where they were fed a standard breakfast consisting of two pieces of whole wheat toast with ½ tbs butter and 1 tbs jam, 4 oz orange juice and 1 cup skim milk. Participants were permitted to drink their usual amount of coffee or tea, as determined prior to study entry, in order to avoid caffeine withdrawal. Subjects remained in the laboratory, refrained from eating or drinking anything except water, and engaged in sedentary activities of their own choosing until 11:00 a.m. At this time, an intracath was inserted into the antecubital fossa region of the distal hand of each subject to permit blood samplings throughout the afternoon.

Lunch was eaten between 12:15 p.m. and 12:45 p.m. The carbohydrate meal was six lunch bars which supplied 105 g carbohydrate, .7 g protein, 42.7 g fat, and 799 calories. The protein lunch consisted of 318.8 g of turkey breast with mayonnaise which supplied 105 g protein, 33.3 g fat, and 780 calories. The balanced lunch was six lunch bars which supplied 76 g carbohydrate, 27.7 g protein, 40 g fat, and 774 calories.

Blood was drawn prior to lunch, and also four times following the meal. In addition, mood and performance were assessed before and four times after eating lunch. All behavioral assessments involved paper and pencil tests. Measures of mood were the Stanford Sleepiness Scale (SSS), the Profile of Mood States (POMS), and the Visual Analog Mood Scales (VAMS). At each assessment subjects were asked to rate their mood "right now." Measures of performance were the Digit Symbol Substitution Test (DSST), Letter Cancellation, and a test of Addition.

Blood samples were analyzed for plasma glucose, serum insulin, and plasma amino acids, the latter by means of a Beckman automated amino acid analyzer.

Data were analyzed by repeated measures analysis of variance with planned contrasts comparing test meals to fasting for selected post-lunch assessments. Analysis of the primary mood variable, POMS Fatigue, indicated that at 2 hours after lunchtime subjects reported significantly greater fatigue after eating the carbohydrate lunch than after skipping lunch. Neither the balanced nor the protein meal increased fatigue significantly when compared to fasting. Mean differences in performance between carbohydrate and fasting did not reach significance for these seven subjects.

Analysis of the blood constituents revealed that the carbohydrate meal, as compared to fasting, significantly elevated plasma glucose levels throughout the afternoon. The balanced lunch also elevated plasma glucose but the protein lunch did not substantially affect glucose. Both the carbohydrate and the balanced lunches significantly raised serum insulin throughout the afternoon. The increase in insulin following the protein meal was considerably smaller.

As expected, neither fasting nor the balanced lunch altered the tryptophan/LNAA ratio from the pre- to the post-lunch assessments. However, consistent with prior results, by 1.5 hours after lunch, the carbohydrate lunch increased the ratio significantly and this elevation persisted throughout the afternoon. Also as predicted, the protein meal lowered the tryptophan ratio for much of the afternoon.

Since only the carbohydrate lunch induced significant fatigue, but the carbohydrate and balanced lunches were similar in hedonic properties, it appears unlikely that psychological factors such as taste play a major role in generating the drowsiness that normal adults report following a carbohydrate meal. Moreover, fatigue following a carbohydrate lunch could not in these normal subjects be attributed to hypoglycemia, since glucose remained elevated. Nor could fatigue be explained by differences in insulin, since carbohydrate and balanced meals affected serum insulin similarly, but only the former caused fatigue. Since fatigue occurred at approximately the same time that the carbohydrate meal began to elevate the tryptophan/LNAA ratio, enhanced brain serotonin synthesis represents a plausible underlying mechanism.

The current study replicates and extends prior findings indicating that meals high in carbohydrate and low in protein induce drowsiness 2 hours after eating. At assessments beginning 30 minutes after eating, no evidence was found to support the popular belief that carbohydrate foods trigger a high-energy mood in normal subjects. At this level of caloric intake (slightly less than 800 calories), post-lunch fatigue occurred relatively specifically following unbalanced carbohydrate-rich meals, and not following meals that are rich in protein. The hedonic features of the meal or its effects on glucose and insulin appear unlikely to account for the effects of carbohydrate on mood. However, effects on brain serotonin synthesis represent a possible underlying mechanism.

References

Conners, C.K., Caldwell, J., Caldwell, L., et al. Experimental studies of sugar and aspartame on autonomic, cortical and behavioral responses to sugar. *Nutr. Rev. (Suppl.).* (In press).

Fernstrom, J.D., and Wurtman, R.J. Brain serotonin content: Increase following ingestion of carbohydrate diet. *Science,* 174:1023–1025, 1971.

Fernstrom, J.D., and Wurtman, R.J. Brain serotonin content: Physiological regulation by plasma amino acids. *Science,* 178:414–416, 1972.

Lieberman, H., Spring, B., and Garfield, G. The behavioral effects of food constituents: Strategies used in studies of amino acids, protein, carbohydrate, and caffeine. *Nutr. Rev. (Suppl.).* (In press).

Spring, B., Lieberman, H., Swope, G., and Garfield, G. Effects of carbohydrates on mood and behavior. *Nutr. Rev. (Suppl.).* (In press).

Spring, B., Maller, O., Wurtman, J., et al. Effects of protein and carbohydrate meals on mood and performance: Interactions with sex and age. *J. Psychiatr. Res.,* 17:155–167, 1983.

Mouse Strain Differences in Acquisition of Discrete Lever-Press and Shuttle Avoidance Responses, and Drug Effects Thereon

Hisashi Kuribara, Ph.D.,[1] and Sakutaro Tadokoro, M.D., Ph.D.[1]

It has been well known that there are marked differences among strains of mice in their behavioral characteristics as well as in the sensitivities to psychoactive drugs (Bovet et al., 1969; Oliverio, 1974; Wahlsten, 1972). In respect to conditioned avoidance response in mice, a shuttle avoidance has been commonly applied to investigate genetic influence on the acquisition processes and to study the drug effects.

Recently, the authors newly assembled an operant box for lever-press avoidance in mice (Kuribara and Tadokoro, 1983a, 1984), and have studied characteristics of the acquisition processes and the psychoactive drug-induced changes in the discrete lever-press and shuttle avoidance responses in the dd strain of mice (Kuribara and Tadokoro, 1983a, 1983b, 1984, 1986; Kuribara et al., 1985). These experiments demonstrated that the drug-induced changes in the lever-press and shuttle avoidance responses were sometimes different according to types of the drugs, and that the difference in the response topographies between the lever-press and shuttle avoidances should be considered when the drug effects were investigated (Kuribara et al., 1985).

Hence, the purposes of this study were to investigate the acquisition processes of the discrete lever-press and shuttle avoidance responses, and to investigate the effects of methamphetamine and morphine, prototypes of central stimulant and narcotic analgesic, respectively, on these avoidance responses in three strains of mice (dd, ICR, and C57). Furthermore, the effects of the drugs on the ambulatory activity were examined in these three strains of mice.

Method

Animals

The experimental animals were male mice of dd (Institute of Experimental Animal Research, Gunma University School of Medicine), ICR (Charles River Japan, Inc.) and C57 (Charles River Japan, Inc.) strains. These mice had been housed in groups of 8 to 10 in aluminum cages in a controlled room (light period; 6:00–18:00, and temperature; 23 ± 2°C) with a free access to food (MF: Oriental Yeast Co.) and tap water except during the avoidance sessions. When the mice were 10 weeks old, and weighed 28 to 32 g in the dd and ICR strains and 23 to 28 g in the C57 strain, the training in either of the discrete lever-press or shuttle avoidance situations was started.

Discrete Avoidance

The experimental box for the lever-press avoidance (GT-8310; O'Hara & Co. Ltd.), 18 (w) × 9 (d) × 10 (h) cm, was attached by a stainless steel lever which could be activated with a force of more than 1.5 g. A speaker for presenting a warning stimulus was set in the ceiling.

Two different sizes of the experimental boxes for the shuttle avoidance were used in the present experiment. The dimensions of the larger box (GT-7750; O'Hara & Co. Ltd.) were 50 (w) × 15 (d) × 20 (h) cm with 2 photobeams arranged 36 cm apart, and the dimensions of the smaller box (GT-8450; O'Hara & Co. Ltd.) were 30 (w) × 9 (d) × 15 (h) cm with 2 photobeams arranged 18 cm apart. A speaker for presenting a warning stimulus was set in the ceiling of each box.

The temporal parameters of the discrete avoidance schedule (Hoffman et al., 1961) were an inter–trial interval of 25 sec and a warning duration of 5 sec. The warning stimulus was an 800 Hz pure tone from the speaker. The shock was an electric current of 100 to 150 V, 0.3 to 0.5 mA, 50 Hz AC, and was given to the mouse through the stainless steel floor grid of the experimental box. The maximum duration of the shock presentation was 3 sec and an escape contingency was considered in the schedule during the training sessions. During the drug-testing sessions, the shock duration was fixed to 0.5 sec. Each session consisted of 1 hr performance/day, and was held every other day during the training period, and every day during the drug-testing period. The indices of the avoidance response were response rate (number of lever-pressings or shuttlings/min) and avoidance rate (number of avoidance responses/number of avoidance trials). After 12 to 15 sessions of the training, the mice that achieved a critical level of the avoidance rate of higher than 75 percent were selected as good-performing mice, and the drug-testing was carried out in these mice.

---

[1] Division for Behavior Analysis, Behavior Research Institute, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi 371, Japan.

Ambulatory Activity

For measurement of the ambulatory activity of the mouse, a tilting-type ambulometer, 20 cm in diameter (AM-10; O'Hara & Co. Ltd.) (Hirabayashi et al., 1978), was used. A mouse was put into the activity cage, and the ambulatory activity counts were recorded for 0.5 and 1 hr before and after the drug administration, respectively.

Drug Treatments

The drugs and the doses tested in the avoidance experiments were methamphetamine HCl (MAP) (Philopon: Dainippon Pharm. Co.; 0.13, 0.25, 0.5, and 1 mg/kg s.c.) and morphine HCl (MOR) (Takeda Pharm. Co.; 1.3, 2.5, 5, and 10 mg/kg s.c.). The doses were expressed in terms of the salt forms. MAP and MOR were dissolved in physiological saline vehicle, and each volume administered was fixed at 1 ml/100 g body weight. Each drug was administered immediately before the start of the avoidance session, and the avoidance response was observed for 1 hr thereafter. The drug-testing sessions were held twice a week at intervals of 3 to 4 days, and physiological saline was administered as the control session the day before. Administration of MAP was done first, followed by MOR, and the doses of each drug-testing were changed from the lower to the higher. When the drug-testing was changed from MAP to MOR, the mice were allowed to rest for 1 week.

After completion of the drug-testing in the avoidance experiments, the mice used were administered MAP (1 mg/kg s.c.) and MOR (10 mg/kg s.c.), which were the highest doses tested in the avoidance experiments, and their ambulatory activity was observed for 1 hr. In the control experiment, physiological saline was administered. The administration was carried out in an order of physiological saline, MAP and MOR at intervals of 3 to 4 days.

Results

Acquisition of Avoidance Responses

The acquisition processes of the discrete lever-press and shuttle avoidance responses in the dd, ICR, and C57 strains as well as the BALB/c, C3H, and DBA strains have been reported elsewhere (Kuribara and Tadokoro, 1986). The characteristic points are as follows:

After 15 sessions of the training in the lever-press situation, nearly 80 percent of the dd strain achieved a critical level of the avoidance rate (75%), whereas only 30 to 40 percent of the ICR and C57 strains achieved the critical level.

Within 10 sessions of the training in the shuttle situation of the larger box, approximately 80 percent of the dd strain achieved the critical level of the avoidance rate. However, there was no case that exhibited the critical level in the ICR and C57 strains although they were trained for 15 sessions or more. Therefore, the drug-testing by using the ICR and C57 strains could not be carried out in the shuttle situation of the larger box.

The acquisition of the shuttle avoidance response in the smaller box was faster than those in the lever-press situation and in the shuttle situation of the larger box. Further-

best copy available

more, the avoidance rates as well as the percentages of the mice that achieved to show the critical level of the avoidance rate were higher in the smaller box than in the other two situations. In particular, all the mice of the C57 strain excellently acquired the shuttle avoidance response in the smaller box by the second session of the training, showing the best acquisition among the three strains, although this strain exhibited the poorest avoidance response in the lever-press situation and in the shuttle situation of the larger box. In contrast, the ICR strain demonstrated the poorest result in this situation as well as in the lever-press situation and in the shuttle situation of the larger box.

Drug Effects on the Avoidance Responses

Figures 1 and 2 show dose-effect relationships for MAP and MOR, respectively, in the lever-press situation (left panels), shuttle situation of the larger box (middle panels), and shuttle situation of the smaller box (right panels), respectively, in the 3 strains of mice. As mentioned above, the data of the shuttle avoidance response in the larger box in the ICR and C57 strains are not shown in these figures.

The baseline response rate in the lever-press situation was comparatively higher in the ICR strain than in the dd and C57 strains. In the shuttle situation of the smaller box, the baseline response rates were higher in an order of ICR > dd > C57 strains.

MAP increased the response rate in the dd and ICR strains in the lever-press situation almost in a dose-dependent manner, except in the case of the ICR strain at 0.5 to 1 mg/kg, whereas the C57 strain exhibited a dose-dependent decrease in the response rate after MAP. MAP increased the response rate in the dd, ICR, and C57 strains in the shuttle situations of the larger and/or smaller boxes in a dose-dependent manner. The avoidance rate slightly but sometimes significantly increased in the dd strain in the lever-press situation, and in the dd, ICR, and C57 strains in the shuttle situations. However, the C57 strain exhibited a dose-dependent decrease in the avoidance rate in the lever-press situation after MAP.

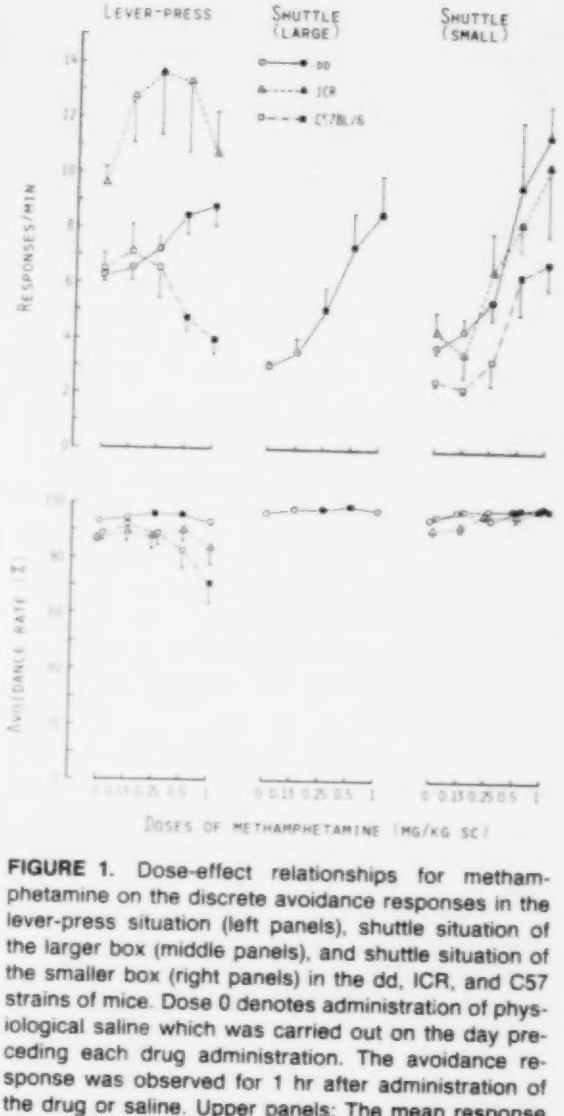


FIGURE 1. Dose-effect relationships for methamphetamine on the discrete avoidance responses in the lever-press situation (left panels), shuttle situation of the larger box (middle panels), and shuttle situation of the smaller box (right panels) in the dd, ICR, and C57 strains of mice. Dose 0 denotes administration of physiological saline which was carried out on the day preceding each drug administration. The avoidance response was observed for 1 hr after administration of the drug or saline. Upper panels: The mean response rates with S.E.M. Lower panels: The mean avoidance rates with S.E.M. The closed symbols indicate a significant difference as compared with the control value (dose = 0) within the same strains of mice ($p < 0.05$). Ten to 40 mice were used in this experiment. However, the data in the ICR and C57 strains in the shuttle situations of the larger box are not shown in this figure due to the reason mentioned in the text.

MOR decreased markedly the response rate in the ICR strain in the lever-press situation, while it tended to increase the rate in the C57 strain. On the other hand, MOR increased the response rate in the dd, ICR, and

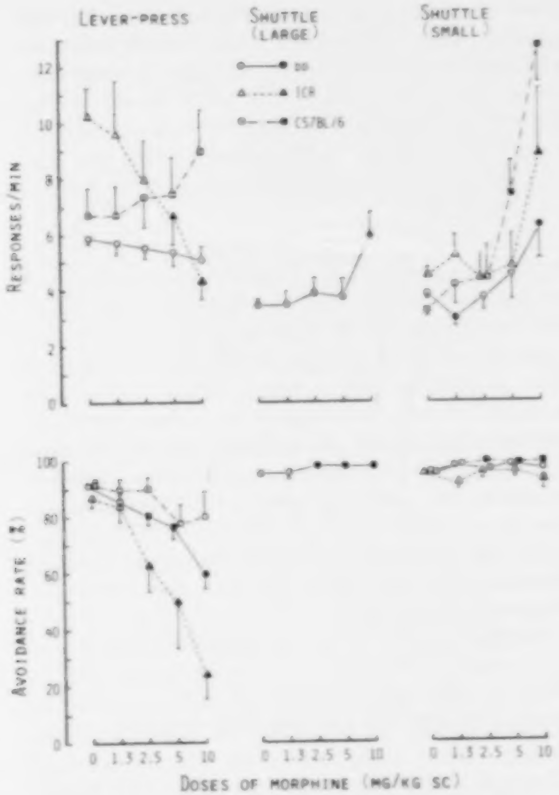


FIGURE 2. Dose-effect relationships for morphine on the discrete avoidance responses in the lever-press situation, shuttle situation of the larger box and shuttle situation of the smaller box in the dd, ICR, and C57 strains of mice. The data are shown in the same way as in Figure 1.

C57 strains in the shuttle situations of both the larger and smaller boxes. In particular, the C57 strain demonstrated the highest increase in the rate after MOR. The avoidance rate decreased in the dd and ICR strains in the lever-press situation after administration of MOR in a dose-dependent manner. In contrast, MOR increased the avoidance rate in the dd and C57 strains in the shuttle situations of the larger box and smaller box, respectively, at the high doses.

Effects of the Drugs on the Ambulatory Activity

Figure 3 shows the mean overall ambulatory activity counts during a 1 hr observation period after administration of saline, MAP (1 mg/kg), and MOR (10 mg/kg). After administration of saline, the C57 strain showed comparatively lower activity count than the dd and ICR strains. MAP and MOR increased the ambulatory activity in the three strains. The rank orders of the increased ambulatory activity were dd ≑ ICR > C57 strains after MAP, and C57 > dd ≑ ICR strains after MOR.

Discussion

Prior to evaluating the behavioral effects of psychoactive drugs, the characteristics of the experimental animals, such as the baseline levels of the behaviors and the sensitivities to standard drugs, should be investigated.

The present experiment demonstrated that there were marked differences in the acquisition of the discrete lever-press and shuttle avoidance responses among the dd, ICR, and C57 strains of mice. The results obtained in the lever-press situation and in the shuttle situation of the larger box were almost identical with those reported by Bovet et al. (1969), Oliverio (1974), and Sekiguchi (1982) that

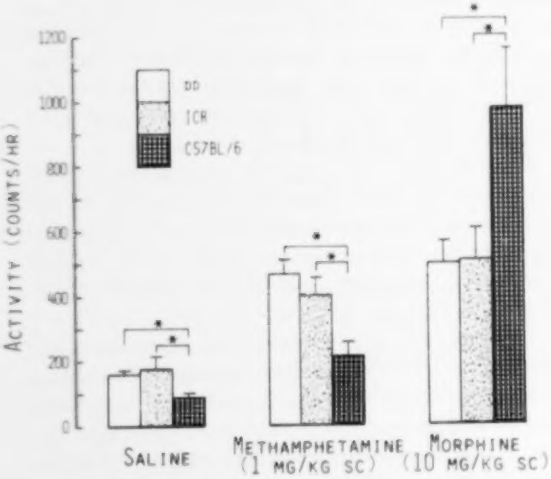


FIGURE 3. Effects of methamphetamine (1 mg/kg s.c.) and morphine (10 mg/kg s.c.) on the ambulatory activity in the dd, ICR, and C57 strains of mice. The doses administered were the highest doses tested in the avoidance experiment. The ambulatory activity of each mouse was measured for 1 hr after administration of the drugs. * indicates significant difference between strains ($p < 0.05$). N = 20 to 50.

the ICR and C57 strains exhibited poor avoidance response in the shuttle situation. However, when the dd, ICR, and C57 strains of mice were trained in the shuttle situation of the smaller box, the acquisition progressed more rapidly than in those trained in the larger box. These results strongly suggest that the acquisition of the shuttle avoidance response is affected by the size of the experimental box. In particular, the acquisition of the C57 strain was superior to that of the dd strain which has been considered to be a good-performing strain (Kuribara and Tadokoro, 1984; Kuribara et al., 1985). In the shuttle situation, the mouse has to move in the experimental box to avoid the shocks. Thereby, the general activity level of the mouse might affect the acquisition of the shuttle avoidance response as suggested by Messeri et al. (1972). The C57 strain exhibited a much lower ambulatory activity as well as a lower response rate in the shuttle situation. It is therefore considered that the inferior avoidance response in the C57 strain, which was demonstrated in the lever-press situation and in the shuttle situation of the larger box, is not simply due to a lower learning ability, but rather reflects a lower level of the general activity. In contrast, the ICR strain exhibited an inferior avoidance response in the three types of the avoidance situations, suggesting that the learning ability of the ICR strain is lower than the dd and C57 strains in the avoidance situation.

Furthermore, it can be considered from the present results that the acquisition of the avoidance response in the shuttle situation of the smaller box is easier than those in the lever-press situation or in the shuttle situation of the larger box.

The present experiment also demonstrated that there were strain differences in the drug-induced changes in the avoidance responses and in the ambulatory activity. Although the sensitivities were different among the strains, both MAP and MOR increased the ambulatory activity in the three strains, clearly reflecting the behavior-stimulating effects of these drugs (Chiuech and Moore, 1975; Cheney and Goldstein, 1971; Rethy et al., 1971), and such changes were well correlated with the MAP- and MOR-induced facilitations of the shuttle avoidance response as demonstrated with a dose-dependent increase in the response rate. However, the drug-induced changes in the lever-press avoidance response were not always identical with those in the shuttle avoidance response and the ambulatory activity. These results strongly suggest that the drug effects vary depending on the types of behavior.

The mouse strain differences in the acquisition processes of the avoidance responses as well as the sensitivities to psychoactive drugs are considered to be due to differences in the neural activities in the brain. In this study, the authors did not carry out the neurochemical investigation. It has been reported that there are differences in the acetylcholine, catecholamines, serotonin, GABA systems, etc., among strains of mice (cf. Al-Ani et al., 1970; Durkin et al., 1983). However, the authors could not find definite correlations between the present data and the neurochemical data.

Furthermore, it is considered that there are colony differences in the characteristics even in the same strain of mice. Hence, a further study is required to elucidate the mouse strain differences in the behavioral pharmacology. However, it can be concluded from the present results that there are marked differences in the acquisition processes of conditioned avoidance response as well as the drug effects thereon depending on the strains of mice, types of behavior, experimental situations, etc., and that these factors should be considered in the behavioral procedures of drug evaluation.

References

Al-Ani, A.T., Tunnicliff, G., Rick, G.T., and Kerkut, G.A. GABA production, acetylcholinesterase activity and biogenic amine levels in brain for mouse strains differing in spontaneous activity and reactivity. *Life Sci.*, 9:21–27, 1970.

Bovet, D., Bovet-Nitti, F., and Oliverio, A. Genetic aspects of learning and memory in mice. *Science*, 163:139–149, 1969.

Cheney, D.L., and Goldstein, A. The effect of p-chlorophenylalanine on opiate-induced running, analgesis, tolerance and physical dependence in mice. *J. Pharmacol. Exp. Ther.*, 177:309–315, 1971.

Chiuech, C.C., and Moore, K.E. d-Amphetamine-induced release of "newly synthesized" and "stored" dopamine from the caudate nucleus. *J. Pharmacol. Exp. Ther.*, 192:642–653, 1975.

Durkin, T.P., Hashem-Zadeh, H., Mandel, P., Kempf, J., et al. Genotypic variation in the dopaminergic inhibitory control of striatal and hippocampal cholinergic activity in mice. *Pharmacol. Biochem. Behav.*, 19:63–70, 1983.

Hirabayashi, M., Iizuka, M., and Tadokoro, S. Simple and easy method for measurement of ambulatory activity in mice. *Folia Pharmacol. Japon.*, 74:629–639, 1978. (Abs. in English and text in Japanese.)

Hoffman, H.S., Fleshler, M., and Chorney, H. Discriminated bar press avoidance. *J. Exp. Anal. Behav.*, 4:309–316, 1961.

Kuribara, H., and Tadokoro, S. Comparison of susceptibilities to the effects of antipsychotic drugs on lever-press avoidance responses between mice and rats. *Jpn. J. Pharmacol.*, 33:1127–1133, 1983a.

Kuribara, H., and Tadokoro, S. Differences in cholinergic agonist- and cholinergic antagonist-induced changes in avoidance responses between dd mice and Wistar rats. *Jpn. J. Psychopharmacol.*, 3:139–149, 1983b.

Kuribara, H., and Tadokoro, S. Conditioned lever-press avoidance responses in mice: Acquisition processes and effects of diazepam. *Psychopharmacology*, 82:36–40, 1984.

Kuribara, H., Haraguchi, H., and Tadokoro, S. Comparisons between discrete lever-press and shuttle avoidance responses in mice: Acquisition processes and effects of psychoactive drugs. *Jpn. J. Pharmacol.*, 38:141–151, 1985.

Kuribara, H., and Tadokoro, S. Differences in acquisition of discrete lever-press and shuttle avoidance responses in 6 strains of mice. *Jpn. J. Pharmacol.*, 40:303–310, 1986.

Messeri, P., Oliverio, A., and Bovet, D. Relation between avoidance and activity: A diallel study in mice. *Behav. Biol.*, 7:733–742, 1972.

Oliverio, A. Genetic factors in the control of drug effects on the behaviour of mice. In: Van Abeelen, J.H.F. (ed.), *The Genetics of Behaviour*. Amsterdam: North-Holland Pub. Co., 1974, pp. 375–395.

Rethy, C.R., Smith, C.B., and Villarreal, J.E. Effects of narcotic analgesics upon the locomotor activity and brain catecholamine content of the mouse. *J. Pharmacol. Exp. Ther.*, 176:472–479, 1971.

Sekiguchi, S. Strain differences of mice for open field behaviour, circadian rhythms, and morphine reactivity. *Med. Educ. Shiga Univ. Hum. Soc. Ped.*, No. 32:93–107, 1982.

Wahlsten, D. Genetic experiments with animal learning: A critical review. *Behav. Biol.*, 7:143–182, 1972.

Differential Erythropoietic Response to Oxiracetam in Alzheimer's Disease and Multi-Infarct Dementia: A Potential Biological Marker

Roland J. Branconnier, M.A.,[1] Eric C. Dessain, M.D.,[1] Maureen E. McNiff, M.Ed.,[1] Nancy E. Harto, Ph.D.,[1] Karen F. Spera, B.A.,[1] Richard Katz, Ph.D.,[2] Frank Stallone, Ph.D.,[2] Joseph DeVeaugh-Geiss, M.D.,[2] and Jonathan O. Cole, M.D. [1]

Introduction

Dementia has been described as a clinical syndrome associated with chronic diffuse cerebral hemispheric dysfunction resulting in deterioration of intellectual capacity characterized by multiple involvement of cognition, memory, language, visual-spatial skills, and personality (Wells, 1979). However, dementia is a generic term that does not imply a specific etiology, but a group of diseases that present with similar clinical features (Schneck et al., 1982).

Dementia is observed principally in the aged. Differential diagnostic studies of aged patients with dementia revealed that in 80 percent of the cases the underlying specific diseases causing the dementia were Alzheimer's disease (AD) (50 percent), multi-infarct dementia (MID) (12 percent), or combination of both (18 percent). The remaining 20 percent had a broad spectrum of disorders such as normal pressure hydrocephalus, metabolic or endocrine diseases, drug toxicity, depressive pseudodementia, or intracranial masses (Wells, 1979).

Early differential diagnosis of the etiology of the dementia is critical since effective medical management and psychosocial intervention can minimize the functional disability of the demented patient. For example, although AD is a chronic, progressive, irreversible neurological disease, during the early stages of the disease, reality orientation and remotivation therapy can contribute to maintaining the patient's ability to cope with activities of daily living (West, 1983). Patients with MID can be helped by slowing the progression of the dementia by effectively preventing further infarction with control of risk factors for cerebral atherosclerosis, vascular surgery to alleviate stenosis or occlusion of cerebral arteries, or pharmacologic treatment with vasodilators, anticoagulants, or antiplatelet agents (Meyer, 1981). Lastly, dementia resulting from such diseases as normal pressure hydrocephalus, metabolic or endocrine disorders are usually completely reversible if specific therapy is applied before permanent brain damage has occurred (Besdine, 1982). While the differential diagnosis of dementia arising from the latter group of diseases can be made accurately with special laboratory procedures, the differential diagnosis of AD and MID is more difficult.

The most valid and reliable instrument for differentiating AD and MID is the Hachinski Ischemia Scale (HAS) (Hachinski et al., 1975; Hachinski, 1983). However, the accuracy of the HAS is dependent on a careful neurological examination and detailed history of the onset and progression of the dementia. Since these data are often unavailable, a reliable biological marker for MID would be a valuable adjunct in the differential diagnosis of dementia. Preliminary findings suggest that the nootropic, oxiracetam, differentially affects erythropoiesis in AD and MID, and therefore may be a potential biological marker for MID.

Method

Fourteen male and female patients who met DSM-III criteria for dementia were studied. Following an extensive differential diagnostic screening that included a detailed history, Hachinski Ischemia Scale (Hachinski et al., 1975), physical and neurological examinations, ECG, EEG, chest x-ray, clinical laboratory battery, and CT scan, 3 male and 5 female patients met DSM-III criteria for primary degenerative dementia, and 3 male and 3 female patients met DSM-III criteria for MID. All patients were rated as mild to moderate severity (GDS 3 to 5) on the Global Deterioration Scale of Reisberg et al. (1982).

---

[1] Institute for Psychopharmacologic Research, 1842 Beacon St., Brookline, MA 02146.

[2] CIBA-GEIGY Pharmaceuticals, Summit, NJ 07901.

This was a multi-center, single-blind, dose-ranging study of oxiracetam in the treatment of the cognitive symptoms of AD and MID. Qualified patients were given one placebo tablet h.s. for 2 weeks. On their second visit active treatment was initiated at 400 mg oxiracetam h.s. for 1 week. If no untoward effects were encountered the dosage was raised to 400 mg b.i.d. for the second week then 800 mg b.i.d. for the next 2 weeks. The dosage was then titrated to 1000 mg b.i.d., 1200 mg b.i.d. and 1600 mg b.i.d. each for a 4-week period.

Results

The demographic characteristics of the study sample are shown in Table 1. No significant differences in age, sex, degree of cognitive impairment or baseline depression were observed between the AD and MID groups. In contrast, the MID group had significantly higher scores on the HAS, and higher systolic and diastolic blood pressures than the AD group.

Following oxiracetam treatment, hematologic studies that were normal at baseline revealed that oxiracetam lowered hematocrit (HCT). Hematocrit data were analyzed by a Two-Factor Mixed-Design ANOVA. The between–group, nonrepeated factor was diagnosis. The within group, repeated factor was time. Results showed that there was no significant main effect for diagnosis, $F(1,12) = 0.24, p > 0.05$. Likewise, there was no statistically significant main effect for time, $F(3,10) = 1.33, p > 0.05$. In contrast, there was a highly statistically significant diagnosis × time interaction detected, $F(3,10) = 12.75, p < 0.001$ that indicated that the MID group was selectively affected.

Likewise, red blood cell counts showed that there was no significant main effect for diagnosis $F(1,12) = 0.01, p > 0.05$ or for time, $F(3,10) = 1.72, p > 0.05$. However, a highly statistically significant diagnosis × time interaction was observed, $F(3,10) = 13.16, p < 0.001$.

Analysis of the hemoglobin data revealed that, overall, there was no significant difference between diagnostic groups, $F(1,12) = 0.15, p > 0.05$. Similarly, there was no main effect for time, $F(3,10) = 1.59, p > 0.05$, and only a trend toward a significant diagnosis × time interaction, $F(3,10) = 3.07, p < 0.08$.

A discriminative validity analysis was also performed. If a 2-percent drop in HCT was used as a cutting score, diagnostic groups could be correctly classified with 100-percent accuracy, Fisher Exact, $p < 0.0003$. Thus, as a diagnostic test, a 2-percent drop in HCT has a sensitivity and specificity of 100 percent.

Investigation into the mechanism of the drop in HCT showed that the reduction in HCT did not result from occult blood loss (negative guaiac and blood in urine) or he-

TABLE 1. Demographic Characteristics of Study Sample.

Variable	AD[1] ($n = 8$)	MID[2] ($n = 6$)	t	p
Age	65.0 ± 2.6	68.5 ± 3.2	1.09	0.298
Sex[*] (%Female)	63	50	–	0.670
Mini-Mental State	17.1 ± 1.7	16.5 ± 1.1	0.28	0.784
Global Deterioration	3.7 ± 0.3	3.8 ± 0.2	0.84	0.212
Hamilton Depression	5.8 ± 1.7	5.5 ± 1.7	0.10	0.920
Hachinski Ischemia	0.8 ± 0.3	8.7 ± 0.5	14.18	<0.001
Supine Systolic BP	124.1 ± 4.8	142.7 ± 5.4	2.56	0.025
Supine Diastolic BP	69.8 ± 3.2	81.8 ± 4.2	2.31	0.039
Supine Pulse Rate	66.5 ± 3.6	68.8 ± 2.9	0.48	0.640

Data expressed as Mean (± SE).

[*] Fisher Exact Test.

[1] Alzheimer's disease.

[2] Multi-infarct dementia.

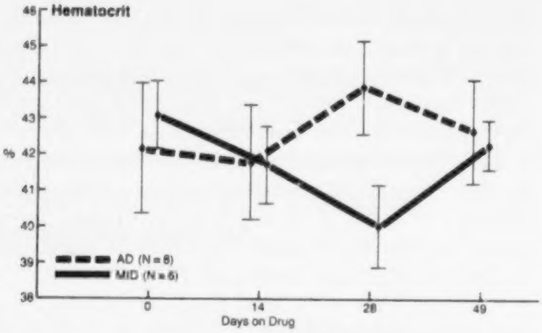


FIGURE 1. Time-response curve for hematocrit.

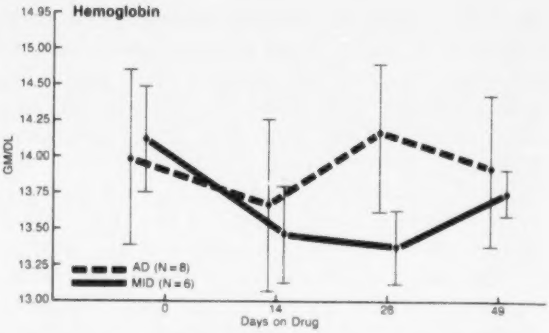


FIGURE 3. Time-response curve for hemoglobin.

molysis (negative antihuman globulin titer and normal bilirubin), but appeared to be related to reduced erythropoiesis since reticulocyte counts did not increase. While this suggests a bone marrow suppression, platelet estimates, and white blood cell counts were normal, and erythropoietin (EPT) levels were low, not high as would be expected in marrow suppression. This latter finding indicates that the reduction in erythropoiesis was probably secondary to decreased bone marrow stimulation by EPT.

Discussion

Oxiracetam is an analog of piracetam, a nootropic drug of putative value in the treatment of the cognitive/behavioral symptoms of dementia (Nicholas, 1982). Agents of this class have been shown to stimulate the conversion of adenosine diphosphate (ADP) to adenosine triphosphate (ATP) under hypoxic conditions, and it is this mechanism of action that is hypothesized to be the basis for its putative therapeutic effect in dementia (Gobert, 1972; Blass, 1980). This mechanism may also account for the differential effect of oxiracetam on erythropoiesis in AD and MID.

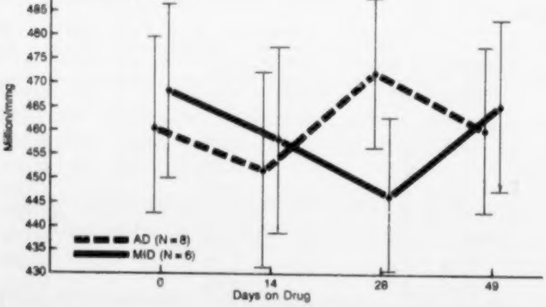


FIGURE 2. Time-response curve for red blood cell counts.

Erythropoiesis is regulated by tissue oxygenation. Under conditions of tissue hypoxia, the kidney is stimulated to secrete an enzyme, renal erythropoietic factor (REF). REF then cleaves a circulating precursor protein of erythropoietin to yield the active glycoprotein hormone, erythropoietin (EPT). Active EPT stimulates committed stem cell proliferation in the bone marrow and erythrocyte production is increased (Guyton, 1981).

It is hypothesized that the metabolic enhancing effect of oxiracetam, and probably other piracetam analogs as well, may improve tissue oxygenation in hypoxic tissue affected by atherosclerosis. As a response to this stimulus, erythropoietin levels are reduced, and erythropoietic activity is lowered. Since tissue hypoxia secondary to athersclerosis is probably more severe in MID than AD, this may be the basis for the differential erythropoietic response to oxiracetam. Thus, the findings suggest that it may be possible to administer oxiracetam and measure erythropoietin suppression as a diagnostic test for MID.

References

Besdine, R.W. Dementia. In: Rowe, J.W., and Besdine, R.W. (eds.), *Health and Disease in Old Age.* Boston: Brown and Co., 1982, pp. 97–114.

Blass, J.P. Metabolic dementias. In: Amaducci, L., Davidson, A.N., and Antuono, P. (eds.), *Aging of the Brain and Dementia*. New York: Raven Press, 1980, pp. 261–270.

Gobert, J.G. Genese d'un medicament: le piracetam metabolisation et recherche biochemique. *J. Pharmacol. Belg.*, 27:281, 1972.

Guyton, A.C. (ed.), *Textbook of Medical Physiology*, 6th edition. Philadelphia: W.B. Saunders, 1981.

Hachinski, V.C., Iliff, L., DuBoulay, G.H., et al. Cerebral blood flow in dementia. *Arch. Neurol.*, 32:632–637, 1975.

Hachinski, V.C. Differential diagnosis of alzheimer's disease: multi-infarct dementia. In: Reisberg, B. (ed.), *Alzheimer's Disease: The Standard Reference*. New York: The Free Press, 1983, pp. 188–192.

Meyer, J.S. Strategies for drug development in multi-infarct dementia. In: Crook, T., and Gershon, S. (eds.), *Strategies for the Development of an Effective Treatment for Senile Dementia*. New Canaan, CN: Mark Powley Associates, 1981, pp. 209–213.

Nicholas, B.J.R. Chemistry and pharmacology of nootropics. *Drug Develop. Res.*, 2:463–474, 1982.

Reisberg, B., Ferris, S.H., DeLeon, M.J., and Crook, T. The global deterioration scale for assessment of primary degenerative dementia. *Am. J. Psychiatry*, 139:1136–1139, 1982.

Schneck, M.K., Reisberg, B., and Ferris, S.H. An overview of the current concepts of alzheimer's disease. *Am. J. Psychiatry*, 139:165–173, 1982.

Wells, C.E. Diagnosis of dementia. *Psychosomatics*, 20:517–522, 1979.

West, H.L. Therapeutic interventions with the elderly. In: Ernst, N.A., and Glazer-Waldman, H.R. (eds.), *The Aged Patient: A Sourcebook for the Allied Health Professional*. Chicago: Year Book Medical Publishers, 1983, pp. 257–267.

Thioridazine Metabolism and Effects on Stereotyped Behavior in Mentally Retarded Patients

Mark H. Lewis, Ph.D.,[1] Robert A. Steer, Ed.D.,[3] Judith Favell, Ph.D.,[2] James McGimsey, M.D.,[2] Luther Clontz, M.D.,[2] Carole Trivette,[2] Wendy Jodry,[2] Stephen R. Schroeder, Ph.D.,[1] Robert C. Kanoy, Ph.D.,[1] and Richard B. Mailman, Ph.D.[1]

Introduction

Thioridazine is one of the most frequently prescribed psychotropic drugs for behavioral control of mentally retarded patients (Aman & Singh, 1980; Lipman, 1970). Despite this, its efficacy in this population has not been adequately established (Aman & Singh, 1980; Davis, 1971; Davis, Sprague, & Werry, 1969; Heistad et al., 1982; Singh & Aman, 1981). The psychopharmacology of this drug is particularly interesting as thioridazine is believed to have at least two metabolites that contribute significantly to its behavioral effects. Recently, these S-oxidized metabolites (mesoridazine and sulforidazine) have been shown to be 2 to 100 times more potent than thioridazine depending on the *in vitro* test being used (Kilts et al., 1985; Lewis et al., 1983; Niedzwiecki et al., 1984). Thus, although circulating concentrations of thioridazine have been found to be poor predictors of behavioral outcome (Axelsson, 1977; Axelsson & Martensson, 1977), quantification of the drug plus its metabolites might increase this correlation markedly.

The present study sought to establish the efficacy of thioridazine for the control of stereotyped movement disorder. In addition, the study investigated whether the concentrations of the parent drug plus metabolites could better predict behavioral outcome. Finally, the question of whether abrupt withdrawal from chronically administered thioridazine would result in increased stereotyped behavior, other withdrawal emergent symptoms, or tardive dyskinesia was also studied.

The effects of thioridazine on the stereotyped behavior of institutionalized mentally retarded patients were determined using a double-blind, placebo-controlled, crossover design. Daily rates of several stereotyped behaviors were quantified over a 3- to 4-month period for each subject using computer-supported observational recording methods. Serum concentrations of thioridazine and its metabolites were determined over time for each subject by high performance liquid chromatography (HPLC). Three subjects went through an abrupt withdrawal design while three subjects were drug free at the start of the study and dose was titered to a preselected therapeutic range of active drug and metabolites.

Methods

Subjects

Six adult institutionalized mentally retarded patients exhibiting high levels of stereotyped movements (e.g., body rocking, head rolling, and hand flapping) participated in the study. Half the subjects had been free from antipsychotic medication for at least 6 months while the other half had been receiving at least 100 mg/day of thioridazine for at least the previous 6 months. Informed consent was obtained from the parent or guardian of each participant.

Experimental Design

A double-blind, placebo-controlled, crossover design was used to assess the effects of

---

[1] Biological Sciences Research Center and Departments of Psychiatry and Pharmacology, University of North Carolina School of Medicine, Chapel Hill, NC 27514.
[2] Western Carolina Center, Morganton, NC.
[3] Department of Psychiatry, University of Medicine and Dentistry of New Jersey — SOM, Camden, NJ 08103.

Address all correspondence to: Dr. Mark H. Lewis, Biological Sciences Research Center, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

either abrupt withdrawal from thioridazine or initiation of thioridazine treatment in drug-free patients. Four conditions with alternating on-drug and off-drug phases (withdrawal experiment) or alternating off-drug, on-drug phases (prospective experiment) were employed. Typically, each condition lasted approximately 4 weeks. One major difference in the prospective experiment was the adjustment of drug dose dependent upon rapid (24 hr) analysis of parent drug and metabolite blood levels. Each client was started on 100 mg of thioridazine with the desired endpoint that blood concentrations of "total active thioridazine metabolites" be equal to approximately 1000 ng "thioridazine equivalents"/ml.

Behavioral Measures

Continuous recording of selected behavioral topographies was carried out either three or four times each day for 30 minute periods by trained observers using electronic digital data collectors (Lewis et al., 1985). The effects of abrupt discontinuation of thioridazine were also assessed by the Abnormal Involuntary Movement Scale (AIMS).

Drug and Metabolite Determinations

Circulating concentrations of thioridazine and its major S-oxidized and *N*-demethylated metabolites (thioridazine-2-sulfoxide, thioridazine-2-sulfone, thioridazine-5-oxide, nor-thioridazine) were determined in serum by the HPLC method of Kilts et al. (1982).

Data Analysis

Time-series analysis employing the C-statistic was used to determine if changes in the rate of stereotyped responding following initiation or cessation of thioridazine treatment were statistically significant (Tryon, 1982; Young, 1941).

Results

Thioridazine and Metabolite Levels

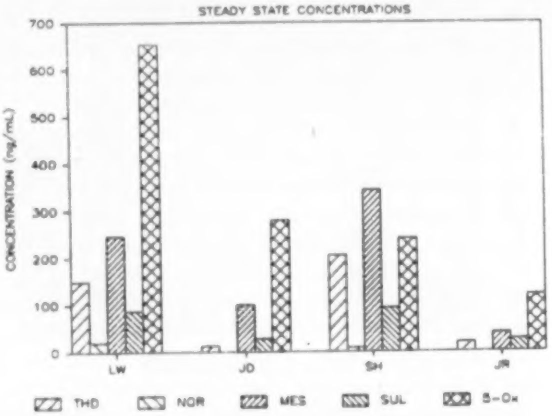


FIGURE 1. Drug and metabolite concentrations in patients on identical doses (100 mg/day) of thioridazine.

Discontinuation of thioridazine resulted in nondetectable blood levels of drug or metabolites 48 to 72 hours after the last dose. Both the absolute concentration and the relative proportion of drug and metabolites differed widely in individuals taking a constant dose or even identical doses of thioridazine (Figure 1). In all cases, the concentration of the parent drug was exceeded by one or both of the active S-oxidized metabolites. The ratio of active to inactive metabolites, which proved to be an indicator of behavioral outcome, was also variable across subjects (Figure 2) and not systematically related to dose. While total antidopaminergic activity and dose were positively correlated, abrupt increases in antidopaminergic activity were seen at specific dosage increments (Figure 3). [Total antidopaminergic activity was deter-

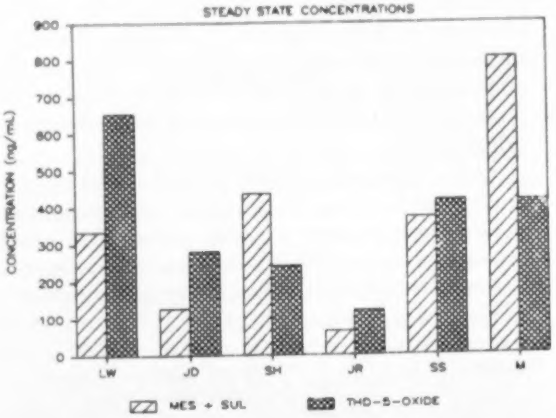


FIGURE 2. Ratio of active to inactive metabolites of thioridazine in all subjects.

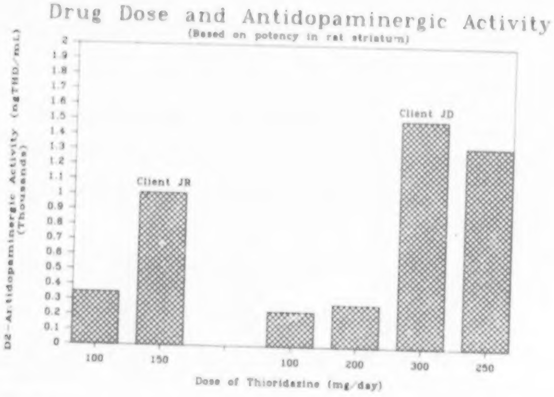


FIGURE 3. Total antidopaminergic activity in blood as a function of dose of thioridazine for two subjects.

mined by computing the sum of parent drug plus active metabolites weighted by their *in vitro* potencies in competing with ^{3}H-spiperone in rat striatal homogenates (Bylund, 1981; Kilts et al., 1985; Lewis et al., 1983)].

Thioridazine and Stereotyped Behavior

The results of the time series analyses employing the C-statistic showed that the initiation and cessation of thioridazine administration were significantly related to changes in the rates of responding for a variety of stereotypic behaviors. However, the pattern of results was inconsistent across subjects, with thioridazine increasing the rate of stereotyped responding in subjects SH and M (e.g., Figure 4) not appreciably affecting the rate in JR, JD, and SS (data not shown), and decreasing the rate in LW (Figure 5). Within the same individual, thioridazine administration or discontinuation was found to have similar effects on different stereotyped behavioral topographies.

Analysis of the AIMS data showed no evidence of tardive dyskinesia or withdrawal dyskinesias in any of the patients studied. Moreover, there did not appear to be evidence for withdrawal emergent symptoms. Indeed, only in one patient was there a clear indication of behavioral deterioration in the off-drug condition. This patient exhibited increases in screaming and pacing while showing decreases in stereotyped behavior following thioridazine discontinuation.

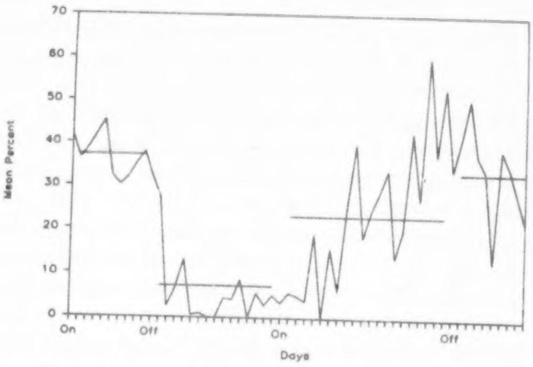


FIGURE 4. Rate of stereotyped body rocking for subject M during both thioridazine and placebo conditions.

Blood Levels and Behavioral Response

Relatively high levels of the parent drug and its active S-oxide metabolites coupled with relatively low levels of the inactive metabolite thioridazine-5-sulfoxide were associated with an increase in stereotyped behavior (subjects SH and M, Figure 2). The reverse was associated with either no change (subjects SS, JR, JD, Figure 2) or some improvement in behavior (subject LW, Figure 2). Neither dose nor total antidopaminergic activity appeared to be related to behavioral outcome. No evidence for a differential effect of drug administration or drug and metabolite blood levels on specific behavioral topographies was observed. For example, thioridazine administration or discontinuation had the same effect on three different stereotyped behaviors of subject M.

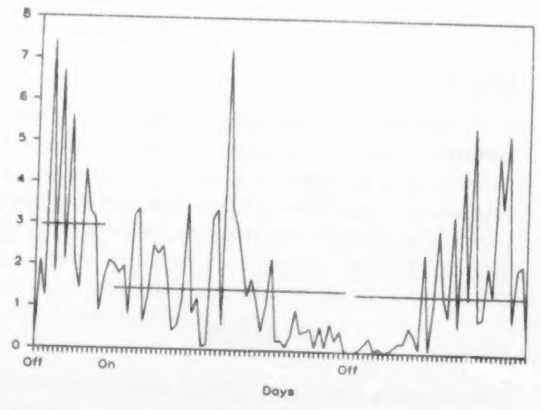


FIGURE 5. Rate of self-injurious behavior for subject LW during both thioridazine and placebo conditions.

Discussion

A number of reviewers have documented the serious methodological problems that have plagued psychopharmacological studies with mentally retarded patients (Freeman, 1970; Lipman et al., 1978; Sprague & Werry, 1971). As a result, the effects of thioridazine and other antipsychotic drugs on stereotyped responding or other behavioral categories have not been adequately demonstrated. The present study examined the effects of thioridazine on stereotyped behavior using a series of double-blind, placebo-controlled, intensive, single-case designs. Despite the fact that a frequently reported benefit of thioridazine is a reduction in stereotyped behavior (Heistad et al., 1982), we could find little support for such a position. Indeed, our data suggest that thioridazine in dosages typically used with this population may exacerbate stereotyped responding. These conclusions, while based on a relatively small number of subjects, are drawn from an intensive 3- to 4-month examination of each patient's behavior in several settings with concomitant determinations of drug and metabolite blood levels.

Thioridazine has been reported to suppress stereotypies at 2.0 to 2.5 mg/kg with either no improvement or behavioral deterioration observed at higher doses (Breuning, 1982; Singh & Aman, 1981). Our data suggest that even relatively low doses of thioridazine (100 mg/day) may exacerbate stereotyped responding depending on parent drug and metabolite levels. Heistad et al. (1982), however, have reported an 18-percent increase in stereotyped responding following thioridazine withdrawal. This effect was observed despite patients being maintained on relatively high doses of thioridazine.

A major conclusion to be drawn from the present study is the importance of quantifying parent drug and metabolite concentrations in mentally retarded clients when examining the behavioral effects of thioridazine. The wide variation in concentration supports the importance of blood level determinations and suggests that even fixed-dose studies may be inadequate. Another observation of some significance is the lack of withdrawal emergent symptoms observed in our subjects despite using an abrupt withdrawal design and patients on long-term thioridazine.

The lack of effect of thioridazine on stereotyped behavior may be due to its potent anti-cholinergic effects (Bylund, 1981) or lack of effect on striatal dopamine function (Bunney, 1984). However, the importance of establishing the effects of thioridazine on various classes of behavior seen in mentally retarded patients is underscored by its widespread use. Specific behavioral topographies must be intensively examined with appropriate attention paid to the role of drug metabolism. The results reported here suggest that thioridazine will not effectively suppress stereotyped behavior in dosages typically employed but may increase such responding. Low concentrations of active metabolites relative to inactive metabolites may be associated with some suppression of stereotyped behavior.

Acknowledgments

The authors wish to thank the staff and residents of the developmental center for their assistance and cooperation. The assistance of Ms. Susan McGimsey, Ms. Dorothy Billings, and Mr. Jerry Poteet is greatly appreciated. Requests for reprints should be sent to Dr. Richard B. Mailman. This research was supported by PHS Grants HD–16834, MH–37404, and Center Grant HD–03110.

References

Aman, M.G., and Singh, N.N. The usefulness of thioridazine for treating childhood disorders — fact or folklore? *Am. J. Ment. Def.*, 84:331–338, 1980.

Axelsson, R. On the serum concentrations and antipsychotic effects of thioridazine, thioridazine side-chain sulfoxide and thioridazine side-chain sulfone, in chronic psychotic patients. *Curr. Therap. Res.*, 21:588–589, 1977.

Axelsson, R., and Martensson, E. The concentration pattern of nonconjugated thioridazine metabolites in serum by thioridazine treatment and its relationship to physiological and clinical variables. *Curr. Therap. Res.*, 21:561–586, 1977.

Breuning, S.E. An applied dose response curve of thioridazine with the mentally retarded: aggressive, self-stimulatory, intellectual, and workshop behaviors—a preliminary report. *Psychopharm. Bull.*, 18:57–59, 1982.

Bylund, D.B. Interactions of neuroleptic metabolites with dopaminergic, alpha-adrenergic and muscarinic cholinergic receptors. *J. Pharm. Exper. Therap.*, 217:81–86, 1981.

Bunney, B.S. Antipsychotic drug effects on the electrical activity of dopaminergic neurons. *Trends Neurosci.*, 7:212–215, 1984.

Davis, K.V. The effect of drugs on stereotyped and non-stereotyped operant behaviors in retardates. *Psychopharm.*, 22:195–213, 1971.

Davis, K.V., Sprague, R.L., and Werry, J.S. Stereotyped behavior and activity level in severe retardates: The effect of drugs. *Am. J. Ment. Def.*, 73:721–727, 1969.

Heistad, G.T., Zimmermann, R.L., and Doebler, M.I. Long-term usefulness of thioridazine for institutionalized mentally retarded patients. *Am. J. Ment. Def.*, 87:243–251, 1982.

Kilts, C.D., Knight, D., Widerlov, E., et al. Effects of thioridazine and its metabolites on dopaminergic function. Drug metabolism as a determinant of the *in vivo* antidopaminergic actions of thioridazine. *J. of Pharmacol. Exper. Therap.*, 231:334–342, 1984.

Kilts, C.D., Patrick, K.S., Breese, G.R., and Mailman, R.B. Simultaneous determination of thioridazine and its S-oxidized and *N*-demethylated metabolites using HPLC on radially compressed silica. *J. Chromat.*, 232:377–391, 1982.

Lewis, M.H., Baumeister, A.A., McCorkle, D.L., and Mailman, R.B. A computer-supported method for analyzing behavioral observations: studies with stereotypy. *Psychopharm.*, 85:204–209, 1985.

Lewis, M.H., Staples, L., McCorkle, D., and Mailman, R.B. Thioridazine pharmacodynamics: *in vitro* correlations and dependence on drug metabolism. *Soc. Neurosci. Abs.*, 9:432, 1983.

Lipman, R.S. The use of psychopharmacological agents in residential facilities for the retarded. In: Menolascino, F.J. (ed.), *Psychiatric Approaches to Mental Retardation*. New York: Basic Books, 1970.

Niedzwiecki, D.M., Mailman, R.B., and Cubeddu, L.X. Greater potency of mesoridazine and sulforidazine than thioridazine on striatal dopamine autoreceptors. *J. Pharmacol. Exper. Therap.*, 228:686–689, 1984.

Singh, N.N., and Aman, M.G. Effects of thioridazine dosage on the behavior of severely mentally retarded persons. *Am. J. Ment. Def.*, 85:580–587, 1981.

Sprague, R.L., and Werry, J.S. Methodology: psychopharmacological studies with the retarded. In: Ellis, N.R. (ed.), *Int. Rev. Res. Ment. Ret.* Vol. 5. New York: Academic Press, 1971.

Tryon, W.W. A simplified time-series analysis for evaluating treatment interventions. *J. App. Beh. Anal.*, 15:423–429, 1982.

Young, L.C. On randomness in ordered sequences. *Ann. Math. Stat.*, 12:293–300, 1941.

*U.S. GOVERNMENT PRINTING OFFICE: 1986-491-327:21003

The *Psychopharmacology Bulletin* is available on subscription from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Subscription price $19.00 per year for the United States. All other countries add $4.75 for postage. This price was in effect at time of printing. Prices are subject to change. Please make check or money order payable to the Superintendent of Documents. An annual subscription for four quarterly issues begins with the next issue following receipt of the order. Single copies and back issues may also be ordered from the Superintendent of Documents. The expiration date is printed on the top line of the address label. Change of address and complaints about non-receipt of issues should be sent to the Superintendent of Documents, and should include the old address, perferably a mailing label, as well as the new address.

ORDER FORM Mail To: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

Enclosed is $________ ☐ check,
(U.S. Currency Only)
☐ money order, or charge to my
Deposit Account No.
☐☐☐☐☐☐☐–☐

Order No.______________

VISA
master charge

Credit Card Orders Only

Total charges $________ Fill in the boxes below

Credit Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiration Date Month/Year ☐☐☐☐

Please enter my subscription to: **PSYCHOPHARMACOLOGY BULLETIN [PSBU]**
@ $19.00 domestic, @ $23.75 foreign

Name—First, Last

Street address

Company name or additional address line

City **State** **ZIP Code**

(or Country)

PLEASE PRINT OR TYPE

For Office Use Only.

	Quantity	Charges
Enclosed		
To be mailed		
Subscriptions		
Postage		
Foreign handling		
MMOB		
OPNR		
UPNS		
Discount		
Refund		

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
Alcohol, Drug Abuse, and Mental
Health Administration
Rockville MD 20857

Official Business
Penalty for Private Use $300

SPECIAL FOURTH CLASS MAIL
POSTAGE AND FEES PAID
PHS/ADAMHA
PERMIT NO. G-283

DHHS Publication No. (ADM) 86-173
Printed 1986

22/4

PSYCHOPHARMACOLOGY BULLETIN

NATIONAL INSTITUTE OF MENTAL HEALTH

LD S & T C
U.S. DOCUMENTS
NEWARK PUBLIC LIBRARY

Special Feature:

Treatment Research With the Mentally Retarded Mentally Ill

1986
Vol. 22, No. 4

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

HE 20.8109:

Editor-in-Chief:

Nina R. Schooler, Ph.D.
NIMH, Rockville, Md.

Special Features Editor:

Allen Raskin, Ph.D.
Lafayette Clinic, Wayne State University
Detroit, Mich.

Editorial Assistant:

Anne J. Ambler, M.A.
NIMH, Rockville, Md.

Associate Editors:

Jonathan O. Cole, M.D.
McLean Hospital, Belmont, Mass.

Seymour Fisher, Ph.D.
University of Texas Medical Center
Galveston, Texas

Arnold J. Friedhoff, M.D.
New York University School of Medicine

Gerald L. Klerman, M.D.
Cornell University Medical Center, New York

David J. Kupfer, M.D.
Western Psychiatric Institute & Clinic
University of Pittsburgh School of Medicine

Judith L. Rapoport, M.D.
NIMH, Bethesda, Md.

Donald S. Robinson, M.D.
Bristol-Myers Pharmaceuticals
Wallingford, Conn.

The *Psychopharmacology Bulletin* is prepared by the Division of Clinical Research of the National Institute of Mental Health. Its purpose is to facilitate the dissemination and exchange of information among the national and international scientific community. This emphasis is on rapid, informal reporting of work which has not appeared in the more formal literature. In accordance with new policy set forth by our Associate Editors, we are no longer accepting unsolicited papers for publication in the *Bulletin*.

All material published in the *Psychopharmacology Bulletin* is in the public domain unless otherwise noted. Publication in the *Bulletin* therefore does not preclude publication elsewhere.

Vol. 22, No. 4 1986

PSYCHOPHARMACOLOGY BULLETIN

Table of Contents

Methodological Issues in Treatment Research of Mental Illness in the Mentally Retarded—

1045 Introduction—*Shervert Frazier*

1046 Overview of Research in Psychopharmacological Treatment of the Mentally Ill/Mentally Retarded—*Ronald S. Lipman*

1055 Limiting Factors in the Use of *DSM-III* Criteria With Mentally Ill/Mentally Retarded Persons—*Robert Sovner*

1060 The Nature and Types of Mental Illness in the Mentally Retarded—*Frank J. Menolascino, Andrew Levitas, and Carl Greiner*

1072 Psychometric and Demographic Characteristics of the Psychopathology Instrument for Mentally Retarded Adults—*Michael G. Aman, Janine E. Watson, Nirbhay N. Singh, Sarah H. Turbott, and Catherine P. Wilsher*

1077 Components of the Design of Psychopharmacology Studies—*Barbara Geller*

1081 Treatment Outcome Research for Depression in Mentally Retarded Children and Youth: Methodological Issues—*Johnny L. Matson*

1086 Summary: Challenges for Research—*Eleanor D. Dibble*

Neuropeptides and Psychoneuroimmunology—

1089 Neuropeptides as Modulators of Immune Function—*John E. Morley and Neil Kay*

1093 Life Events, Depression, and Natural Killer Cell Activity—*Michael Irwin, Marcia Daniels, Eda T. Bloom, and Herbert Weiner*

1097 Methionine Enkephalin: Immunomodulator in Normal Volunteers (*in Vivo*)—*Nicholas P. Plotnikoff, Gerald C. Miller, Suman K. T. Solomon, Robert E. Faith, Larry D. Edwards, and Anthony J. Murgo*

The Forum—

1101 Issues in the Diagnosis of Attention Deficit Disorder: A Cautionary Note on the Gordon Diagnostic System—*Richard Milich, William E. Pelham, and Stephen P. Hinshaw*

B1 **Psychopharmacology—A Recurring Bibliography—**

NEWARK PUBLIC LIBRARY

DEC 17 1986

U. S. GOVT. PUBS.
DEPOSITORY 376

Methodological Issues in Treatment Research of Mental Illness in the Mentally Retarded[1]

Co-Chairs:

Ronald S. Lipman, Ph.D.
Friends Hospital
Philadelphia, PA

Eleanor D. Dibble, D.S.W.
National Institute of Mental Health
Rockville, MD

Introduction

The reorganization of the National Institute of Mental Health in October 1985 gave special emphasis to research on disorders of children and adolescents. Clinical, biological, and treatment studies were consolidated into a single branch, the Child and Adolescent Disorders Research Branch in the Division of Clinical Research. One of the most important problems receiving new emphasis in this Branch is the population of mentally retarded who are also mentally ill. This population is one of the largest with a serious and chronic illness, but effective clinical research has been hampered by several problems. Prevalence of these disorders in the community, where most of these patients now reside following deinstitutionalization, is difficult to establish. The diagnosis of specific mental disorders is complicated by the presence of retardation. The applicability of diagnostic criteria and assessment measures validated in research with individuals of normal intelligence cannot be assumed. Finally, specialized assessment techniques and research designs may be needed in order to assess the efficacy of treatments for mental disorders among the mentally retarded.

The following papers, presented at a special workshop for this population, reflect a beginning effort to resolve some of the research problems. The National Institute of Mental Health is committed to encouraging the research needed for more adequate treatment of the mentally retarded who are also mentally ill. This overview provides an assessment of the state-of-the-art, and we hope it proves useful to future research in this underdeveloped area.

Shervert H. Frazier, M.D.
Director
National Institute of Mental Health

---

[1] This workshop was held on May 30, 1986, in conjunction with the New Clinical Drug Evaluation Unit (NCDEU) meeting.

Overview of Research in Psychopharmacological Treatment of the Mentally Ill/Mentally Retarded

Ronald S. Lipman, Ph.D.[1]

Introduction

Estimates of the prevalence of mental retardation vary from less than 1 percent to 12 to 13 percent. In general, 3 percent is taken as the prevalence figure and that translates to about 7,250,000 mentally retarded people (Breuning and Poling 1982). About 3 percent reside in institutions and the majority of those that are institutionalized are severely or profoundly retarded; that is, have IQs of less than 40 on the Wechsler Adult Intelligence Scale (WAIS; Wechsler 1955), or 35 on the Stanford-Binet test (Terman & Merrill 1973). The very large majority of retarded persons in the United States, 89 percent, are classified by IQ test scores as mildly retarded (IQs between 55 and 69 on the WAIS).

The most generally accepted definitions of mental retardation, both by the American Association of Mental Deficiency (Grossman 1983) and in the *DSM-III: Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980), include three defining characteristics: (a) subaverage intellectual functioning (usually 2 or more standard deviations below the mean on a standard IQ test), (b) concurrent deficits in personal independence and social responsibility, and (c) onset before the age of 18.

Chromosomal abnormality—mainly Downs syndrome—accounts for roughly 15 percent of mental retardation; metabolic and nutritional disorders such as phenylketonuria are responsible for about 2 or 3 percent; about another 5 to 10 percent of cases of retardation are attributable to such factors as drug intoxication, infections, brain injury, or disease. The large majority of the mentally retarded—mostly the mildly and moderately retarded—are thought to owe their condition to environmental-cultural factors broadly grouped under such categories as psychosocial disadvantage and sensory deprivation.

Prevalence of Drug Usage

Institutional Settings

In a 1966–67 survey of drug usage in institutions for the retarded that included 142 State and 31 private institutions, Lipman (1970) found that 51 percent of residents were receiving psychotropic drugs and that two phenothiazine medications—thioridazine (Mellaril) and chlorpromazine (Thorazine)—accounted for 58 percent of all psychotropic drug prescriptions. These two drugs were the most frequently prescribed agents in 91 percent of the institutions participating in the survey. Moreover, 25 percent of these institutions typically used psychotropic medication from 4 years to an "indefinite" time period for their residents who received medication. While typical dosages were usually within the manufacturer's suggested range, it was not unusual to find maximal dosages well above the upper limits suggested by the pharmaceutical firms. The issue of polypharmacy was not examined in this survey.

Sprague (1977) reviewed the medical files on 1,094 residents of a large midwestern institution and found that 64 percent were receiving a psychotropic and/or antiepileptic medication. Thioridazine and chlorpromazine were prescribed for 34 and 5 percent of the residents, respectively. Polypharmacy was very much in evidence. While the median dose of thioridazine was 200 mg/day, the maximal dose was 1200 mg/day.

In another study, Marker (1975) reviewed the records for all the retarded residents in four State mental hospitals in a southern State. It was reported that about 60 percent of the residents were receiving phenothiazines with thioridazine and chlorpromazine being the most widely used. Moreover, 75 percent of the residents were receiving two or more drugs;

---

[1] Friends Hospital, Philadelphia, PA.

Reprint requests: Ronald S. Lipman, Ph.D., Friends Hospital, Roosevelt Boulevard and Adams Avenue, Philadelphia, PA 19124.

"many of these persons were receiving 4-5 drugs and some were receiving as many as 7-8 drugs" (p. 1).

DiMascio (1975), in a survey of two northwestern State institutions, found, in contrast to the Sprague and Marker results, much less polypharmacy. At one institution 53 percent of the residents were receiving a psychotropic drug, while at the other institution, 25 percent were on medication. The most frequently used psychotropic drug in both institutions was thioridazine, with chlorpromazine characterized as a "distant second."

Other surveys by Tu (1979) in Canada and Pulman, Pook, and Singh (1979) in New Zealand reported high rates of psychotropic drug usage, 42 and 47 percent, respectively. The treatment prevalence rates rose to roughly 60 percent when antiepileptic drugs were also included in the total.

Hill, Balow, and Bruininks (1985) reported the results of a national survey of drug usage conducted in 1978/1979 at the 1985 Pharmacotherapy and Mental Retardation Workshop sponsored by NIMH. They found a prevalence rate of 38 percent, excluding psychotropic drugs prescribed for epilepsy (36.3%). The major tranquilizers accounted for about 80 percent of psychotropic drug prescriptions. Roughly 3 percent of these medications were given for psychiatric conditions; the remainder were given for "overactive behavior" (p. 283).

Drug Usage in Community Settings

There is a more limited data base of the prevalence of psychotropic drug usage in the community or with children attending special education classes. In an Illinois survey of 3,306 trainable retarded children aged 3 to 21, it was found that about 7 percent received psychotropic medication for the management of behavior disorders, primarily hyperactivity (Gadow & Kalachink 1981). Roughly 12 percent of the sample was on antiepileptic medication.

Of real interest was the fact that stimulant medication tended to be the drug class of choice, although the major tranquilizers, primarily thioridazine, were a very close second. In general, doses were far lower than the dosage patterns observed in institutions.

In a second survey of about 2,600 handicapped children 3 to 5 years old attending special education class, Gadow (1981) found a 7.9 percent prevalence of psychotropic drug usage. Stimulant medications were used almost five times as frequently as neuroleptics. Again, these medications were prescribed for behavior disorders in which hyperactivity was present.

The most extensive study of drug usage in community residential facilities for the retarded was the one conducted by Hill and his associates cited above (1985). A true-probability sample of about 1,000 residents was selected from a nationally defined sample. Hill found that 25.9 percent were receiving psychotropic medication and 21.5 percent were receiving antiepileptic medications. About two thirds of these medications were neuroleptics. A small minority of these medications were given for a "psychiatric condition"; the great majority of medications were prescribed for "overactive behavior" (Hill et al. 1985, p. 283).

Data obtained by Agran and Martin (1985) on about 250 mentally retarded adults receiving services from a comprehensive community retardation agency found results quite similar to those reported by Hill; roughly half (48%) of the adults surveyed were receiving a psychotropic and/or anticonvulsant medication. About two thirds (66%) of the group received neuroleptics.

Psychotropic drug prevalence was also reported for retarded residents of public and community facilities by Intagliata and Rinck (1985). The study sample consisted of 295 clients randomly selected from the total of 3,600 individuals who resided in Missouri's community residential facilities and 171 clients randomly selected from the roughly 2,000 residents of the State's public residential facilities. The typical pattern of psychotropic drug usage was found. Thus, 54 percent of residents in public institutions and 36 percent of residents in community facilities were receiving psychotropic medications. The comparable rates for anticonvulsant drug use were 41.5 percent and 20.7 percent. As before, major tranquilizers—thioridazine, chlorpromazine, and haloperidol, in that order—were the most frequently used psychotropic medications, and stimulants were the least frequently used. Antidepressant drugs were also used infrequently in both residential groups. Polypharmacy was examined and dosage information was presented. While some polypharmacy was noted—4 percent in community residential facility clients and 13.4 percent in public residential facility clients—it was not judged to represent dangerous drug combinations. In general, dosage levels seemed more conservative than those found earlier by Lipman (1970).

These data taken as a whole suggest that about 35 to 50 percent of mentally retarded persons living in public institutions and about 25 to 35 percent of community residents are on psychotropic medications. When anticonvulsant medications are also considered, these prevalence rates rise from 20 to 30 percent. Clearly, then, these data support Aman's characterization of the retarded as among "the most medicated people in society" (Aman & Singh 1983).

Rationale for Pharmacotherapy in the Mentally Retarded

In some ways this workshop brings to mind the story of the man who had lost his car keys and was looking for them under the light of a nearby lamp post. He was asked by a well-meaning passerby why he was looking for his keys under the lamp post when his car was parked a few hundred yards away. He replied, "This is where the light is; this is where I can see." While there is undoubtedly "light" in the pharmacotherapy of the mentally retarded who have a dual diagnosis of schizophrenia or depression or mania, there is no question but that drugs are being prescribed for other reasons. One has only to look at the recent national survey by Hill and his associates (1985) to find that only a small minority of the mentally retarded in institutions and in community facilities who were receiving drugs were receiving them for a "psychiatric condition." Specifically 5.2 percent of the institutionalized and 2.9 percent of those residing in a community facility were said by those staff members most familiar with each resident to be receiving psychotropic drugs for a psychiatric condition. The overwhelming majority were on medication for "overactive behavior" (Hill et al. 1985, p. 283). These survey data confirm the view of the many reviewers of the pharmacotherapy literature involving retarded persons (Aman & Singh 1983; Lipman et al. 1978; Sprague & Werry 1971) who characterize the prescribing of psychotropic drugs as "usually prescribed to suppress maladaptive and nonconforming behavior" (Aman & Singh 1983, p. 318). These maladaptive and nonconforming behaviors include behaviors characterized as "aggressive," "assaultive," "hostile," "acting-out," "hyperactive," "self-injurious," "self-stimulating," and "stereotypic."

The actual literature on the efficacy of psychotropic drugs for psychiatric conditions in the retarded is very limited. Is this because the retarded are protected from other psychiatric disorders such as schizophrenia, major depressive disorder, or generalized anxiety disorder—or because most clinicians assume that schizophrenia will respond to antipsychotic medication regardless of the IQ of the patient and do not mount studies to investigate the question? In this regard, Eaton and Menolascino (1982) surveyed the extent of psychiatric illness in a sample of community-based mentally retarded people living in the Omaha, Nebraska, area. Of 168 individuals receiving psychiatric evaluation, about two thirds (68%) were given a psychiatric diagnosis. The most common diagnoses were organic brain syndromes occurring with transient behavioral or psychotic reactions (30%), followed by personality disorder (27%), adjustment reactions (21%), and schizophrenia (21%). No affective disorders and only one case of psychoneurosis were diagnosed. The diagnosis of organic brain syndrome was based on findings from mental status, physical and neurological examinations, and/or on a history of etiologically significant factors. The diagnosis of organic brain syndrome with behavioral reaction was used for that subgroup of retarded individuals who frequently displayed inappropriate acting-out behavior (e.g., emotional liability, impulsivity, poor judgment in social situations, and frequent temper tantrums).

The absence of diagnosed cases of affective illness in the Eaton and Menolascino (1982) survey probably reflects the low prevalence of this disorder among retarded persons, since Sovner and Hurley (1983) have reported that individuals with mental retardation were found to manifest the full range of affective disorders, i.e., depression and mania. They point out that individuals with all levels of severity of retardation can be adequately diagnosed as suffering from an affective illness. In the mildly and moderately impaired, standard *DSM-III* criteria can be employed. Gualtieri and Keppel (1985) believe that the standard diagnostic categories may be particularly tricky to apply to the severely and profoundly impaired but that to at least some degree traditional psychiatric categories are relevant. However, they also see merit in the development of a new psychiatric taxonomy which pays more attention to the behavioral position of psychologists like Baumeister and Rollings (1976), who maintain that psychiatric taxonomies are irrelevant to such problems as self-injurious behavior or aggression. It would also seem pertinent to screen for various types of conduct disorder and attention deficit disorder with or without hyperactivity in retarded children. Clearly, it would be helpful to support state-of-the-art diagnostic studies across the spectrum of severity of mental retardation and in cohorts of the mentally retarded living in public institutions, in various types of community residence facilities, and at home.

This author's intuition and sense of the literature suggest that mildly and moderately retarded individuals with a dual diagnosis will respond in keeping with expectations for their psychiatric diagnosis: i.e., mentally retarded schizophrenics will respond to neuroleptics much as nonretarded schizophrenics; retarded individuals with an affective disorder will respond to antidepressants and lithium as do the nonretarded; retarded hyperactive children will respond to stimulants as do normal IQ hyperactive children. But there is apt to be more variability in response to pharmacotherapy among the severely and profoundly retarded. In part, however, these anticipated differences are likely to reflect differences in the basic taxonomy of the psychiatric diagnoses and an overlay of organic and neurological impairment in the more severely retarded.

The anticipated similarity of therapeutic response in retarded and nonretarded schizophrenic patients is supported, in the main, by the results of a recent study comparing the relative efficacy of two neuroleptic medications. Menolascino and associates (1985) randomly assigned a total of 61 patients, about equally grouped into a retarded and nonretarded subsample of schizophrenics, to a 3-month trial of either thioridazine (Mellaril) or thiothixene (Navane). In this rater-blind study, it was concluded that thiothixene and thioridazine were as effective in the retarded schizophrenic as in the nonretarded schizophrenic. The following differences were observed: Optimal dose levels were lower in the retarded, and thiothixene alleviated symptoms reliably faster than thioridazine in the retarded but not in the nonretarded. Side effects were similar in both groups with drowsiness and sedation observed more frequently in the thioridazine-treated patients, and extrapyramidal symptoms (which responded well to symptomatic therapy) seen more often in thiothixene-treated patients. Menolascino indicates that thiothixene is the preferred drug not only because of its faster action in the retarded but because of its low incidence of drowsiness and sedation, which was judged likely to avoid further impairment in cognition.

Unfortunately, there is a dearth of literature on the treatment of affective illness in the mentally retarded. Naylor and associates (1974) studied 17 retarded inpatients who evidenced major depression and bipolar disorders. In the 14 patients who completed the 2-year placebo-controlled, double-blind trial with lithium, a statistically significant decrease in the "number of weeks ill" was noted. Actual episodes of illness were not significantly reduced. In another study involving patients with mood swings, Rivinus and Harmatz (1979) tested four patients with bipolar disorder and one patient with mania. These patients were judged to have had a statistically significant response to lithium and to have relapsed within about 6 months after double-blind placebo substitution. Again, in the main, similarities in therapeutic response between the retarded and nonretarded seem to outweigh differences.

If there are studies employing psychotropic medications for the treatment of anxiety disorders in the retarded, they have escaped the notice of reviewers (Aman & Field 1985; Lipman 1982). As with other classes of psychotropic medications, those studies which have employed the minor tranquilizers in the treatment of the mentally retarded have focused on behavioral symptoms such as hyperactivity, aggressiveness, and self-injurious behavior. The few better controlled symptom-focused studies suggest that the minor tranquilizers may actually increase hyperactivity and distractibility and decrease desirable behavior such as constructive play (cf. La Veck & Buckley 1961; Zrull et al. 1963).

Gadow (1985) has recently reviewed the literature regarding the stimulant drug treatment of hyperactive retarded and nonretarded children. This area is particularly difficult since hyperactivity is a symptom which may occur in the context of attention deficit disorder, in the context of conduct disorder, and in the context of organic brain syndrome. While the stimulant medications have been found very beneficial in the treatment of children with attention deficit disorders both behaviorally and on many laboratory tests of attention, vigilance, and memory, they are of arguable benefit for children with conduct disorders. Campbell and her colleagues (1982), concluded that stimulants failed to produce a satisfactory response. Minimal support for the efficacy of *d*-amphetamine in delinquents is provided in an early study by Eisenberg and colleagues (1963) and in a later study by Maletzky (1974). Diagnostic criteria were not spelled out in either study. In the Maletzky study, those delinquents who showed the best response were those who were most hyperactive prior to treatment and may well have met criteria for attention deficit disorder.

In his review, Gadow concludes that the response to stimulant medications among the more moderately impaired mentally retarded is similar to that of "hyperactive" nonretarded children: that is, mainly beneficial. In the more severely and profoundly retarded, response to the stimulants is primarily negative. These findings are probably tied to the presence of different diagnostic groupings in the different IQ levels studied. Diagnostic differences are also implicated in the relative efficacy with which Aman (1983) views the stimulants as contrasted with Gadow (1985). In this regard, Aman (1983) does not see the stimulants as "having a major role to play in the treatment of the mentally retarded." Very clearly, further studies are needed employing well-defined samples of retarded and normal children with attention deficit disorders and conduct disorders in which stimulant medications are tested in double-blind, placebo-controlled studies.

With regard to the pharmacotherapy of conduct disorders, there is a growing consensus that lithium carbonate is effective for the treatment of such symptoms as aggression, hyperactivity, and hostility. In a recent publication, Campbell and associates (1984) found lithium to be significantly more therapeutic than placebo in decreasing behavioral symptoms of hospitalized, aggressive children with conduct disorder. This was a well-designed and well-analyzed study and in a companion paper (Platt et al. 1984), Campbell and her colleagues reported that lithium had few, if any, adverse cognitive effects. Other studies have also shown a beneficial effect for lithium on aggression and hostility. These studies are reviewed by Campbell (Campbell et al. 1982). Behavioral symptoms of aggressiveness, self-injurious behavior, and chronic hyperactivity were reported to respond positively to lithium in a series of case studies reviewed by Aman and Singh (1983). Sovner and Hurley (1981) have also reviewed the literature in this area and conclude that "the available data lend tentative support for the use of lithium to manage behavior disorders in retarded individuals which are characterized by lifelong hyperactivity, aggressiveness, and/or self-mutilation" (p. 191).

It seems clear from the available literature that the response to lithium in the retarded and nonretarded vis-a-vis conduct disorder and/or the cardinal behavioral symptoms associated with the aggressive subtype of conduct disorder is essentially continuous across the chronological and mental age spectrum.

To make this point more generally, although time does not permit a full explication, there seems to be a qualitatively similar response to psychotropic drugs across the chronological and mental age spectrum for most disorders known to this writer. This issue was particularly salient with regard to stimulant medication where much of the early literature talked of a paradoxical response to stimulants in hyperactive children. However, the research of Rapoport and her associates (1980) and Werry and colleagues (Aman et al. 1984; Werry & Aman 1984) has indicated a qualitative similarity in response in normal children and adults as well as in hyperactive children. In general, all three groups showed a facilitation of cognitive performance and a reduction in physical activity.

Until some 5 years ago there was a real

question about whether or not children could be depressed and, if so, whether or not they could be helped by antidepressant medication. The answer to both questions was yes. Although there have not been many studies focused on the treatment of depression in the retarded, the review of the limited literature by Sovner and Hurley (1983) suggests that antidepressants and lithium may play a role in individuals with these dual diagnoses.

As has already been indicated in this paper, both retarded and nonretarded schizophrenic adults have been shown to respond favorably to neuroleptics by Menolascino and colleagues (1985) and there is evidence that children with autism and/or schizophrenia respond therapeutically to neuroleptics (cf. Fish et al. 1966), particularly to the more stimulating neuroleptics such as thiothizene. It is this author's impression that many of the neuroleptic studies conducted with hospitalized autistic and/or schizophrenic children included many children who were functionally mentally retarded.

In general, then, the literature tends to support the hypothesis that neither chronological age nor mental age is an important modifier of drug response, given reasonable diagnostic correspondence among samples.

Given that pharmacotherapy with the mentally retarded is overwhelmingly focused on the suppression of maladaptive behavior symptoms such as hyperactive, aggressive, or self-injurious behavior, how effective are psychotropic drugs? Here it should be pointed out that the vast majority of pharmacotherapy studies with the retarded fail to meet the basic criteria of adequate scientific trials, which have been clearly set forth in the excellent review by Sprague and Werry (1971).

Sprague and Werry (1971) indicated six minimal criteria that should be incorporated into any scientifically sound drug study. These criteria include (a) the use of placebo controls; (b) random assignment to treatment conditions; (c) "blind" evaluation of drug effects to protect against potential observer bias; (d) standardized dosages; (e) standardized evaluations; and (f) appropriate statistical tests. Unfortunately, most drug studies that employed retarded individuals do not meet acceptable methodological criteria. Aman and Singh (1983) added the additional criterion that clinical drug trials should be free of other confounding medications and noted how often this self-evident criterion had been violated in drug studies with retarded people.

It is interesting that although the data base of psychotropic drug studies with the retarded is particularly lacking in scientific merit, the quality of scientific reviews is particularly good. The most recent review in that tradition is by Michael Aman (1983). He concluded that the minor tranquilizers seem contraindicated and the antidepressants have not been adequately tested in well-designed studies. This author finds lithium carbonate promising. The efficacy of the stimulants is questionable; well-designed, diagnostically focused studies would be required to sort out whether these patients manifest behavioral problems in the context of attention deficit disorders, conduct disorders, organic brain syndromes, or childhood psychosis.

Major Tranquilizers

In a comprehensive review of 174 psychotropic drug studies with retarded persons, Lipman and associates (1978) reported that 60 percent of these studies dealt with the major tranquilizers. We have also seen that the bulk of psychotropic prescriptions written in institutional and community living facilities are for the major tranquilizers, primarily thioridazine, chlorpromazine, and the butyrophenone haloperidol. This is also the area of greatest concern since the long-term use of the phenothiazines, particularly in higher dosages, has been shown both to produce cognitive impairment and to be associated with the occurrence of a devastating abnormal involuntary movement disorder called tardive dyskinesia (TD). Aman has recently reviewed the literature relating drugs and learning in retarded individuals and, with the usual caveat that the literature is methodologically poor, reaches the same general conclusion as other previous reviewers of this literature (cf. Sprague & Werry 1971; Lipman 1979): the "preponderance of evidence suggests . . . the antipsychotics . . . are capable of depressing performance, especially at high doses" (Aman 1984, p. 159). The dose issue is a very important one since Werry and Aman (1975) found that high and low doses (0.05 mg/kg/day vs. 0.025 mg/kg/day) of haloperidol had opposite cognitive effects in nonretarded, aggressive, conduct disorder children. The low dose facilitated performance on a continuous performance task, whereas the high dose caused some deterioration on a test of short-term memory. Using somewhat higher doses of haloperidol needed to produce a clinically therapeutic effect with hospitalized aggressive children with conduct disorder, Campbell and associates (Platt et al. 1984) found that haloperidol, relative to placebo, caused significant decreases in Porteus Maze Test quotient scores and a slowing of reaction time on a simple reaction time task. These studies with the nonretarded as well as a few reasonably well-controlled studies with retarded persons (Adamson et al. 1958; Buck & Menolascino 1968; Claghorn 1972; Ucer & Kreger 1969) have indicated a therapeutic effect for haloperidol, both relative to placebo and to other phenothiazines, on acting-out and self-injurious behaviors. A few short-term studies support the efficacy of thioridazine on such behavior as well as on stereotyped behaviors such as rocking (Alexandris & Lundell 1968; Davis 1971; Davis et al. 1969; Le Vann 1970). Pimozide was also recently reported by White and Aman (1985) to be significantly more effective than placebo in reducing irritability and hyperactivity/noncompliance in a small sample of moderately to profoundly retarded residents. This drug seems particularly promising since at the 6 mg/day dosage used, it did not interfere with the learning of a discrimination learning task.

When one turns to concerns regarding the iatrogenic induction of TD via the use of neuroleptics, the literature is rather bleak in that we still have no effective active treatment for this abnormal involuntary movement disorder and the prevalance of the disorder is high enough to pose a real public health concern (Gardos & Cole 1980). A good general presentation of this area has been made by Gardos and Cole (1980) and an excellent study with retarded persons has just been published by Gualtieri and colleagues in the April issue of the *Archives of General Psychiatry* (Gualtieri et al. 1986). In this systematic neuroleptic withdrawal study, the prevalence of TD was 34 percent. The diagnosis of TD was used only when symptoms of abnormal movement persisted for at least 16 weeks after complete neuroleptic withdrawal. Moreover, 5 of the 13 patients with TD, 13 percent of the total sample, continued to be characterized by moderate to severe TD after 3 years of followup. Needless to say, these percentages translate into literally hundreds of thousands of retarded persons who are probably diagnosable as having TD. It should be stressed that Gualtieri and associates (1986) were able to identify only 3 of the 13 diagnosed cases of TD during maintenance neuroleptic therapy. They suggest that in order to detect early (presumably mild and reversible) forms of TD, a drug-free period of at least 4 weeks' duration be periodically employed. It should also be noted that in their data only total neuroleptic dose, and not the number of drug holidays, was related to the risk of developing severe TD.

The use of any treatment regimen should always involve (a) the assessment of potential benefits and risks; (b) a weighing of potential benefits and risks of alternative treatments (if they exist); and (c) the consideration of the risks involved in doing nothing. While this is obviously a complex judgment, it is, nevertheless, a critically important decision that should be based on solid scientific knowledge.

Conclusion

What, then, is the bottom line? Here this writer would agree with the position espoused by Gualtieri and Keppel (1985). Basically, the neuroleptics have a role in the short-term treatment of acutely disturbed mentally retarded persons *but* given the substantial risk of TD and the likelihood of cognitive impairment, long-term treatment might better employ behavior modification procedures.

From a research perspective, emphasis should be given to psychotropic medications which are less likely to result in cognitive impairment and serious side effects. Prime candidates for more systematic study are lithium and the psychostimulants such as methylphenidate and magnesium pemoline. In general, psychotropic drug studies should include measures of clinical efficacy, cognitive learning performance, and, whenever possible, behavioral alternatives. The National Institute of Mental Health and the National Institute of Child Health and Human Development should stimulate and encourage research in this area and might sponsor future workshops focused on issues of diagnosis and the development of objective, reliable, sensitive, and valid rating scales.

The relevant Institutes should encourage meaningful research in this area by the use of administrative devices such as the Request for Proposals and Request for Applications. It is not enough for the Institutes to play a reactive role to the field; they must encourage, stimulate, lead, and nourish, or progress in this area will continue to be slow and spotty.

References

Adamson, W.C.; Nellis, B.P.; Runzo, G.; Cleland, C.; and Killian, E. Use of tranquilizers for mentally deficient patients. *J. Disabled Children* 96:159–164, 1958.

Agran, M., and Martin, J.E. Establishing socially validated drug research in community settings. *Psychopharmacol. Bull.* 21:285–290, 1985.

Alexandris, A., and Lundell, F.W. Effect of thioridazine, amphetamine and placebo on the hyperkinetic syndrome and cognitive area in mentally deficient children. *Can. Med. Assoc. J.* 98:92–96, 1968.

Aman, M.G. Psychoactive drugs in mental retardation. In: Matson, J.C. and Andrasik, F., eds. *Treatment Issues and Innovations in Mental Retardation.* New York: Plenum Press, 1983. pp. 455–513.

Aman, M.G. Drugs and learning in mentally retarded persons. In: Burrows, C.D. and Werry, J.S., eds. *Advances in Human Psychopharmacology.* Vol. 3. Greenwich, CT: JAI Press, 1984. pp. 121–163.

Aman, M.G., and Field, C.J. Pharmacological management. In: Singh, N.N., and Wilton, K.M., eds. *Mental Retardation in New Zealand: Provisions, Services and Research.* Christchurch, N.Z.: Whiteoulls, 1985. pp. 223–249.

Aman, M.G., and Singh, N.N. Pharmacological intervention. In: Matson, J.L. and Malick, S.A., eds. *Handbook of Mental Retardation.* New York: Pergamon Press, 1983. pp. 317–337.

Aman, M.G.; Vamos, M.; and Werry, J.S. Effects of methylphenidate in normal adults with reference to drug action in hyperactivity. *Aust. N.Z. J. Med.* 18:86–88, 1984.

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders.* 3d ed. Washington, DC: The Association, 1980.

Baumeister, A.A., and Rollings, P. Self-injurious behavior. In: Ellis, N.R., ed. *International Review of Research in Mental Retardation.* Vol. 8. New York: Academic Press, 1976. pp. 1–34.

Breuning, S.E., and Poling, A.D. *Drugs and Mental Retardation.* Springfield, IL: Charles C Thomas, 1982.

Burk, H.W., and Menolascino, F.J. Haloperidol in emotionally disturbed mentally retarded individuals. *Am. J. Psychiatry* 124:147–149, 1968.

Campbell, M.; Cohen, I.L.; and Small, A.M. Drugs in aggressive behavior. *J. Am. Acad. Child Psychiatry* 21:107–117, 1982.

Campbell, M.; Small, A.M.; Green, W.F.; Jennings, S.J.; Perry, R.; Bennett, W.G.; and Anderson, L. Behavioral efficacy of haloperidol and lithium carbonate. *Arch. Gen. Psychiatry* 41:650–656, 1984.

Claghorn, J.L. A double-blind comparison of haloperidol (Haldol) and thioridazine (Mellaril) in outpatient children. *Curr. Ther. Res.* 14:785–789, 1972.

Davis, K.V. The effect of drugs on stereotyped and non-stereotyped operant behaviors in retardates. *Psychopharmacology* (Berlin) 22:195–213, 1971.

Davis, K.V.; Sprague, R.L.; and Werry, J.S. Stereotyped behavior and activity level in severe retardates: The effect of drugs. *Am. J. Ment. Defic.* 73:721–727, 1969.

DiMascio, A. "Review and analysis of actual psychotropic drug use in 2,000 mental retardates in two state institutions." Paper presented at meeting of the American Association on Mental Deficiency, Portland, OR, May 1975.

Eaton, L.F., and Menolascino, F.J. Psychiatric disorders in the mentally retarded: Types, problems, and challenges. *Am. J. Psychiatry* 139:1297–1303, 1982.

Eisenberg, L.; Lachman, R.; Molling, [illegible].; Lockner, A.; Mizelle, J.D.; and Conners, C.K. A psychopharmacologic experiment in a training school for delinquent boys. *Am. J. Orthopsychiatry* 33:431–447, 1963.

Fish, B.; Shapiro, T.; and Campbell, M. Long-term prognosis and the response of schizophrenic children to drug therapy. *Am. J. Psychiatry* 123:32–39, 1966.

Gadow, K.D. Prevalance of drug treatment for hyperactivity and other childhood behavior disorders. In: Gadow, K.D., and Loney, J., eds *Psychosocial Aspects of Drug Treatment for Hyperactivity.* Boulder, CO: Westview Press, 1981. pp. 13–76.

Gadow, K.D. Prevalance and efficacy of stimulant drug use with mentally retarded children and youth. *Psychopharmacol. Bull.* 21:291–303, 1985.

Gadow, K.D., and Kalachnik, J. Prevalance and pattern of drug treatment for behavior and seizure disorders of TMR students. *Am. J. Ment. Defic.* 85:588–595, 1981.

Gardos, G., and Cole, J.O. Overview: Public health issues in tardive dyskinesia. *Am. J. Psychiatry* 137:776–781, 1980.

Grossman, H.J. *Manual of Terminology and Classification in Mental Retardation.* Washington, DC: American Association on Mental Deficiency, 1983.

Gualtieri, C.T., and Keppel, J.M. Psychopharmacology in the mentally retarded and a few related issues. *Psychopharmacol. Bull.* 21:304-309, 1985.

Gualtieri, C.T.; Schroeder, S.R.; Hicks, R.E.; and Quade, D. Tardive dyskinesia in young mentally retarded individuals. *Arch. Gen. Psychiatry* 43:335-340, 1986.

Hill, B.K.; Balow, E.A.; and Bruininks, R.H. A national study of prescribed drugs in institutions and community residential facilities for mentally retarded people. *Psychopharmacol. Bull.* 21:279-284, 1985.

Intagliata, J., and Rinck, C. Psychoactive drug use in public and community residential facilities for mentally retarded persons. *Psychopharmacol. Bull.* 21:268-278, 1985.

LaVeck, G., and Buckley, P. The use of psychopharmacological agents in retarded children with behavior disorders. *J. Chronic Dis.* 13:174-183, 1961.

LeVann, L.J. Clinical experience with tarasan and thioridazine in mentally retarded children. *Appl. Therapeutics* 12:30-33, 1970.

Lipman, R.S. The use of psychopharmacological agents in residential facilities for the retarded. In: Menolascino, F.J., ed. *Psychiatric Approaches to Mental Retardation.* New York: Basic Books, 1970. pp. 387-398.

Lipman, R.S. Psychotropic drugs in mental retardation: The known and the unknown. In: Gadow, K.D., and Bialer, I., eds. *Advances in Learning and Behavioral Disabilities.* Vol. 1. Greenwich, CT: JAI Press, 1982. pp. 261-282.

Lipman, R.S.; DiMascio, A.; Reatig, N.; and Kirson, P. Psychotropic drugs and mentally retarded children. In: Lipton, M.A.; DiMascio, A.; and Killam, K.F., eds. *Psychopharmacology: A Generation of Progress.* New York: Raven Press, 1978. pp. 1437-1449.

Maletzky, B.M. *d*-Amphetamine and delinquency. *Dis. Nerv. Syst.* 35:543-547, 1974.

Marker, G. "The use of phenothiazines (major tranquilizers) on mentally retarded persons—A review of the research literature." Unpublished manuscript, 1975. (Available from Mental Health Law Project, 2021 L St., N.W., Washington, DC 20036.)

Menolascino, F.J.; Ruedrich, S.L.; Golden, C.J.; and Wilson, J.E. Diagnosis and pharmacotherapy of schizophrenia in the retarded. *Psychopharmacol. Bull.* 21:316-322, 1985.

Naylor, G.J.; Donald, J.M.; LePoidevin, D.; and Reid, A.H. A double-blind trial of long-term lithium therapy in mental defectives. *Br. J. Psychiatry* 124:52-57, 1974.

Platt, J.E.; Campbell, M.; Green, W.H.; and Grega, D.M. Cognitive effects of lithium carbonate and haloperidol in treatment-resistant aggressive children. *Arch. Gen. Psychiatry* 41:657-662, 1984.

Pulman, R.M.; Pook, R.B.; and Singh, N.N. Prevalence of drug therapy for institutionalized mentally retarded children. *Aust. J. Ment. Retardation* 5:212-214, 1979.

Rapoport, J.L.; Buchsbaum, M.S.; Weingartner, H.; Zahn, T.P.; Ludlow, C.; and Mikkelsen, E.J. Dextroamphetamine—Its cognitive and behavioral effects in normal and hyperactive boys and normal men. *Arch. Gen. Psychiatry* 37:933-943, 1980.

Rivinus, T.M., and Harmatz, J.S. Diagnosis and lithium treatment of affective disorder in the retarded: Five case studies. *Am. J. Psychiatry* 136:551-554, 1979.

Sovner, R., and Hurley, A. The management of chronic behavior disorders in mentally retarded adults with lithium carbonate. *J. Nerv. Ment. Dis.* 169:191-195, 1981.

Sovner, R., and Hurley, A.D. Do the mentally retarded suffer from affective illness? *Arch. Gen. Psychiatry* 40:61-67, 1983.

Sprague, R.L. Overview of psychopharmacology for the retarded in the United States. In: Mittler, P., ed. *Research to Practice in Mental Retardation: Biomedical Aspects.* Vol. 3. Baltimore, MD: University Park Press, 1977. pp. 199-202.

Sprague, R.L., and Werry, J.S. Methodology of psychopharmacological studies with the retarded. In: Ellis, N.R., ed. *International Research in Mental Retardation.* Vol. 5. New York: Academic Press, 1971. pp. 147-219.

Terman, L.M., and Merrill, M.A. *Stanford-Binet Intelligence Scale. Manual for the Third Revision, Form L-M.* Boston: Houghton Mifflin, 1973.

Tu, J. A survey of psychotropic medication in mental retardation facilities. *J. Clin. Psychiatry* 40:125-128, 1979.

Ucer, E., and Kreger, K.C. A double-blind study comparing haloperidol with thioridazine in emotionally disturbed, mentally retarded children. *Curr. Ther. Res.* 11:278-283, 1969.

Wechsler, D. *Manual for the Wechsler Adult Intelligence Scale.* New York: Psychological Corporation, 1955.

Werry, J.S., and Aman, M.G. Haloperidol and methylphenidate in children: Effects on cognitive function. *Arch. Gen. Psychiatry* 32:790-795, 1975.

Werry, J.S., and Aman, M.G. Methylphenidate in hyperactive and enuretic children. In: Greenhill, L., and Shopsin, B., eds. *The Psychobiology of Childhood.* Jamaica, NY: Spectrum Publications, 1984. pp. 183-195.

White, T.R., and Aman, M.G. Pimozide treatment in disruptive severely retarded patients. *Aust. N.Z. J. Psychiatry* 19:92-94, 1985.

Zrull, J.P.; Westman, J.C.; Arthur, B.; and Bell, W.A. A comparison of chlordiazepoxide, *d*-amphetamine, and placebo in the treatment of the hyperkinetic syndrome in children. *Am. J. Psychiatry* 120:590-591, 1963.

Limiting Factors in the Use of *DSM–III* Criteria With Mentally Ill/Mentally Retarded Persons

Robert Sovner, M.D.[1]

Introduction

The treatment of psychiatric disorders in mentally retarded adults is severely hampered by the lack of diagnostic criteria which take into account the presence of developmental disabilities. However, current concepts regarding psychiatric disorders as discrete syndromes and their applicability, when there is coexisting mental retardation, are not at issue here. There is ample evidence that mentally retarded persons develop the full range of psychiatric disorders (Carlson 1979; Corbett 1979; Lund 1985; Reid 1972*a*, 1972*b*; Sovner & Hurley 1983), and that *DSM–III: Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980) categories are valid—but not necessarily inclusive (Menolascino 1972)—for classifying behavioral-emotional disturbances in the developmentally disabled.

Nevertheless, the *DSM–III* was designed for mentally disordered persons with normal intelligence and psychosocial functioning. The effects of developmental disabilities upon the diagnostic process were not taken into account. As a result, *DSM–III* criteria are difficult to use when evaluating mentally retarded individuals, especially those with severe disabilities.

Effects of Mental Retardation on Clinical Presentation

Mental retardation affects the types of information which can be used for diagnostic decision-making and the diagnostic process itself. The interactions between mental retardation and mental illness are the result of four factors (see Table 1). These factors reflect the profound biopsychosocial effects of developmental disabilities.

Intellectual Distortion

Intellectual distortion refers to the effects of the mentally retarded person's diminished ability to think abstractly and communicate intelligibly. Deficits in the ability to observe and describe one's own behavior and feeling states severely hamper the elicitation of diagnostically relevant information (Carlson 1979; 1981) because the specific symptom criteria for most Axis I diagnoses rely on self-reports of essentially subjective experiences.

These difficulties are compounded by the poor communication skills of mentally retarded persons. They may have any combination of speech impediments, limited vocabulary, concrete thinking, hearing deficits, and receptive and expressive aphasia. There may also be the complete absence of language function.

TABLE 1. Four Nonspecific Factors Associated With Mental Retardation Which Influence the Diagnostic Process.

Factor	Definition	Clinical Impact
Intellectual Distortion	Concrete thinking and impaired communication skills	Inability of patient to label own experiences and report them
Psychosocial Masking	Impoverished social skills and life experiences	Unsophisticated presentation and lack of poise during interview can result in missed symptoms and misattribution of nervousness and silliness as psychiatric features.
Cognitive Disintegration	Stress-induced disruption of information processing	Bizarre presentation and psychotic-like state may be misdiagnosed as schizophrenia.
Baseline Exaggeration	Increase in severity of pre-existing cognitive deficits and maladaptive behaviors	Creates difficulty in establishing illness features, target symptoms, and outcome measures.

---

[1] Mount Auburn Hospital, Cambridge, MA.

Reprint requests: Robert Sovner, M.D., Suite 101, 697 Cambridge Street, Brighton, MA 02135.

A main effect of intellectual distortion is that it is virtually impossible for an examiner to identify the characteristic features of psychotic disorders in patients with an IQ below 50 (Corbett 1979; Heaton-Ward 1977; Reid 1972*b*, 1976). Describing the form and content of hallucinations and delusions is beyond the ability of most mentally retarded persons with moderate or greater disabilities.

In addition, intellectual distortion subverts the clinical interview as the principal data collection mode for diagnosis. Psychiatry, as it is currently practiced, is based upon the supposition that a dialog between the patient and clinician is a reliable and valid way to elicit evidence of psychiatric illness (McHugh & Slavney 1983). Through the interview, the patient shares subjective, but diagnostically relevant information (e.g., guilt feelings).

However, the clinical interview has limited utility with regard to diagnosing psychoses in the mentally retarded, especially in those with moderate or greater disabilities or who are nonverbal. Through the interview process, the clinician may learn that the client is experiencing emotional distress, but not much will be learned about the cause of that distress. Thus, in many cases, the clinician must rely on the impressions and behavioral data collected by caregivers who work with the patient on a daily basis.

Psychosocial Masking

Psychosocial masking refers to effect of the developmental disabilities upon the content of psychiatric symptoms. By definition, the mentally retarded have deficits in interpersonal/social skills as well as diminished intelligence, and, as a consequence, are less likely to have had the wide range of life experiences enjoyed by their chronologically aged counterparts of normal intelligence.

This lack of real world experience contributes to a bland clinical presentation during a psychiatric illness. When self-reports are available, they are usually devoid of the richness of conception and detail that is associated with the symptoms of the major psychiatric disorders.

Delusional percepts may lack inventiveness and resemble the nonspecific fears of young children. Manic expansiveness may lack the usual grandiosity associated with this disorder. The grandiose content may go unrecognized unless the presence of mental retardation is taken into account: "When the normal person becomes manic, he thinks he's God. When the mentally retarded person becomes manic, he thinks he's not retarded" (Menolascino 1986).

Cognitive Disintegration

Cognitive disintegration refers to the tendency of mentally retarded persons to become disorganized under emotional stress (Menolascino 1983). Predisposed by organic deficits and concrete coping mechanisms, exogenous or endogenous stress can cause a deterioration in intellectual functioning and a clinically significant behavioral regression (Hucker et al. 1979).

The process of cognitive disintegration is similar to that which occurs in pseudodementia. During an acute episode of a psychiatric illness such as an affective disorder, an elderly person with compromised but compensated intellectual function develops many of the signs of a full-fledged organic brain syndrome. However, this cognitive deterioration remits when the acute psychiatric illness has been treated (Caine 1981). In addition, there is evidence that an acute affective illness, per se, may produce impairments in general intellectual ability and abstract thinking (Clark et al. 1985).

An analogous process may occur in mentally retarded persons. They are exquisitely vulnerable to stress-induced intellectual and emotional decompensation. Stress may overload their cognitive functioning, and, as a result, breakdowns in reality testing may occur. They may become transiently psychotic and present with the signs and symptoms of a brief reactive psychosis in response to seemingly minimal stress. Vague ideas reference or illusions may develop. Patients may withdraw and talk to themselves, creating or resurrecting an imaginary friend.

The effects of cognitive disintegration may be superimposed upon the features of a psychiatric illness so that clinical presentation may be quite atypical. Visual hallucinations have been reported to occur in mentally retarded persons with mania (Gordon 1919; Penrose 1963) and depression (Russell & Tanguay 1981). Penrose (1963) believed that mentally retarded manics were more likely to hallucinate than their counterparts of normal intelligence, and Schneider (1959, p. 71) suggested that the mentally retarded have difficulty modulating strong negative affects and tend to hallucinate "through fear and anxiety."

Thus, a bizarre presentation in a mentally retarded patient has little diagnostic significance. It may not even indicate that a psychotic process is present.

Baseline Exaggeration

Mentally retarded persons have a variety of cognitive and psychosocial deficits such as distractibility and poor judgment. These are seen in the absence of any mental illness. In addition, they may have developed a variety of maladaptive behaviors (e.g., self-injury) which serve as attention-getting and demand-avoidance maneuvers.

Baseline exaggeration refers to the fact that during a period of emotional stress, these deficits and maladaptive behaviors may significantly increase in severity. Thus, the signs and symptoms of a psychiatric illness may be a mix of new behaviors and an increase in severity of pre-existing ones. For example, chronic self-injury or aggression which occurs infrequently may suddenly increase in severity. Mania may cause an increase in the level of pre-existing distractibility and poor judgment. This phenomenon is particularly common in individuals who have a pervasive childhood developmental disorder and then go on to develop an affective illness or schizophrenia (Gilberg 1985; Reid 1976).

In some cases, it is therefore the exacerbation rather than the onset of behavioral problems which may be diagnostically relevant. This is of particular significance since the symptom criteria for most *DMS-III* Axis I disorders represent qualitatively abnormal disturbances of psychological function. If the significance of changes in the severity of pre-existing problems is unappreciated, diagnostically relevant information will be missed.

Approaches to Development of Diagnostic Criteria for Mentally Retarded Persons

The degree to which the diagnostic process is affected by the pathoplastic effects of mental retardation is a function of both the severity of the patient's developmental disabilities and his overall life experiences. For individuals with mild developmental disabilities, classic *DSM-III* criteria can often be employed. But even in these cases, sufficient cognitive disintegration and baseline exaggeration may be present to confuse the inexperienced practitioner.

Consequently, many clinicians, when working with individuals who have moderate or greater disabilities, are forced to adopt an intuitive approach to diagnosis because of the lack of diagnostic criteria which control for the pathoplastic effects of mental retardation. Gaps in the diagnostic picture are usually filled in with hypotheses, e.g., the patient's self-injury is a sign of dysphoria.

One approach to this problem has been to modify standard criteria. Hucker and associates (1979) published diagnostic criteria for depression and mania based upon the research criteria of Feighner and associates (1972), but adapted for use with mentally retarded persons. However, these criteria still contained items dependent on adequate communication and self-assessment skills (e.g., self-reproach/guilt).

A more promising approach is to use a diagnostic framework similar to that which has been developed for diagnosing affective disorders in children (Cantwell 1983). Children present many of the same diagnostic difficulties as do the mentally retarded, on account of their cognitive and psychosocial immaturity (Carlson 1981). This has led to the development of empirically derived diagnostic criteria based upon the presentation of depression in children.

Distortion-Free Diagnostic Criteria for Affective Disorders

The affective disorders are a good starting point for the development of distortion-free diagnostic criteria for the mentally retarded. The presence of neuro-vegetative features and specific responses to antidepressant and antimanic therapy make them relatively easy to diagnose, even in severely retarded persons (Reid 1976).

Table 2 lists behavioral criteria for major depression and mania. The types of behaviors which have been included are based upon the types of symptoms and behaviors which have

TABLE 2. Diagnostic Criteria for Major Depression and Mania for Use With Mentally Retarded Persons.

Major Depression	Mania
I. A disturbance of mood characterized by sadness, withdrawal, or agitation	I. A disturbance of mood characterized by elation, irritability, or excitability
II. Any 4[a] of the following 9 symptoms: • change in sleep • change in appetite and/or weight • onset or increase in severity of self-injurious behavior • apathy • psychomotor retardation • loss of activity of daily living skills, e.g., onset of urinary incontinence • catatonic stupor and/or rigidity • spontaneous crying • fearfulness	II. Any 4[b] of the following 7 symptoms: • decreased sleep • overactivity • biphasic course • onset or increase in severity of distractibility • increase in rate or frequency of verbalizations • onset or increase in severity of aggressiveness • onset or increase in severity of noncompliance

[a] Only 3 symptoms needed if there is a positive history of depression in a first degree relative.

[b] Only 3 symptoms needed if there is a positive history of bipolar disorder in a first degree relative.

been observed in affectively ill, developmentally disabled persons by the author and other clinicians (Carlson 1979; Corbett 1979; Heaton-Ward 1977; Hucker et al. 1979; Reid 1972*a*; Sovner & Hurley 1983). In addition, several elements have been introduced to increase the sensitivity of the criteria.

Family History

First, a positive family history for an affective disorder has been used to reduce the number of symptoms needed for a diagnosis. In some cases, clinical presentation is so confounded by cognitive disintegration and baseline exaggeration that it is difficult to find four diagnosis-specific symptoms, even when an affective disorder is strongly suspected. In those cases, family history data are often used to confirm the diagnosis.

Given the strong genetic component to the affective disorders (Winokur 1978) and the presence of an affective disorder in first degree family members of many symptomatic mentally retarded persons (Carlson 1979), the use of a positive family history is a reasonable way to increase the sensitivity of the criteria.

Biphasic Course

Biphasic course is a classic sign of bipolar illness and one which can be observed in mentally retarded persons irrespective of the severity of their disabilities (Reid 1976; Reid & Leonard 1977; Wallace 1983). It is often used to justify treatment with lithium carbonate (Reid & Leonard 1977), and, therefore, has been incorporated as a symptom criterion for the diagnosis of bipolar disorder.

Catatonia

A number of clinical reports have noted an association between catatonia and mental retardation (Earl 1934; Keegan et al. 1974; Rollin 1946; Zlotlow & Kleiner 1965) and there is a preponderance of evidence that catatonia is usually a sign of an affective disorder rather than schizophrenia (Reis 1985). In addition, the author has seen a number of depressed mentally retarded persons whose catatonic signs were related to an antidepressant-responsive affective illness. Thus, catatonia has been utilized as a depressive feature.

Conclusion

The confluence of intellectual distortion, psychosocial masking, cognitive disintegration, and baseline exaggeration makes it difficult to use *DSM-III* operational criteria in their current form. Future versions of the *Diagnostic and Statistical Manual of Mental Disorders* must recognize the limitations of diagnostic schema developed for individuals with normal intellectual and psychosocial functioning when applied to the mentally retarded with mental illness.

References

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. Washington, DC: The Association, 1980.

Caine, E. Pseudodementia. *Arch. Gen. Psychiatry* 38:1359–1364, 1981.

Cantwell, D.P. Depression in childhood: Clinical picture and diagnostic criteria. In: Cantwell, D.P., and Carlson, G.A., eds. *Affective Disorders in Childhood and Adolescence*. New York: SP Medical & Scientific Books, 1983. pp. 3–18.

Carlson, G.A. Affective psychoses in mental retardates. *Psychiatr. Clin. North Am.* 2:499-510, 1979.

Carlson, G.A. Affective disorder and cognitive immaturity. In: Belmaker, R.H., and VanPraag, H.M., eds. *Mania: An Evolving Concept.* New York: Spectrum Books, 1981. pp. 281-289.

Clark, D.C.; Clayton, P.J.; Andreason N.C.; Collins L.; Fawcett, J.; and Scheftner, W.A. Intellectual functioning and abstraction ability in major affective disorders. *Compr. Psychiatry* 26:313-325, 1985.

Corbett, J. Psychiatric morbidity and mental retardation. In: James, F.E., and Snaith, R.P., eds. *Psychiatric Illness and Mental Handicap.* London: Gaskell Press, 1979. pp. 11-25.

Earl, C.J.C. The primitive catatonic psychosis of idiocy. *Br. J. Med. Psychol.* 14:230-253, 1934.

Feighner, J.; Robins, E.; Guze, S.B.; Woodruff, R.A.; Winokur, G.; and Munoz, R. Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiatry* 26:57-63, 1972.

Gillberg, C. Asperger's syndrome and recurrent psychosis—A case study. *J. Autism Devel. Dis.* 15:389-397, 1985.

Gordon, A. Psychoses in mental defectives. *Am. J. Insanity* 75:489-499, 1919.

Heaton-Ward, A. Psychosis in mental handicap. *Br. J. Psychiatry* 130:525-533, 1977.

Hucker, S.J.; Day, K.A.; George, S.; Roth, M. Psychosis in mentally handicapped adults. In: James, F.E., and Snaith, R.P., eds. *Psychiatric Illness and Mental Handicap.* London: Gaskell Press, 1979. pp. 27-35.

Keegan, D.L.; Pettigrew, A; and Parker, Z. Psychosis in Down's syndrome treated with amitriptyline. *Can. Med. Assoc. J.* 110:1128-1129, 1974.

McHugh, P.R., and Slavney, P.R. *The Perspectives of Psychiatry.* Baltimore: The Johns Hopkins University Press, 1983.

Menolascino, F.J. Primitive, atypical, and abnormal-psychotic behavior in institutionalized mentally retarded children. *J. Autism Child. Schiz.* 3:49-64, 1972.

Menolascino, F.J. Overview. In: Menolascino, F.J., and McCann, B.M., eds. *Mental Health and Mental Retardation: Bridging the Gap.* Baltimore: University Park Press, 1983. pp. 3-64.

Menolascino, F.J. "Differential Diagnosis: Clinical Research Challenges in the Mentally Ill/Mentally Retarded." Paper presented at the 26th annual meeting of the New Clinical Drug Evaluation Unit (NCDEU), Key Biscayne, FL, May 1986.

Penrose, L.S. *The Biology of Mental Defect.* 3d ed. Revised by Berg, J.M., and Lang-Brown, H. London: Sidgwick & Jackson, Ltd., 1963.

Reid, A.H. Psychoses in adult mental defectives: I. Manic-depressive psychosis. *Br. J. Psychiatry* 120:205-212, 1972*a*.

Reid, A.H. Psychoses in adult mental defectives: II. Schizophrenic and paranoid psychoses. *Br. J. Psychiatry* 120:213-218, 1972*b*.

Reid, A.H. Psychiatric disturbances in the mentally handicapped. *Proc. R. Soc. Lond.* 69:509-512, 1976.

Reid, A.H., and Leonard, A. Lithium treatment of cyclical vomiting in a mentally defective patient. *Br. J. Psychiatry* 130:316, 1977.

Reis, R.K. *DSM-III* implications of the diagnoses of catatonia and bipolar disorder. *Am. J. Psychiatry* 142:1471-1474, 1985.

Rollin, H.R. Personality in mongolism with special reference to the incidence of catatonic psychosis. *Am. J. Ment. Defic.* 51:219-237, 1946.

Russell, A.P., and Tanguay, P.E. Mental illness and mental retardation: Cause or coincidence? *Am. J. Ment. Defic.* 83:570-574, 1981.

Schneider, K. *Clinical Psychopathology.* New York: Grune & Stratton, Inc., 1959.

Simmons, J.Q. Emotional problems in mental retardation: Utilization of psychiatric services. *Psychiatr. Clin. North Am.* 15:957-967, 1968.

Sovner, R., and Hurley, A.H. Do the mentally retarded suffer from affective illness? *Arch. Gen. Psychiatry* 40:61-67, 1983.

Wallace, J.G. Affective disorders in the mentally retarded. *Am. J. Psychiatry* 140:1539-1540, 1983.

Winokur, G. Mania and depression: Family studies and genetics in relation to treatment. In: Lipton M.; DiMascio, A.; and Kellam, F., eds. *Psychopharmacology: A Generation of Progress.* New York: Raven Press, 1978. pp. 1213-1222.

Zlotlow, M., and Kleiner, S. Catatonic schizophrenia associated with tuberous sclerosis. *Psychiatr. Q.* 39:466-475, 1965.

The Nature and Types of Mental Illness in the Mentally Retarded

Frank J. Menolascino, M.D.,[1] Andrew Levitas, M.D.,[1] and Carl Greiner, M.D.[1]

Introduction

The various degrees of mental retardation bring unique challenges relative to the risk of development of clusters of maladaptive behaviors. In general, persons with mental retardation are nearly twice as likely to have severe behavioral problems or mental illness as are the non-mentally retarded (Balthazar & Stevens 1975; Beier 1964; Eaton & Menolascino 1982; May & May 1979; Menolascino 1975; Penrose 1966; Pollock 1958). This risk may result in part from the person's difficulty in processing information; allied medical, physical, or sensorial difficulties; actual organic problems; cultural-familial factors; and society's nonacceptance of retarded persons with resultant elements of raw prejudice toward them. Other factors involve the inability of some retarded persons to communicate their feelings. This impairment is particularly important in the clinical setting wherein mentally retarded/mentally ill citizens have great difficulty in realizing the subjective and historical perspective of their behavioral status. Even those who appear to have superficially adequate language have extreme difficulty in processing abstract feelings and emotions. Many severe behavioral problems are caused by the way we teach or do not teach mentally retarded persons to become integrated into society. Globally, all of these problems are affected by society's role in the acceptance and support of people with special needs.

Undeniably, maladaptive behaviors are frequently reinforced and increase unnecessarily due to such reinforcement. For example, Johnny might throw objects on the floor in the classroom because he is frustrated. His frustration may be a condition of his inability to express himself. But if the teacher demands retribution, behavior could likely increase because he is getting the attention he might not otherwise receive. Paradoxically, the teacher's punishment becomes the child's reward; his maladaptive behavior is a means of avoiding the particular task, and the punishment allows him to avoid it. Over time this child can develop a cluster of "primitive" behaviors which enable him to gain control over an unresponsive world. If constantly punished, he would likely submit to his teacher, but he would not bond with the teacher. He would not learn the value inherent in human presence and participation, in equitable interpersonal transactions.

Examining the various levels of mental retardation shows its behavioral at-risk nature. Persons with *severe* and *profound* mental retardation often have major central nervous system disorders, sensory handicaps such as deafness and blindness, and severe motor and physical disabilities such as cerebral palsy and allied seizure disorders. These conditions all make the person more likely to have difficulty with interpersonal transactions, dealing with stress, and even what we might regard as minor changes in daily routine (Chess et al. 1971). Many persons with severe/profound mental retardation cannot express themselves without intensive teaching and ongoing support. They can easily learn to withdraw from the world through autistic-like behaviors (e.g., rocking, finger flicking, arm waving, and other perseverative behaviors) as an alternative to seeking others out and living independently. The lack of expressive language in many can easily lead to "primitive" communication in the form of aggressive, self-injurious, or self-stimulatory behaviors. These are often attempts to interact with, respond to, or master an otherwise overly complex or unresponsive world. *Moderately* retarded persons, besides their obvious developmental delays, have difficulty primarily with processing abstract information (Webster 1970). Most possess some degree of receptive and expressive language and are able to adapt well functionally in the world. In general, they can easily be taught the basic parameters of language, a wide repertoire of self-care and daily living skills, and vocational skills. Yet, they are also highly at risk to develop behavioral problems. Often their functionally adaptive and communicative abilities are a facade. The caregiver too often assumes that a moderately retarded person is adequately processing and dealing with complex situations such as the death of a loved one, the loss of a job, loneliness, etc., when actually such events can be overwhelming—in terms of both the person's comprehension and expression. Such complex and abstract human events may lead to severe "behavioral" problems. If retarded persons in crisis are not fully understood, enabled to express themselves, or actively supported in times of stress, they may display their emotions through what we would term "maladaptive" behaviors such as excessive sadness, withdrawal, or avoidance—beyond what is considered normal. In reality, these may be "normal" responses, given their ability to understand, communicate, and emotionally express themselves. Without adequate and sensitive support, a person with moderate mental retardation might rather quickly succumb to structured mental illness, such as an adjustment disorder, as a stepping stone to more serious illness (i.e., depression).

---

[1] Department of Psychiatry, University of Nebraska Medical Center, College of Medicine, Omaha, NE.

Reprint requests: Frank J. Menolascino, M.D., Department of Psychiatry, University of Nebraska Medical Center, College of Medicine, 42nd and Dewey Avenue, Omaha, NE 65105-1065.

Diagnostic and Treatment Challenges

The diagnostic and treatment challenges of providing services for mentally retarded citizens who have allied emotional or behavioral needs is a topic that has recently taken on increased importance in view of significant changes in society's care and treatment of its retarded citizens. Deinstitutionalization has not only changed the physical site of service delivery, bringing persons with mental retardation into the mainstream of community life, but has also dramatically highlighted the need for teaching and treatment strategies for persons with mental retardation and allied behavioral challenges. No longer are these persons automatically hidden away in State institutions. No longer are punishment and restraint practices endured away from public scrutiny. Increasingly, many persons with both mental retardation and mental illness now live in their community in a societal climate which critically questions the demeaning and "put them away" practices of the past and present (United States Senate 1984).

The recent movement of retarded persons from institutional back wards into the community has literally changed the definitions of normal and abnormal behavior. Behaviors that were traditionally "expected" or "tolerated" in institutionalized retarded citizens are viewed as abnormal within the community mainstreams of our society. For example, the clinical phenomena of rocking, rumination, and headbanging are frequent behaviors in institutionalized persons; within the institution they are expected behaviors and their abnormality is tolerated at best and severely restrained at worst. It should be pause for reflection that such behaviors are rarely seen in retarded citizens who have been raised at home and matriculated through their home community system of educational-vocational-residential services.

As mentally retarded/mentally ill persons move from institutions into the mainstream of community life, they present caregivers with new diagnostic and treatment challenges. Diagnosis becomes important so that caregivers can gain therapeutically helpful insights into the underlying causes of "behavioral problems" and "noncompliant behaviors" and thereby apply similar treatment approaches to persons with similar behavioral needs.

A major issue in the care of retarded persons with severe behavioral problems is the widespread use of high levels and chronic usage of psychoactive medications for chemical restraint (Donaldson 1984; Lipman 1970; Lipman et al. 1978; Wilson 1983) rather than as entrees to learning. Another major issue is the relative lack of a sufficient number of community-based support systems for persons with mental retardation and allied mental illness (Menolascino & McCann 1983).

A number of major concepts, issues, and trends are relevant to the relationships between mental illness and mental retardation. The definition of mental retardation as found in the diagnostic system of the American Association on Mental Deficiency (AAMD; Grossman 1983) posits the presence of subaverage intellectual functioning and associated deficits in social-adaptive behavior. The majority of the disorders listed as capable of producing the symptom of mental retardation, however, are more descriptive of syndromes than of specifically understood diagnostic entities (especially in AAMD categories VII and VIII; see Table 1).

It should be noted that defining or describing the known/unknown causes of the symptom of mental retardation may say much (i.e., psychosis as part of the PKU syndrome and likewise for Lesch-Nyhan; tuberous sclerosis, etc.) or very little about expected behaviors beyond rough guidelines for social-adaptive accomplishments at different levels of retardation.

Similar perplexity may exist in the delineation of the causes and manifestations of mental illness in a given individual. (We define mental illness as occurring at that time when a cluster of behavioral signs and symptoms come together and become overly disruptive of the person's ability to function smoothly within the mainstreams of his/her family and community settings.)

Mentally retarded persons have been noted to display the vast majority of the major psychiatric disorders, that is, classically described instances of mental illness co-exist with mental retardation. The one does not exclude the other, even in severe/profound mental retardation. Some mental illnesses can cause pervasive developmental delays which may be separated only with great difficulty from strikingly similar developmental manifestations of mental retardation (e.g., infantile autism). When the uncertainty of primary causes of mental retardation are combined with the problems of clinical description in mental illness, an area of possible clinical confusion arises: symptomatic behaviors (although produced by different causes) can have the *same* final symptom(s) pathway: abnormal behavior. For example, the origins of an 8-year-old retarded child's hyperactivity may range from motor expression of anxiety to manifestations of cerebral dysfunction, or it may arise from both. Similarly, a shortened attention span in a mentally retarded 4-year-old child may be the end product of factors ranging from inadequate parenting relationships in infancy (suggesting that the parents were unable to operate as a selective stimulation barrier for the child) to actually impaired midbrain neurologic screening of incoming stimuli. The adult with moderate mental retardation can surely have a seizure disorder and also display schizophrenia along with his/her "old" developmental manifestations of mental retardation. Combined diagnoses are clearly indicated in these frequent instances of mixed disorders. Failure to describe and delineate multiple disorders in the same individual sharply limits both professional understanding and effective treatment.

TABLE 1. Classification of the Causes of Mental Retardation.

O.	Infections and intoxications (e.g., prenatal and postnatal infections)
I.	Trauma or physical agent (e.g., post-traumatic injury)
II.	Metabolism or nutrition (e.g., inborn errors of metabolism)
III.	Gross brain disease (postnatal) (e.g., neurocutaneous dysplasia)
IV.	Unknown prenatal influence (e.g., malformations of the brain)
V.	Chromosomal abnormality (e.g., Down's syndrome)
VI.	Gestational disorders (e.g., prematurity)
VII.	Following psychiatric disorder (e.g., childhood schizophrenia)
VIII.	Environmental influences (e.g., psychosocial disadvantages)
IX.	Other conditions (e.g., defects of special senses)

SOURCE: American Association on Mental Deficiency (Grossman 1983).

The symptomatic nature of mental retardation, however, coupled with multiple causes of an associated behavioral disorder, not only increases the possible number of causes but also presents challenging opportunities for alert professionals to initiate the necessarily wide array of specific treatment interventions which are so often needed. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980) and its revised *DSM-III(R)* (American Psychiatric Association 1985) embrace most of the symptomatic and developmental parameters that are so important here. These considerations suggest that a description of mental illness in the mentally retarded should include behavioral patterns that produce serious conflicts within retarded individuals, their families, and the greater circle of their community transactions. A constellation of persistent personality traits, coupled with pervasive anxiety at a time of personal-social crisis, will significantly reduce a retarded person's effectiveness in intellectual and social-adaptive spheres.

Nature of Mental Illness in the Retarded

One reason frequently given for institutionalizing persons with mental retardation has been concern about their unmanageable behavior as they approach mid-adolescence or adulthood. Although such persons show a higher incidence of epilepsy and motor, special sensory, and allied handicapping conditions (Menolascino & Egger 1978), the tremendous improvements in medical treatment of these problems during the last 20 years have made possible revolutionary changes in our approach. Similarly, improved mental health treatment approaches have permitted a dramatic decrease in overly restrictive procedures and practices: isolation rooms, restraints, locked units, and excessive pharmacologic regimens have become associated with the professional practices of the past and, where still present, they are increasingly questioned by professionals and parents alike.

Improvements in the treatment of mental illness in the mentally retarded have flowed from an increased understanding of the nature (i.e., especially the etiological and developmental factors) and manifestations of mental illness in persons who are mentally retarded. Further exploration has made it abundantly clear that any condition which renders one less capable of handling reality-based demands makes one more susceptible to mental illness. Some of the factors that make persons with mental retardation vulnerable to mental illness are:

1. Relative inability to understand the demands of culture secondary to the presence of intellectual and social-adaptive limitations.

2. Major handicaps secondary to central nervous system impairments. These often lead to secondary behavior manifestations (e.g., self-stimulation as an external replacement for impaired inner resources).

3. Constricted emotional and personality growth secondary to delayed self-concept (i.e., differentiating the self from the nonself). Allied components are sensory and motor handicaps, and delayed integrative functions. These include poor reality perceptions and retained primitive thinking (e.g., magical thinking, confusion of reality/fantasy; problems in handling aggression, difficulty in pinpointing sources of frustration).

4. Delayed language development, with particular reference to delayed ability to express appropriate needs and decreased exploration of the world. Lack of ability to understand the interpersonal world around them leads to a very concrete cause-and-effect understanding of that world.

5. Impaired memory and transfer of learning. This leads to lowered inner control and decreased ability to delay responses and plan alternative methods of action. Thinking tends to be concrete and rigid, leading to poor responses to external and internal stress.

6. Low self-esteem fostered by early attendance at special schools. This leads to a sense of "differentness" and, eventually, a self-image of deviancy. The client perceives he or she failed the parents, leading to an increased need for praise and approval. Repeated nonapproval from peers leads to an increasing sense of incompetence and ineffectiveness. Peer rejection and lowered family and group expectations are reflected in lowered individual motivation.

7. Atypical personality defenses include increased obsessional behavior. This helps to control new situations and to control and/or cope with the environment. Fears, however, are retained longer and defenses are more fixed, leading to rigidity of lifestyle and increased utilization of nonadaptive defenses (e.g., denial, compulsive rigidity, withdrawal, regression, projection, etc.).

8. Vulnerability in adulthood. Continuation of the previously noted factors in childhood and adolescence directly leads to longer dependence, social and vocational limitations, and interference with heterosexual experiences. Failure to master key adaptational tasks at developmentally appropriate milestones in childhood and adolescence, when coupled with the lowered global intelligence, culminates in poor judgment.

Influences of the Level of Retardation

Severe Mental Retardation

The factors noted above are further affected by the level of mental retardation present. For example, in the severely retarded the presence of major central nervous system impairments tends to impair greatly their ability to assess or participate in social transactions. Without gentle and stable interpersonal support systems, the severely retarded tend to respond adversely to instances of gross interpersonal stress with stereotypical and out-of-contact behaviors that mimic autism. Similarly, their severe language delay (which is usually present) seriously restricts complex personality development, thus enhancing vulnerability to emotional under- or over-reactivity. A study by Chess, Korn, and Fernandez (1971) clearly noted that if severely retarded infants (in this study they were also blind and deaf secondary to rubella) were provided with early and ongoing interpersonal and developmental stimuli, they tended primarily to show delayed (i.e., primitive) behaviors that were consistent with their level of retardation. Chess and colleagues also noted, however, that in those instances where these early sets of interventive experiences were *not* provided, the infants consistently displayed "blindisms," prolonged rocking, marked irritability, persistent obstinancy, and "organic autism." Such learned responses often led to gross forms of harsh parental punishment and restraint. Thus the lack of early preventive intervention (including parental supports) so often, in reality, creates the very "problems" it later seeks to eradicate. Thus, if the handicaps were energetically treated, the impact on the person would be developmental delay but behavioral intactness; without these intervening developmental-treatment experiences the impact is a wide array of very disturbed and out-of-contact behaviors.

Moderate Mental Retardation

In the moderately retarded a set of personality characteristics is noted that can either lead to maximal developmental growth or become the focal point for mental illness. Specifically, during an extensive study of young moderately retarded children, Webster (1970) noted a consistent set of personality characteristics that he termed the primary psychopathology of moderately retarded youngsters:

1. benign autism;
2. repetitiousness;
3. relative inflexibility (rapid external changes leading to a heightened propensity for personality disorganization);
4. passivity (a protective posture secondary to perceived failure);
5. simplicity of emotional life (secondary to delayed personality development and allied symptoms such as motor and special sensory handicaps);
6. marked language delay.

The benign autism, nonobsessive repetitiousness, relative inflexibility, passivity, and simplicity of emotional life are all fertile ground for both the initiation of behavioral disorders (if highly supportive family or necessary program services are not provided) and misdiagnosis. Regarding the latter, one must be careful not to view the personality characteristics of persons with moderate mental retardation as signs or symptoms of mental illness. The few available autobiographies of moderately retarded individuals are helpful (e.g., Hunt 1967) since they illustrate the portrayal of the basic personality features without symptoms or signs of allied mental illness.

Mild Mental Retardation

Mildly retarded persons have a unique set of stresses. Their often nearly normal appearance tends to preclude their identification by others as disabled. This state of affairs can lead them and their loved ones to unrealistic expectations and major interpersonal failures. At the same time, these individuals are capable of developing some insight into their limitations.

Mental illness in the mildly retarded often is the result of the individual's being labeled as deviant, while being concomitantly enmeshed in the dynamic interplay of disturbed family transactions. The frequent delay in establishing that these youngsters have a distinct disability (usually not confirmed until 6 to 8 years of age) is a common source of anxiety. Low self-esteem is very frequent in persons with mild degrees of mental retardation; the stigma of attending segregated classes and adverse encounters with the social-interpersonal environment tend to make them feel even more ineffective and different. This life status is compounded by their inability to integrate the normal developmental sequences at the appropriate times. For example, during the late childhood period of personality integration, mildly retarded persons have considerable difficulty understanding the symbolic abstractions of schoolwork and the ongoing complexities of social-adaptive expectations from both family and peer group. At this stage they often gain some understanding of their limitations. Unfortunately, by early adolescence they have all too often established an identity that incorporates both mental retardation and behavioral deviancy. They are so often not buffered (or redirected) by loved ones into new interpersonal coping styles that could help them to correct earlier misconceptions about their self-identity. Without a source of ongoing family or community support and direction, they are at high risk for developing patterns of severe behavioral problems or marginal identities. In our experience with persons with mild mental retardation it is not uncommon to deal with severe psychosexual disorders, suicide attempts, and transgressions with the legal system. These personal-social developmental problems are primarily due to the lack of ongoing family and community support systems.

Persons with *mild* retardation primarily have difficulty with the societal acceptance of their "differentness" (Menolascino & McCann 1983). Society's posture of devaluation of retarded persons often leads to segregation and a superimposed subculture of deviancy. Raw prejudice can lead to more deviancy, which in turn can lead to more socially unacceptable behaviors. Most often, the mildly mentally retarded are all too cognizant of their cognitive limitations and understand the consequences of their actions. Yet, through naivete, misdirection, exploitation, or the pressures of social conforming, their behavior can become outside their direct control and lead to severe behavioral problems or mental illness more easily than in the population at large.

Lastly, a major complicating factor in the diagnosis and treatment of mental illness in the mentally retarded is the possible presence of any of a number of allied medical or developmental disabilities. The most common ones are cerebral palsy, the various types of epilepsy, auditory disorders, visual disorders, diabetes mellitus, and hypothyroidism (Ruedrich & Menolascino 1984).

Frequency and Types of Mental Illness in the Retarded

A few introductory comments on clinical diagnostic assessment are in order before the frequencies and types of mental illness in the mentally retarded are discussed.

The 1970s brought mental health and mental retardation professionals to a realization that mental illness can frequently hinder the intellectual and social adaptive growth of mentally retarded individuals. Nevertheless, there has been only minor change in the management of mentally ill/mentally retarded children or adults; their clinical diagnostic assessment is too often accomplished only with much difficulty and too little understanding of the manifestations of mental illness in persons with mental retardation.

It should be stressed at the outset that the mental status examination of a mentally retarded individual—whether to confirm the primary diagnosis of mental retardation, to assess the possibility of "pseudo-retardation," or to confirm the coexistence of mental illness with mental retardation—cannot be accomplished in isolation from general diagnostic procedures. In short, a psychiatrist ideally should carry out his or her own physical and neurological examinations and should be able to interpret pediatric, internal medicine, and neurologic consultations, as well as such studies as psychological evaluations and electroencephalograms. Direct caregivers play a key role in providing concrete objective data in these consultations. With these types of information the mental health professional is in a much better position to see the whole person and to piece together the diagnostic puzzle that mental illness can present in the mentally retarded person. To cast the mental health professional in the role of a "complete professional" may appear to be asking too much, but failure to assess clearly all parameters of behavior can result in many of the major diagnostic errors made with persons with mental retardation. It seems that exclusive focus on the mental status examination has perpetuated the classic split between the *psyche* and the *soma* in evaluating and treating persons with these special needs.

Studies concerning the frequency and types of mental illness in the mentally retarded have some major methodological problems. Before 1960, studies were carried out primarily in institutions. Frequency rates reported range from 16 percent (Penrose 1966) to 28 percent (Beier 1964) and as high as 40 percent (Pollock 1958). These studies, as well as more recent investigations of institutionalized persons (Balthazar & Stevens 1975; May & May 1979; Menolascino 1975) are questionable guides to the true frequency of mental illness in the mentally retarded because institutionalization traditionally has been used as society's mechanism for "managing" persons with social-behavioral difficulties. The more recent studies may also reflect the increasing referral of "community rejects" to institutions (Menolascino 1970). In other words, are these individuals disturbed because of personality deficits secondary to their underlying mental retardation, or are they disturbed because of the way they are treated by society?

Many reports on mentally retarded individuals living with their natural families or in their primary communities have appeared (Berman 1977; Chess 1962, 1970; Dewan 1948; Eaton & Menolascino 1966, 1967, 1982; Menolascino 1967, 1969; Webster 1970). These studies report that persons with mental retardation fall prey to the same types of mental illness that befall people with normal intellectual abilities. Recent professional literature repeats the theme that persons with mental retardation have the same range of psychoses, neuroses, personality disorders, behavior disorders, and adjustment reactions as the general population. Other investigators report a different spectrum and a higher incidence of mental illness among retarded persons than in the general population (Beier 1964; Garfield 1963; Phillips & Williams 1966). Some suggest that there are qualitative differences as well, so that some psychiatric conditions seen in retarded persons may represent unique syndromes (Bender 1970; Menolascino & Egger 1978; Webster 1970). Yet there have been few studies that have looked specifically at the frequency and types of mental illness in this population.

The data in Table 2 summarize the types of mental illness found in a review of 543 admissions of mentally retarded persons with mental illness to an acute psychiatric care setting over a 5-year period. (This review was conducted by the authors at the Nebraska Psychiatric Institute, Omaha, Nebraska.)

TABLE 2. Mental Illness in the Mentally Retarded.

Psychiatric Diagnosis	Ages								
	1–5	6–10	11–15	16–20	21–25	26–30	31–35	36+	Total
Schizophrenic Disorders									
Catatonic Type			1	4	2	1		2	10
Paranoid Type				8	5	3	4	10	30
Undifferentiated Type				15	8	10	5	15	53
Residual Type					4	13	13	15	45
									138
Organic Brain Disorders									
Behavioral Reaction		4	11	7	13	6	8	6	55
Psychotic Reaction	1	1	2	2	10	14	8	5	43
Presenile Dementia								7	7
									105
Adjustment Disorders									
Childhood and Adolescent	5	4	10	25					44
Disturbance of Conduct		3	5	10					18
Adulthood					15	12	9	5	41
									103
Personality Disorders									
Schizoid				2	4				6
Paranoid						2	1		3
Narcissistic						2	4	1	7
Avoidant				1	2	1	1	2	7
Passive Aggressive				5	4	2	5	6	22
Anti-Social				1	8	7	2	5	23
									68

TABLE 2. Mental Illness in the Mentally Retarded (*continued*).

	Ages								
Psychiatric Diagnosis	**1–5**	**6–10**	**11–15**	**16–20**	**21–25**	**26–30**	**31–35**	**36+**	**Total**
Affective Disorders									
Unipolar Manic Disorder				4	2	1			7
Biopolar Affective					2			3	5
Major Depression, Recurrent			5	4	4	9	5	5	32
Cyclothymic Disorder					1				1
									45
Psychosexual Disorders									
Fetishism				1					1
Transvestism				2	1			1	4
Zoophilia			1						1
Pedophilia			1	1	4	2	1	3	12
Exhibitionism			1	1	2	1		1	6
Ego-dystonic Homosexuality			1	1					2
Disorder Not Elsewhere Classified				3	2	1	1	1	8
									34
Anxiety Disorders									
Generalized Anxiety Disorder				2	1	2	2	2	9
Post Traumatic Stress Disorder				2	2	1	2	3	10
Obsessive Compulsive Disorder								1	1
									20
Other Mental Disorders									
Pervasive Developmental Disorder	2	5	7	2					16
Anorexia Nervosa			3	2	1				6
Oppositional Disorder			2						2
Substance Use Disorder					3		1	2	6
									30

NOTE: A review of mentally retarded/mentally ill patients at the Nebraska Psychiatric Institute, Omaha, NE (unduplicated count) July 1, 1979, through June 30, 1985. *N* = 543.

A similar spectrum of types of mental illness was noted in a study of 115 mentally retarded citizens, all of whom lived in their primary homes or a community-based program. They were seen, in an outpatient setting, for diagnosis and treatment.

Review of Tables 2 and 3 shows that the mentally retarded can, and do, fall prey to any of the major psychiatric syndromes.

TABLE 3. Psychiatric Disorders in a Community-Based Sample of 115 Retarded Persons, by Level of Retardation.

Diagnosis	**Mild (*n* = 50)**	**Moderate (*n* = 41)**	**Severe (*n* = 24)**
Schizophrenia	13	8	4
Personality Disorder	22	7	2
Anxiety Disorders	1	0	0
Adjustment Disorders	9	14	1
Organic Brain Syndrome			
With transient behavioral reaction	2	8	11
With transient psychotic reaction	3	4	6

Even when persons with mental retardation are emotionally well adjusted, they experience some difficulty functioning independently or semi-independently in their community. If their lives are complicated by mental illness, their adjustment difficulties are obviously compounded. Recent studies rather consistently have reported a 25 to 30 percent frequency rate of emotional disturbances and have suggested strongly that clinical focus must be placed on the diagnosis and subsequent treatment of the combined findings of mental illness and mental retardation.

Childhood Schizophrenia and Mental Retardation

Psychotic reactions of childhood have presented a major challenge to caregivers because the psychotic child frequently functions at a mentally retarded level. Early observers believed that all psychotic children "deteriorated." In 1943, "early infantile autism" was described (Kanner 1943); yet labeling a child "autistic" presents some formidable diagnostic and treatment problems. A number of followup studies (Bender 1959, 1970; Menolascino 1970; Rimland 1964; Rutter & Schopler 1978; Schain & Yannet 1960), along with the literal rediscovery of the wide variety of primitive behavioral repertoires in retarded persons, have tended to mute the earlier clinical enthusiasm concerning the interrelationship between functional psychoses and early infantile autism. It is striking to observe bizarre behavior, persistent withdrawal, echolalic speech, and the affective unavailability of some persons in early adolescence who had clearly regressed from an earlier higher level of functioning.

Because treatment-prognosis guidelines may differ for youngsters with autistic reactions and the combined mental retardation-childhood schizophrenia syndrome noted above, the differential diagnosis is therapeutically significant beyond mere academic interest. For example, the vast majority of autistic youngsters seem to profit greatly from mental retardation services and secondary mental health consultations (Rutter & Schopler 1978). Conversely, the retarded youngster who develops schizophrenia has a primary need for mental health services, with mental retardation services filling a secondary role until the functional psychosis subsides.

Adult Schizophrenia and Mental Retardation

Instances of paranoid schizophrenia are noted in both verbal and nonverbal persons. Examples in the authors' recent clinical work include three nonverbal adults who drew their attackers on paper, complete with nonverbal gestures. One young man labeled his separate fingers as the "source" of his common delusions, which he portrayed symbolically in crude drawings. In the entire group of people with combined diagnoses of mental retardation and schizophrenia, the schizophrenia was clearly marked by altered affective responses, bizarre rituals, and interpersonal distancing.

Personality Disorders

Personality disorders are characterized by chronically maladaptive patterns of behavior (e.g., antisocial personality, passive-aggressive personality, etc.) which are qualitatively different from psychotic or anxiety disorders (American Psychiatric Association 1980). It is interesting to note that the schizoid personality has been reported only rarely in retarded persons. The authors have diagnosed and treated a number of such persons. The personality disorders occurred in individuals whose behavior was based primarily on extrinsic factors; none had causal relationships to the symptom of mental retardation. The presence of personality disorders can be an allied disability for mentally retarded persons.

Anxiety Disorders

Early reviews (Beier 1964; Garfield 1963) of the occurrence of psychoneurotic disorders in retarded persons suggested that their frequency was quite low. The type of psychoneuroses reported was limited to such disorders as anxiety and depressive reactions. Recent reviews (Balthazar & Stevens 1975; May & May 1979), however, dispute the concept of the incompatibility between neuroses and retardation. They are quite explicit regarding the diagnostic criteria and attribute the neurotic phenomena to factors associated with atypical developmental patterns and disturbed family functioning. For example, anxiety disorders in retarded children clearly link symptoms of anxiety (e.g., fear of failure and insecurity) to external factors such as chronic frustration, unrealistic family expectations, and persistent interpersonal deprivations. Interestingly, these reports suggest that psychoneurotic disorders are more common in individuals in the high-moderate and mild levels of mental retardation. This has prompted speculation that the complexity of psychoneurotic transactions is beyond the adaptive limits of more severely retarded persons. Alternatively, the manifestations of psychoneuroses may not be as obvious, or may present differently, in the supervised and regimented lives of the more severely retarded.

Adjustment Disorders of Childhood, Adolescence, or Adulthood

Although the category of adjustment disorders is perhaps overutilized in the assessment of nonretarded persons, it is only infrequently employed during the clinical assessment of emotional disturbances in the retarded population. Because mentally retarded individuals have a predisposition to overreact to stimuli and a limited understanding of social-interpersonal expectations, they are more likely to exhibit personality disorganization after minimal interpersonal stress. The adjustment disorders may be caused by continuing inappropriate social-adaptive expectations or unexpected and frequent changes in externally imposed life patterns. Clinically, these disorders respond rapidly to environmental adjustment (when coupled with the realignment of parental, residential, and educational personnel's expectations and goals), brief utilization of psychopharmacological adjuncts, supportive counseling, or a combination of these treatments.

Depressive Disorders

An area which has attracted little attention until recently is the appearance and recognition of depression in persons with mental retardation. Yet if we consider the language and communication problems of retarded persons as well as their limited social skills and lack of social networks, it makes sense that the retarded person is highly at risk to develop depressive reactions (Berman 1977; Matson 1982*a*, 1982*b*; Schloss 1982). The authors have often seen persons develop severe behavioral problems due to the loss of loved ones or transitions in family life. Caregivers may misunderstand these behavioral problems unless they are sensitized to the full sentient nature of persons with mental retardation and to the difficulty which many have in dealing with abstract phenomena. Indeed, the retarded person may display signs of depression different from those of the nonretarded population. Vegetative signs will be found, however, as will a high frequency of family histories and biochemical parameters compatible with, and indicative of, affective disorders.

In summary, persons with mental retardation, because of their high incidence of central nervous system impairment and their diminished interpersonal coping abilities, present a greater than average risk for developing associated mental illness. The reported frequency of mental illness in mentally retarded individuals suffers from the myopia of the reporters. As May and May (1979) noted, well-recognized forms of major personality dysfunctions (i.e., the symptom clusters noted in alcoholism or suicide) are only rarely reported in the current literature on the dual diagnosis of mental retardation and mental illness.

Conclusion

Caregivers need to understand the at-risk nature of persons with mental retardation which is related to a variety of factors—both intrinsic and extrinsic. Many of the predisposing conditions can be eliminated through ongoing supports which prevent mental illness. Others may be "given" predispositions which have to be worked around and dealt with in a compassionate, caring, and respectful way. Just as important, caregivers must understand that any clustering of behaviors which equates with a major mental illness requires active intervention; that such intervention requires the teaching or reteaching of new behaviors; and that persons with these needs require more integration and support, not less, if they are to live in the confluence of family life. They require sensitive caregivers and often a restructuring of their personal and social reality by such means as increased caregiver support to help them pass through times of acute stress.

The caregiver is essentially responsible for intervening at points of risk in a person's life to help that person make the transition from at-risk points to emotional stability. At these moments the caregiver becomes the person's emotional mediator.

Understanding the nature and underlying causes of mental illness in the mentally retarded is only the beginning. It provides the caregiver with insight into the person's problems and a roadmap for ongoing care and treatment. Regardless of the types or intensity of behaviors, the caregiver's fundamental goal should be to break through whatever avoidant, self-injurious, disruptive, or destructive behaviors might exist, and to respectfully and gently move the person from these states to human interdependence. Clearly, persons with the dual diagnosis of mental retardation and mental illness present a persistent challenge to the clinician and require specialized service models if their needs are to be appropriately met. These persons can be appropriately served if a range of psychiatric, medical, educational, vocational, and residential services and supports are available. On the surface, the continuum of care for this population appears to be no different from that utilized for the mentally retarded population in general. However, the services differ in their treatment intensity relative to staffing competency, staffing patterns, and the availability of psychiatric support services. Professionals need to develop specific acute care, subacute care, and ongoing long-term management approaches which utilize a balanced range of treatment techniques to ensure the optimal social reintegration of these complex retarded persons.

Mental retardation is a given. Some of the physiological causes of mental illness may be givens. The question is: How can caregivers bring persons with mental retardation from a disengaged state—a state in which their behaviors block them from meaningful human interactions—to a state in which they can participate fully in family and community life? The entire need for change does not rest with the person with mental retardation. Caregivers need to discover personal and social change strategies to help persons with special needs live fully in family and community life.

References

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. Washington, DC: The Association, 1980.

American Psychiatric Association. "DSM-III(R): Diagnostic and Statistical Manual of Mental Disorders, Revised." Washington, DC: The Association, 1985. In development.

Balthazar, E.E., and Stevens, H.S. *The Emotionally Disturbed, Mentally Retarded: A Historical and Contemporary Perspective*. Englewood Cliffs, NJ: Prentice Hall, 1975.

Beier, D.C. Behavioral disturbances in the mentally retarded. In: Stevens, H.A., and Heber, R., eds. *Mental Retardation*. Chicago: University of Chicago Press, 1964. pp. 453–487.

Bender, L. Autism in children with mental deficiency. *Am. J. Ment. Defic.* 64:81–86, 1959.

Bender, L. The life course of children with autism and mental retardation. In: Menolascino, F.J., ed. *Psychiatric Approaches to Mental Retardation*. New York: Basic Books, 1970. pp. 149–191.

Berman, M.I. Mental retardation and depression. *Ment. Retard.* 5:19–21, 1977.

Chess, S. Psychiatric treatment of the mentally retarded child with behavioral problems. *Am. J. Orthopsychiatry*. 32:863–869, 1962.

Chess, S. Emotional problems in mentally retarded children. In: Menolascino, F.J., ed. *Psychiatric Approaches to Mental Retardation*. New York: Basic Books, 1970. pp. 55–67.

Chess, S.; Korn, S.; and Fernandez, P. *Psychiatric Disorders of Children with Congenital Rubella*. New York: Brunner/Mazel, Inc., 1971.

Dewan, J.G. Intelligence and emotional stability. *Am. J. Psychiatry* 104:548–554, 1948.

Donaldson, J.Y. Specific psychopharmacological approaches and rationale for mentally ill-mentally retarded children. In: Menolascino, F.J., and Stark, J.A., eds. *Handbook of Mental Illness in the Mentally Retarded*. New York: Plenum Press, 1984. pp. 171–187.

Eaton, L., and Menolascino, F.J. Psychotic reactions of childhood: Experience of a mental retardation pilot project. *Nerv. Ment. Dis.* 143:55–67, 1966.

Eaton, L., and Menolascino, F.J. Psychoses of childhood: A five-year follow-up of experiences in a mental retardation clinic. *Am. J. Ment. Defic.* 72:370–380, 1967.

Eaton, L., and Menolascino, F.J. Psychiatric disorders in the mentally retarded: Types, problems and challenges. *Am. J. Psychiatry* 139:1297–1303, 1982.

Garfield, S.L. Abnormal behavior and mental deficiency. In: Ellis, N.R., ed. *Handbook of Mental Deficiency*. New York: McGraw-Hill, 1963. pp. 574–601.

Grossman, H.J. *Manual of Terminology and Classification in Mental Retardation*. Washington, DC: American Association on Mental Deficiency, 1983.

Hunt, N. *The World of Nigel Hunt*. New York: Toplinger, 1967.

Kanner, L. Autistic disturbances of affective contact. *Nerv. Child* 2:217–250, 1943.

Lipman, R.S. The use of psychopharmacological agents in residential facilities for the retarded. In: Menolascino, F.J., ed. *Psychiatric Approaches to Mental Retardation*. New York: Basic Books, 1970. pp. 387–398.

Lipman, R.S.; DiMascio, A.; Reating, N.; and Kirson, T. Psychotropic drugs and mentally retarded children. In: Lipton, M.A.; DiMascio, A.; and Killam, K.F., eds. *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978. pp. 1437–1449.

Matson, J.L. Depression in the mentally retarded: A review. *Educ. Train. Ment. Retarded* 17:159–163, 1982*a*.

Matson, J.L. The treatment of behavioral characteristics of depression in the mentally retarded. *Behavior Therapy* 13:209–218, 1982*b*.

May, J., and May, J. "Overview of emotional disturbances in mentally retarded individuals." Paper presented at the Annual Convention of the National Association for Retarded Citizens, Atlanta, GA, 1979.

Menolascino, F.J. Mental retardation and comprehensive training in psychiatry. *Am. J. Psychiatry* 124:249–466, 1967.

Menolascino, F.J. Emotional disturbances in mentally retarded children. *Am. J. Psychiatry* 126:54-62, 1969.

Menolascino, F.J. *Psychiatric Approaches to Mental Retardation.* New York: Basic Books, 1970.

Menolascino, F.J. Community psychiatry and mental retardation. In: Bellack, L., and Barten, H., eds. *Progress in Community Mental Health.* New York: Brunner/Mazel, Inc., 1975. pp. 140-178.

Menolascino, F.J., and Egger, M.L. *Medical Dimensions of Mental Retardation.* Lincoln, NE: University of Nebraska Press, 1978.

Menolascino, F.J., and McCann, B.M. *Mental Health and Mental Retardation: Bridging the Gap.* Baltimore: University Park Press, 1983.

Penrose, L. The contribution of mental deficiency research to psychiatry. *Br. J. Psychiatry* 112:747-755, 1966.

Phillips, I., and Williams, N. Psychopathology and mental retardation: I. Psychopathology. *Am. J. Psychiatry* 112:1265-1271, 1966.

Pollock, H. Brain damage, mental retardation, and childhood schizophrenia. *Am. J. Psychiatry* 115:422-427, 1958.

Rimland, B. *Infantile Autism.* New York: Appleton-Century-Crofts, 1964.

Ruedrich, S.R., and Menolascino, F.J. Dual diagnosis of mental retardation and mental illness: An overview. In: Menolascino, F.J., and Stark, J.A., eds. *Handbook of Mental Illness in the Mentally Retarded.* New York: Plenum Press. 1984. pp. 45-81.

Rutter, M., and Schopler, E. *Autism: A Reappraisal of Concepts and Treatments.* New York: Plenum Press, 1978.

Schain, R., and Yannet, H. Infantile autism. *J. Pediatr.* 57:560-567, 1960.

Schloss, P.J. Verbal interaction patterns of depressed and nondepressed institutionalized mentally retarded adults. *Appl. Res. Ment. Retard.* 3:1-12, 1982.

United States Senate. *Enforcement of Section 504 of the Rehabilitation Act: Institutional Care and Services for Retarded Citizens.* Hearing before the Subcommittee on the Handicapped Committee on Labor and Human Resources. Washington, DC: U.S. Govt. Print. Off., 1984.

Webster, T.G. Unique aspects of emotional development in mentally retarded children. In: Menolascino, F.J., ed. *Psychiatric Approaches to Mental Retardation.* New York: Basic Books, 1970. pp. 3-54.

Wilson, J.E. Psychopharmacologic agents in mental retardation. In: Menolascino, F.J., and McCann, B.M., eds. *Mental Health and Mental Retardation: Bridging the Gap.* Baltimore: University Park Press, 1983. pp. 171-186.

Forthcoming Issues—1987

Volume 23

No. 1. Annual NCDEU Meeting (1986)—Abridged Proceedings.

No. 2. "Applications of Microcomputers to Clinical Trials in Psychopharmacology"—a workshop held in conjunction with the 1986 NCDEU meeting. (Guest Editor Joanne B. Severe, M.S.)

No. 3. Annual ACNP Meeting (1986)—Selected Proceedings.

No. 4. "The Anxiety Disorders: A Consensus on Diagnosis and Treatment." (Guest Editor Gerald L. Klerman, M.D.)

Psychometric and Demographic Characteristics of the Psychopathology Instrument for Mentally Retarded Adults[1]

Michael G. Aman, Ph.D.,[2] Janine E. Watson, B.Sc. (Hons.),[3] Nirbhay N. Singh, Ph.D.,[3] Sarah H. Turbott, B.Sc.,[2] and Catherine P. Wilsher, M.Sc.[2]

Introduction

Recently, Senatore, Matson, and Kazdin (1985) described an inventory of psychopathology for mentally retarded adults. Called the Psychopathology Instrument for Mentally Retarded Adults, or simply PIMRA, the instrument is available in both a Self-Report and an Informant version. The PIMRA is based on the *DSM-III: Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980) and its 57 items resolve into eight subscales as follows: Schizophrenia, Affective Disorder, Psychosexual Disorder, Adjustment Disorder, Anxiety Disorder, Somatoform Disorder, Personality Disorder, and Poor Mental Adjustment.

Such an inventory could be important to the clinical application of psychotropic drugs in mental retardation for several reasons. First, it is important to have psychometrically robust tools to enable psychopharmacological research to make progress in looking for subject-treatment interactions. Second, such an instrument could facilitate the day-to-day clinical use of psychotropic medication. Third, given substantial evidence of overuse of psychotropic agents with this population (Aman & Singh in press), availability of suitable instruments may help to stem the tide of inappropriate treatment.

The authors became interested in the PIMRA as a possible means of studying psychopathology in mentally retarded individuals. The authors employed the Self-Report version developed by Senatore and associates (1985) but, because of some difficulty in obtaining the Informant version, generated a slightly different informant questionnaire by rewording the Self-Report version for completion by third parties. Data from the novel informant version will be presented elsewhere. In this paper data are presented from 160 mentally retarded adults on the psychometric properties of the Self-Report version as well as the effects of salient demographic variables. As the developers of the PIMRA have pointed out, it is essential that data be available on the reliability and validity of such instruments before they are assimilated for routine use in the field.

Method

Subjects

Criteria for subject selection were that the person under study be judged capable of understanding and responding to questions within the PIMRA, and that at least one caregiver be available who knew the individual well. The subjects were 160 mentally retarded adults drawn from two settings. Those in the first and larger group ($n = 95$) lived in the community and attended a workshop training center caring for 180 individuals. The second group ($n = 65$) was drawn from a residential institution caring for approximately 600 individuals. Characteristics of the two samples, including age, sex, and functional level are presented in Table 1. As is clear from Table 1, subjects within the institution tended to be older, predominantly male, and more severely impaired.

---

[1] This research was supported in part by grants from the University of Canterbury to Dr. N. Singh and from the Medical Research Council to Dr. M. Aman.

The authors wish to thank Helen Rainsford, who conducted the interviews, and Dr. G. Elkind for assistance with the statistical analyses. The authors are grateful to the administration and staff members of Templeton Hospital for supporting and providing practical assistance on this study.

[2] Department of Psychiatry and Behavioural Science, School of Medicine, University of Auckland, Auckland, New Zealand.

[3] Department of Psychology, University of Canterbury, Christchurch, New Zealand.

Reprint requests: Michael G. Aman, Ph.D., Department of Psychiatry and Behavioural Science, School of Medicine, University of Auckland, P.B., Auckland 795-780, New Zealand.

TABLE 1. Subject Characteristics Presented by Setting.

Variable	Community ($n = 95$)	Institution ($n = 65$)	Total ($n = 160$)
Age (Yrs.)			
Mean	24.08	36.03	29.38
SD	6.02	13.07	11.40
Range	18–52	18–67	18–67
Sex (%)			
Males	48.4	70.8	57.5
Severity of Retardation (%)[a]			
Borderline	24.2	12.3	19.4
Mild	62.1	26.2	47.5
Moderate	13.7	61.5	33.1

[a] Based on the American Association on Mental Deficiency (Grossman 1983) classification.

Procedure

Informed consent was obtained from the administration of the institution concerned and from parents of the community subjects, as well as from all subjects who took part.

Subjects completed the Self-Report version of the PIMRA during an interview led by a female research assistant who had 10 years' experience working with mentally retarded people. The interviewer stated each item to the subjects and recorded their response (yes or no). If necessary, the question was repeated or further questions asked to clarify the subject's response.

To assess interviewer accuracy, three additional observers scored 38 of the 160 interviews (24%). Spearman reliability correlations between scores ranged from .95 to .97, indicating high accuracy in interpreting subjects' replies and in coding these answers.

Five months after the initial ratings were obtained, a second set of ratings was collected on a random sample of 32 subjects.

In summary, the Self-Report version of the PIMRA was filled in for 160 mentally retarded adults residing either in the community or in a public residential facility. Assessments of interviewer coding showed that scoring of subject responses was very accurate. As a means of assessing stability over time, ratings were repeated for 32 subjects after 5 months.

Results

In general the data from the community sample and the institutional group were analyzed separately because of marked differences in age and sex distributions for the two samples. Insofar as it was possible to do so, the same statistical tests that were employed by Matson and associates (1984) and Senatore and associates (1985) were used here.

Psychometric Characteristics

Internal consistency. Coefficient alpha is a measure of internal consistency based on the average correlation among items, and it provides an estimate of the extent to which questions on a given subscale assess the same attribute. Alpha coefficients were calculated for each combination of setting and subscale. Alpha ranged from .45 to .73 with a mean of .64 (*see* Table 2).

TABLE 2. Alpha Coefficients Presented by Setting and Subscale.

Subscale	Community	Institution
Schizophrenia	.66	.62
Affective Disorder	.66	.63
Psychosexual Disorder	.64	.67
Adjustment Disorder	.64	.69
Anxiety Disorder	.61	.70
Somatoform Disorder	.45	.66
Personality Disorder	.56	.73
Mental Adjustment	.60	.71

Item-whole correlations. Internal consistency was also analyzed by computing the correlation between each item and its respective subscale total (Spearman correlations). The *mean* correlations (i.e., for each group of seven or eight items comprising each subscale) broken down by setting and subscale are presented in Table 3. These ranged from a low of .30 to a high of .54. Ninety-three of 114 items (82%) correlated significantly ($p < .05$) with total subscale scores, and the mean item-total correlation was .39.

Stability of ratings. Ratings were repeated after 5 months for 32 subjects. Because of the smallness of the sample, it was not possible to analyze separately for setting. Spearman correlations are presented in Table 4. Only three of eight subscales were found to correlate signifi-

TABLE 3. Mean Item-Total Correlations Presented by Setting and Subscale (Spearman Correlations).

Subscale	Community	Institution
Schizophrenia	.36	.39
Affective Disorder	.48	.41
Psychosexual Disorder	.32	.37
Adjustment Disorder	.41	.50
Anxiety Disorder	.53	.51
Somatoform Disorder	.28	.30
Personality Disorder	.38	.36
Mental Adjustment	.36	.34

cantly over this interval, and the mean correlation for all eight subscales was .31.

Effects of Demographic Characteristics and Setting

Age, sex, and functional level. Subscale scores were also analyzed as a function of age (treated as a continuous variable), sex, and functional level (mild and borderline vs. moderate mental retardation) using the general linear models procedure from the Statistical Analysis System (SAS; Ray 1982). As there were pronounced differences in subject composition across the two settings, these analyses were initially conducted separately for each sample.

Age. Within the community sample, no age effects were found. Within the institution, age was directly associated with scores on one subscale, Somatoform Disorder ($p<.05$, regression coefficient = .031).

Sex. Within the community group, there were no sex differences. However, in the institution, sex was associated with significant differences on Psychosexual Disorder ($p<.05$). Female residents had a mean score of .50 compared with .27 for males.

TABLE 4. Spearman Correlations Between Test and Retest for Subscale and Total Scores ($n=32$).

Subscale	Correlation
Schizophrenia	.29
Affective Disorder	.26
Psychosexual Disorder	−.15
Adjustment Disorder	.34
Anxiety Disorder	.29
Somatoform Disorder	.56***
Personality Disorder	.47**
Inappropriate Mental Adjustment	.40*
Total	.65***

* $p < .05$; ** $p < .01$; *** $p < .005$.

Functional level. No differences occurred due to functional level within either sample.

Summary. To recap, one comparison each showed an effect due to age and sex, but functional level had no measurable influence on psychopathology scores. Both significant findings were confined to the institutional group.

Effect of setting. Because of extensive age differences between settings, subjects at the two age extremes were deleted from this comparison. The effect of setting was analyzed for subjects between 23 and 40 years of age inclusive ($n = 84$), and the effects of age, sex, and functional level were partialled out by analysis of covariance. None of the subscales discriminated significantly between the community and the institutional sample.

Factor Structure

Factor analyses were performed using a principal components solution followed by varimax rotation. In keeping with the procedure adopted by Matson and associates (1984), all factors with eigenvalues of 1.50 or greater and with at least five items having a loading of .35 or more were included. The result was a four-factor solution (*see* Table 5). Factor I had numerous items relating to worry and mood and, as in the report by Matson and associates, it has been labeled Anxiety. Factor II dealt with orientation to other people and, as in the previous report, has been labeled Social Adjustment. Factor III is new and describes problems with sexual identification and reality orientation and has been titled Identity/Reality Problem. Finally, factor IV included an amorphous collection of problems (hearing voices, experiencing pain, need to make others happy), and it has not been labeled.

Discussion

In general, the statistics relating to the PIMRA's psychometric characteristics were not as convincing in this study as in the original reports. Coefficient alpha was substantially less with a mean alpha value of .64 as compared

TABLE 5. PIMRA Items Grouped by Factor.

Item No.*	Loading	Item Description
Factor I: Anxiety		
4	.47	Do you get real upset when things get confusing?
5	.56	Do you worry a lot?
12	.69	Are you a very nervous person?
13	.35	Do you have trouble thinking about one thing at a time?
20	.44	Do you get angry and fight with other people?
21	.42	Do you worry about making friends?
23	−.39	Do you care about what other people say to you?
29	.45	When things go bad for you, do you feel OK?
33	.40	Have things been bad for you?
42	.53	Are you real happy some days, and real sad other days?
44	.35	Do you hate rules . . . .
45	.40	Do you feel relaxed most of the time?
46	−.35	Is it bad to be sick?
53	.59	Are you nervous most of the time?
Factor II: Social Adjustment		
15	.40	Do you enjoy things that are funny?
22	.36	Do you breathe well?
26	.42	Do you feel happy most of the time?
30	.55	Do you think you will live a long time?
31	.39	Do people understand you?
32	.51	Do people like to be with you?
37	.39	Do you like talking to new people?
41	.75	Do you like living with other people?
50	.50	Do you like being with groups of people?
52	.40	Do you get along well with people at home and at work?
56	.49	Do you like to be alone most of the time?
Factor III: Identity/Reality Problem		
8	.43	Do you get along well with lots of other people?
11	.66	Do you wish that you were (opposite sex)?
28	.79	Do you take things that only belong to you?
35	.70	Do you ever take all your clothes off outside . . . . ?
36	.53	Can you do most things on your own?
48	.52	Do you wish that you were a tree . . . . ?
49	.36	Do you like to collect unusual things like old papers or garbage?
Factor IV: Unlabeled		
3	−.44	Are you happy that you are a (same sex)?
9	.42	Do you hear voices that upset you?
14	.43	Do you have a lot of pain?
19	−.40	Do you try real hard to act like a (same sex)?
39	.38	Do you get excited a lot?
43	.36	Do you get a real excited feeling when you see stockings or underwear?
55	.48	Do you always try to make other people happy?

*Item numbers do not necessarily correspond to those in the original scale.

with .85 reported by Senatore and associates (1985). Item-whole correlations were actually higher in this study than in the initial report ($r_s = .39$ as compared with .31). Nevertheless, in 21 of 114 comparisons, the items failed to correlate significantly with their respective subscales, and these items should perhaps be re-examined for their appropriateness.

The stability of the Self-Report version was substantially lower than in the original article (Senatore et al. 1985) with only three of eight subscales (as well as the Total score) showing a significant correspondence between original and subsequent ratings. The mean correlation of .31 obtained in this study was also substantially lower than the figure of .56 reported by Senatore and associates.

Demographic variables such as age, sex, and functional level had surprisingly little effect on psychopathology scores. However, this is basically what the developers of the instrument also found (Senatore et al. 1985). There are numerous reasons to speculate that individuals residing in an institution might show greater psychopathology than those living in the community, but these data do not bear this prediction out.

Finally, the factor structure was remarkably similar to that reported by Matson and associates (1984), although this analysis produced two additional factors. Anxiety and Social Adjustment emerged as the first two factors in both analyses with the addition of Identity/Reality Problem and another, difficult-to-label, factor in this study.

Conclusions

Certain problems with the psychometric characteristics of the Self-Report version were noted in this study. Therefore, further studies of both the Self-Report and the Informant versions of PIMRA appear to be indicated. Informant instruments have had a lengthy tradition of use in child psychology and psychiatry (Boyle & Jones 1985; Conners 1969; Costello et al. 1985; Quay 1979), whereas self-rating instruments have been relatively uncommon. Furthermore, many of the difficulties encountered in work with children are analogous to those confronted with mentally retarded adults. In view of these considerations, the Informant version of the PIMRA may well prove to be a more valuable tool than the Self-Report version.

Finally, there have now been several attempts in child psychiatry to validate the *DSM-III* diagnostic scheme (e.g., Koriath et al. 1985; Reeves et al. in press) and certainly not all have been confirmatory. The PIMRA is an attempt to extend that diagnostic system to mentally retarded individuals, but the presumed underlying dimensions again need validation. The factor analysis carried out here, together with that by Matson and associates (1984), raises the important question of whether the present scoring system for this instrument is appropriate for this population. The authors are presently conducting a cluster analysis with these data to take a more detailed look at this issue.

References

Aman, M.G., and Singh, N.N. Overview of psychopharmacology: Drug prevalance, measurement techniques, unorthodox treatments, and future trends. *Analysis and Intervention in Developmental Disabilities* (Special Issue on Psychopharmacology), in press.

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. Washington, DC: The Association, 1980.

Boyle, M.H., and Jones, S.C. Selecting measures of emotional and behavioral disorders of childhood for use in general populations. *J. Child Psychol. Psychiatry* 26:137-159, 1985.

Conners, C.K. A teacher rating scale for use in drug studies with children. *Am. J. Psychiatry* 126:152-156, 1969.

Costello, E.J.; Edelbrock, C.S.; and Costello, A.J. Validity of the NIMH Diagnostic Interview Schedule for Children: A comparison between psychiatric and pediatric referrals. *J. Abnorm. Child Psychol.* 13:579-595, 1985.

Grossman, H.J. *Manual of Terminology and Classification in Mental Retardation*. Washington, DC: American Association on Mental Deficiency, 1983.

Koriath, U.; Gualtieri, T.; Van Bourgondien, M.E.; Quade, D.; and Werry, J.S. Construct validity of clinical diagnosis in pediatric psychiatry: Relationship among measures. *J. Am. Acad. Child Psychiatry* 24:429-436, 1985.

Matson, J.L.; Kazdin, A.E.; and Senatore, V. Psychometric properties of the psychopathology instrument for mentally retarded adults. *Appl. Res. Ment. Retard.* 5:81-89, 1984.

Quay, H.C. Classification. In: Quay, H.C., and Werry, J.S., eds. *Psychopathological Disorders of Childhood*. 2d ed. New York: Wiley, 1979. pp. 1-42.

Ray, A.A. *SAS User's Guide: Statistics*. Cary, NC: SAS Institute, 1982.

Reeves, J.C.; Werry, J.S.; Elkind, G.S.; and Zametkin, A. Attention deficit, conduct, oppositional and anxiety disorders in children: II. Clinical characteristics. *J. Abnorm. Child Psychol.*, in press.

Senatore, V.; Matson, J.L.; and Kazdin, A.E. An inventory to assess psychopathology of mentally retarded adults. *Am. J. Ment. Defic.* 89:459-466, 1985.

Components of the Design of Psychopharmacology Studies[1]

Barbara Geller, M.D.[2]

This paper addresses the various components of the experimental design of psychopharmacology studies with particular reference to the dually diagnosed population, i.e., the population diagnosed as both mentally retarded and suffering from a major psychiatric disorder as described in the *DSM-III: Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980).

Component I. Rationale

The rationale for these studies is that the problems in diagnosis and assessment in the dually diagnosed population are sufficiently different from those of the nonretarded population as to require separate study. In this way, the dually diagnosed are similar to other groups (e.g., pediatric) who require separate study.

Component II. Aims

There are two essential aims of drug studies:

A. To demonstrate that the benefits of pharmacotherapy are significantly better than placebo.

B. To demonstrate that the benefits significantly outweigh the risks.

Component III. Long Range Goal

Historically, the administration of psychotropic drugs to the mentally retarded population has been directed toward the management of behavioral problems (e.g., aggression). The use of drugs for a concomitant *DSM-III* psychiatric diagnosis is an understudied area. In this respect, the dually diagnosed are similar to other groups (e.g., pediatric, geriatric) that require special consideration. For studies of dually diagnosed populations, aiming at a psychiatric disorder could potentially lessen the reported prevalence of nonspecific polypharmacy and of indefinite lengths of treatment.

Component IV. Preliminary Studies

Prior to undertaking the double-blind placebo-controlled studies necessary to fully evaluate the effectiveness and safety of a particular drug, one needs to investigate whether or not it is feasible to give these drugs in a systematic manner. These preliminary studies should include the following six areas:

A. Assessment instruments specific for both IQ and age range should be developed to establish the *DSM-III* psychiatric disorder diagnosis. Similarly, specific instruments need to be developed for monitoring severity at baseline and during the protocol.

B. IQ and age-specific instruments for measuring and monitoring side effects should be developed. Scales developed to assess and monitor symptoms and side effects in the dually diagnosed that are modifications of those used in the nonretarded population will facilitate comparison of data between the retarded and nonretarded populations. Further, the use of the pediatric technique of interviewing the subject and an observer (parent, guardian, nurse, etc.) to arrive at a rating should also be advantageous for the dually diagnosed.

C. Drugs selected to be used in studies of the dually diagnosed should have the same characteristics as those chosen for other special populations (e.g., pediatrics). These are:

1. They have been well studied in non-mentally retarded populations to avoid, as much as possible, confounding issues such as previously undescribed adverse effects.
2. Sedative effects are low relative to other drugs of their class so as to impair, as little

---

[1] This work was supported by NIMH Grants MH-40273 and MH-40646.

[2] Childhood Affective Disorders Program, William S. Hall Psychiatric Institute, University of South Carolina School of Medicine, Columbia, SC.

Reprint requests: Barbara Geller, M.D., William S. Hall Psychiatric Institute, P.O. Box 202, Columbia, SC 29202.

as possible, the already compromised cognitive abilities of the subjects.

3. The incidence of anticholinergic side effects should also be low because of the relative difficulty the retarded population may have in reporting those anticholinergic effects that are less observable (e.g., urinary retention).
4. Relatively low extrapyramidal and other neurological adverse effects are especially important for the dually diagnosed where prior extensive drug usage is frequent.

D. Open drug trials are useful in establishing:

1. The dose range for optimizing efficacy.
2. The dose range for minimizing side effects.
3. The half-life of various agents in this population—to be able to develop an appropriate dosage regimen.
4. Plasma level monitoring where it has been shown to be clinically useful in the nonretarded population.

E. The length of study used in open trials should be at least as long as that used with the nonretarded population. The investigator may wish to run a trial for a week or two longer, however, in order to be sure that the length of time to response in the dually diagnosed population is not longer than that in the nonretarded population.

F. Training the staff in psychoeducation is essential because the parents, spouses, and other relatives of the retarded population often maintain the expectation that when the psychiatric disorder improves, so will the patient's cognitive ability. Although cognitive ability may improve to a certain extent after recovery from the psychiatric disorder (because of better concentration, etc.), improvement is unlikely to be sufficient for the patient to gain normal cognition.

Component V. Defining the Study Population

The general purpose of defining the study population is to obtain a homogenous group of subjects in order to obtain generalizable data. Further, obtaining a homogenous group for study permits using similar assessment instruments for all the subjects. For example, if subjects from both the pediatric and geriatric age groups are included or subjects from different *DSM-III* mentally retarded groups are included, different assessment instruments will be needed. Both inclusion and exclusion criteria are needed in order to define the study population.

A. Inclusion criteria include the following:

1. Descriptive criteria should give the age range (pediatric, adult, geriatric), sex, socioeconomic status and residential status (inpatient, outpatient, group home, etc.) of the subjects.
2. Diagnostic criteria should include the *DSM-III* psychiatric disorder under study. A statement is also needed as to the inclusive IQ range and whether mentally retarded of all etiologies, or only certain ones, will be considered for study.
3. The length of time that the psychiatric disorder has been present in order for the subject to qualify for study should be specified.

B. Exclusion criteria address the following issues:

1. The IQ ranges and etiologies not included.
2. The exclusion of other *DSM-III* psychiatric disorders.
3. Exclusive medical conditions.
4. Exclusive neurological conditions.
5. Prior drug usage and how long the subjects need to be drug-free prior to entry into study. The latter is defined as the time it takes for the previous drugs to disappear from the body plus 1 week. Finding inactive metabolites of neuroleptics in the urine over a period of months is not ordinarily taken as an exclusion criterion.
6. Alcohol and other substance abusers should be excluded (unless they are the specific target population).
7. Because many patients in this population have been chronically treated with neuroleptics, some of them will have tardive dyskinesia or its variants. The investigator should specify which dyskinesias will be excluded. It may also be useful to aim for subjects who will have had equivalent amounts of neuroleptic exposure (i.e., the maximum total life dose of neuroleptic).

Component VI. Assessments

This category refers to the instruments to be used to screen subjects and to collect data. The following types of assessments are useful in psychopharmacology studies:

A. Diagnostic scales to establish the *DSM-III* psychiatric diagnosis.

B. Diagnostic scales to establish IQ and other cognitive abilities.

C. Scales that yield numerical values to measure the severity of the *DSM-III* psychiatric disorder under study. These are administered at baseline and then weekly or at other intervals during the protocol in order to monitor change over time.

D. Severity scales for monitoring IQ and cognitive measures during the protocol.

E. Instruments to measure adaptation in the residential, school, and/or work environments.

F. Psychosocial schedules, including items that measure life history events prior to and during the illness.

G. Physical measure scales used to monitor possible adverse effects (e.g., electrocardiogram tracings, height, and weight). These should specify the time of day and the conditions of eating and clothing.

H. Side-effect scales.

I. Family history schedules.

J. Baseline physical examination and screening laboratory measures (e.g., complete blood count, urinalysis, SMA 25, etc.).

Component VII. Issues in Assessment Implementation

To facilitate the use of assessment instruments and maximize the value of the data collected, the following are important:

A. Raters who are performing the assessment scales should have the appropriate experience and education, especially for clinical semi-structured interviews.

B. Interrater reliability among the raters for a particular study must be established. Even if the assessment scale has been used extensively by the investigator, it is important that new raters hired for a study be trained until they attain reliability.

C. Specifying the time of day that ratings are performed is important in terms of both the disorder being studied and the pharmacokinetics of the medications. For example, in disorders with a diurnal variation such as a major depressive disorder, performing some scales in the morning and some in the afternoon may provide nonvalid data because of the natural diurnal variation in the illness. For medications such as those used for the hyperactivity syndromes where improvement may correspond with peak plasma levels, it is important to state the time of day the drug is given and the time of day that ratings are given and to decide beforehand whether these will coincide.

D. The validity of the data is strengthened if baseline assessments and end-of-study assessments are performed by a different rater from the one who performs the ratings during the protocol.

Component VIII. Study Medication

Issues important in assuring that the patient is receiving the medication systematically include:

A. The specific hour(s) the drug will be administered should be scheduled.

B. The drug should be packaged in a way that makes it easy for the person giving the medication to follow instructions. This is especially important for those patients who will be in nonhospital residential settings.

C. Placebos should be prepared by the manufacturer or compounded in the facility pharmacy. Placebo medication prepared by placing a nonidentical tablet or capsule in an opaque capsule is an inadequate blinding technique for the mentally retarded population, where biting, chewing, or general curiosity may lead to breaking the blind.

D. The dispensing facility should be able to follow the protocol requirements for packaging and distribution.

Component IX. Compliance

To help ensure compliance with medication regimens:

A. Assure that the person who administers the drug to the patient is reliable. The retarded population should be treated similarly to the pediatric population and have all medication administered by another person.

B. Employ techniques that ensure swallowing, such as encouraging the person to swish water around in the mouth after taking the pill.

C. Dispense an exact number of pills for no longer than a week's period of time and perform pill counts to detect unused pills.

D. Monitor compliance by such direct measures as plasma and/or saliva levels which can be very helpful in detecting noncompliance in subjects and in caretakers who may not report their own noncompliance.

Component X. Double-Blind Placebo-Controlled Study Design

The two essential phases of a double-blind, placebo-controlled study begin after baseline studies have been completed.

Since psychopharmacological agents often have high placebo response rates, the *first phase* of the study should be a *2-week single-blind period* during which all subjects receive placebo. This will eliminate many placebo responders, permit a smaller number of subjects in the double-blind phase, and avoid administration of active medication to subjects who do not need it.

At the end of Weeks 1 and 2, subjects who are below the predecided criteria of recovery on the severity scales are discontinued.

The remaining subjects enter the *second phase*, the *double-blind, placebo-controlled protocol*, in *randomized* order. During this phase, interval monitoring should be performed. A sample of such a protocol for a theoretical 6-week study is given in Table 1.

The length of the double-blind, placebo-controlled study should be no shorter than the duration of similar studies of the drug in nonretarded populations.

Cross-over designs refer to protocols in which subjects sequentially receive active drug and placebo in randomized order. This type of investigation is useful for chronic, noncycling illnesses where natural recovery due to the length of time is not a factor.

Discontinuation studies are performed to determine the length of time a drug needs to be continuously administered following recovery in order for the recovery to be maintained. These protocols permit comparison of relapse rates after discontinuation at varying lengths of time.

TABLE 1. Sample Protocol for Double-Blind Placebo-Controlled Study.

	Phases							
	Single-Blind		Double-Blind Placebo-Controlled					
Weeks of Phase	1	2	1	2	3	4	5	6
Ratings								
Symptoms	X	X	X	X	X	X	X	X
Side Effects	X	X	X	X	X	X	X	X
Physical Measures	X	X	X	X	X	X	X	X
Plasma Measures	X	X	X	X	X	X	X	X
Week of Total Study	1	2	3	4	5	6	7	8

Component XI. Statistical Issues

A. It is imperative to perform *power analyses* to determine the number of subjects needed to detect a significant effect. For double-blind, placebo-controlled studies, it will be necessary to have expected rates of active and of placebo response during the protocol. For the dually diagnosed, the expected rates of response can be estimated from the reported studies of the nonretarded population.

B. The end of study analysis (e.g., χ^2 statistic) will compare active to placebo response rates based on predecided criteria of response on the severity scales.

C. Multivariate analyses should be performed to find predictors of response, which are important for future research and clinical work.

The components presented here are common to psychopharmacology studies. However, each clinical trial and every drug present unique problems that are the challenge to psychopharmacology investigators. Attention to standards of experimental design such as those offered here free the investigator to turn creative energy to the solution of those problems.

Reference

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. Washington, DC: The Association, 1980.

Treatment Outcome Research for Depression in Mentally Retarded Children and Youth: Methodological Issues

Johnny L. Matson, Ph.D.[1]

Diagnosis

Childhood depression is a topic that has only recently begun to receive much attention. As recently as 1978 there was debate on whether or not this phenomenon was evident in young persons (LefkoWitz & Burton 1978). However, the rapid change in views of professionals is evident since entire books and many articles have now been written on the topic (Cantwell & Carlson 1983). Initially, a very broad list of symptoms had been used to describe the syndrome. Thus, in addition to symptoms such as dysphoria, irritability, low self-esteem, self-deprecation, hopelessness, suicidal ideation, and social withdrawal, indirect responses such as aggression and noncompliance were noted. Current research, however, suggests that the symptoms of childhood depression are similar to those reported in adults. Using adult criteria, recent research suggests that a group of depressed children can clearly be delineated (Carlson & Cantwell 1980; Kazdin et al. 1983).

Also, related to the diagnosis of depression in children is the clear differential diagnosis of particular disorders. It has been demonstrated empirically that children identified as mentally retarded are less likely to have their symptoms of emotional disorders identified as such. Rather, clinicians typically attribute those behaviors to the child's mental retardation. This concept is defined as diagnostic *overshadowing* and it has been demonstrated empirically (Reiss & Szyszko 1983). It has been found that approximately 30 percent of a group of adolescents who were identified as conduct disordered and who could not function acceptably even in a behaviorally disordered class meet criteria for depression (Matson & Nieminen 1986; Nieminen & Matson 1985). It is this author's view that children may be afflicted with *multiple emotional problems simultaneously*. This conceptualization differs from previous points of view where the symptoms were attributed to the same disorder as in the case of masked depression. The conception of multiple disorders should enhance the accuracy of differential diagnosis and fits into the conceptualization of diagnostic *overshadowing* noted above. Also, there is no other well-delineated method of dealing with these overlapping symptoms.

Rate of Depression

Substantial numbers of emotionally disturbed children evince depression, and this has been noted by several researchers (Albert & Peck 1975; Carlson & Cantwell 1979). However, the group of depressed children and youth who are also mentally retarded is one that has been completely ignored. This group constitutes more than 3 percent of the total childhood population, and perhaps as much as 10 to 15 percent of the emotionally disturbed group. These handicapped children and youth exhibit the wide range of childhood psychopathology found in the population at large. In addition, the rates of emotional disturbance are much higher in these children. For example, Chazan (1964), who studied mildly mentally retarded children in school settings, found the rate of emotional disturbance to be twice that of the general population. Similarly, Chess and Hassibi (1970) studied 52 noninstitutionalized children aged 5 to 11 with IQs between 50 and 75 and found that over half of them evinced emotional problems. In the Isle of Wight studies, several thousand developmentally disabled children were rated and emotional disturbance was in excess of 30 percent, a rate four to five times that of the general population (Rutter et al. 1976). Many other studies of this type exist (Matson & Barrett 1982). What all of these studies show is that a serious problem is present, and that these children and youth are

---

[1] Department of Psychology, Louisiana State University, Baton Rouge, LA.

Reprint requests: Johnny L. Matson, Ph.D., Department of Psychology, Louisiana State University, Baton Rouge, LA 70803-5501.

much more likely to evince emotional problems than the general population of young children.

Methodology Issues

To date, little research on the treatment of depressed children has occurred, and no studies specific to the mentally retarded population have been reported. Yet there are issues specific to the mentally retarded population which should be considered in the development of effective treatments. Differential diagnosis and the development of methods sensitive to the evaluation of treatment effectiveness are of particular concern. These and related issues considered of importance in evaluating treatment outcome research will be reviewed. Also, the use of single case and control group outcome studies as means to evaluate treatment effectiveness will be discussed.

Assessment

The issue of assessment is a critical one in evaluating treatment outcome research both in establishing the severity and type of depression and in measuring all or at least many of the behaviors which are likely to be affected by a particular treatment. Thus, in conducting meaningful treatment research the first order of business is the development of measures for which the psychometric properties for the mentally retarded population have been established. Given that approximately 98 percent of the mentally retarded population is in the mild or moderate range and given that these persons typically have some verbal skills, retarded youth belonging to this group would seem to be the most likely candidates for initial research attention.

Differential Diagnosis

Differential diagnosis is particularly complex with the mentally retarded child. Involved are not only the typical developmental issues, but also diagnostic overshadowing. Thus, age, level and type of mental retardation, type and severity of mental retardation, and cultural and sex issues are among those which should be considered. In previous research the authors have demonstrated that with mildly to severely mentally retarded adults, reading and paraphrasing remarks to the patient are very important. Also, since persons with the milder forms of mental retardation are more likely to be socially deprived and poorly educated, these methods may also be employed with the parents in reports on their children. The authors have used simplified language, paraphrasing, examples the patients and/or their parents can identify with, and visual aids. The visual aids may include pictorial representations of differing types of affect. Similarly, with Likert 3 point scales (more points than 3 often are beyond the conceptual grasp of the patients) bar graphs taped on the wall have proven useful (Matson, Kazdin, et al. 1984). A small bar for 1, a larger bar for 2, and the largest bar for 3 are taped on the wall behind the tester, who uses them for illustrative purpose. These procedures are also recommended for younger, normal IQ children.

Treatment Outcome

Evaluating treatment outcome differs to some degree from differential diagnosis. The major consideration is that discrete responses are necessary in this latter situation to ensure that effects will be measurable. This problem has been common in much of the published literature. Also, it is critical that a wide range of responses across settings and raters be conducted. This method will ensure the broadest picture of the overall effects of the treatment. Matson (1983) proposes that among the dimensions measured should be chronic nature of the condition, the unipolar-bipolar continuum, and affect and social/interpersonal skills. Obviously, before adequate treatment outcome research can be attempted, the psychometric properties of a number of assessment instruments will need to be established for mentally retarded children and youth. Taking this factor into account, several measures are likely to prove useful and are proposed for study prior to initiation of an extensive program of treatment research.

At a minimum, treatment evaluation should include direct observation and checklists. Direct measures should include operationally defined behaviors which can be assessed on frequency and severity within a number of domains. Some of those include sadness, hopelessness, sleep disturbance, psychomotor retardation, loss of pleasure, low self-esteem, decreased concentration, suicidal statements, social disturbances, marked decreases in school performance, and somatic complaints (Connell 1972; Kuhn & Kuhn 1972; Matson 1983). These behaviors are best evaluated in naturalistic environments such as the school.

A substantial number of checklists have recently been developed to assess depression of children. It is recommended that self-report, teacher report, and parent measures be collected where possible. Among the many instruments currently used, some of those which may prove of value are the Child Depression Inventory (Kovacs & Beck 1977), Child Depression Scale (Reynolds 1985), and the Bellevue Index of Depression (Petti 1978).

It is also suggested that researchers measure a broad range of responses other than depression, being mindful that overlap in types of psychopathology may exist. General measures of child psychopathology may also be considered. One measure that has been extensively studied in the past is the Child Behavior Profile, which has been standardized and factor analyzed on 259 mildly and moderately mentally retarded adolescents (Cullinan et al. 1984; Matson, Epstein, et al. 1984). Given that this measure screens for a range of typical childhood conditions, it could prove useful in augmenting the overall profile of particular children. This measure is unlikely to be particularly sensitive to treatment effects, however.

Initial evaluative studies with single case methodology (Barlow & Hersen 1984) are suggested to develop pharmacological and psychological interventions. Considering the idiosyncratic nature of these problems in mentally retarded children, factors such as level of mental retardation, age, ability to communicate, severity and length of the depression, and a host of other variables dictating the potential efficacy of the treatment are needed. With mentally retarded children and youth it is recommended that psychological treatments be combined with pharmacotherapy when the latter approach is used, given the social and interpersonal problems evident with this population. Adapting treatments to these variables is best accomplished with initially small numbers of subjects. This method is of course more cost effective as well.

An example of a single case depression treatment study is presented by Frame, Matson, Sonis, Fialkov, and Kazdin (1982). They studied a 10-year-old boy with an IQ of 79. He evinced acute depression including a recent history of suicidal thoughts and gestures, violent temper outbursts, and poor school performance. He was hospitalized at Western Psychiatric Institute and Clinic, a component of the University of Pittsburgh School of Medicine. In this instance a much more extensive series of assessment measures was employed. In addition to meeting the criteria of *DSM-III: Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980) for a major depressive episode, he completed the Child Depression Inventory, Child Behavior Profile, and the Bellevue Index of Depression [using Weinberg criteria (Weinberg et al. 1973)]. He far exceeded criteria for depression on all measures. Also, the Depression Adjective Checklist (Lubin 1965) was used on video-taped interviews to rate specific operationally defined behaviors, including inappropriate body position (hands over face, torso bent forward and/or away from interviewer), lack of eye contact, and poor speech quality. Two students independently rated these target responses and reliability ranged from .83 to .99 on Pearson Product Moment correlations for each target behavior. Treatment was psychological in nature with social learning components of instructions, modeling, role playing, performance feedback, and social reinforcement. Treatment proved to be highly effective.

The next step, once particular treatments have been demonstrated to be useful, is to initiate large scale experimental control group designs. The single case approach should also have proven useful in determining parameters of the group of mentally retarded depressed children and youth for study. Also, the parameters that are most important for matching children across conditions should be better established through previous single case research.

Given the transient nature of many forms of depression, severity and type of depression should also dictate length of treatment and followup. A sizable treatment and control group should be used since differences among characteristics and relief from symptoms in this cohort can be followed and evaluated also. Thus, it may be that some subgroups of depressed mentally retarded children are more amenable to certain treatments than others.

Conclusions

The emphasis in this paper has been on issues specific to conducting treatment research in childhood psychopathology. A conscious effort to avoid discussions of particular treatments and/or statistical approaches has been made. This approach has been taken since these latter topics have been covered extensively elsewhere. The major points made here have been that differential diagnosis and multiple measures of assessment are essential in determining the effectiveness of particular treatments and the extent of their effects across a range of problem behaviors. The fact that some children and youth may suffer from two or more emotional disorders further argues for this approach. It is suggested that a major shortcoming of a good deal of the treatment outcome research that has occurred in the child psychiatry and psychology literature is the failure to use more comprehensive and treatment-sensitive dependent variables. Such problems can lead to inaccurate or premature conclusions about treatment effectiveness. Also of concern is careful matching of subjects across treatment conditions. This issue is perhaps the most important to consider along with comprehensive assessment; it is often one of those most frequently overlooked.

Once measurement and intervention procedures have been worked out in single case studies, large group studies are needed. Of course large group studies are not possible in some areas of mental retardation research such as self-injurious behavior, where the cases are few and the problems are idiosyncratic. However, such would not seem to be the case with mildly and moderately mentally retarded children and youth, particularly with respect to unipolar depression. Also, given that spontaneous remission is likely for many persons who fit these criteria (conjecture only, since ample data with this group are not currently available) an *n* of 25 to 30 in the treatment and control groups would be optimal. In this way the course of the disorder could be followed more accurately, and a more realistic evaluation of treatment effectiveness could be obtained.

A final issue pertains to matching subjects in a yoking procedure with random assignment of one member to each condition employed in the study. This process is far from easy. Most importantly, a large number of children and adolescents will need to be screened to obtain adequate numbers of subjects. Some of these persons identified as depressed may not meet criteria for inclusion in the study. Alternate ways of ensuring treatment for these persons must be made available. Furthermore, it has been pointed out that the children and youth will need to be matched on a number of criteria including level of mental retardation, age, sex, severity and type of depressive symptoms, and chronicity of the disorder. A ranking system with point values given to each of these factors will be necessary to ensure that the closest fit (unlikely to be perfect) can be made. Statistical adjustments such as analysis of covariance can then be used. However, it should be strongly emphasized that no substitute exists for careful matching.

An effort has been made here to review some important methodological issues in treatment research of depression in mentally retarded children. It should be stressed that many of these same factors apply to other groups of people and problem behaviors. Much has been accomplished in the treatment of childhood emotional disorders in a short period of time. However, much is yet to be done and this paper addresses some points to consider in additional research in the area.

References

Albert, N., and Peck, A.T. Incidence of depression in early adolescence: A preliminary study. *J. Youth Adolesc.* 4:301-307, 1975.

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders.* 3d ed. Washington, DC: The Association, 1980.

Barlow, D., and Hersen, M. *Single Case Research Designs.* New York: Academic Press, 1984.

Cantwell, O.P., and Carlson, G.A. *Affective Disorders in Childhood and Adolescents: An Update.* New York: SP Medical and Scientific Books, 1983.

Carlson, G.A., and Cantwell, D.P. A survey of depressive symptoms, syndrome and disorder in child psychiatric population. *J. Child Psychol. Psychiatry* 21:19–25, 1979.

Carlson, G.A., and Cantwell, D.P. Unmasking masked depression in children and adolescents. *Am. J. Psychiatry* 137:445–449, 1980.

Chazan, M. The incidence of maladjustment among children in schools for the educationally subnormal. *Br. J. Educ. Psychol.* 34:294–304, 1964.

Chess, S., and Hassibi, M. Behavior deviations in mentally retarded children. *J. Am. Acad. Child Psychiatry* 9:282–297, 1970.

Connell, H.M. Depression in childhood. *Child Psychiatry Hum. Dev.* 4:71–85, 1972.

Cullinan, D.; Epstein, M.H.; Matson, J.L.; and Rosemier, R.A. Behavior problems of mentally retarded and nonretarded adolescent pupils. *School Psychol. Rev.* 13:381–384, 1984.

Frame, C; Matson, J.L.; Sonis, W.A.; Fialkov, M.J.; and Kazdin, A.E. Behavioral treatment of depression in a prepubertal child. *J. Behav. Ther. Exp. Psychiatry* 13: 239–243, 1982.

Kazdin, A.E.; French, N.H.; and Unis, A.S. Child, mother and father evaluations of depression in psychiatric inpatient children. *J. Abnorm. Child Psychol.* 11: 167–180, 1983.

Kovacs, M., and Beck, A.T. An empirical-clinical approach toward a definition of childhood depression. In: Schulterbrandt, J.G., and Raskin, A., eds. *Depression in Childhood: Diagnosis, Treatment, and Conceptual Models.* New York: Raven Press, 1977.

Kuhn, V., and Kuhn, R. Drug therapy for depression in children: Indications and methods. In: Annell, A.L., ed. *Depressive States in Childhood and Adolescents.* Stockholm: Almquist & Wiksell, 1972.

LefkoWitz, M.M., and Burton, N. Childhood depression: A critique of the concept. *Psychol. Bull.* 85:716–726, 1978.

Lubin, B. Adjective check lists for measurement of depression. *Arch. Gen. Psychiatry* 12:57–62, 1965.

Matson, J.L. Depression in the mentally retarded: Toward a conceptual analysis of diagnosis. In: Hersen, M.; Eisler, R.; and Miller, P.M., eds. *Progress in Behavioral Modification.* New York: Academic Press, 1983. pp. 58–74.

Matson, J.L., and Barrett, R.P. Affective disorders. In: Matson, J.L., and Barrett, R.P., eds. *Psychopathology in the Mentally Retarded.* New York: Grune and Stratton, 1982. pp. 121–146.

Matson, J.L.; Epstein, M.H.; and Cullinan, D. A factor analytic study of the Quay-Peterson Scale with mentally retarded adolescents. *Educ. Train. Ment. Retarded* 19:150–154, 1984.

Matson, J.L.; Kazdin, A.E.; and Senatore, V. Psychometric properties of the Psychopathology Instrument for Mentally Retarded Adults. *Appl. Res. Ment. Retard.* 5:81–89, 1984.

Matson, J.L., and Nieminen, G. "A validity study of measures of depression, conduct disorder and anxiety." Unpublished manuscript.

Nieminen, G., and Matson, J.L. "A study of depression, anxiety and conduct disorder in emotionally disturbed adolescents." Unpublished manuscript.

Petti, T.A. Depression in hospitalized child psychiatry patients: Approaches to measuring depression. *J. Am. Acad. Child Psychiatry* 17:49–59, 1978.

Reiss, S., and Szyszko, J. Diagnostic overshadowing and professional experience with mentally retarded persons. *Am. J. Ment. Defic.* 87:396–402, 1983.

Reynolds, W.M.; Anderson, G.; and Bartell, N. Measuring depression in children: A multimethod assessment investigation. *J. Abnorm. Child Psychol.* 13:513–526, 1985.

Rutter, M.; Tizard, J.; Yule, W.; Graham, P; and Whitmore, K. Research report: Isle of Wight Studies, 1964–1974. *Psychol. Med.* 6:313–332, 1976.

Weinberg, W.A.; Rutman, J.; Sullivan, L.; Penick, E.C.; and Dietz, S.G. Depression in children referred to an educational diagnostic center: Diagnosis and treatment. *J. Pediatr.* 83:1065–1072, 1973.

Summary: Challenges for Research

Eleanor D. Dibble, D.S.W.[1]

Studies have already shown that the mentally retarded may have the same range of psychiatric disorders as the non-mentally retarded (Sovner & Hurley 1983, Eaton & Menolascino 1982). What is at issue is differentiating whether the psychiatric behaviors are a continuation/exaggeration of mentally retarded behaviors or of the basic personality characteristics, or distinctly psychopathological. Determining whether a client is mentally ill as well as mentally retarded—a condition frequently referred to as "dually diagnosed"—presents a problem for both treatment and research. Increasingly, the problems of the mentally ill/mentally retarded are being given attention at the national level with conferences of large numbers of professionals and the establishment of the National Association for the Dually Diagnosed. The National Institute of Mental Health is also emphasizing the need for research with this under-researched population. To stimulate research was the goal of the workshop "Methodological Issues in Treatment Research of Mental Illness in the Mentally Retarded."

Research in pharmacologic treatment of the mentally retarded has not developed very far in the last 15 years despite the fact that available research reports that mentally retarded persons are particularly prone to develop severe and sometimes incapacitating behavior disorders (Gillberg et al. 1986). Dr. Lipman, chair of the workshop, made the first survey of psychotropic drug use in the institutionalized mentally retarded in 1968 (Lipman 1970). Other surveys followed in the early 1970s for both institutionalized and home and community care facilities. Little has been done since then. The National Strategy Conference on Mental Retardation and Mental Health convened by the President's Committee on Mental Retardation in October 1985 (unpublished transcript) made extensive recommendations about the research needed for this population. Recommendations included epidemiologic research on the prevalance of the disorders, development of nosology, and research on the effectiveness of various treatments. For this workshop NIMH chose to focus on what appears to be the primary methodological issue: the development of instruments for uniformity in sample selection and experimental design. As Aman (1983) reported, much of the research on neuroleptics in the mentally retarded is uninformative because of poor experimental controls and failure to assess specific functions.

In the first of the workshop papers presented here in the *Bulletin*, Dr. Lipman sets the stage by reviewing the state-of-the-art in pharmacological treatment. Dr. Sovner's paper addresses the research issue of using *DSM-III* criteria (American Psychiatric Association 1980) in differentiating and diagnosing mental illness in the mentally retarded. Dr. Sovner suggests that supplementary criteria are needed in assessing the mentally retarded to allow for their differences from normals. Dr. Menolascino, in the succeeding paper, suggests other criteria which must be considered in diagnosing mental illness in the mentally retarded.

The first research challenge then is to incorporate the appropriate diagnostic criteria and procedures into an instrument which will provide uniformity of diagnoses across research samples. One instrument which has been developed, the Psychopathology Instrument for Mentally Retarded Adults (PIMRA), was reviewed and its testing is reported by Dr. Aman. The PIMRA includes 57 items for diagnosing eight major psychiatric disorders. The PIMRA can be either a self-report or an informant report. Although evaluation of the instrument's self-report version showed similar test results for internal consistency and test-retest reliability to the original informant report version, the majority of the tests fell short of original levels. Further studies of the PIMRA are indicated. From this beginning the challenge is to develop an instrument which can assure more homogeneous study populations and thus provide more useful data.

---

[1] National Institute of Mental Health, Rockville, MD.

Reprint requests: Eleanor D. Dibble, D.S.W., Child and Adolescent Disorders Branch, NIMH, 5600 Fishers Lane, Rm. 10-104, Rockville, MD 20857.

The essentials of good experimental design in psychopharmacology studies are addressed in the papers by Dr. Geller and Dr. Matson. Dr. Geller has consolidated her experience in the study of pharmacologic treatments in a set of guidelines for psychopharmacology studies. Review of these guidelines may be useful to those designing research projects and measuring treatment outcome. Dr. Matson describes specific research approaches assessing pathology in mentally retarded children. These suggestions may also be helpful to researchers.

Investigators stimulated by these papers to do research with this population may find the proceedings of an earlier workshop conducted under NIMH sponsorship useful to review (Reatig 1985). In addition, consultation about research support (e.g., application procedures, protection of human subjects requirements, funding, etc.) is available both from NIMH, where emphasis is on research in mental illness in the mentally retarded, and from the National Institute of Child Health and Human Development (NICHHD), where emphasis is on basic research in mental retardation. Address inquiries to Dr. Eleanor Dibble at NIMH, and to Dr. Peter Vietze at NICHHD.

The papers presented here demonstrate that the current need is for basic diagnostic procedures in research experimental studies and the application of clinical trials methodology to this population. Eventually, researchers can begin to investigate possible etiologic relationships between specific causes of mental retardation and specific mental disorders. The fruits of this research may be more adequate treatment for those who are "dually diagnosed."

References

Aman, M.G., and Singh, N.M. Pharmacological interventions. In: Matson, J.L., and Mulick, J.A., eds. *Handbook of Mental Retardation*. New York: Pergamon Press, 1983. pp. 317-338.

American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. Washington, DC: The Association, 1980.

Eaton, L.F., and Menolascino, F.J. Psychiatric disorders in the mentally retarded: Types, problems and challenges. *Am. J. Psychiatry* 139:1297-1303, 1982.

Gillberg, C.; Persson, E.; Grufman, M.; and Themner, U. Psychiatric disorders in mildly and severely mentally retarded urban children and adolescents: Epidemiological aspects. *Br. J. of Psychiatry* 149:68-74, 1986.

Lipman, R.S. The use of psychopharmacological agents in residential facilities for the retarded. In: Menolascino, F.J., ed. *Psychiatric Approaches in Mental Retardation*. New York: Basic Books, 1970. pp. 387-397.

President's Committee on Mental Retardation. Unpublished proceedings of the National Strategy Conference on Mental Retardation and Mental Health, Washington, DC, October-November 1985.

Reatig, N., ed. Pharmacotherapy and mental retardation workshop. *Psychopharmacol. Bull.* 21:258-326, 1985.

Sovner, R., and Hurley, A.D. Do the mentally retarded suffer from affective illness? *Arch. Gen. Psychiatry* 40:61-67, 1983.

ANNOUNCEMENT

NCDEU ANNUAL MEETING

The annual meeting of the New Clinical Drug Evaluation Unit (NCDEU), sponsored by the Pharmacologic and Somatic Treatment Research Consortium, Division of Clinical Research of the National Institute of Mental Health (NIMH), will take place on May 26–28, 1987, in Key Biscayne, Florida.

This will be the 27th annual meeting of the NCDEU program. The program was established in 1959 by the NIMH as the Early Clinical Drug Evaluation Unit (ECDEU) program with 15 grantees. It has developed into the current format of planned symposia and free communications. Sessions focus on recent research findings in psychopharmacology, methodologic problems and advances in clinical trials in this area, and updates or reviews of significant issues in the field.

As in previous years, the Winter issue of the *Bulletin* will be devoted to summaries of papers presented at the NCDEU meeting. These summaries are designed to provide early availability of the substance of the meeting to *Bulletin* readers. Publication in the *Bulletin* does not prejudice formal publication of the full papers elsewhere at a later time.

To register for the meeting or for further information, contact:

Elaine G. Pearl, NCDEU Coordinator
Pharmacologic and Somatic Treatments
Research Consortium, NIMH
Room 10C–06
5600 Fishers Lane
Rockville, MD 20857.

Neuropeptides and Psychoneuroimmunology[1]

Chair:

Nicholas P. Plotnikoff, Ph.D.
Oral Roberts University
Tulsa, OK

Neuropeptides as Modulators of Immune Function

John E. Morley, M.D.[2] and
Neil Kay, M.D.[3]

> *It is important and salutary to speak also of incomprehensible things.*
>
> —Carl Gustav Jung

The role of the central nervous system (CNS) as a potential modulator of disease was first recognized by Galen who felt that melancholy women were more prone to cancer than sanguine women. Sir William Osler pointed out that to predict the outcome of tuberculosis, it was more important to understand what was going on in a man's head than in his chest. The scientific basis of CNS regulation of the immune system was based on lesion studies such as that of Brooks and associates (1982) which demonstrated that lesions of the anterior hypothalamus decreased concanavalin A reactivity of spleen cells, whereas lesions of the amygdala increased it. Over the last decade an increasing number of studies have suggested that a number of neuropeptides are responsible for linking CNS function to immune function.

More recently, it has been recognized that the immune system makes peptides which not only modulate immune functions but also produce effects on the CNS. Thus, thymosin fraction 5 is a potent stimulator of adrenocorticotropic hormone (ACTH) and cortisol secretion (McGillis et al. 1985) and alpha-interferon produces analgesia and catatonia (Reyes-Vazquez et al. 1984). Woloski and associates (1985) found that monokines produced in response to inflammatory challenge, such as hepatocyte stimulating factor and interleukin-1, stimulate pituitary tumor cells (AtT-20) to produce ACTH. It should be pointed out that the role of the thymus as an endocrine modulator was first recognized as early as 1903 when C.E. de M. Sajous reported " . . . the thymus gland supplies some substances which directly or indirectly stimulate the secretory functions of the adrenals and thereby enhances the activity of the oxidation process."

Neuropeptides that have been reported to directly modify immune function include neurotensin, vasoactive intestinal peptide, porcine histidine isoleucine, substance P, somatostatin, bombesin, and opioid peptides.

Opioid Peptides and Immune Function

In 1974, Brown and associates found that peripheral blood lymphocytes have reduced proliferative responses to mitogens. Subsequently, multiple studies have demonstrated a modulatory effect of opioid peptides on a variety of immune functions (Table 1; *see* Teschemacher & Schweigerer, 1985, for a review). It would appear that a number of the effects of opioids on the immune system are mediated through prostaglandin release. Thus, Brown and Van Epps (1985) found that opioid-induced chemotaxis is inhibited by the prostaglandin inhibitor, indomethacin. Another particularly interesting effect of beta-endorphin and other opioids is their ability to activate superoxide dismutase and free radical generation in polymorphonuclear leukocytes and macrophages (Sharp et al. 1985). In view of the well-known release of beta-endorphin during stress (Morley 1981) and the possibility that free radical generation may accelerate the aging process (Gordon 1974), these findings suggest a linkage between stress, opioids, and the aging process.

---

[1] This symposium took place in December 1985 in Maui, Hawaii, as a sanctioned meeting held in conjunction with the 24th Annual Meeting of the American College of Neuropsychopharmacology.

[2] Geriatric Research, Education and Clinical Center, Sepulveda Veterans Administration Medical Center, Sepulveda, CA.

[3] Minneapolis Veterans Administration Center, Minneapolis, MN.

Reprint requests: John E. Morley, M.D., Geriatric Research, Education and Clinical Center, Sepulveda V.A. Medical Center, Sepulveda, CA 91343.

The authors' interest in opioids and the immune system has centered on the role of endogenous opioids as activators of natural killer (NK) cells. Peripheral blood lymphocyte NK cell activity is a spontaneous cytotoxic function that is thought to be important in mediating host defense to viral and other infections and in natural resistance toward malignant cells. Of particular note is the fact that in patients with low or absent NK function, there is an increased incidence of primary or secondary malignancies (Kay & Zarling 1984). Studies by Kay, Allen, and Morley (1984) confirmed the original studies of Matthews and associates (1983) and Plotnikoff and associates (1985) that beta-endorphin and methionine-enkephalin enhanced NK activity. Gamma-endorphin was more potent than beta-endorphin in this system (Kay et al. 1984). Further studies showed that the des-tyrosine endorphins were more potent enhancers of NK activity than were either gamma- or beta-endorphins (Morley et al. 1985). The authors' fragment studies suggested that the NK stimulatory activity of endorphins rests predominantly in the (6–9) amino acid fragment, i.e., the alpha-helix portion of the molecule. As the NK activity of des-tyrosine endorphin (2–16) is blocked by naloxone, it appears that the NK-cell opioid receptor may be a two-site receptor with the (6–9) portion acting as the address site and the (1–5) portion representing the active opioid site. A similar double site receptor has been proposed for dynorphin based on *in vitro* (Chavkin & Goldstein 1981) and *in vivo* data (Morley & Levine 1983).

TABLE 1. Effects of Opioid Peptides on the Immune System.

1. C–terminal of beta-endorphin binds to complement SC5B-9 and 5B-9(m).
2. C–terminal of beta-endorphin modulates proliferative response of T-lymphocytes.
3. Methionine-enkephalin increases percentage of T-cell rosettes in normal and lymphoma patients.[a]
4. Beta-endorphin and methionine-enkephalin stimulate monocyte chemotaxis.[a]
5. Beta-endorphin and dynorphin stimulate superoxidase dismutase activity in polymorphonuclear lymphocytes and macrophages.[a]
6. Methionine-enkephalin enhances endothelial prostacyclin production and thus inhibits granulocyte adherence to endothelium.[a]
7. Methionine-enkephalin antagonizes prostaglandin inhibition of IgE-mediated serotonin release from mast cells.[a]
8. Opioids release histamine from mast cells.[a]
9. Opioids enhance natural killer cell activity.[a]

SOURCES: Data abstracted from Teschemacher and Schweigerer 1985, Morley et al. 1985, Plotnikoff et al. 1985, and Pert et al. 1985.
[a] Naloxone reversible.

In other studies the authors have demonstrated that recombinant alpha-interferon and recombinant interleukin-2 stimulation of NK cell activity was reversed by naloxone (Kay et al. 1984; Morley et al. 1985). Preliminary data suggest that beta-endorphin and interleukin-2 have synergistic effects on NK activity. Based on this data, the authors suggest that activation of NK cells is produced by a cascade in which interleukin-2 releases alpha-interferon which, in turn, releases beta-endorphin. This type of cascade is similar to that proposed for the neuropeptide regulation of appetite (Morley 1980; Morley & Levine 1985).

One further question suggested by these data is whether the release of pituitary beta-endorphin plays a physiological role in immune modulation. Beta-endorphin is increased during exercise and exercise transiently increases NK activity (Brahmi et al. 1985). Thus, it is possible that the pituitary release of opioids is responsible for the NK enhancement that occurs during exercise.

Other Neuropeptides and Immune Function

O'Dorisso and associates (1985) have demonstrated the presence of vasoactive intestinal peptide (VIP) receptors on molt 4B lymphocytes. These receptors cross-react with porcine histidine isoleucine (PHI) and growth hormone releasing factor. Both VIP and PHI activate cyclic adenosine monophosphate (AMP) in this cell line, while growth hormone releasing factor fails to produce activation of this second messenger. VIP enhances NK activity when preincubated with peripheral blood lymphocytes, but is inhibitory when added at the time of the assay (Rola-Pleszcywski et al. 1985).

Somatostatin has been demonstrated to bind specifically to monocytes and lymphocytes whereas glucagon binds specifically only to monocytes (Bhathena et al. 1981). Somatostatin inhibits the proliferation of T-lymphocytes (Payan et al. 1984), stimulates histamine release from mast cells (Theoharides & Douglas 1978), and inhibits its release from basophils (Goetzl et al. 1984). A number of other peptides stimulate histamine release from mast cells. These include neurotensin, VIP, substance P, and bradykinin (Shanahan et al. 1985).

Substance P meets many of the requirements of the mediator of the local inflammatory response. It produces vasodilatation, increases vascular permeability, produces margination and endothelial adherence of polymorphonuclear white cells and monocytes, and degranulates mast cells (Payan et al. 1984). Substance P cross-reacts with the chemotaxis receptor on rabbit neutrophils, orientates the neutrophil, and is chemotactic (Marasco et al. 1981). Ruff, Wahl, and associates (1985) reported that substance P is also chemotactic for human monocytes at concentrations as low as 10^{-13} M. Substance P also enhances ^{3}H-thymidine incorporation into stimulated T-lymphocytes (Payan et al. 1983). Payan and associates (1984) have suggested that substance P and somatostatin are the neurotransmitters released from peripheral nerves in response to local surgery.

Ruff, Schiffman, and associates (1985) have demonstrated that the tetradecapeptide bombesin is a potent chemo-attractant for human monocytes and small cell lung carcinoma cells. The closely related gastrin releasing peptide was also chemo-attractant for human tumor cells and monocytes. Ruff, Pert, and associates (1985) have also shown that there are high-affinity benzodiazepine sites on purified monocytes, and benzodiazepines enhance chemotactic activity. The endogenous ligand for the benzodiazepine receptor is a neuropeptide (Ferrero et al. 1984).

Conclusion

With the discovery of neuropeptides as linkages between the CNS and the immune system, the field of psychoneuroimmunology has taken a giant leap forward. It is clear that many of the acute effects of stress on the immune system are mediated by peptides acting either in a paracrine (local regulatory), humoral, or neurotransmitter mode. Pert and associates (1985) have named this system a "psychosomatic network." Human ability to piece together the jigsaw that represents the neuropeptide immunomodulatory system is at present rudimentary. It is thus useful to conclude this review by recalling the words of the English philosopher Emerson Pugh: "If the human brain were so simple that we could understand it, we would be so simple that we couldn't."

References

Bhathena, S.J.; Schechter, G.P.; Redman, R.S.; Wahl, L.; and Recant L. Identification of human mononuclear leukocytes bearing receptors for somatostatin and glucagon. *Diabetes* 30:127–131, 1981.

Brahmi, Z.; Thomas, J.E.; Park, M.; Park, M; and Dowdeswell, I.R. The effect of acute exercise on natural killer-cell activity of trained and sedentary subjects. *J. Clin. Immunol.* 5:321–328, 1985.

Brooks, W.H.; Cross, R.J.; Roszmon, T.L.; and Markesbery, W.R. Neuroimmunomodulation: Neural anatomical basis for impairment and facilitation. *Ann. Neurol.* 12:56–61, 1982.

Brown, S.L., and Van Epps, D.E. Suppression of T-lymphocyte chemotactic factor production by the opioid peptides beta-endorphin and met-enkephalin. *J. Immunol.* 134:3384–3389, 1985.

Brown, S.M.; Stemmel, B.; and Taub, R.N. Immunologic dysfunction in heroin addicts. *Arch. Intern. Med.* 134:1001–1006, 1974.

Chavkin, C., and Goldstein, A. Specific receptor for the opioid peptide dynorphin and the kappa opioid receptor in feeding. *Peptides* 4:797–800, 1981.

Ferrero, P.; Guidotti, A.; Conte-Tronconi, B.; and Costa, E. A brain octadecaneuropeptide generated by tryptic digestion of DBI (diazepam binding inhibitor) functions as a proconflict ligand of benzodiazepine recognition sites. *Neuropharmacology* 23:1359–1362, 1984.

Goetzl, E.J., and Payan, D.G. Inhibition by somatostatin of the release of mediators from human basophils and rat leukemic basophils. *J. Immunol.* 133:3255–3258, 1984.

Gordon, P. Free radical and the aging process. In: Rockstein, M. ed. *Theoretical Aspects of Aging.* New York: Academic Press Inc., 1974. pp. 61–82.

Kay, N.E., and Zarling, J.M. Impaired natural killer activity in patients with chronic lymphocytic leukemia is associated with a deficiency of azurophilic cytoplasmic granules in putative NK cells. *Blood* 63:305–309, 1984.

Kay, N.E.; Allen, J.; and Morley, J.E. Endorphins stimulate normal peripheral blood lymphocyte natural killer activity. *Life Sci.* 35:53–59, 1984.

Marasco, W.A.; Showell, H.J.; and Becker, E.L. Substance P binds to the formylpeptide chemotaxis receptor on the rabbit neutrophil. *Biochem. Biophys. Res. Commun.* 99:1065–1072, 1981.

Matthews, P.M.; Froelich, C.J.; Sibbit, W.L.; and Bankhurst, A.D. Enhancement of natural cytotoxicity by β-endorphin. *J. Immunol.* 130:1658–1662, 1983.

McGillis, J.P.; Hall, N.R.; Vahouny, G.V.; and Goldstein, A.L. Thymosin fraction 5 causes increased serum corticosterone in rodents in vivo. *J. Immunol.* 134:3952–3955, 1985.

Morley, J.E. The neuroendocrine control of appetite: The role of the endogenous opiates, cholecystokinin, TRH, gamma-amino butyric acid and the diazepam receptor. *Life Sci.* 27:355–368, 1980.

Morley, J.E. The endocrinology of the opiates and the opioid peptides. *Metabolism* 30:195–209, 1981.

Morley, J.E., and Levine, A.S. Involvement of dynorphin and the kappa opioid receptor in feeding. *Peptides* 4:797–800, 1983.

Morley, J.E., and Levine, A.S. Pharmacology of eating behavior. *Annu. Rev. Pharmacol. Toxicol.* 25:127–146, 1985.

Morley, J.E.; Kay, N.; Allen, J.; Moon, T.; and Billington, C.J. Endorphins, immune function and cancer. *Psychopharmacol. Bull.* 21:485–488, 1985.

O'Dorisso, M.S.; Wood, C.L.; Wenger, G.D.; and Vassalo, L.M. Cyclic AMP-dependent protein kinase in Molt 4b lymphoblasts: Identification by photoaffinity labeling and activation in intact cells by vasoactive intestinal polypeptide (VIP) and peptide histidine isoleucine (PHI). *J. Immunol.* 134:4078–4086, 1985.

Payan, D.G.; Brewster, D.R.; and Goetzl, E.J. Specific stimulation of human T-lymphocytes by substance P. *J. Immunol.* 131:1613–1615, 1983.

Payan, D.G.; Levine, J.D.; and Goetzl, E.J. Modulation of immunity and hypersensitivity by sensory neuropeptides. *J. Immunol.* 132:1601–1603, 1984.

Pert, C.B.; Ruff, M.R.; Weber, R.J.; and Herkenheim, M. Neuropeptides and their receptors: A psychosomatic network. *J. Immunol.* 135:8205–8265, 1985.

Plotnikoff, N.P.; Murgo, A.J.; Miller, G.C.; Corder, C.N.; and Faith, R.E. Enkephalins: Immunomodulators. *Fed. Proc.* 44:118–122, 1985.

Reyes-Vasquez, C.; Weisbrodt, N.; and Dafny, N. Does interferon exert its action through opiate receptors? *Life Sci.* 35:1015–1021, 1984.

Rola-Pleszcywski, M.; Bolduc, D.; and St. Pierre, S. The effects of vasoactive intestinal peptide on human natural killer cell function. *J. Immunol.* 135:2569–2573, 1985.

Ruff, M.R., Pert, C.B., Weber, R.J., Wahl, L.M., Wahl, S.M., and Paul, S.M. Benzodiazepine receptor mediated chemotaxis of human monocytes. *Science* 229:1281–1283, 1985.

Ruff, M.R.; Schiffman, E.; Terranova, V.; and Pert, C.B. Neuropeptides are chemoattractants for human tumor cells and monocytes: A possible mechanism for metastasis. *Clin. Immunol. Immunopath.* 37:387–396, 1985.

Ruff, M.R.; Wahl, S.M.; and Pert, C.B. Substance P receptor-mediated chemotaxis of human monocytes. *Peptides* 6:(Suppl. 2):107–111, 1985.

Shanahan, F.; Denburg, J.A.; Fox, J.; Bienenstock, J.; and Befus, D. Mast cell heterogeneity: Effects of neuroenteric peptides on histamine release. *J. Immunol.* 135:1331–1336, 1985.

Sharp, B.M.; Keane, W.F.; Suh, H.J.; Gekker, G.; Tsukayama, D.; and Peterson, P.K. Opioid peptides rapidly stimulate superoxide production by human polymorphonuclear leukocytes and macrophages. *Endocrinology* 117:793–795, 1985.

Teschemacher, H., and Schweigerer, L. Opioid peptides: Do they have immunological significance? *Trends Pharmacol. Sci.* 6:368–370, 1985.

Theoharides, T.C., and Douglas, W.W. Somatostatin induces histamine secretion from rat peritoneal mast cells. *Endocrinology* 102:1637–1641, 1978.

Woloski, B.M.; Smith, E.N.; Meyer, W.J., III; Fuller, G.M.; and Blalock, J.E. Corticotropin-releasing activity of monokines. *Science* 230:1035–1037, 1985.

Life Events, Depression, and Natural Killer Cell Activity[1]

Michael Irwin, M.D.,[2] Marcia Daniels, M.D.,[3] Eda T. Bloom, Ph.D.,[4] and Herbert Weiner, M.D.[3]

Introduction

Both bereavement (Bartrop et al. 1977; Schleifer et al. 1983) and depression (Schleifer et al. 1984) are associated with impaired immune function. While these findings suggest that depression or "stress" may affect immune function (Guillemin et al. 1985; Tecoma & Huey 1985), measurement of lymphocyte responses to mitogens is a general immune parameter and may not have clinical significance (Guillemin et al. 1985). Another parameter of immune function is natural killer (NK) cell activity. NK cells are cytolytic cells that are considered important in the immunologic surveillance of tumor cells and cells infected with viruses (Herberman & Ortaldo 1981).

NK activity may be regulated by neural mechanisms (Tecoma & Huey 1985). An impairment of NK activity has been reported in depressed, anxious, and lonely persons (Locke et al. 1984; Kiecolt-Glaser, Ricker, et al. 1984; Kiecolt-Glaser, Garner, et al. 1984) and recently correlated with Hamilton ratings of depression in women anticipating and undergoing bereavement (Irwin et al. 1986). The effects of other life experiences on NK activity have not yet been clearly demonstrated. Some have reported life changes to have significant effects on NK activity (Kiecolt-Glaser, Ricker, et al. 1984), while others have not found this relationship (Kiecolt-Glaser, Garner, et al. 1984).

In this study the authors measured NK activity at several times in 38 women who differed in the severity of depression and in the magnitude of changes in their lives.

Methods

Sample

The subjects consisted of three groups of women: those whose husbands had died from lung cancer during the previous 6 months ($n = 12$); the wives of men alive but diagnosed with incurable lung cancer ($n = 16$); and women whose husbands were well and living with them ($n = 11$). The subjects were free of chronic medical disorders associated with alterations in immunity, and no subject was tested who had a recent (< 1 week) history of infectious disease. None were taking drugs known to affect immune function, nor abusing alcohol or other substances. Only 2 subjects smoked tobacco.

The subjects had a mean age of 59.3 (range 40–71) and were in the middle range of socioeconomic status. Thirty-two of the subjects were white, 6 were black.

Study Design

Each subject was interviewed to evaluate severity of depression, number of major life changes, and recent health status. Blood was drawn from the subjects at each interview. Subjects were tested over a 1- to 3-month period, and of the 38 subjects, 18 were tested three times, 15 were evaluated four to five times, and 5 were seen six or more times. All testing occurred in the morning between 9 and 11 a.m. At each session the subject met with a psychiatrist, who carried out a 30-minute struc-

---

[1] This research was supported by two grants from the National Institutes of Health: Biomedical Research Support Grant RR-05756 and National Cancer Institute Grant CA-30187.

The authors wish to thank Dr. Edward L. Korn for expert statistical advice, Dr. T. Makinodan for critical review of the manuscript, Jane Babbitt for technical help in the natural killer cell assay, Dr. L.J. West for his enthusiastic support of this project, and finally, the Hematology-Oncology Service of the West Los Angeles Veterans Administration Medical Center.

[2] Alcohol Research Center, San Diego Veterans Admininstration Medical Center, San Diego, CA.

[3] Neuropsychiatric Institute, University of California at Los Angeles, Los Angeles, CA.

[4] Geriatric Research, Education and Clinical Center, West Los Angeles Veterans Administration Medical Center, Los Angeles, CA.

Reprint requests: Michael Irwin, M.D., Psychiatry Service (116A), V.A. Medical Center, 3350 La Jolla Village Drive, San Diego, CA 92161.

tured interview consisting of the Social Readjustment Scale (SRS) of recent (< 1 month) life events (Holmes & Masuda 1974), the General Health Questionnaire (GHQ; Goldberg 1972), an evaluation of recent changes in health status or medication use, and the Hamilton Depression Rating Scale (Endicott et al. 1981). At the end of this interview the subject was weighed and a 10 cc blood sample was obtained by venipuncture.

Cell Isolation

Peripheral blood lymphocytes from subjects were isolated by sedimentation over ficoll-hypaque (Ficoll-Paque, Pharmacia, Piscataway, NJ) followed by treatment with carbonyl iron as described by Bloom and Korn (1983). This procedure yields a cell suspension that typically contains 99 percent lymphocytes (Bloom & Babbitt 1985). The medium used for suspending the cells throughout the assay was RPMI-1640 containing 10 percent fetal bovine serum (Sterile Systems, Logan, UT), 1 percent l-glutamine, and 0.1 percent gentamicin.

Cytotoxicity Assay

The 4-hour chromium release assay was performed in 0.2 mL volume in U-bottom microplates as described by Bloom and Babbitt (1985). Cell populations were titrated for cytolytic activity against 5000 51-chromium labeled K562 target calls. Effector cell suspensions were adjusted to 2×10^6 cells/mL; and effector:target cell ratios of 40:1, 20:1, 10:1, and 5:1 were tested in triplicate. Plates were centrifuged for 2 minutes at 500 × g prior to incubation for 4 hours at 37°C in 5 percent CO_2, and again prior to harvesting of 100 μL of supernatant from each well. Radioactivity in the supernatant was determined by a gamma counter and the percentage of 51-chromium released in each effector:target cell ratio was calculated.

Since it is crucial to measure and to express cytotoxic activities accurately, lytic units were obtained by fitting scale families of curves to our data (Bloom & Korn 1983). In this case, each curve was fit separately to the modified exponential family of equations. One lytic unit was defined as the number of effector cells killing 20 percent of the target cells. Data are presented as the number of lytic units in 10^6 cells.

Data Analysis

The mean of the measurement of life events (SRS), subjective symptoms (GHQ), depression (Hamilton score), and NK activity was determined for each individual. NK activity was related to life change, depression, and subjective symptoms using Kendall Tau correlations.

Results

The magnitude of changes in these women's lives was related to an impairment of NK function (r = .32, $p < .005$). When the subjects were divided into three groups that differed in the magnitude of changes in their lives, those women who had few changes in their lives had higher NK activity (mean ± SE = 40.2 ± 8.4) than did women with a moderate (10.9 ± 4.2) or severe number of life changes (21.9 ± 5.6) (Figure 1). Bereavement, per se, was not related to changes in NK activity even though NK activity tended to decrease in women anticipating or undergoing bereavement (Table 1). No subject had a weight change of 5 percent of her baseline body weight during the study period.

Impaired NK function was related to the Hamilton subscale item, depressed mood (r = .27, $p < .02$). While total Hamilton depression and subscales, including anxiety, insomnia, and somatic symptoms, were correlated with NK function in the same direction, they did not reach statistical significance. Self-report of symptoms on the GHQ was not related to changes in NK function.

Evaluation of depression with the Hamilton Scale was correlated with self-report of depressive symptoms (GHQ) (r = .56, $p <.0001$).

TABLE 1. Relation of Bereavement to Immune Function.

Variable	Not Bereaved ($n = 11$)	Anticipating Bereavement ($n = 16$)	Bereaved ($n = 12$)
NK Activity	29.7 ± 8.2	25.8 ± 4.5	18.2 ± 3.8

Values represent the mean ± SE.
Using Kruskal Wallis Test (χ^2 approximation), p = .41.

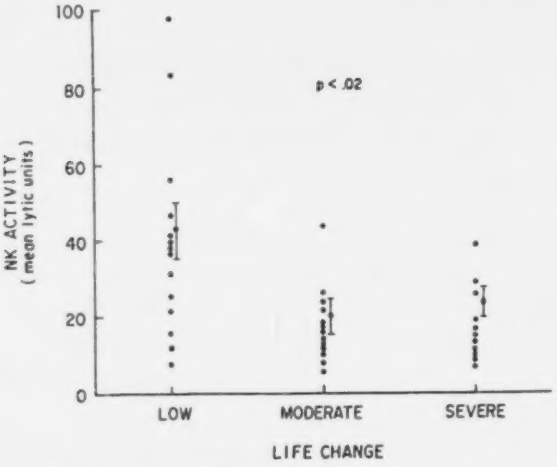


FIGURE 1. NK activity in peripheral blood lymphocytes. $N = 38$ women: 13 with few life changes; 14 with moderate changes; and 11 with severe changes in their lives.

Measures of life change were significantly related to depression ($r = .28$, $p < .01$), depressed mood ($r = .39$, $p < .001$), and somatic symptoms ($r = .32$, $p < .005$), but were not related to self-report of symptoms on the GHQ.

Discussion

Lymphocyte NK function of women who were depressed and experiencing major changes in their lives was compared with the function of matched subjects who had neither Hamilton depression nor major life changes. Hamilton depressed mood and magnitude of life changes were correlated with impaired NK activity. While measures of NK activity are known to fluctuate, repeated sampling of these two parameters minimizes the influence of this variability and strengthens our findings.

Hamilton depressed mood was related to impaired NK cell function, but the overall Hamilton score and scores on anxiety and insomnia were not. Others have described an association between impaired NK function and the self-report of depression and anxiety (Locke et al. 1984; Kiecolt-Glaser, Ricker, et al. 1984). In contrast, this study controlled for the use of tobacco and alcohol and changes in weight, rated depression by clinician observation (rather than self-report), and possibly studied a population that was less depressed and anxious. All of these subjects were only moderately depressed (Hamilton < 25). Schleifer and associates (1985) have found changes in lymphocyte responses to mitogens in severely depressed subjects but not in subjects with Hamilton scores less than 25.

The effects of depression on immune function may be relatively more important than effects associated with life events. Some moderate number of changes in the subjects' lives (such as illness of husband) was associated with lower NK activity, but severe changes including bereavement were not associated with further effects on NK activity. The authors have followed women longitudinally during bereavement and demonstrated in a recent study that severity of depression (but not the bereavement event) is related to impaired NK function (Irwin & Weiner in press). Locke and associates (1984) have also reported that lower cytotoxic activity is predicted by psychiatric symptoms but not by retrospective report of life change.

These results represent progress in understanding the association of depression and impaired immune function. NK function has been related to medical illnesses and is altered in women who are depressed. Whether these alterations in immunity are clinically significant and affect disease susceptibility is unknown but must be addressed in prospective evaluation of these women's health status. Moreover, the processes that modulate NK activity and link bereavement, depressive symptoms, and immune function remain largely unexplored.

References

Bartrop, R.W.; Lazarus, L.; Luckherst, E.; and Kiloh, L.G. Depressed lymphocyte function after bereavement. *Lancet* 1:834–836, 1977.

Bloom, E.T., and Babbitt, J.T. Monocyte mediated augmentation of human natural cell-mediated cytotoxicity. *Cell Immunol.* 91:21–32, 1985.

Bloom, E.T., and Korn, E.L. Quantification of natural cytotoxicity by human lymphocyte subpopulations isolated by density: Heterogeneity of the effector cells. *J Immunol.* 58:323–335, 1983.

Endicott, J.; Cohen, J.; Nee, J.; Fleiss, J.; and Sarantakos, S. Hamilton depression rating scale. *Arch Gen. Psychiatry* 38:98–103, 1981.

Goldberg, D. The detection of psychiatric illness by questionnaire: A technique for the identification and assessment of non-psychotic psychiatric illness. *Inst. Psych. Maudsley Mono.* 21:1–30, 1972.

Guillemin, R.; Cohen, M.; and Melnechuk, T., eds. *Neural Modulation of Immunity.* New York: Raven Press, 1985.

Herberman, R.B., and Ortaldo, J.R. Natural killer cells: Their role in defenses against disease. *Science* 214:24–30, 1981.

Holmes, T.H., and Masuda, M. Life change and illness susceptibility. In: Dohrenwend, B.S., and Dohrenwend, B.P., eds. *Stressful Life Events: Their Nature and Effects.* New York: Wiley, 1974.

Irwin, M.; Daniels, M.; Bloom, E.T.; Smith, T.L.; and Weiner, H. "Life events, depressive symptoms, and immune function." Paper presented at the annual meeting of the American Psychiatric Association, May 1986.

Irwin, M., and Weiner, H. Depressive symptoms and immune function during bereavement. In: Zisook, S., ed. *Biopsychosocial Dimensions of Grief and Bereavement.* Washington, DC: American Psychiatric Association Press, in press.

Kiecolt-Glaser, J.K.; Garner, W.; Speicher, C.; Penn, G.M.; Holliday, J.; and Glaser, R. Psychosocial modifiers of immunocompetence in medical students. *Psychosom. Med.* 46:7–14, 1984.

Kiecolt-Glaser, J.K.; Ricker, D.; George, J.; Messick, G.; Speicher, C.E.; Garner, W.; and Glaser, R. Urinary cortisol levels, cellular immunocompetency, and loneliness in psychiatric inpatients. *Psychosom. Med.* 46:15–23, 1984.

Locke, S.E.; Kraus, L.; Leserman, J.; Hurst, M.W.; Heisel, J.S.; and Williams, R.M. Life change stress, psychiatric symptoms, and natural killer cell activity. *Psychosom. Med.* 46:441–453, 1984.

Schleifer, S.J.; Keller, S.E.; Camerino, M.; Thornton, J.C.; and Stein, M. Suppression of lymphocyte stimulation following bereavement. *JAMA* 250:374–377, 1983.

Schleifer, S.J.; Keller, S.E.; Meyerson, A.T.; Raskin, M.J.; Davis, K.L.; and Stein, M. Lymphocyte function in major depressive disorder. *Arch. Gen. Psychiatry* 41:484–486, 1984.

Schleifer, S.J.; Keller, S.E.; Siris, S.G.; Davis, K.L.; and Stein, M. Depression and immunity: Lymphocyte function in ambulatory depressed patients, hospitalized patients, and patients hospitalized for herniorrhaphy. *Arch. Gen. Psychiatry* 42:129–133, 1985.

Tecoma, E.S., and Huey, L.Y. Minireview: Psychic distress and the immune response. *Life Sci.* 36:1700–1812, 1985.

Methionine Enkephalin: Immunomodulator in Normal Volunteers (*in Vivo*)[1]

Nicholas P. Plotnikoff, Ph.D.,[2] Gerald C. Miller, Ph.D.,[3] Suman K.T. Solomon, M.D.,[3] Robert E. Faith, D.V.M.,[2] Larry D. Edwards, M.D.,[4] and Anthony J. Murgo, M.D.[5]

Introduction

Methionine enkephalin (met-enkephalin) was originally discovered to be one of the endogenous ligands for morphine receptors (Hughes et al. 1975). However, Plotnikoff and associates (1976) discovered antidepressant, antianxiety, and anticonvulsant effects of the enkephalins, identifying a much broader spectrum of pharmacological effects than originally anticipated.

Earlier studies by several researchers have identified enkephalin receptors on human T-cells, granulocytes, complement, platelets, and B-cells (Hazum et al. 1979; Lopker et al. 1980; Schweigerer et al. 1982; Wybran et al. 1979). Plotnikoff and associates (Plotnikoff 1982; Plotnikoff & Miller 1983) explored the possibility that methionine enkephalin might have an immunomodulatory role. Other investigators studied similar effects with the endorphins (Blalock & Smith 1980; Gilman et al. 1982; Mathews et al. 1983). In mice, Plotnikoff and Miller (1983) identified enhanced lymphocyte blastogenesis with phytohemagglutinin and also increased size of thymus (Plotnikoff et al. 1985). In rats, Plotnikoff and associates (1984) showed similar effects on the thymus gland.

Studies in humans (*in vitro*) identified enhanced active T-cell rosettes and natural killer (NK) cell activity in normal volunteers as well as in cancer patients (Faith et al. 1984).

The present study is an evaluation of the *in vivo* effects of methionine enkephalin on levels and activities of T-cells in human volunteers.

Patients and Methods

Male subjects aged 21 to 39 were recruited and informed consent forms signed. Subjects abstained from all drugs, including alcohol and tobacco, for at least 3 weeks prior to the study. All subjects were within 20 percent of ideal body weight and free of acute and chronic cardiovascular, renal, metabolic, and neurological diseases. Those subjects satisfying admission criteria were admitted to the hospital the evening prior to the study, given the drug infusion in the morning of the second day, and discharged on the third day.

Methionine Enkephalin Formation

A sterile solution of met-enkephalin was prepared. Met-enkephalin (Sigma-Aldrich Chemical Co., St. Louis) was dissolved in sterile saline and filter sterilized by the pharmacy. Met-enkephalin has the following characteristics: molecular weight 574, water soluble and amino acid sequence Try-Gly-Gly-Phe-Met-OH. It was dissolved in 60 mL of saline at a concentration sufficient to infuse at 2 mL/min for 30 min to give a delivered dose of 1, 10, or 50 μg/kg body weight.

Immunologic Tests

Total and Active T Lymphocyte Rosette Determination

Peripheral blood was collected by antecubital venipuncture, diluted with RPMI 1640 me-

---

[1] This work was supported by grants from TNI Pharmaceuticals, Inc., Tulsa, OK, and Travenol Laboratories, Morton Grove, IL.

[2] Department of Pharmacology, School of Medicine, Oral Roberts University, Tulsa, OK.

[3] Immuno-Diagnostic Laboratory, Tulsa, OK.

[4] Department of Medicine, School of Medicine, Oral Roberts University, Tulsa, OK.

[5] Section of Hematology-Oncology, Department of Medicine, West Virginia University School of Medicine, Morgantown, WV.

Reprint requests: Nicholas P. Plotnikoff, School of Medicine, Oral Roberts University, 8181 South Lewis Avenue, Tulsa, OK 74137.

dium, layered over a Ficoll-Paque gradient and centrifuged for 30 min at 400 × g. The mononuclear band was collected, washed twice, and resuspended in RPMI 1640. Total T rosettes were quantified by mixing one million lymphocytes with sheep red blood cells in RPMI supplemented with 10 percent fetal calf serum at 4°C overnight. The cells were gently resuspended and the rosettes quantified. The active T-cells were determined by mixing 0.1 mL volume of 1 × 10^7 cells/mL and an equal volume of fetal calf serum and incubated at 37°C for 60 min. Sheep red blood cells (2 × 10^{-7}) were added, the cell suspension centrifuged at 200 × g for 5 min, gently resuspended, and rosette-forming cells quantified with a hemocytometer.

Results

Active T-Cell Rosettes

Significant increases in the levels of active T-cell rosettes were observed in all 6 volunteers at all dose levels (1, 10, and 50 μg/kg). The increases ranged from 26 to 633 percent over control levels (Table 1).

Total T-Cell Rosettes

Only a slight increase in total T-cell rosettes was seen in 5 of the volunteers. However, Volunteer 3 demonstrated a very marked increase of 98 and 82 percent over control levels (Table 2). A significant increase in 11 out of 12 (6 of 6 at 2 hours and 5 of 6 at 24 hours) volunteer samples was obtained with ranges of 4 to 35 percent.

Conclusion

The present *in vivo* study of met-enkephalin at doses of 1, 10, and 50 μg/kg confirms and extends the authors' original *in vivo* studies (Plotnikoff 1982; Plotnikoff & Miller 1983). In fact the minute doses of met-enkephalin employed (1, 10, and 50 μg/kg) correspond to 10^{-7} mg/mL blood, which was a high dose range of the authors' *in vitro* studies. Marked activity on T-cells and NK cells was seen at concentrations of 10^{-6} to 10^{-14} mg/mL blood.

Such increases in active T-cell rosettes may have implications in the immunomodulatory control of infectious and neoplastic diseases (Herberman 1982; Wybran & Fudenberg

TABLE 1. Active T-Cell Rosettes

Volunteer	1 μg/kg		10 μg/kg		50 μg/kg	
	#1	#2	#3	#4	#5	#6
Baseline	17/200	31/200	30/200	34/200	33/200	6/200
2 hours	29/200 (71%↑)	77/200 (148%↑)	85/200 (183%↑)	77/200 (126%↑)	82/200 (148%↑)	14/200 (133%↑)
24 hours	26/200 (53%↑)	17/200 (45%↓)	61/200 (103%↑)	43/200 (26%↑)	15/200 (54%↓)	44/200 (633%↑)

$p < .05$—*t*-test paired difference (10 of 12 samples); significant positive increase over control values.

TABLE 2. Total T-Cell Rosettes

Volunteer	1 μg/kg		10 μg/kg		50 μg/kg	
	#1	#2	#3	#4	#5	#6
Baseline	100/200	116/200	62/200	113/200	95/200	110/200
2 hours	106/200 (6%↑)	124/200 (4%↑)	123/200 (98%↑)	117/200 (4%↑)	128/200 (35%↑)	102/200 (7%↑)
24 hours	108/200 (8%↑)	110/200 (3%↑)	113/200 (82%↑)	123/200 (9%↑)	117/200 (23%↑)	134/200 (21%↑)

$p < .05$—*t*-test paired difference; 11 of 12 volunteer samples show statistically significant increases over control samples.

1973). Certainly the elevations of blood levels of enkephalin in times of stress have now been documented by several researchers (Farrell et al. 1982; Gilman et al. 1982; Hanbauer et al. 1982; Udenfriend & Kilpatrick 1983; Viveros et al. 1980). It is possible that the enkephalins have a reciprocal relationship with the steroid hormones in modulating immune function in times of stress (Ader 1981; Besedovsky et al. 1983; Laszlo et al. 1983; Lotzova 1983; Miller et al. 1984; Prange et al. 1972; Riley 1981; Rossier et al. 1981; Targan et al. 1981; Vaught & Takemori 1979; Wybran et al. 1980).

It is hoped that the administration of met-enkephalin to patients with infections as well as cancerous tumor growth will be found useful in modulating the immune system, as measured by its restorative effects on T-cells.

References

Ader, R., ed. *Psychoneuroimmunology*. New York: Academic Press, 1981.

Besedovsky, H.O.; del Rey, A.E.; and Sorkin, E. What do the immune system and brain know about each other? *Immunol. Today* 4:342-346, 1983.

Blalock, J.E., and Smith, E.M. Human leukocyte interferon: Structural and biological relatedness to adrenocorticotropic hormone and endorphins. *Proc. Nat'l. Acad. Sci. USA* 77:5972-5974, 1980.

Faith, R.E.; Liang, H.J.; Murgo, A.J.; and Plotnikoff, N.P. Neuroimmunomodulation with enkephalins: Enhancement of human natural killer (NK) cell activity *in vitro*. *Clin. Immunol. Immunopathol.* 31:412-418, 1984.

Farrell, P.A.; Getes, W.K.; Maksud, M.G.; and Morgan, W.P. Increases in plasma beta-endorphin/beta-lipotropin immunoreactivity after treadmill running in humans. *J. Appl. Physiol.* 52:1245-1249, 1982.

Gilman, S.C.; Schwartz, J.M.; Milner, R.J.; Bloom, F.E.; and Feldman, J.D. Beta-endorphin enhances lymphocyte proliferative responses. *Proc. Nat'l Acad. Sci. USA* 79:4226-4230, 1982.

Hanbauer, J.; Kelly, G.D.; Saiani, L.; and Yang, H.Y.T. Met-enkephalin-like peptides of adrenal medulla: Release by nerve stimulation and functional implications. *Peptides* 3:469-473, 1982.

Hazum, E.; Chang, K.J.; and Cuatrecasas, P. Specific non-opiate receptors for beta-endorphins. *Science* 205:1033-1035, 1979.

Herberman, R.B., ed. *NK Cells and Other Natural Effector Cells*. New York: Academic Press, 1982.

Hughes, I.; Smith, T.W.; Kosterlitz, H.W.; Fotergill, L.A.; Morgan, B.A.; and Morriss, H.T. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 258:577-579, 1975.

Laszlo, J; Huang, A.T.; Brenckman, W.D.; Jeffs, C.; Koren, H.; Cianciolo, G.; Metzgar, R.; Cashdollar, W.; Cox, E.; Buckley, C.E., III; Tso, C.Y.; and Lucas, V.S., Jr. Phase I study of pharmacological and immunological effects of human lymphoblastoid interferon given to patients with cancer. *Cancer Res.* 43:4458-4466, 1983.

Lopker, A.; Abood, L.G.; Hoss, W.; and Lionetti, F.J. Stereoselective muscarinic, acetylcholine and opiate receptors in human phagocytic leukocytes. *Biochem. Pharmacol.* 29:1361-1365, 1980.

Lotzova, E. Function of natural killer cells in various biological phenomena. *Surv. Synth. Pathol. Res.* 2:41-45, 1983.

Mathews, P.M.; Froelich, C.J.; Sibbitt, W.L., Jr.; and Bankhurst, A.D. Enhancement of natural cytotoxicity of beta-endorphin. *J. Immunol.* 130:1658-1662, 1983.

Miller, G.C.; Murgo, A.J.; and Plotnikoff, N.P. Enkephalins-enhancement of active T-cell rosettes from normal volunteers. *Clin. Immunol. Immunopathol.* 31:132-137, 1984.

Plotnikoff, N.P. The central nervous system control of the immune-system-enkephalins: Anti-tumor activities. *Psychopharmacol. Bull.* 18(4):148, 1982.

Plotnikoff, N.P.; Kastin, A.J.; Coy, D.H.; Christensen, C.W.; Schally, A.V.; and Spirtes, M.A. Neuropharmacological actions of enkephalin after systemic administration. *Life Sci.* 19:1283-1288, 1976.

Plotnikoff, N.P., and Miller, G.C. Enkephalins as immunomodulators. *Int. J. Immunopharmacol.* 5:437-441, 1983.

Plotnikoff, N.P.; Murgo, A.J.; and Faith, R.E. Neuroimmunomodulation with enkephalins: Effects on thymus and spleen weights in mice. *Clin. Immunol. Immunopathol.* 32:52-56, 1984.

Plotnikoff, N.P.; Murgo, A.J.; Miller, G.C.; Corder, C.N.; and Faith, R.E. Enkephalins: Immunomodulators. *Fed. Proc.* 44:118-122, 1985.

Prange, A.J., Jr.; Lara, P.P.; and Wilson, J.C. Effects of thyrotropin-releasing hormone in depression. *Lancet* 2:999-1002, 1972.

Riley, V. Psychoneuroendocrine influences on immunocompetence and neoplasia. *Science* 212:1100-1109, 1981.

Robbins, D.S.; Donnan, G.G.; Fudenberg, H.H.; and Strelkauskas, A.J. Functional subsets of human T cells defined by 'active' rosette formation. *Cell. Immunol.* 59:205-218, 1981.

Rossier, J.; Dean, D.M.; Livett, B.G.; and Udenfriend, S. Enkephalin congeners and precursors are synthesized and released by primary cultures of adrenal chromaffin cells. *Life Sci.* 28:781-789, 1981.

Schweigerer, L.; Bhakdi, S.; and Teschemacher, H. Specific non-opiate binding sites for human beta-endorphin on the terminal complex of human complement. *Nature* 296:572-574, 1982.

Targan, S.; Britvan, L.; and Dorey, F. Activation of human NKCC by moderate exercise: Increased frequency of NK cells with enhanced capability of effector-target lytic interactions. *Clin. Exp. Immunol.* 45:352-360, 1981.

Udenfriend, S., and Kirkpatrick, D.L. Biochemistry of the enkephalins and enkephalin-containing peptides. *Arch. Biochem Biophys.* 221:309-323, 1983.

Vaught, J.L., and Takemori, A.E. Differential effects of leucine and methionine enkephalin on morphine-induced analgesia, acute tolerance and dependence. *J. Pharmacol. Exp. Ther.* 208:86-90, 1979.

Viveros, O.H.; Diliberto, E.J.; Hazum, E.; and Chang, K.J. Enkephalins as possible adrenomedullary hormones: Storage, secretion, and regulation of synthesis. *Adv. Biochem. Psychopharmacol.* 22:191-204, 1980.

Wybran, J., and Fudenberg, H.H. Thymus-derived rosette-forming cells in various human disease states: Cancer, lymphoma, bacterial and viral infections and other diseases. *J. Clin. Invest.* 52:1026-1032, 1973.

Wybran, J.; Appelboom, T.; Famaey, J.P.; and Govaerts, A. Suggestive evidence for receptors for morphine and methionine-enkephalin on normal human blood T lymphocytes. *J. Immunol.* 123:1068-1070, 1979.

Wybran, J; Appelboom, T.; Famaey, J.P.; and Govaerts, A. In: Serrou, B., and Rosenfeld, C., eds. *International Symposium on New Trends in Human Immunology and Cancer Immunotherapy.* Paris: Doin Press, 1980.

ANNOUNCEMENT

INTERNATIONAL CONGRESS ON SCHIZOPHRENIA RESEARCH

An International Congress on Schizophrenia Research will be held March 28-April 1, 1987, at the Belleview-Biltmore Hotel in Clearwater, Florida. The meeting will host leading scientists actively working on basic and/or clinical research, who will present their work in paper or poster sessions. There has been a great increase in the enthusiasm of schizophrenia researchers recently, and the International Congress will provide a setting for both formal presentation of current research and informal discussion by attendees. In addition, the NIMH will sponsor a Young Investigators Program so that investigators early in their career can be supported to attend the meeting and present their work.

The meeting is being organized by Drs. Charles Schulz of NIMH and Carol Tamminga of the University of Maryland. For further information about the meeting contact:

Susan M. Nusbaum
Maryland Psychiatric Research Center
Box 21247
Baltimore, MD 21228.

The Forum

With this issue we inaugurate a new feature, **The Forum**, which will appear twice a year in issues 2 and 4. Its goal is to provide an opportunity for discussion on issues that are topical and new in psychopharmacology. Consider submitting comments on papers that have appeared in the *Bulletin* (e.g., the paper by Dr. Richard Milich and colleagues presented here). Raise questions that may stimulate responses from others. Material for **The Forum** should be submitted to:

The Forum
Psychopharmacology Bulletin
5600 Fishers Lane, Room 10C-06
Rockville, MD 20857 USA

Submissions will be reviewed by the *Bulletin* Associate Editors. We hope **The Forum** will be a place for lively debate.

—Nina R. Schooler, Ph.D.
Editor-in-Chief

Issues in the Diagnosis of Attention Deficit Disorder: A Cautionary Note on the Gordon Diagnostic System

Richard Milich, Ph.D.,[1] William E. Pelham, Ph.D.,[2] and Stephen P. Hinshaw, Ph.D.[3]

Introduction

In a recent paper Gordon (1986) has compared the strengths and weaknesses of traditional microcomputer-based assessment of attention deficit disorder (ADD) with those offered by the Gordon Diagnostic System (GDS; Gordon & McClure 1983; 1984). Not surprisingly, although careful not to overstate the case, he finds the GDS to be an improvement over the use of standard microcomputers. Nevertheless, several of his criticisms of microcomputers seem forced, and he tends to downplay some of the more serious concerns associated with the GDS. Given that the GDS is receiving widespread attention, with nationwide marketing procedures underway, it seems fitting to examine its strengths and weaknesses independently as compared to more traditional methods of assessment of attention deficit disorder. To facilitate this goal the history of the GDS will be reviewed, since in its relatively brief life several important events have already occurred.

In 1979 the first paper by Gordon in the area of ADD appeared. He presented the results of a study comparing 20 hyperactive

---

[1] Department of Psychology, University of Kentucky, Lexington, KY.

[2] Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA.

[3] Department of Psychology, University of California, Berkeley, CA.

Reprint requests: Richard Milich, Ph.D., Department of Psychology, University of Kentucky, Lexington, KY 40506.

and 20 clinic-referred nonhyperactive children on a differential reinforcement of low-rate behavior (DRL) task. The results of this study were quite promising and, as Milich and Kramer (1984) note, offered an intriguing way in which to define and measure the problems in impulsivity exhibited by ADD children. Approximately 3 to 4 years following the publication of this first article, but before the appearance of any subsequent articles, a commercially marketed version of the GDS was made available (Clinical Diagnostics, Inc., 300 E. Mineral Ave., Littleton, CO 80122). Admittedly, Gordon was in the process of collecting large scale normative data, and within the last year an article has appeared replicating the results of the first study (Gordon & McClure 1984). Nevertheless, it does not seem too rash to state that the appearance of the GDS as a commercially available product was premature.

In its original format the GDS contained only the DRL. Halfway through the standardization process a continuous performance test (CPT), modeled after the one originally produced by Rosvold and associates (1956), was included. In its current format the GDS sells for $1295 (originally $2500). For an additional $150 a data analysis program compatible with either the Apple II or IBM-PC microcomputer is available. For an additional $18 a newsletter is available, published four times a year, that deals with attention deficit disorder in general and the GDS specifically.

Argument

Although Gordon (1986) discusses the flexibility of the GDS, basically the DRL and the CPT are the only two tasks that can be run on the machine. The question raised is whether the information obtained justifies the relatively high cost of the apparatus. It is important to keep in mind that for the same expenditure of funds one could purchase a relatively sophisticated microcomputer system with printer and two disc drives, at least. Such a system would give one markedly improved flexibility, in terms of software available for assessment procedures, word processing capabilities, and data analysis programs, to name just several of the common uses for microcomputers.

As noted, purchasing the Gordon Diagnostic System involves a relatively major financial investment, money that could perhaps be spent in a more cost-efficient fashion. Therefore, the question becomes whether the GDS is supplying valuable information that cannot be obtained in a more economical manner. To answer this question it may be helpful to examine the research available on the GDS. We will summarize briefly the research for the two different tasks: the Delay task, as the DRL is now called, and the Vigilance task, as the CPT task is named.

As noted, two published studies exist to date supporting the validity of the Delay task in differentiating, with a relatively high rate of accuracy, ADD and non-ADD clinic-referred children. However, as Gordon (1985) himself notes, the validity of an assessment instrument can be no greater than the measures employed to establish the criterion groups against which the new instrument is being validated. Thus, for example, when the criterion groups (ADD vs. non-ADD) were established by meeting cutoffs on three rating scales and one laboratory test (the Matching Familiar Figures Test), the Delay task was found to agree with the criterion measures on 15 of 16 cases (94%). When the children were classified as ADD or not by meeting criteria on three of the measures, agreement with the GDS was found in 29 of 32 cases (91%). Although such results certainly offer support for the sensitivity of the GDS in identifying ADD children, they also indicate that four relatively inexpensive and easily obtained measures can do a comparable job of identification.

There are two other aspects of the Delay task that are somewhat disquieting when considering its role in the assessment of ADD. First, the normative data (*see* Gordon & McClure 1983) have not found gender differences in performance on the Delay task. Such a finding contrasts markedly with the accepted prevalence figures for ADD, which range anywhere from 4:1 to 10:1, boys to girls. Whereas Gordon (1985) suggests that there may be many girls with significant deficits in attention who are being overlooked, the Delay task is one of the few measures in the ADD field that fails to find sex differences.

Furthermore, the Delay task has not consistently been shown to be drug sensitive. For example, Barkley (1985) found none of the three measures from the Delay task (rewards, responses, efficiency ratio) to differentiate among placebo and two dosages of methylphenidate (.3 and .5 mg/kg). In contrast, most of the other measures he collected, including parent and teacher ratings, playroom observations, and the Vigilance task, all showed evidence of drug sensitivity. Considering that most measures employed in the assessment of ADD routinely show sensitivity to drug effects, this lack of sensitivity of the Delay task gives one pause as to the utility of this procedure.

Along these lines, it is interesting to note that Gordon (1985), in one of his most recent presentations summarizing the current research on the GDS, focuses entirely on the Vigilance task. His motivation for this decision is not clear but it may well reflect this task's greater sensitivity to stimulant medication. In fact, in the Barkley (1985) study, the Vigilance task was one of the few measures also to differentiate low and high dosages of methylphenidate. It is certainly not surprising that the Vigilance task should exhibit such sensitivity; these procedures have been around for 30 years, and a wealth of studies have documented their drug sensitivity and ability to differentiate ADD and non-ADD children (*see* Douglas 1983). The questions then become whether the GDS Vigilance task offers a significant improvement over more conventional CPT procedures and whether its validity and utility justify its great expense. To answer these questions we will examine Gordon's (1986) criticisms of conventional microcomputer assessments.

Gordon (1986) notes basically three limitations of conventional microcomputers in the assessment of ADD: their size and cumbersomeness, the unreliability of administration, and their delicacy. It is obvious that the first and third points deal with issues of practicality and utility, rather than validity per se. Although at one time the GDS may have been more mobile and hence practical than portable microcomputers, the ones currently available are no more cumbersome, and considerably less expensive, than the GDS. For example, an Apple II-C, which is small and easily portable, can be obtained for approximately $700, and a number of relatively inexpensive CPT tasks compatible with the II-C are available in the public domain. Similarly, Gordon's third point regarding the delicacy of the machines does not seem to be a real issue. Altogether we have administered a variety of information processing tasks on Apple II microcomputers to several hundred ADD children, with no unusual problems and no damage to hardware or software.

Thus, the only substantive issue regarding microcomputer assessment raised by Gordon (1986) concerns the reliability of the evaluation. Here Gordon means that different systems present the stimuli in slightly different fashions and may require different responses (e.g., pressing a spacebar vs. a single letter). In one sense, Gordon is correct in that different CPT programs or microcomputers may produce slightly different response patterns, making it difficult to establish specific cutoff or criterion scores to arrive at a formal diagnosis. The GDS, which presents the same stimuli in a standardized fashion to anyone who uses the machine, could generate such criteria.

First, however, the issue of norms is crucial to such an endeavor. The standardization sample reported by Gordon and McClure (1984) contains 700 boys and girls from ages 3 through 16. Thus, at any given age and gender level, there may be fewer than 30 subjects. In addition, the cutoff scores presented by Gordon and McClure are not separated by gender, a problem noted earlier regarding the GDS. Thus, the viability of these norms for diagnostic use may be questionable.

Second, as Gordon (1986) himself notes, a diagnosis should not be based upon a single score on a single instrument. Instead, it must be derived from the convergence of multiple sources of data. From that perspective, the score on the GDS is, by itself, no more diagnostically significant than that obtained from teacher rating scales or systematic classroom observations. In fact, one could argue that the presentation of formalized normative data and cutoff scores may inadvertently encourage clinicians to rely primarily or even solely on such a measure, at the expense of other information. This is a realistic possibility, given the lack of standardized criteria in the field and given particularly the designation of "Diagnostic System" to the hardware and procedures of the GDS. The problems inherent in single-instrument diagnoses have been noted by Ullmann and associates (1985) with respect to the use of cutoff scores from the Conners (1973) Abbreviated Teacher Rating Scale to diagnose ADD. There is no reason to suspect that a single score from a continuous performance test will escape such problems.

Furthermore, although performance on a CPT task is currently thought to be useful in defining and thus diagnosing ADD, there is sufficient disagreement among professionals regarding the precise nature of the attention deficit in ADD children (*see* Douglas 1983) that currently popular versions of the CPT task, including Gordon's, may not be thought relevant in future diagnostic systems. If one uses a microcomputer to administer an attention task, one is able to acquire new software when accepted diagnostic tasks change. The GDS, however, lacks such flexibility.

Conclusion

The GDS, especially the Vigilance task, appears to have some utility in aiding with the diagnosis of ADD. However, legitimate concerns can be raised regarding the cost efficiency of purchasing such an apparatus, especially when apparently comparable information can be obtained at considerably less expense. Further, the apparent simplification of the diagnostic process may predispose clinicians to resort to simplistic assessment procedures. Finally, we feel the need to reiterate our concern regarding the aggressive nature in which the GDS has been marketed, especially given the relatively meager data available when the apparatus was first offered for sale and the inherent limitations of any single instrument for the purpose of diagnosis.

References

Barkley, R.A. "Assessment of stimulant drug responding in ADD-H children." Paper presented at the 93rd Annual Meeting of the American Psychological Association, Los Angeles, CA, August 1985.

Conners, C.K. Rating scales for use in drug studies with children. *Psychopharmacol. Bull.* (Special Issue, *Pharmacotherapy of Children*), 24-84, 1973.

Douglas, V.I. Attentional and cognitive problems. In: Rutter, M., ed. *Developmental Neuropsychiatry*. New York: Guilford Press, 1983. pp. 280-329.

Gordon, M. The assessment of impulsivity and mediating behaviors in hyperactive and nonhyperactive children. *J. Abnorm. Child Psychol.* 7:317-326, 1979.

Gordon, M. Microprocessor-based assessment of attention deficit disorders. *Psychopharmacol. Bull.* 22:288-290, 1986.

Gordon, M. "Current GDS research: The vicissitudes of validation." Paper presented at the 93rd Annual Meeting of the American Psychological Association, Los Angeles, CA, August 1985.

Gordon, M., and McClure, F.D. "The objective assessment of attention deficit disorder." Paper presented at the 91st Annual Meeting of the American Psychological Association, Anaheim, CA, August 1983.

Gordon, M., and McClure, F.D. "Assessment of attention deficit disorders using the Gordon Diagnostic System." Paper presented at the 92nd Annual Meeting of the American Psychological Association, Toronto, Canada, August 1984.

Milich, R., and Kramer, J. Reflections on impulsivity: An empirical investigation of impulsivity as a construct. In: Gadow, K.D., ed. *Advances in Learning and Behavioral Disabilities*. Greenwich, CT: JAI Press, 1984. pp. 57-94.

Rosvold, H.E.; Mirsky, A.F.; Sarason, I.; Bransome, E.D.; and Beck, L.H. A continuous performance test of brain damage. *J. Consult. Psychol.* 20:343-350, 1956.

Ullmann, R.K.; Sleator, E.K.; and Sprague, R.L. A change of mind: The Conners Abbreviated Teacher Rating Scales reconsidered. *J. Abnorm. Child Psychol.* 13:567-577, 1985.

Psychopharmacology—A Recurring Bibliography

The bibliographies below are offered to our readers to alert them to recent papers on psychopharmacology from the world literature. They were computer-generated by the Medical-Literature Analysis and Retrieval System (MEDLARS) of the National Library of Medicine, National Institutes of Health, and represent papers which were entered into the system during the 9 months before the *Bulletin* went to press. Because the preceding issue (Vol. 22, No. 3) was unusually large, we did not include a bibliography in that issue. We are fortunate to be able to include in the current issue three bibliographies, from the second, third, and fourth quarters of 1986. The earliest culling from the *Index Medicus* appears first, followed by the more recent ones.

The subject headings from the *Index Medicus* were selected by the National Institute of Mental Health to reflect significant current interests of the international scientific community. Some nonrelevant citations may appear, and some relevant ones may be absent, but this is customary for machine-generated searches.

BIBLIOGRAPHY

ACEPROMAZINE

Attempted suicide with acepromazine maleate: a case report. Clutton RE. **Vet Hum Toxicol** 1985 Oct;27(5):391

ACETYLCHOLINE

Sarin and soman depress [3H]acetylcholine secretion in guinea-pig ileum myenteric plexus. Alberts P, et al. **Acta Physiol Scand** 1985 Oct;125(2):347-8

Release of an insulin-like peptide from perfused extirpated cat legs in response to electrical stimulation of the sciatic and brachial nerves and to administration of ACh, bombesin, oxytocin and glibenclamide. Posloncec B, et al. **Acta Physiol Scand** 1985 Oct;125(2):195-203

The kinetics of adrenal catecholamine secretion elicited by splanchnic nerve stimulation or by Ach is consistent with non-exocytotic, multivesicular release on cation exchange basis. Uvnäs B, et al. **Acta Physiol Scand** 1985 Mar;123(3):249-59

Halothane effects on synaptosomal acetylcholine metabolism [letter] Becker GL. **Anesth Analg** 1986 Jan;65(1):103-4

Gabapentin decreases monoamine release without affecting acetylcholine release in the brain. Schlicker E, et al. **Arzneimittelforschung** 1985;35(9):1347-9

Antigenic sites of the nicotinic acetylcholine receptor [letter] Barkas T, et al. **Biochem J** 1985 Oct 1;231(1):245

Antigenicity of the sequence 152-167 in alpha subunits of Torpedo acetylcholine receptor [letter] Lindstrom J, et al. **Biochem J** 1985 Oct 1;231(1):247

Antigenicity of synthetic peptides 159-169 and 151-169 of Torpedo acetylcholine receptor alpha chain [letter] McCormick DJ, et al. **Biochem J** 1985 Oct 1;231(1):245-6

Effects of haloperidol and low dose clozapine on the acetylcholine turnover rate in rat forebrain structures. Bluth R, et al. **Biomed Biochim Acta** 1985;44(10):1531-9

Mechanism of inhibitory effect of calcium on negative inotropic activity of acetylcholine in guinea pig atria. Mehrotra M, et al. **Biomed Biochim Acta** 1985;44(5):785-93

Cholinesterase activity and exposure time to acetylcholine as factors influencing the muscarinic inhibition of [3H]-noradrenaline overflow from guinea-pig isolated atria. Fuder H, et al. **Br J Pharmacol** 1985 Dec;86(4):905-14

Modulation of the endogenous acetylcholine release from rat striatal slices. Alberch J, et al. **Brain Res** 1985 Nov 4;346(2):353-6

The effect of the acetylcholine transport blocker 2-(4-phenylpiperidino)cyclohexanol (AH5183) on the subcellular storage and release of acetylcholine in mouse brain. Carroll PT. **Brain Res** 1985 Dec 9;358(1-2):200-9

Maitotoxin activates quantal transmitter release at the neuromuscular junction: evidence for elevated intraterminal Ca2+ in the motor nerve terminal. Kim YI, et al. **Brain Res** 1985 Nov 4;346(2):357-62

Effects of 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (AH5183) on rat cortical synaptosome choline uptake, acetylcholine storage and release. Otero DH, et al. **Brain Res** 1985 Dec 16;359(1-2):208-14

Anticholinergic agents do not block light-induced circadian phase shifts. Pauly JR, et al. **Brain Res** 1985 Nov 25;348(1):163-7

Acetylcholine responses in snail neurons: increase and decrease in potassium conductance succeeding inward currents. Witte OW, et al. **Brain Res** 1985 Nov 18;347(2):313-20

Effect of tranquilizers on the total acetylcholine content and acetylcholinesterase activity in the brain tissue of Arvicanthis niloticus. Fathi MM, et al. **Comp Biochem Physiol** [C] 1985;82(2):467-74

Acetylcholine and carnitine sensitive growth in a Drosophila cell line. Gingle AR. **Comp Biochem Physiol** [C] 1985;82(1):235-41

Induced rewarming by central stimulation in hypothermic hamsters. Resch GE, et al. **Cryobiology** 1985 Oct;22(5):490-4

Interaction of acetylcholine and gastric inhibitory polypeptide on endocrine and exocrine rat pancreatic secretion: augmentation of acetylcholine-induced amylase and volume secretion by the insulinotropic action of gastric inhibitory polypeptide. Müller MK, et al. **Digestion** 1986;33(1):45-52

Effect of Rumex nepalensis extracts on histamine, acetylcholine and carbachol evoked responses on isolated guinea pig ileum, frog rectus abdominis muscle, rabbit heart and blood pressure of dog. Aggarwal P, et al. **Indian J Exp Biol** 1985 Aug;23(8):447-51

Leukotriene B4 induces airway hyperresponsiveness in dogs. O'Byrne PM, et al. **J Appl Physiol** 1985 Dec;59(6):1941-6

Measurement of quantal secretion induced by ouabain and its correlation with depletion of synaptic vesicles. Haimann C, et al. **J Cell Biol** 1985 Nov;101(5 Pt 1):1953-65

Acetylcholine depolarizes barnacle photoreceptors. Timpe LC, et al. **J Exp Biol** 1985 Jul;117:481-5

Incorporation of acetate into acetylcholine, acetylcarnitine, and amino acids in the Torpedo electric organ. Corthay J, et al. **J Neurochem** 1985 Dec;45(6):1809-19

Serotonin inhibits acetylcholine release from rat striatum slices: evidence for a presynaptic receptor-mediated effect. Gillet G, et al. **J Neurochem** 1985 Dec;45(6):1687-91

BIBLIOGRAPHY

ACETYLCHOLINE

N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine increases acetylcholine and decreases dopamine in mouse striatum: both responses are blocked by anticholinergic drugs. Hadjiconstantinou M, et al. **J Neurochem** 1985 Dec;45(6):1957-9

The occurrence of long openings in the purified cholinergic receptor channel increases with acetylcholine concentration. Labarca P, et al. **J Neurosci** 1985 Dec;5(12):3409-13

Noradrenergic modulation of cortical acetylcholine release is both direct and gamma-aminobutyric acid-mediated. Beani L, et al. **J Pharmacol Exp Ther** 1986 Jan;236(1):230-6

Activation of acetylcholine synthesis in cat sympathetic ganglia: dependence on external choline and sodium-pump rate. Birks RI, et al. **J Physiol (Lond)** 1985 Oct;367:401-17

Inactivation of acetylcholine release from Torpedo synaptosomes in response to prolonged depolarizations. Birman S, et al. **J Physiol (Lond)** 1985 Nov;368:293-307

Effect of excitatory amino acids and analogues on [3H]acetylcholine release from amacrine cells of the rabbit retina. Cunningham JR, et al. **J Physiol (Lond)** 1985 Sep;366:47-62

Role of calcium mobilization in mediation of acetylcholine-evoked chloride currents in Xenopus laevis oocytes. Dascal N, et al. **J Physiol (Lond)** 1985 Sep;366:299-313

Presynaptic regulation by ACh of the NE mediated responses in the rat vas deferens. Miranda HF, et al. **J Recept Res** 1985;5(4):231-43

Measurement of acetylcholine and choline in brain by HPLC with electrochemical detection. Bymaster FP, et al. **Life Sci** 1985 Nov 11; 37(19):1775-81

The binding of 3H-acetylcholine to cholinergic receptors in bovine cerebral arteries. Shimohama S, et al. **Life Sci** 1985 Nov 18; 37(20):1887-93

Neuroanatomy. Antibodies to acetylcholine at last [news] Eckenstein F. **Nature** 1985 Nov 21-27;318(6043):236

The calcium channel activator, Bay K 8644, enhances K+-evoked efflux of acetylcholine and noradrenaline from rat brain slices. Middlemiss DN. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):114-6

The effect of tityustoxin and ruthenium red on the release of acetylcholine from slices of cortex of rat brain. Gomez MV, et al. **Neuropharmacology** 1985 Nov;24(11):1103-7

Changes in body temperature after administration of acetylcholine, histamine, morphine, prostaglandins and related agents: II. Clark WG, et al. **Neurosci Biobehav Rev** 1985 Fall;9(3):479-552 (741 ref.)

Independent co-release of acetylcholine and somatostatin from cardiac vagal neurones in toad. Campbell G, et al. **Neurosci Lett** 1985 Sep 16; 60(1):47-50

High- and low-affinity binding of [3H]acetylcholine at nicotinic cholinergic receptors in rat brain. Reulecke M, et al. **Neurosci Lett** 1985 Sep 6;59(3):271-6

Number and distribution of putative cholinergic neurons in the cat retina. Schmidt M, et al. **Neurosci Lett** 1985 Sep 6;59(3):235-40

Acetylcholine-induced change in intracellular Cl- activity of the mouse lacrimal acinar cells. Saito Y, et al. **Pflugers Arch** 1985 Sep; 405(2):108-11

Evidence for multiple dopamine receptors involved in the modulation of acetylcholine release in the striatum. Hársing LG Jr, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):383-96

Ion channel block by acetylcholine, carbachol and suberyldicholine at the frog neuromuscular junction. Ogden DC, et al. **Proc R Soc Lond [Biol]** 1985 Sep 23;225(1240):329-55

On the mechanism of renal vasoconstriction induced by acetylcholine in indomethacin-treated dogs. Ho SS, et al. **Renal Physiol** 1985; 8(6):310-20

[Activity of single acetylcholine-activated ion channels in the sympathetic neuron] Derkach VA, et al. **Dokl Akad Nauk SSSR** 1985; 284(2):495-8 **(Rus)**

[Importance of calcium ions for the process of nonquantum acetylcholine secretion from the motor nerve endings in mice] Voronin VA, et al. **Dokl Akad Nauk SSSR** 1985;285(4):1019-21 **(Rus)**

[Effect of prostaglandin E2 and its derivatives on the reaction of isolated mollusk neurons to acetylcholine] Bragintseva LM, et al. **Farmakol Toksikol** 1985 Sep-Oct;48(5):39-42 (Eng. Abstr.) **(Rus)**

[Effect of histamine on motor and vascular effects on the small intestine induced by acetylcholine] Lavrova ZS, et al. **Fiziol Zh SSSR** 1985 Sep; 71(9):1156-63 (Eng. Abstr.) **(Rus)**

[Effect of acetylcholine on migration of mature eosinophils from the bone marrow into the circulating blood] Deshevoi IuB. **Patol Fiziol Eksp Ter** 1985 Sep-Oct;(5):48-50 (Eng. Abstr.) **(Rus)**

[Changes in the effect of acetylcholine on septo-hippocampal reactions after serotonin administration to rabbits] Kozhedub RG. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):914-9 (Eng. Abstr.) **(Rus)**

ADJUSTMENT DISORDERS

Psychostimulant treatment of depressive disorders secondary to medical illness. Woods SW, et al. **J Clin Psychiatry** 1986 Jan;47(1):12-5

Sulfate and glucuronide conjugates of 3-methoxy-4-hydroxyphenylglycol (MHPG) in urine of depressed patients: central and peripheral influences. Peyrin L, et al. **J Neural Transm** 1985;63(3-4):255-69

[Depression, anxiety and neurotic disorders] Wilmotte J. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):469-79 (Eng. Abstr.) **(Fre)**

AFFECTIVE DISORDERS

Antidepressant effects of estrogen [letter] Price WA, et al. **J Clin Psychiatry** 1985 Nov;46(11):506

Psychiatric evaluation of premenstrual changes. Harrison WM, et al. **Psychosomatics** 1985 Oct;26(10):789-92, 795, 798-9

AFFECTIVE DISORDERS, PSYCHOTIC

Cholinesterases in primary affective disorders. Thakar JH, et al. **Clin Biochem** 1985 Oct;18(5):308-10

Effects of carbamazepine on noradrenergic mechanisms in affectively ill patients. Post RM, et al. **Psychopharmacology (Berlin)** 1985; 87(1):59-63

AFFECTIVE SYMPTOMS

Nomifensine for emotional incontinence in the elderly. Sandyk R, et al. **Clin Neuropharmacol** 1985;8(4):377-8

AGGRESSION

Behavioral, autonomic and motor effects of neuroleptic drugs in cats: motor impairment and aggression. Beleslin DB, et al. **Brain Res Bull** 1985 Sep;15(3):353-6

Acute changes in plasma steroids and agonistic behavior in male Japanese quail. Ramenofsky M. **Gen Comp Endocrinol** 1985 Oct;60(1):116-28

Evidence of norepinephrine-mediated suppression of para-chlorophenylalanine-induced muricidal behavior. Puciłowski O, et al. **Pharmacol Res Commun** 1985 Oct;17(10):983-9

Elicitation of conspecific attack or defense in the male rat by intraventricular injection of a GABA agonist or antagonist. Depaulis A, et al. **Physiol Behav** 1985 Sep;35(3):447-53

Effects of dopamine agonists on hypothalamic defensive attack in cats. Maeda H, et al. **Physiol Behav** 1985 Jul;35(1):89-92

The effects of isolation, grouping and aggressive interactions on indole- and catecholamine levels and apparent turnover in the hypothalamus and midbrain of the male golden hamster. Payne AP, et al. **Physiol Behav** 1985 Jun;34(6):911-6

Effects of taurine and taurine analogues on aggressive behavior. Mandel P, et al. **Prog Clin Biol Res** 1985;179:449-58

Specific anti-aggressive effects of fluprazine hydrochloride. Flannelly KJ, et al. **Psychopharmacology (Berlin)** 1985;87(1):86-9

[Pharmaco-ethological analysis of agonistic behavior between resident and intruder mice: effects of adrenergic beta-blockers] Yoshimura H, et al. **Yakubutsu Seishin Kodo** 1985 Sep;5(3):223-9 (Eng. Abstr.) **(Jpn)**

[Genetic factors in the regulation of the hypophyseo-adrenal system in aggressive and sexual interactions of male laboratory mice] Osadchuk AV, et al. **Zh Obshch Biol** 1985 Sep-Oct;46(5):711-6 (Eng. Abstr.) **(Rus)**

AMINO ACIDS

Rapid separation of phosphoamino acids including the phosphohistidines by isocratic high-performance liquid chromatography of the orthophthalaldehyde derivatives. Carlomagno L, et al. **Anal Biochem** 1985 Sep;149(2):344-8

Influences of metal ions on the reaction of amino and imino acids with fluorogenic reagents. Miyano H, et al. **Anal Biochem** 1985 Oct; 150(1):125-30

Microdetermination of serum D-amino acids. Nagata Y, et al. **Anal Biochem** 1985 Oct;150(1):238-42

Reactions of proteins with oxidizing lipids. 1. Analytical measurements of lipid oxidation and of amino acid losses in a whey protein-methyl linolenate model system. Nielsen HK, et al. **Br J Nutr** 1985 Jan; 53(1):61-73

Plasma amino acids in relation to cerebrospinal fluid monoamine metabolites in schizophrenic patients and healthy controls. Bjerkenstedt L, et al. **Br J Psychiatry** 1985 Sep;147:276-82

The role of putative excitatory amino acid neurotransmitters in the initiation of locomotion in the lamprey spinal cord. II. The effects of amino acid uptake inhibitors. Brodin L, et al. **Brain Res** 1985 Dec 23; 360(1-2):149-58

The role of putative excitatory amino acid neurotransmitters in the initiation of locomotion in the lamprey spinal cord. I. The effects of excitatory amino acid antagonists. Brodin L, et al. **Brain Res** 1985 Dec 23;360(1-2):139-48

Possible excitatory amino acid afferents to nucleus raphe dorsalis of the rat investigated with retrograde wheat germ agglutinin and D-[3H]aspartate tracing. Kalén P, et al. **Brain Res** 1985 Dec 23; 360(1-2):285-97

Plasma tyrosine/neutral amino acid ratio correlated with clinical response to nortriptyline in endogenously depressed patients. Møller SE, et al. **J Affective Disord** 1985 Nov;9(3):223-9

High-performance liquid chromatographic support for the baseline separation of all phenylthiohydantoin amino acids. Kruggel WG, et al. **J Chromatogr** 1985 Aug 9;342(2):376-9

Acylamino boronic acids and difluoroborane analogues of amino acids: potent inhibitors of chymotrypsin and elastase. Kinder DH, et al. **J Med Chem** 1985 Dec;28(12):1917-25

Immobilization decreases amino acid concentrations in plasma but maintains or increases them in brain. Kennett GA, et al. **J Neurochem** 1986 Jan;46(1):208-12

Effect of excitatory amino acids and analogues on [3H]acetylcholine release from amacrine cells of the rabbit retina. Cunningham JR, et al. **J Physiol (Lond)** 1985 Sep;366:47-62

Fetomaternal placental transfer mechanisms of aromatic amino acids in Macaca mulatta. Pueschel SM, et al. **J Reprod Med** 1985 Nov; 30(11):879-83

Excitatory amino acids inhibit stimulation of phosphatidylinositol metabolism by aminergic agonists in hippocampus. Baudry M, et al. **Nature** 1986 Jan 23-29;319(6051):329-31

Amino acid and monoamine transport in primary astroglial cultures from defined brain regions. Hansson E, et al. **Neurochem Res** 1985 Oct; 10(10):1335-41

2-Amino-6-trifluoromethoxy benzothiazole, a possible antagonist of excitatory amino acid neurotransmission--II. Biochemical properties. Benavides J, et al. **Neuropharmacology** 1985 Nov;24(11):1085-92

Excitatory and inhibitory responses of Purkinje cells, in the rat cerebellum in vivo, induced by excitatory amino acids. Quinlan JE, et al. **Neurosci Lett** 1985 Sep 16;60(1):39-46

Differences of neuronal sensitivity to amino acids and related compounds in the rat hippocampal slice. Stone TW. **Neurosci Lett** 1985 Sep 6; 59(3):313-7

Neurochemical relation between excitatory and inhibitory amino acids in hippocampus. Baba A, et al. **Prog Clin Biol Res** 1985;179:271-9

Peptide and amino acid electropharmacology of cultured mammalian central neurons and clonal pituitary cells. Barker JL, et al. **Regul Pept [Suppl]** 1985;4:14-22

Retrograde labeling of dorsal root ganglion neurons after injection of tritiated amino acids in the spinal cord of rats and cats. Barbaresi P, et al. **Somatosens Res** 1985;3(1):57-74

AMITRIPTYLINE

Construction of ion-selective electrodes for chlorpromazine, amitriptyline, propantheline and meperidine: analytical study and application to pharmaceutical analysis. Mitsana-Papazoglou A, et al. **Analyst** 1985 Sep; 110(9):1091-4

Effects of psychotropic drugs on thermal responses to radiofrequency radiation. Jauchem JR, et al. **Aviat Space Environ Med** 1985 Dec; 56(12):1183-8

A controlled trial of amitriptyline and cianopramine in major depression. Mellsop GW, et al. **Clin Ther** 1985;7(6):699-703 (8 ref.)

Self-rating data as a selecting factor in clinical trials of psychotropic drugs. Baumann U, et al. **Eur Arch Psychiatry Neurol Sci** 1985; 235(2):65-70

Peripheral adrenoceptors and serotonin receptors in depression. Changes associated with response to treatment with trazodone or amitriptyline. Healy D, et al. **J Affective Disord** 1985 Nov;9(3):285-96

Effective column extraction from decomposed tissue in a suspected overdose case involving maprotiline and amitriptyline. Fernandez GS, et al. **J Anal Toxicol** 1985 Sep-Oct;9(5):230-1

Arterio-venous plasma concentration differences in amitriptyline overdose. Baud FJ, et al. **J Toxicol Clin Toxicol** 1985; 23(4-6):391-406

Effects of some antidepressant drugs on apomorphine concentration in the central nervous system of rats and apomorphine-induced stereotypy. Rurak A, et al. **Pol J Pharmacol Pharm** 1985 Jul-Aug;37(4):509-15

[Controlled trial of amitriptyline in a group of patients with so-called functional pseudorheumatic pain (letter)] Limon J, et al. **Presse Med** 1985 Nov 30;14(41):2107 **(Fre)**

[Correlation between serum levels of amitriptyline and the Hamilton scale of depression using high-pressure liquid chromatography] Cruz Igartúa A, et al. **Bol Asoc Med PR** 1935 Sep;77(9):375-80 **(Spa)**

AMOBARBITAL

N-Glucosidation of amobarbital in the cat. Carro-Ciampi G, et al. **Can J Physiol Pharmacol** 1985 Oct;63(10):1263-6

AMPHETAMINE

Stereoselectivity and isoenzyme selectivity of monoamine oxidase inhibitors. Enantiomers of amphetamine, N-methylamphetamine and deprenyl. Robinson JB. **Biochem Pharmacol** 1985 Dec 1; 34(23):4105-8

Differences between the release of radiolabelled and endogenous dopamine from superfused rat brain slices: effects of depolarizing stimuli, amphetamine and synthesis inhibition. Herdon H, et al. **Brain Res** 1985 Dec 2;348(2):309-20

Enduring enhancement in frontal cortex dopamine utilization in an animal model of amphetamine psychosis. Robinson TE, et al. **Brain Res** 1985 Sep 23;343(2):374-7

Analysis of dopamine D1 and D2 receptor involvement in d- and l-amphetamine-induced anorexia in rats. Gilbert DB, et al. **Brain Res Bull** 1985 Oct;15(4):385-9

Effect of methylphenidate pretreatment on the behavioral and biochemical responses to amphetamine. Kolta MG, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):279-82

The acute effects of methamphetamine, amphetamine and p-chloroamphetamine on the cortical serotonergic system of the rat brain: evidence for differences in the effects of methamphetamine and amphetamine. Peat MA, et al. **Eur J Pharmacol** 1985 Oct 8; 116(1-2):11-6

Hyper-reactivity to amphetamine in rats with dopaminergic grafts. Herman JP, et al. **Exp Brain Res** 1985;60(3):521-6

Use of bonded-phase silica sorbents for rapid sampling of impurities in illicit amphetamine for high-performance liquid chromatographic analyses. Lambrechts M, et al. **J Chromatogr** 1985 Sep 6; 331(2):339-48

Analysis of the long-lasting antagonistic effect of caerulein on amphetamine hyperactivity in rats. Matsubara K, et al. **Jpn J Pharmacol** 1985 Aug;38(4):381-90

Time course of the development of the enhanced behavioral and biochemical responses to amphetamine after pretreatment with amphetamine. Kolta MG, et al. **Neuropharmacology** 1985 Sep; 24(9):823-9

Amphetamine, but not reserpine, protects mice against dopaminergic neurotoxicity of MPTP. Melamed E, et al. **Neuropharmacology** 1985 Sep;24(9):923-5

Stressor invoked exacerbation of amphetamine-elicited perseveration. Anisman H, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):173-83

Amphetamine-haloperidol discrimination: effects of chronic drug treatment. Haenlein M, et al. **Pharmacol Biochem Behav** 1985 Dec; 23(6):949-52

Haloperidol blocks amphetamine induced recovery of binocular depth perception after bilateral visual cortex ablation in cat. Hovda DA, et al. **Proc West Pharmacol Soc** 1985;28:209-11

A comparison between the growth hormone responses to amphetamine and clonidine [letter] Siever LJ, et al. **Psychiatry Res** 1985 Sep; 16(1):79-82

Depletion of brain serotonin by 5,7-dihydroxytryptamine alters the response to amphetamine and the habituation of locomotor activity in rats. Gately PF, et al. **Psychopharmacology (Berlin)** 1985;87(4):400-5

[Conditioned reactions of hippocampal neurons during amphetamine poisoning and its counteraction with haloperidol] Zhavoronkova LA, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):957-63 (Eng. Abstr.) **(Rus)**

AMPHETAMINES

Information on 'Ecstasy' [letter] Greer G, et al. **Am J Psychiatry** 1985 Nov;142(11):1391

Techniques for the detection and identification of amphetamines and amphetamine-like substances. Rasmussen KE, et al. **Bull Narc** 1985 Jan-Mar;37(1):95-112 (63 ref.)

The acute effects of methamphetamine, amphetamine and p-chloroamphetamine on the cortical serotonergic system of the rat brain: evidence for differences in the effects of methamphetamine and amphetamine. Peat MA, et al. **Eur J Pharmacol** 1985 Oct 8; 116(1-2):11-6

The scheduling of MDMA: a pharmacist's perspective. Riedlinger JE. **J Psychoactive Drugs** 1985 Jul-Sep;17(3):167-71

A bit on the Wilde side: MDMA abuse. Mack RB. **NC Med J** 1985 Dec; 46(12):641-2

Serotonergic stimulation of prolactin and corticosterone secretion is mediated by different pathways from the mediobasal hypothalamus. Van de Kar LD, et al. **Neuroendocrinology** 1985 Nov;41(5):380-4

Method for the preparation of N-isopropyl-p-(1231)-iodoamphetamine with an assessment of radiochemical purity. Lyall D. **Nucl Med Commun** 1985 Aug;6(8):485-8

Mechanistic studies on DOM as a discriminative stimulus. Glennon RA, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):937-41

Comparison of 1-methyl-4-(p-chlorophenyl)-1,2,3,6-tetrahydropyridine, 1-methyl-4-phenyl-1 2,3,6-tetrahydropyridine (MPTP) and p-chloroamphetamine as monoamine depletors. Fuller RW, et al. **Res Commun Chem Pathol Pharmacol** 1985 Oct;50(1):57-65

ANGER

Carbamazepine treatment of a patient with Klüver-Bucy syndrome. Stewart JT. **J Clin Psychiatry** 1985 Nov;46(11):496-7

ANOREXIA NERVOSA

Alterations in vitamin A and thyroid hormone status in anorexia nervosa and associated disorders. Curran-Celentano J, et al.

Am J Clin Nutr 1985 Dec;42(6):1183-91

Anorexia nervosa. Elston T, et al. **Child Care Health Dev** 1985 Nov-Dec; 11(6):355-73 (102 ref.)

Anorexia nervosa and related eating disorders. Warren MP. **Clin Obstet Gynecol** 1985 Sep;28(3):588-97

Anorexia nervosa and bulimia: a review of clinical issues. Dickstein LJ. **Hosp Community Psychiatry** 1985 Oct;36(10):1086-92 (45 ref.)

Platelet alpha 2-adrenoceptor and adenylate cyclase in patients with anorexia nervosa and bulimia. Heufelder A, et al. **J Clin Endocrinol Metab** 1985 Dec;61(6):1053-60

The responses of plasma adrenocorticotropin and cortisol to corticotropin-releasing hormone (CRH) and cerebrospinal fluid immunoreactive CRH in anorexia nervosa patients. Hotta M, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):319-24

Response of ACTH and cortisol to corticotropin-releasing hormone in anorexia nervosa [letter] Cavagnini F, et al. **N Engl J Med** 1986 Jan 16;314(3):184-5

ANTIDEPRESSIVE AGENTS

Tolerance to antidepressants [letter] **Am J Psychiatry** 1985 Dec; 142(12):1519-20

Psychoses associated with bupropion treatment. Golden RN, et al. **Am J Psychiatry** 1985 Dec;142(12):1459-62

Continuation drug therapy for major depressive episodes: how long should it be maintained? Prien RF, et al. **Am J Psychiatry** 1986 Jan; 143(1):18-23

Behavioural pharmacology of imidazole, a potential antidepressant agent. Ferrari F. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):303-12

Effects of chlorpromazine and the antidepressant drugs amitriptyline, clomipramine and mianserin on the Ca-depleted rat uterus. Villar A, et al. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):264-71

Prescribing hints for the treatment of anxiety and depression. Horgan D. **Aust Fam Physician** 1985 Sep;14(9):872-5

A double-blind out-patient trial of indalpine vs mianserin. Naylor GJ, et al. **Br J Psychiatry** 1985 Sep;147:306-9

Clinical management of benzodiazepine dependence [letter] Marks J. **Br Med J [Clin Res]** 1985 Oct 26;291(6503):1201-2

Clinical management of benzodiazepine dependence [letter] Tyrer P. **Br Med J [Clin Res]** 1985 Nov 23;291(6507):1507

Interaction of antidepressant drugs with lipid bilayers studied by high-resolution carbon-13 (13C-) and high-power deuterium nuclear magnetic resonance (2H-NMR) spectroscopy: the manner of binding as deduced from the differential line-broadening of 13C-NMR signals. Tabeta R, et al. **Chem Pharm Bull (Tokyo)** 1985 May;33(5):1793-807

Pharmacokinetics of bupropion and its major basic metabolites in normal subjects after a single dose. Laizure SC, et al. **Clin Pharmacol Ther** 1985 Nov;38(5):586-9

The tolerance and antidepressive activity of fluvoxamine as a single dose compared to a twice daily dose. Siddiqui UA, et al. **Curr Med Res Opin** 1985;9(10):681-90

The disposition of bupropion and its metabolites in healthy male volunteers after single and multiple doses. Posner J, et al. **Eur J Clin Pharmacol** 1985;29(1):97-103

Prenatal exposure of rats to antidepressants enhances agonist affinity of brain dopamine receptors and dopamine-mediated behaviour. De Ceballos ML, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):257-62

Phospholipid liposomes potentiate the inhibitory effect of antidepressant drugs on immobility of rats in a despair test (constrained swim). Drago F, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):179-84

DMI, Wy-45,030, Wy-45,881 and ciramadol inhibit locus coeruleus neuronal activity. Haskins JT, et al. **Eur J Pharmacol** 1985 Sep 24; 115(2-3):139-46

3[H]-Sulpiride labels mesolimbic non-dopaminergic sites that bind antidepressant drugs. Csernansky JG, et al. **Experientia** 1985 Nov 15; 41(11):1419-21

Current treatment of depression. Bowden CL. **Hosp Community Psychiatry** 1985 Nov;36(11):1192-200

Evaluation of long-term use of antidepressant medication. Risse SC, et al. **Hosp Community Psychiatry** 1985 Nov;36(11):1215-6

Effect of anticonvulsants, centazolone and centpropazine, on gamma amino butyric acid metabolism in mouse brain. Tripathi LM, et al. **Indian J Exp Biol** 1985 Aug;23(8):452-5

Simultaneous panic and depressive disorder: response to antidepressant treatments. Grunhaus L, et al. **J Clin Psychiatry** 1986 Jan;47(1):4-7

Antidepressant effects of estrogen [letter] Price WA, et al. **J Clin Psychiatry** 1985 Nov;46(11):506

Antidepressant treatment of bulimia: a two-year follow-up study. Pope HG Jr, et al. **J Clin Psychopharmacol** 1985 Dec;5(6):320-7

3-Phenyl-1-indanamines. Potential antidepressant activity and potent inhibition of dopamine, norepinephrine, and serotonin uptake. Bøgesø KP, et al. **J Med Chem** 1985 Dec;28(12):1817-28

The effects of manipulation of presynaptic 5-HT nerve terminals on postsynaptic 5-HT1 and 5-HT2 binding sites of the rat brain. Hall H, et al. **J Neural Transm** 1985;64(2):129-43

Studies on the role of alpha 2-adrenoceptors in the control of synaptosomal [3H]5-hydroxytryptamine release: effects of antidepressant drugs. Ellison DW, et al. **J Neurochem** 1986 Jan; 46(1):218-23

Behavioral effects of perinatal administration of antidepressant drugs in the rat. Drago F, et al. **Neurobehav Toxicol Teratol** 1985 Sep-Oct; 7(5):493-7

Prenatal exposure of rats to antidepressant drugs down-regulates beta-adrenoceptors and 5-HT2 receptors in cerebral cortex. Lack of correlation between 5-HT2 receptors and serotonin-mediated behaviour. De Ceballos ML, et al. **Neuropharmacology** 1985 Oct; 24(10):947-52

Effects of neuroleptics displaying antidepressant activity on behavior of rats in the forced swimming test. Górka Z, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):203-6

Chronic administration of sulbutiamine improves long term memory formation in mice: possible cholinergic mediation. Micheau J, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):195-8

Increased low-affinity 3H-spiroperidol binding to rat cortical membranes after chronic antidepressant treatments. Antkiewicz-Michaluk L, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):317-23

Central effects of repeated treatment with bupropion. Klimek V, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):243-52

The efficiency of ECT: II. Correlation of specific treatment variables to response rate in unilateral ECT. Rich CL, et al. **Psychiatry Res** 1985 Oct;16(2):147-54

Clinical studies of the effect of (+) and (-)-oxaprotiline upon noradrenaline uptake. Checkley SA, et al. **Psychopharmacology (Berlin)** 1985;87(1):116-8

Effect of the experimental antidepressant AHR-9377 on performance during differential reinforcement of low response rate. O'Donnell JM, et al. **Psychopharmacology (Berlin)** 1985;87(3):283-5

Stability of bupropion and its major metabolites in human plasma. Laizure SC, et al. **Ther Drug Monit** 1985;7(4):447-50

[3 cases of agranulocytosis during polytherapy including indalpine] Laaban JP, et al. **Rev Med Interne** 1985 Oct;6(4):433-5 **(Fre)**

[Vivalan] Geysen F, et al. **Soins Psychiatr** 1985 Apr;(54):I-II **(Fre)**

[Adverse actions of antidepressives] Faust V, et al. **Med Monatsschr Pharm** 1985 Nov;8(11):336-40 **(Ger)**

[The activating effect of MCI-2016 (bifemelane hydrochloride) on EEG in cats] Egawa M, et al. **No To Shinkei** 1985 Aug;37(8):759-65 (Eng. Abstr.) **(Jpn)**

[Effect of antidepressants on the balance of biogenic amines and their metabolites in the rat brain] Kamysheva VA, et al. **Farmakol Toksikol** 1985 Sep-Oct;48(5):22-4 (Eng. Abstr.) **(Rus)**

ANXIETY

Comparison of paracetamol and aminophenazone plus diazepam suppositories for anxiety and pain relief after tonsillectomy in children. Lindgren L, et al. **Acta Anaesthesiol Scand** 1985 Oct;29(7):679-82

Anxiety and epinephrine in multiparous women in labor: relationship to duration of labor and fetal heart rate pattern. Lederman RP, et al. **Am J Obstet Gynecol** 1985 Dec 15;153(8):870-7

Clinical notes in therapeutics: pharmacoanxiolytic therapy in dentistry: the benzodiazepines. Terezhalmy GT, et al. **J Oral Med** 1985 Oct-Dec; 40(4):209-11

Trazodone and m-chlorophenylpiperazine. Concentration in brain and receptor activity in regions in the brain associated with anxiety. Smith TM, et al. **Neuropharmacology** 1985 Nov;24(11):1067-71

The effects of PK 11195, a ligand for benzodiazepine binding sites, in animal tests of anxiety and stress. File SE, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):737-41

Skin conductance reaction (SCR)-habituation test, a tool to detect anxiolytic activity. Its justification by the correlation between SCR-habituation test activities and specific binding potencies in benzodiazepines. Marcy R, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):387-91

Fear-enhanced acoustic startle is not attenuated by acute or chronic imipramine treatment in rats. Cassella JV, et al. **Psychopharmacology (Berlin)** 1985;87(3):278-82

Tolerance to the benzodiazepine diazepam in an animal model of anxiolytic activity. Stephens DN, et al. **Psychopharmacology (Berlin)** 1985;87(3):322-7

Current status of benzodiazepines in South Africa. Proceedings of a symposium on anxiety and its treatment. Johannesburg, June 1985. **S Afr Med J** 1985 Oct 26;Suppl:1-32

Other forms of treatment for anxiety. Pretorius HW. **S Afr Med J** 1985 Oct 26;Suppl:30-2

[Adrenaline, noradrenaline and dopamine excretion and anxiety levels in surgical patients] Barham O, et al. **Arch Psychol (Frankf)** 1985; 137(4):291-5 (Eng. Abstr.) **(Ger)**

ANXIETY DISORDERS

Early treatment response in anxious outpatients treated with diazepam. Downing RW, et al. **Acta Psychiatr Scand** 1985 Dec;72(6):522-8

Imipramine and chlordiazepoxide in depressive and anxiety disorders. II. Efficacy in anxious outpatients. Kahn RJ, et al.

Arch Gen Psychiatry 1986 Jan;43(1):79-85

Drug therapy of anxiety disorders. Desmond P, et al. **Aust Fam Physician** 1985 Sep;14(9):876-9

Prescribing hints for the treatment of anxiety and depression. Horgan D. **Aust Fam Physician** 1985 Sep;14(9):872-5

An approach to stress and anxiety in general practice. Manzie P. **Aust Fam Physician** 1985 Sep;14(9):894-5, 899-900

Randomized comparison of atenolol and placebo in the treatment of anxiety: a double-blind study. Saul P, et al. **Eur J Clin Pharmacol** 1985; 28 Suppl:109-10

Calcium channel blockers in the treatment of panic disorder [letter] Goldstein JA. **J Clin Psychiatry** 1985 Dec;46(12):546

Simultaneous panic and depressive disorder: response to antidepressant treatments. Grunhaus L, et al. **J Clin Psychiatry** 1986 Jan;47(1):4-7

Six-week trial with diazepam: some clinical observations. Rickels K, et al. **J Clin Psychiatry** 1985 Nov;46(11):470-4

Comparison of buspirone and diazepam in generalized anxiety disorder. Jacobson AF, et al. **Pharmacotherapy** 1985 Sep-Oct;5(5):290-6

[Depression, anxiety and neurotic disorders] Wilmotte J. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):469-79 (Eng. Abstr.) **(Fre)**

[New proposals for the development of the concepts of neurotic anxiety, major depression and panic attack] Xhenseval B. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):480-508 (68 ref.) (Eng. Abstr.) **(Fre)**

[Efficacy and kinetics of chlorazepate administered to anxious patients in a single daily dose] Duguay R, et al. **Can J Psychiatry** 1985 Oct; 30(6):414-7 (Eng. Abstr.) **(Fre)**

[Panic attacks in adolescents] Dugas M, et al. **Presse Med** 1985 Nov 9; 14(38):1951-4 (Eng. Abstr.) **(Fre)**

[Alprazolam vs. oxazepam in the treatment of anxious-neurotic patients] Pöldinger W. **Schweiz Rundsch Med Prax** 1985 Oct 29; 74(44):1199-203 (Eng. Abstr.) **(Ger)**

APOMORPHINE

Effect of domperidone on apomorphine inhibition of the copulatory response and exploratory behaviour in the female rat. Sietnieks A, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Sep;57(3):160-5

Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. I: Comparison between systemic and intrastriatal injections. Herrera-Marschitz M, et al. **Acta Physiol Scand** 1985 Nov;125(3):519-27

Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. II: The striatum of the rat is heterogeneously organized for rotational behaviour. Herrera-Marschitz M, et al. **Acta Physiol Scand** 1985 Nov; 125(3):529-35

Studies on the cardiovascular actions of apomorphine in dogs: central versus peripheral mechanisms and role of the adrenal medulla. Montastruc JL, et al. **Arch Int Pharmacodyn Ther** 1985 Sep; 277(1):92-103

Effect of a novel environment on locomotor hyperactivity of rats induced by apomorphine in the nucleus accumbens. Morgenstern R, et al. **Biomed Biochim Acta** 1985;44(10):1517-22

Homocysteine prevents apomorphine-induced decreases in dopamine metabolites. Saller CF, et al. **Brain Res** 1985 Dec 23;360(1-2):407-8

Mechanism of action of apomorphine on rat gastric secretion. Costall B, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):279-85

SKF 38393 and apomorphine modify locomotion and exploration in rats placed on a holeboard by separate actions at dopamine D-1 and D-2 receptors. Fletcher GH, et al. **Eur J Pharmacol** 1985 Nov 19; 117(3):381-5

The enantiomers of SK&F 83566, a new selective D-1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D-2 agonist RU 24213. Molloy AG, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):183-6

Benzamide potentiation of behavioral apomorphine-induced effects; mechanism involved. Piriou F, et al. **Experientia** 1985 Nov 15; 41(11):1409-10

Subchronic methamphetamine treatment selectively attenuates apomorphine-induced decrease in 3,4-dihydroxyphenylacetic acid level in mesolimbic dopaminergic regions. Watanabe H. **Life Sci** 1985 Dec 16;37(24):2319-25

Bilateral lesions of the striatum induced with 6-hydroxydopamine abolish apomorphine-induced yawning in rats. Dourish CT, et al. **Neuropharmacology** 1985 Nov;24(11):1051-5

Differential effects of thioridazine, clozapine and metoclopramide on the induction of adrenomedullary enzymes by apomorphine. Ekker M, et al. **Neuropharmacology** 1985 Nov;24(11):1063-6

Furosemide blocks the apomorphine-elicited Cl-channel activity of rat striatal dopamine receptors functionally reconstituted into bimolecular lipid membrane. Vodyanoy V, et al. **Neurosci Lett** 1985 Nov 20; 62(1):103-6

Different effects of apomorphine on climbing behavior and locomotor activity in three strains of mice. Cabib S, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):555-7

Chronic clorgyline and pargyline increase apomorphine-induced stereotypy in the rat. Campbell IC, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):921-5

Chin rub CRs are elicited by flavors associated with apomorphine, scopolamine, methscopolamine, physostigmine and neostigmine. Smith RJ, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):583-9

Effect of chronic treatment with morphine on the binding of 3H-N-n-propylnorapomorphine to striatal membranes of rats: influence of prolyl-leucyl-glycinamide. Das S, et al. **Pharmacology** 1985; 31(5):241-7

Effects of dopamine agonists on hypothalamic defensive attack in cats. Maeda H, et al. **Physiol Behav** 1985 Jul;35(1):89-92

Effects of some antidepressant drugs on apomorphine concentration in the central nervous system of rats and apomorphine-induced stereotypy. Rurak A, et al. **Pol J Pharmacol Pharm** 1985 Jul-Aug;37(4):509-15

The responsiveness of the endogenous inhibitor of cAMP-dependent protein kinase to apomorphine in rat striatum after prolonged treatment with nomifensin. Szmigielski A, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):285-93

Apomorphine anorexia: a behavioural and neuropharmacological analysis. Willner P, et al. **Psychopharmacology (Berlin)** 1985;87(3):351-6

APPETITE

Dietary effects on brain serotonin synthesis: relationship to appetite regulation. Fernstrom JD. **Am J Clin Nutr** 1985 Nov; 42(5 Suppl):1072-82

Endogenous cholecystokinin and intestinal satiety. Collins SM, et al. **Am J Physiol** 1985 Dec;249(6 Pt 2):R667-71

Dynorphin, an endogenous stimulator of feeding. Morley JE, et al. **Prog Clin Biol Res** 1985;192:293-300

The effect of vagotomy on the increase in food intake induced by the cholecystokinin antagonist, proglumide. Shillabeer G, et al. **Regul Pept** 1985 Oct;12(2):91-9

AROMATIC AMINO ACID DECARBOXYLASES

Inhibition of monoamine oxidase selectively in brain monoamine nerves using the bioprecursor (E)-beta-fluoromethylene-m-tyrosine (MDL 72394), a substrate for aromatic L-amino acid decarboxylase. Palfreyman MG, et al. **J Neurochem** 1985 Dec;45(6):1850-60

AROUSAL

ACTH 4-9 analogue (Org 2766) in depressed elderly patients. II. Effect on memory and vigilance. Frederiksen SO, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):349-57

Suppression of PCP-induced behavioral arousal in the rat by yohimbine pretreatment. Byron K, et al. **Eur J Pharmacol** 1985 Nov 5; 117(2):271-3

Exaggerated psychophysiological reactivity: issues in quantification and reliability. Seraganian P, et al. **J Psychosom Res** 1985;29(4):393-405

Stimulation of dopamine D-1 receptors by SKF 38393 induces EEG desynchronization and behavioral arousal. Ongini E, et al. **Life Sci** 1985 Dec 16;37(24):2327-33

Adrenaline, emotional arousal and memory. Christianson SA, et al. **Scand J Psychol** 1985;26(3):237-48

[The activating effect of MCI-2016 (bifemelane hydrochloride) on EEG in cats] Egawa M, et al. **No To Shinkei** 1985 Aug;37(8):759-65 (Eng. Abstr.) **(Jpn)**

ATTENTION

Benefits of correlating neuroleptic blood level and auditory distractibility [letter] Terkelsen KG. **Am J Psychiatry** 1985 Dec;142(12):1523-4

ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY

Dysthymia and attention deficit disorder in adults [letter] Mattes JA. **Am J Psychiatry** 1986 Jan;143(1):114-5

Attention deficit disorders in adults. Gualtieri CT, et al. **Clin Neuropharmacol** 1985;8(4):343-56

Nortriptyline in attention deficit disorder [letter] Saul RC. **Clin Neuropharmacol** 1985;8(4):382-3

A developmental dose-response analysis of the effects of methylphenidate on the peer interactions of attention deficit disordered boys. Cunningham CE, et al. **J Child Psychol Psychiatry** 1985 Nov; 26(6):955-71

Attention deficit disorder with hyperactivity: differential effects of methylphenidate on impulsivity. Rapport MD, et al. **Pediatrics** 1985 Dec;76(6):938-43

Neuropharmacology of methylphenidate and a neural substrate for childhood hyperactivity. Gualtieri CT, et al. **Psychiatr Clin North Am** 1985 Dec;8(4):875-92

Treatment of attention deficit disorder with DL-phenylalanine. Wood DR, et al. **Psychiatry Res** 1985 Sep;16(1):21-6

AUDITORY PERCEPTION

Benefits of correlating neuroleptic blood level and auditory distractibility [letter] Terkelsen KG. **Am J Psychiatry** 1985 Dec;142(12):1523-4

AUTISM, INFANTILE

Fenfluramine therapy for autism [letter] Pranzatelli MR, et al. **J Autism Dev Disord** 1985 Dec;15(4):439-41

AVOIDANCE LEARNING

A comment on 'coyote control and taste aversion'. Burns RJ, et al. **Appetite** 1985 Sep;6(3):276-81

Coyote control and taste aversion: a predation problem or a people problem? Ellins SR. **Appetite** 1985 Sep;6(3):272-5

Research on forms of conditioned avoidance in coyotes. Lehner PN, et al. **Appetite** 1985 Sep;6(3):265-7

Coyote control and taste aversion. Quick DL, et al. **Appetite** 1985 Sep;6(3):253-64

Brief comments on 'coyote control and taste aversion'. Wade DA. **Appetite** 1985 Sep;6(3):268-71

Effects of preexposure flavor concentration on conditioned aversion and neophobia. Gilley DW, et al. **Behav Neural Biol** 1985 Nov;44(3):503-8

Noradrenergic changes and memory loss in aged mice. Leslie FM, et al. **Brain Res** 1985 Dec 16;359(1-2):292-9

Avfail in color avoidance learning by starlings (Sturnus vulgaris) and red-winged blackbirds (Agelaius phoeniceus). Mason JR, et al. **J Comp Psychol** 1985 Dec;99(4):403-10

The effects of histamine and some related compounds on conditioned avoidance response in rats. Tasaka K, et al. **Life Sci** 1985 Nov 25;37(21):2005-14

Effects of psychoactive drugs on conditioned avoidance response in Mongolian gerbils (Meriones unguiculatus): comparison with Wistar rats and dd mice. Kuribara H, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):1013-8

The effects of clozapine on shuttle-box avoidance responding in rats: comparisons with haloperidol and chlordiazepoxide. Sanger DJ. **Pharmacol Biochem Behav** 1985 Aug;23(2):231-6

Conditioned suppression of sexual behavior in stallions and reversal with diazepam. McDonnell SM, et al. **Physiol Behav** 1985 Jun;34(6):951-6

Is delay of reward mediated by shock-avoidance behavior a critical target for anti-punishment effects of diazepam in rats? Thiebot MH, et al. **Psychopharmacology (Berlin)** 1985;87(4):473-9

AZEPINES

Role of adenosine uptake and metabolism by blood cells in the antiplatelet actions of dipyridamole, dilazep and nitrobenzylthioinosine. Dawicki DD, et al. **Biochem Pharmacol** 1985 Nov 15;34(22):3965-72

Effects of dilazep on the electrophysiological properties of rabbit sinoatrial node cells. Kotake H, et al. **Eur J Pharmacol** 1985 Aug 27;114(3):291-6

Facilitated transport of sodium salicylate across an artificial lipid membrane by Azone. Hadgraft J, et al. **J Pharm Pharmacol** 1985 Oct;37(10):725-7

Relationship between alpha adrenoceptor occupancy and response for the alpha-1 adrenoceptor agonist, cirazoline, and the alpha-2 adrenoceptor agonist, B-HT 933, in canine saphenous vein. Ruffolo RR Jr, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):636-43

Evaluation of immune function in mice exposed to Ordram. Smialowicz RJ, et al. **Toxicology** 1985 Dec;37(3-4):307-14

[Clotiazepam, a new molecule among the anxiolytic agents] **Clin Ter** 1985 Jul 31;114(2):159-62 **(Ita)**

BEHAVIOR

The ethological approach to the assessment of depressive disorders. Fossi L, et al. **J Nerv Ment Dis** 1984 Jun;172(6):332-41

Scientists ponder diet's behavioral effects [news] Simmons K. **JAMA** 1985 Dec 27;254(24):3407-8

BEHAVIOR, ANIMAL

Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. II: The striatum of the rat is heterogeneously organized for rotational behaviour. Herrera-Marschitz M, et al. **Acta Physiol Scand** 1985 Nov;125(3):529-35

Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. I: Comparison between systemic and intrastriatal injections. Herrera-Marschitz M, et al. **Acta Physiol Scand** 1985 Nov;125(3):519-27

Behavioral depression after intraventricular infusion of octopamine in rats. Chance WT, et al. **Am J Surg** 1985 Nov;150(5):577-84

Behavioural pharmacology of imidazole, a potential antidepressant agent. Ferrari F. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):303-12

Differential effects of haloperidol decanoate, a long-acting neuroleptic, in behavioral and biochemical tests. Oka M, et al. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):289-302

Methyl methacrylate induced behavioural and neurochemical changes in rats. Husain R, et al. **Arch Toxicol** 1985 Oct;58(1):33-6

Age-related memory deficits in rats and mice: enhancement with peripheral injections of epinephrine. Sternberg DB, et al. **Behav Neural Biol** 1985 Sep;44(2):213-20

Effect of angiotensin II on some behavioral and neurochemical measures of the central serotonine system. Braszko JJ, et al. **Biomed Biochim Acta** 1985;44(9):1359-68

The functional importance of cerebral noradrenergic processes for the activating action of nootropic drugs in the behavioural despair test in mice. Schmidt J. **Biomed Biochim Acta** 1985;44(5):755-61

The effects of triazolobenzodiazepines in two animal tests of anxiety and in the holeboard. File SE, et al. **Br J Pharmacol** 1985 Nov;86(3):729-35

Monoaminergic involvement in the pharmacological actions of buspirone. Skolnick P, et al. **Br J Pharmacol** 1985 Nov;86(3):637-44

Reduced-5-hydroxytryptamine-dependent behavior in rats following chronic corticosterone treatment. Dickinson SL, et al. **Brain Res** 1985 Oct 14;345(1):10-8

Behavioral and neurochemical effect of daily injection with neurotensin into the ventral tegmental area. Kalivas PW, et al. **Brain Res** 1985 Dec 9;358(1-2):70-6

Dominant social status facilitates the behavioral effects of serotonergic agonists. Raleigh MJ, et al. **Brain Res** 1985 Dec 2;348(2):274-82

Behavioral, autonomic and motor effects of neuroleptic drugs in cats: motor impairment and aggression. Beleslin DB, et al. **Brain Res Bull** 1985 Sep;15(3):353-6

Prenatal exposure of rats to antidepressants enhances agonist affinity of brain dopamine receptors and dopamine-mediated behaviour. De Ceballos ML, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):257-62

Modification of behavioral response to intra-hippocampal injections of noradrenaline and adrenoceptor agonists by chronic treatment with desipramine and citalopram: functional aspects of adaptive receptor changes. Plaznik A, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):245-52

Hyper-reactivity to amphetamine in rats with dopaminergic grafts. Herman JP, et al. **Exp Brain Res** 1985;60(3):521-6

Benzamide potentiation of behavioral apomorphine-induced effects: mechanism involved. Piriou F, et al. **Experientia** 1985 Nov 15;41(11):1409-10

Behavior and kainic acids differential behavioral and biochemical effects of kainic acid and allokainic acid injections in rats. Molla-Hosseini C, et al. **J Pharmacol** 1985 Apr-Jun;16(2):191-6

Modulation of action of kainic acid on the behavior of rats by p-chlorophenylalanine and by gaba-mimetic drugs. Biochemical correlation between behavior and treatments. Molla-Hosseini C, et al. **J Pharmacol** 1985 Jul-Sep;16(3):299-312

Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. Breese GR, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):287-95

Effects of chronic dietary lithium on behavioral indices of dopamine denervation supersensitivity in the rat. Swerdlow NR, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):324-9

delta 9-Tetrahydrocannabinol elicited ipsilateral circling behavior in rats with unilateral nigral lesion. Sakurai Y, et al. **Life Sci** 1985 Dec 9;37(23):2181-5

Substance K, a novel tachykinin injected bilaterally into the ventral tegmental area of rats increases behavioral response. Takano Y, et al. **Life Sci** 1985 Dec 30;37(26):2507-14

Behavioral dependence in rhesus monkeys following chronic THC administration. Beardsley PM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:111-7

Correlating behavior with neural activity: an approach to study the action of drugs in the behaving animal. Deadwyler SA. **Natl Inst Drug Abuse Res Monogr Ser** 1985;62:63-76

Comparative evaluation of the behavioural consequences of prenatal and early postnatal exposure to haloperidol in rats. Cuomo V, et al. **Neurobehav Toxicol Teratol** 1985 Sep-Oct;7(5):489-92

Behavioral effects of perinatal administration of antidepressant drugs in the rat. Drago F, et al. **Neurobehav Toxicol Teratol** 1985 Sep-Oct;7(5):493-7

Time course of the development of the enhanced behavioral and biochemical responses to amphetamine after pretreatment with amphetamine. Kolta MG, et al. **Neuropharmacology** 1985 Sep;24(9):823-9

Intrathecal somatostatin modulates spinal sensory and reflex mechanisms: behavioral and electrophysiological studies in the rat. Wiesenfeld-Hallin Z. **Neurosci Lett** 1985 Nov 20;62(1):69-74

Neuropeptide effects on brain development to be expected from behavioral teratology. Boer GJ, et al. **Peptides (Fayetteville)** 1985;6 Suppl 2:21-8 (121 ref.)

Different effects of apomorphine on climbing behavior and locomotor activity in three strains of mice. Cabib S, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):555-7

Effects of neuroleptics displaying antidepressant activity on behavior of rats in the forced swimming test. Górka Z, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):203-6

Differences between calcium channel inhibitors in their effects on phencyclidine-induced behavioral stimulation in mice. Grebb JA, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):613-8

Changes in drug sensitivity following acute and chronic exercise. McMaster SB, et al. **Pharmacol Biochem Behav** 1985 Aug; 23(2):191-4

Role of dopaminergic system(s) in mediation of the behavioural effects of bombesin. Merali Z, et al. **Pharmacol Biochem Behav** 1985 Aug; 23(2):243-8

Phencyclidine-induced dopamine-dependent behaviors in chronic haloperidol-treated rats. Yamaguchi K, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):803-9

Dopaminergic behavior in frontal decorticated rats. Itoh S, et al. **Physiol Behav** 1985 Jul;35(1):109-12

Central effects of repeated treatment with bupropion. Klimek V, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):243-52

Mesolimbic noradrenaline but not dopamine is responsible for organization of rat behavior in the forced swim test and an anti-immobilizing effect of desipramine. Plaźnik A, et al. **Pol J Pharmacol Pharm** 1985 May-Jun; 37(3):347-57

Behavioral effects of non-opioid fragments of beta-endorphin. van Ree JM, et al. **Prog Clin Biol Res** 1985;192:277-84

Acute and chronic effects of dextropropoxyphene on behaviour and central inhibitory neurotransmission in the rat. Foster-Smith K, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):361-7

Interaction of dietary tryptophan and social isolation on territorial aggression, motor activity, and neurochemistry in mice. Lasley SM, et al. **Psychopharmacology (Berlin)** 1985;87(3):313-21

Behavioral effects of vasopressin and oxytocin within the medial preoptic area of the golden hamster. Albers HE, et al. **Regul Pept** 1985 Nov 7;12(3):257-60

[Effect of lithium, carbamazepine, ca-valproate and diazepam on changes in social isolation-induced behavior in mice] Oehler J, et al. **Biomed Biochim Acta** 1985;44(10):1523-30 (Eng. Abstr.) **(Ger)**

[Behavioral and neurochemical changes in pups prenatally treated with methamphetamine] Fujiwara Y. **Yakubutsu Seishin Kodo** 1985 Sep; 5(3):251-9 (Eng. Abstr.) **(Jpn)**

[Chronological change in abnormal behavior produced by long-term methamphetamine administration in the rat] Kashihara K, et al. **Yakubutsu Seishin Kodo** 1985 Sep;5(3):261-70 (Eng. Abstr.) **(Jpn)**

[Synthesis and the study of the effect of new 3,4,5-trimethoxybenzoic acid derivatives on the central nervous system] Glinka R, et al. **Acta Pol Pharm** 1985;42(2):117-22 (Eng. Abstr.) **(Pol)**

BENACTYZINE

The effects of atropine, benactyzine, and physostigmine on a repeated acquisition baseline in monkeys. Penetar DM. **Psychopharmacology (Berlin)** 1985;87(1):69-76

[Effect of diazepam, meprobamate and amizyl on the emotional reactions of the rabbit to hypothalamic stimulation] Davituliani DS, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):952-6 (Eng. Abstr.) **(Rus)**

BENZAZEPINES

Pharmacokinetics of diltiazem and other calcium entry blockers. Hermann P, et al. **Acta Pharmacol Toxicol (Copenh)** 1985;57 Suppl 2:10-20 (62 ref.)

Calcium blocker diltiazem inhibits platelet activation and stimulates vascular prostacyclin synthesis. Mehta J, et al. **Am J Med Sci** 1986 Jan;291(1):20-4

Effects of diltiazem on the TEA-induced plateau of nodose ganglion action potentials. Ito H, et al. **Arch Int Pharmacodyn Ther** 1985 Sep; 277(1):28-38

The peripheral vascular effects of diltiazem--dose-response characteristics. Finch MB, et al. **Br J Clin Pharmacol** 1985 Nov; 20(5):447-51

SKF 38393 and apomorphine modify locomotion and exploration in rats placed on a holeboard by separate actions at dopamine D-1 and D-2 receptors. Fletcher GH, et al. **Eur J Pharmacol** 1985 Nov 19; 117(3):381-5

The enantiomers of SK&F 83566, a new selective D-1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D-2 agonist RU 24213. Molloy AG, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):183-6

Structural determinants of selective affinity for brain D-1 dopamine receptors within a series of 1-phenyl-1H-3-benzazepine analogues of SK&F 38393 and SCH 23390. O'Boyle KM, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):291-5

The effects of diltiazem and captopril on glycerol-induced acute renal failure in the rat. Functional, pathologic, and microangiographic studies. Lee SM, et al. **Invest Radiol** 1985 Dec;20(9):961-70

The influence of diltiazem and nifedipine on the haemodynamic and tubular responses of the rat kidney to renal nerve stimulation. Herod JJ, et al. **J Auton Pharmacol** 1985 Sep;5(3):251-60

Quantification of R-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-meth benzazepine in brain and blood by use of reversed-phase high-performance liquid chromatography with electrochemical detection. Kilts CD, et al. **J Chromatogr** 1985 Aug 9;342(2):452-7

Calcium channel blockers in the treatment of panic disorder [letter] Goldstein JA. **J Clin Psychiatry** 1985 Dec;46(12):546

Selective alpha-2 adrenoceptor blockade by SK&F 86466: in vitro characterization of receptor selectivity. Hieble JP, et al. **J Pharmacol Exp Ther** 1986 Jan;236(1):90-6

Synaptic facilitation by 3-aminopyridine and its antagonism by verapamil and diltiazem. Riker WK, et al. **J Pharmacol Exp Ther** 1985 Nov; 235(2):431-5

A comparison between dopamine-stimulated adenylate cyclase and 3H-SCH 23390 binding in rat striatum. Andersen PH, et al. **Life Sci** 1985 Nov 25;37(21):1971-83

Stimulation of dopamine D-1 receptors by SKF 38393 induces EEG desynchronization and behavioral arousal. Ongini E, et al. **Life Sci** 1985 Dec 16;37(24):2327-33

Reduction of central epinephrine concentrations is consistent with the continued occurrence of ovulation in rats treated with an inhibitor (LY 134046) of phenylethanolamine N-methyltransferase. Sheaves R, et al. **Neuroendocrinology** 1985 Nov;41(5):432-6

Treatment of mania using a calcium antagonist--preliminary trial. Caillard V. **Neuropsychobiology** 1985;14(1):23-6

The D1 dopamine agonist SKF 38393 functions as a discriminative stimulus in rats. Kamien JB, et al. **Psychopharmacology (Berlin)** 1985; 87(3):368-70

Effects of the putative D-1 antagonist SCH 23390 on stereotyped behaviour induced by the D-2 agonist RU24213. Pugh MT, et al. **Psychopharmacology (Berlin)** 1985;87(3):308-12

[Inhibition of mastocyte granulation by 2 calcium antagonists: verapamil and diltiazem] Manso G, et al. **Arch Farmacol Toxicol** 1985 Aug; 11(2):85-90 (Eng. Abstr.) **(Spa)**

BENZODIAZEPINE TRANQUILIZERS

A third view on benzodiazepines and sleep latency [letter] Rosenbaum JF. **Am J Psychiatry** 1985 Dec;142(12):1524

Another case of alprazolam withdrawal syndrome [letter] Vital-Herne J, et al. **Am J Psychiatry** 1985 Dec;142(12):1515

Combination alprazolam-neuroleptic treatment of the positive and negative symptoms of schizophrenia. Wolkowitz OM, et al. **Am J Psychiatry** 1986 Jan;143(1):85-7

Does the benzodiazepine antagonist Ro 15-1788 reverse the actions of picrotoxin and pentylenetetrazole on social and exploratory behaviour? File SE, et al. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):272-9

Tofisopam and midazolam: differences in clinical effects and in changes of CSF monoamine metabolites. Hovi-Viander M, et al. **Br J Clin Pharmacol** 1985 Nov;20(5):492-6

The effect of repeated doses of temazepam and nitrazepam on human psychomotor performance. Tedeschi G, et al. **Br J Clin Pharmacol** 1985 Oct;20(4):361-7

The effects of triazolobenzodiazepines in two animal tests of anxiety and in the holeboard. File SE, et al. **Br J Pharmacol** 1985 Nov; 86(3):729-35

Abuse potential of benzodiazepines. Ciraulo DA. **Bull NY Acad Med** 1985 Oct;61(8):728-41

Evidence for the pharmacological relevance of benzodiazepine receptors to anticonvulsant activity. Fisher TE, et al. **Can J Physiol Pharmacol** 1985 Nov;63(11):1477-9

Effects of chronic benzodiazepine administration on neuropsychological performance. Bornstein RA, et al. **Clin Neuropharmacol** 1985; 8(4):357-61

Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. Kroboth PD, et al. **Clin Pharmacol Ther** 1985 Nov; 38(5):525-32

Effect of alprazolam on digoxin kinetics and creatinine clearance. Ochs HR, et al. **Clin Pharmacol Ther** 1985 Nov;38(5):595-8

Sublingual use of benzodiazepines [letter] Calis KA, et al. **Drug Intell Clin Pharm** 1985 Nov;19(11):839-40

Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. Borbely AA, et al. **Hum Neurobiol** 1985;4(3):189-94

Preliminary report on the application of a high performance liquid chromatographic method for alprazolam in postmortem blood specimens. Edinboro LE, et al. **J Anal Toxicol** 1985 Sep-Oct; 9(5):207-8

Evaluation of EMIT-TOX Enzyme Immunoassay for the analysis of benzodiazepines in serum: usefulness and limitations in an emergency laboratory. Manchon M, et al. **J Anal Toxicol** 1985 Sep-Oct; 9(5):209-12

Pharmacodynamic interaction between midazolam and a specific benzodiazepine antagonist in humans. Klotz U, et al.

J Clin Pharmacol 1985 Sep;25(6):400-6
Clinical notes in therapeutics: pharmacoanxiolytic therapy in dentistry: the benzodiazepines. Terezhalmy GT, et al. **J Oral Med** 1985 Oct-Dec; 40(4):209-11
Flumezapine and zotepine: 5-hydroxytryptamine antagonism not involved in the lack of synergism of these antipsychotic drugs with amfonelic acid in rats. Fuller RW, et al. **J Pharm Pharmacol** 1985 Oct; 37(10):755-6
Caerulein antagonism by benzodiazepines in the food intake in mice. Kubota K, et al. **Jpn J Pharmacol** 1985 Sep;39(1):120-2
CGS 8216 and CGS 9896, novel pyrazoloquinoline benzodiazepine ligands with benzodiazepine agonist and antagonist properties. Boast CA, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):639-44
Benzodiazepine-induced hyperphagia in the nondeprived rat: comparisons with CL 218,872, zopiclone, tracazolate and phenobarbital. Cooper SJ, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):169-72
Specific antagonism by RO 15-1788 of benzodiazepine-induced increases in food intake in rhesus monkeys. Foltin RW, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):249-52
Autoradiographic demonstration of the selectivity of two 1-N-trifluoroethyl benzodiazepines for the BZD-1 receptors in the rat brain. Wamsley JK, et al. **Pharmacol Biochem Behav** 1985 Dec; 23(6):973-8
Skin conductance reaction (SCR)-habituation test, a tool to detect anxiolytic activity. Its justification by the correlation between SCR-habituation test activities and specific binding potencies in benzodiazepines. Marcy R, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):387-91
Benzodiazepines in the control of anxiety-induced depression. Fairhurst MM. **S Afr Med J** 1985 Oct 26;Suppl:29
Pharmacodynamics of benzodiazepines. Stahmer SD. **S Afr Med J** 1985 Oct 26;Suppl:14-22 (46 ref.)
Pharmacokinetics of the benzodiazepines. Van Rooyen JM, et al. **S Afr Med J** 1985 Oct 26;Suppl:10-3 (18 ref.)
[Benzodiazepines in pharmacy] Hardy P. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):509-21 (Eng. Abstr.) **(Fre)**
[Depression, anxiety and neurotic disorders] Wilmotte J. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):469-79 (Eng. Abstr.) **(Fre)**
[Efficacy and kinetics of chlorazepate administered to anxious patients in a single daily dose] Duguay R, et al. **Can J Psychiatry** 1985 Oct; 30(6):414-7 (Eng. Abstr.) **(Fre)**
[An unusual benzophenone of 3-hydroxydiazepam (temazepam)] Verweij AM, et al. **Arch Kriminol** 1985 Jul-Aug;176(1-2):17-20 **(Ger)**
[Physical dependence in long-term benzodiazepine treatment] Schöpf J. **Nervenarzt** 1985 Nov;56(11):585-92 **(Ger)**
[Alprazolam vs. oxazepam in the treatment of anxious-neurotic patients] Pöldinger W. **Schweiz Rundsch Med Prax** 1985 Oct 29; 74(44):1199-203 (Eng. Abstr.) **(Ger)**
[Effect of benzodiazepines on 5'-nucleotidase activity in rat brain] Korotkina RN, et al. **Biull Eksp Biol Med** 1985 Oct;100(10):438-40 (Eng. Abstr.) **(Rus)**
[Study of the hereditary differences in the cyclic nucleotide content of the blood serum in mice after exposure to stress and administration of phenazepam] Seredinin SB, et al. **Biull Eksp Biol Med** 1985 Nov; 100(11):586-8 (Eng. Abstr.) **(Rus)**

BENZODIAZEPINONES

Does the benzodiazepine antagonist Ro 15-1788 reverse the actions of picrotoxin and pentylenetetrazole on social and exploratory behaviour? File SE, et al. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):272-9
Postprandial pancreatic exocrine secretion in dogs after oral administration of pirenzepine dihydrochloride. Madrid JA, et al. **Arzneimittelforschung** 1985;35(10):1560-2
Muscarinic receptors discriminated by pirenzepine are involved in the regulation of neurotransmitter release in rat nucleus accumbens. de Belleroche J, et al. **Br J Pharmacol** 1985 Oct;86(2):505-8
Muscarinic cholinergic mediation of LHRH-induced LH and FSH secretion in normal men. Chiodera P, et al. **Clin Endocrinol (Oxf)** 1985 Oct;23(4):361-6
Central effects in man of the novel schistosomicidal benzodiazepine meclonazepam. O'Boyle C, et al. **Eur J Clin Pharmacol** 1985; 29(1):105-8
Spectrophotometric determination of pirenzepine dihydrochloride using delta A method. Wahbi AM, et al. **Farmaco [Prat]** 1985 Oct; 40(10):334-8
Determination of clobazam, N-desmethylclobazam and their hydroxy metabolites in plasma and urine by high-performance liquid chromatography. Tomasini JL, et al. **J Chromatogr** 1985 Oct 11; 343(2):369-77
Pharmacodynamic interaction between midazolam and a specific benzodiazepine antagonist in humans. Klotz U, et al. **J Clin Pharmacol** 1985 Sep;25(6):400-6
Mixed bipolar disorder responsive to lithium and clonazepam [letter] Adler LW. **J Clin Psychiatry** 1986 Jan;47(1):49-50
Studies on muscarinic binding sites in human brain identified with [3H]pirenzepine. Lin SC, et al. **J Neurochem** 1986 Jan;46(1):274-9
Imaging of [11C]-labelled Ro 15-1788 binding to benzodiazepine receptors in the human brain by positron emission tomography. Persson A, et al. **J Psychiatr Res** 1985;19(4):609-22
Attenuating effect of diazepam on stress-induced increases in noradrenaline turnover in specific brain regions of rats: antagonism by Ro 15-1788. Ida Y, et al. **Life Sci** 1985 Dec 30;37(26):2491-8
Behavioral effects and benzodiazepine antagonist activity of Ro 15-1788 (flumazepil) in pigeons. Witkin JM, et al. **Life Sci** 1985 Oct 28; 37(17):1587-95
Clonazepam-induced up-regulation of serotonin1 binding sites in frontal cortex of rat. Wagner HR, et al. **Neuropharmacology** 1985 Oct; 24(10):953-6
Specific antagonism by RO 15-1788 of benzodiazepine-induced increases in food intake in rhesus monkeys. Foltin RW, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):249-52
Autoradiographic demonstration of the selectivity of two 1-N-trifluoroethyl benzodiazepines for the BZD-1 receptors in the rat brain. Wamsley JK, et al. **Pharmacol Biochem Behav** 1985 Dec; 23(6):973-8
Endogenous inhibitors of [3H] Ro 5-4864 binding to 'peripheral-type' binding sites for benzodiazepines are present in peripheral tissues and brain. Mantione CR, et al. **Prog Clin Biol Res** 1985;192:167-73
Are 'peripheral-type' binding sites for benzodiazepines in brain related to the convulsant actions of Ro 5-4864? Weissman BA, et al. **Prog Clin Biol Res** 1985;192:197-203
Pharmacodynamics of benzodiazepines. Stahmer SD. **S Afr Med J** 1985 Oct 26;Suppl:14-22 (46 ref.)
Action of pirenzepine, a new muscarinic antagonist drug, on human pancreatic secretion. Nishimura S, et al. **Scand J Gastroenterol** 1985 Oct;20(8):990-4
[Study of the hereditary differences in the cyclic nucleotide content of the blood serum in mice after exposure to stress and administration of phenazepam] Seredinin SB, et al. **Biull Eksp Biol Med** 1985 Nov; 100(11):586-8 (Eng. Abstr.) **(Rus)**
[Relation between the dynamics of EEG indices after a single dose of the tranquilizer phenazepam and its efficacy during a course of treatment of patients with borderline neuropsychological disorders] Uvarova LG, et al. **Zh Nevropatol Psikhiatr** 1985;85(11):1701-9 (Eng. Abstr.) **(Rus)**

BIOGENIC AMINES

Methyl methacrylate induced behavioural and neurochemical changes in rats. Husain R, et al. **Arch Toxicol** 1985 Oct;58(1):33-6
Tofisopam and midazolam: differences in clinical effects and in changes of CSF monoamine metabolites. Hovi-Viander M, et al. **Br J Clin Pharmacol** 1985 Nov;20(5):492-6
Biogenic amines in the snail brain of Helicella virgata (Gastropoda, Pulmonata). Franchini A, et al. **Brain Res** 1985 Nov 11;347(1):132-4
Highly sensitive high-performance liquid chromatographic technique for the simultaneous measurement of histamine, 1-methylhistamine and other biogenic amines. Devalia JL, et al. **J Chromatogr** 1985 Oct 11; 343(2):407-12
Repeated determination of cerebrospinal fluid amine metabolites by automated direct sampling from an implanted cannula in freely moving rats. De La Riva CF, et al. **J Neurosci Methods** 1985 Sep; 14(4):233-40
Cocaine abuse: neurochemistry, phenomenology, and treatment. Gold MS, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:130-50
Amino acid and monoamine transport in primary astroglial cultures from defined brain regions. Hansson E, et al. **Neurochem Res** 1985 Oct; 10(10):1335-41
Studies on brain monoamine neurotransmitters in mice after prenatal exposure to barbiturate. Yanai J, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):215-9
Distribution of non-opioid peptides in the mammalian CNS: relationship to monoamine neurotransmitter systems. Westlund KN. **Prog Clin Biol Res** 1985;192:395-402
Interaction of dietary tryptophan and social isolation on territorial aggression, motor activity, and neurochemistry in mice. Lasley SM, et al. **Psychopharmacology (Berlin)** 1985;87(3):313-21
Comparison of 1-methyl-4-(p-chlorophenyl)-1,2,3,6-tetrahydropyridine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and p-chloroamphetamine as monoamine depletors. Fuller RW, et al. **Res Commun Chem Pathol Pharmacol** 1985 Oct;50(1):57-65
[Circadian rhythm of central monoamine neurotransmitters in mammals] Ye WL. **Sheng Li Ko Hsueh Chin Chan** 1984 Oct;15(4):316-20 **(Chi)**
[Sleep--2. Substances in the mechanism of sleep and wakefulness] Nagasaki H, et al. **Nippon Rinsho** 1985 Jul;43(7):1384-9 (19 ref.) **(Jpn)**
[The response of monoamines in the rat brain to local vibration exposure] Yamaguchi Y. **Sangyo Igaku** 1985 Mar;27(2):73-82 (Eng. Abstr.) **(Jpn)**
[Electrochemical means of determining monoamines in the brain] Gilinskii MA, et al. **Fiziol Zh SSSR** 1985 Oct;71(10):1302-5 **(Rus)**

BIPOLAR DISORDER

Effect of carbamazepine on neuroleptic plasma levels and efficacy [letter] Fast DK, et al. **Am J Psychiatry** 1986 Jan;143(1):117-8

NMR chemistry analysis of red blood cell constituents in normal subjects and lithium-treated psychiatric patients. Domino EF, et al. **Biol Psychiatry** 1985 Dec;20(12):1277-83

Drug treatment of bipolar depression and mania. Cookson JC. **Br J Hosp Med** 1985 Sep;34(3):172-5 (92 ref.)

A double-blind out-patient trial of indalpine vs mianserin. Naylor GJ, et al. **Br J Psychiatry** 1985 Sep;147:306-9

Social support and long-term lithium outcome. O'Connell RA, et al. **Br J Psychiatry** 1985 Sep;147:272-5

Personality diagnosis and illness diagnosis. Brown JH, et al. **Can J Psychiatry** 1985 Oct;30(6):428-33

Affective disorder in an adolescent. Fisman S, et al. **Can J Psychiatry** 1985 Nov;30(7):530-4

Lithium-carbamazepine versus lithium-neuroleptic prophylaxis in bipolar illness. Shukla S, et al. **J Affective Disord** 1985 Nov;9(3):219-22

Mixed bipolar disorder responsive to lithium and clonazepam [letter] Adler LW. **J Clin Psychiatry** 1986 Jan;47(1):49-50

Carbamazepine in bipolar-depressed disorder complicated by tricyclic antidepressant switching: case report. Nurnberg HG, et al. **J Clin Psychiatry** 1985 Nov;46(11):487-8

Treatment of mania using a calcium antagonist--preliminary trial. Caillard V. **Neuropsychobiology** 1985;14(1):23-6

CSF somatostatin in affective illness and normal volunteers. Rubinow DR, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(4):393-400

Amineptine in the management of the depressive syndromes. Scarzella L, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(4):429-39

Prophylaxis and the lithium ratio in bipolar patients. Yassa R, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):423-8

Cerebrospinal fluid monoamine and monoamine metabolite concentrations in melancholia. Roy A, et al. **Psychiatry Res** 1985 Aug;15(4):281-92

Effect of lysine vasopressin in depressed patients on mood and 24-hour rhythm of growth hormone, cortisol, melatonin and prolactin. Zohar J, et al. **Psychoneuroendocrinology** 1985;10(3):273-9

MHPG excretion in endogenous depression: relationship to clinical state and the effects of ECT. Joseph MH, et al. **Psychopharmacology (Berlin)** 1985;87(4):442-8

[Prophylactic efficacy of lithium in recurrent bipolar affective disorders] Yang YY, et al. **Taiwan I Hsueh Hui Tsa Chih** 1985 Jun; 84(6):722-6 (Eng. Abstr.) **(Chi)**

[Lithium prophylaxis, o.k., but for how long?] Slooff CJ, et al. **Ned Tijdschr Geneeskd** 1985 Sep 7;129(36):1729-33 (Eng. Abstr.) **(Dut)**

[Preventive effect of valproic acid amide in affective diseases] Kłosiewicz L. **Psychiatr Pol** 1985 Jan-Feb;19(1):23-9 (Eng. Abstr.) **(Pol)**

BLOOD-BRAIN BARRIER

Permeability of the blood-cerebrospinal fluid and blood-brain barriers to thyrotropin-releasing hormone. Zloković BV, et al. **Brain Res** 1985 Dec 9;358(1-2):191-9

Brain concentrations of cocaine and benzoylecgonine in fatal cases. Spiehler VR, et al. **J Forensic Sci** 1985 Oct;30(4):1003-11

Aging and the blood-brain barrier: changes in the carrier-mediated transport of peptides in rats. Banks WA, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):171-5

BOMBESIN

Release of an insulin-like peptide from perfused extirpated cat legs in response to electrical stimulation of the sciatic and brachial nerves and to administration of ACh, bombesin, oxytocin and glibenclamide. Posloncec B, et al. **Acta Physiol Scand** 1985 Oct;125(2):195-203

A peptide that inhibits the mitogenic stimulation of Swiss 3T3 cells by bombesin or vasopressin. Corps AN, et al. **Biochem J** 1985 Nov 1; 231(3):781-4

Deafferentation causes a loss of presynaptic bombesin receptors and supersensitivity of substance P receptors in the dorsal horn of the cat spinal cord. Massari VJ, et al. **Brain Res** 1985 Sep 23;343(2):268-74

Spantide: failure to antagonize bombesin-induced stimulation of gastrin secretion in dogs. Pappas T, et al. **Peptides (Fayetteville)** 1985 Sep-Oct; 6(5):1001-3

Influence of CCK and bombesin on ACTH and cortisol secretion in the conscious dog. Thomas RM, et al. **Peptides (Fayetteville)** 1985 Jul-Aug; 6(4):703-7

Role of dopaminergic system(s) in mediation of the behavioural effects of bombesin. Merali Z, et al. **Pharmacol Biochem Behav** 1985 Aug; 23(2):243-8

Trophic effect of some regulatory peptides on gastric exocrine and endocrine cells of the rat. Lehy T. **Scand J Gastroenterol [Suppl]** 1984; 101:27-30

BRADYKININ

Effect of leukotrienes, 12-HETE, histamine, bradykinin, and 5-hydroxytryptamine on in vivo rabbit cerebral arteriolar diameter. Kamitani T, et al. **J Cereb Blood Flow Metab** 1985 Dec;5(4):554-9

BUTYLAMINES

The effect of terodiline treatment in women with motor urge incontinence. Results from a double-blind study and long-term treatment. Ulmsten U, et al. **Am J Obstet Gynecol** 1985 Nov 15;153(6):619-22

Allosteric effects of diprobutine on acetylcholine receptors. Chemouilli P, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):205-14

Terodiline in the treatment of urinary frequency and motor urge incontinence. Workshop in Düsseldorf, August 28-29, 1983. **Scand J Urol Nephrol [Suppl]** 1984;87:1-61

Clinical pharmacology of terodiline. Andersson KE. **Scand J Urol Nephrol [Suppl]** 1984;87:13-20

Terodiline in children with diurnal enuresis. Elmér M. **Scand J Urol Nephrol [Suppl]** 1984;87:59-61

Evaluation of long-term safety and clinical benefit of terodiline in women with urgency/urge incontinence. A multicentre study. Fischer-Rasmussen W. **Scand J Urol Nephrol [Suppl]** 1984;87:35-47

The effect of terodiline on patients with detrusor instability. Macfarlane JR, et al. **Scand J Urol Nephrol [Suppl]** 1984;87:51-4

Terodiline in the treatment of urinary frequency and motor urge incontinence. A controlled multicentre trial. Peters D. **Scand J Urol Nephrol [Suppl]** 1984;87:21-33

A symptomatic and cystometric comparison of terodiline with emepronium in the treatment of women with frequency, urgency and incontinence. Sole GM, et al. **Scand J Urol Nephrol [Suppl]** 1984; 87:55-7

BUTYROPHENONE TRANQUILIZERS

Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. arap Mengech HN, et al. **East Afr Med J** 1984 Jun;61(6):435-8

BUTYROPHENONES

In vivo stereospecific [3H]spiperone binding in rat brain: characteristics, regional distribution, kinetics and pharmacological properties. Barone D, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):63-74

Spiperone differentiates multiple 5-hydroxytryptamine responses in rat hippocampal slices in vitro. Beck SG, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):195-7

In vivo quantitative imaging of dopamine receptors in human brain using positron emission tomography and [76Br]bromospiperone. Mazière B, et al. **Eur J Pharmacol** 1985 Aug 27;114(3):267-72

Chronic administration of D-amphetamine increases [3H]spiroperidol binding in cat brain. Trulson ME, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):267-70

Changes in 3H-spiperone, 3H-WB 4101 and 3H-dihydroalprenolol bindings to brain membranes produced by postnatal pretreatment with chlorpromazine in adult rats. Hayashi T, et al. **Jpn J Pharmacol** 1985 Sep;39(1):45-50

D2 dopamine receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in rat striatum. Battaglia G, et al. **Neurosci Lett** 1985 Aug 30;59(2):177-82

Increased low-affinity 3H-spiroperidol binding to rat cortical membranes after chronic antidepressant treatments. Antkiewicz-Michaluk L, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):317-23

CARBAMAZEPINE

Effect of carbamazepine on neuroleptic plasma levels and efficacy [letter] Fast DK, et al. **Am J Psychiatry** 1986 Jan;143(1):117-8

Antidepressant effects of carbamazepine. Post RM, et al. **Am J Psychiatry** 1986 Jan;143(1):29-34

Free thyroxin and free triiodothyronine as measured by equilibrium dialysis and analog radioimmunoassay in serum of patients taking phenytoin and carbamazepine. Liewendahl K, et al. **Clin Chem** 1985 Dec;31(12):1993-6

Direct homogeneous phosphoroimmunoassay for carbamazepine in serum. Sidki AM, et al. **Clin Chem** 1986 Jan;32(1 Pt 1):53-6

Free concentration of carbamazepine and carbamazepine-10,11-epoxide in children and adults. Influence of age and phenobarbitone co-medication. Riva R, et al. **Clin Pharmacokinet** 1985 Nov-Dec; 10(6):524-31

Lithium-carbamazepine versus lithium-neuroleptic prophylaxis in bipolar illness. Shukla S, et al. **J Affective Disord** 1985 Nov;9(3):219-22

Simultaneous determination of carbamazepine and its epoxide metabolite in plasma and urine by high-performance liquid chromatography. Chan K. **J Chromatogr** 1985 Aug 9;342(2):341-7

Carbamazepine in bipolar-depressed disorder complicated by tricyclic antidepressant switching: case report. Nurnberg HG, et al. **J Clin Psychiatry** 1985 Nov;46(11):487-8

CARBAMAZEPINE

Carbamazepine treatment of a patient with Klüver–Bucy syndrome. Stewart JT. **J Clin Psychiatry** 1985 Nov;46(11):496–7

Side–effects of carbamazepine: drug or metabolite? [letter] Tomson T, et al. **Lancet** 1985 Nov 2;2(8462):1010

Effects of carbamazepine on noradrenergic mechanisms in affectively ill patients. Post RM, et al. **Psychopharmacology (Berlin)** 1985; 87(1):59–63

CARBIDOPA

The effect of an increased ratio of carbidopa to levodopa on the pharmacokinetics of levodopa. Kaakkola S, et al. **Acta Neurol Scand** 1985 Oct;72(4):385–91

Sinemet 'abusers'. Nausieda PA. **Clin Neuropharmacol** 1985;8(4):318–27

Effect of L–dopa with and without inhibition of extra cerebral dopa decarboxylase on gastric acid secretion and gastrin release in man. Caldara R, et al. **Gut** 1985 Oct;26(10):1014–7

L–dopa in the treatment of negative schizophrenic symptoms: a single–subject experimental study. Kay SR, et al. **Int J Psychiatry Med** 1985–86;15(3):293–8

CATATONIA

Lorazepam use and catatonic syndrome [letter] Peterson GN. **J Clin Psychopharmacol** 1985 Dec;5(6):359–60

CATECHOL ESTROGENS

Normal and recombinant human growth hormone administered by constant infusion feminize catechol estrogen formation by rat liver microsomes. Jellinck PH, et al. **Endocrinology** 1985 Dec; 117(6):2274–8

Catechol estrogen formation by pig blastocysts during the preimplantation period: biochemical characterization of estrogen–2/4–hydroxylase and correlation with aromatase activity. Mondschein JS, et al. **Endocrinology** 1985 Dec;117(6):2339–46

Estrogen effects on nigral glutamic acid decarboxylase activity: a possible role for catecholestrogen. Nicoletti F, et al. **Eur J Pharmacol** 1985 Sep 24;115(2–3):297–300

CATECHOLAMINES

The kinetics of adrenal catecholamine secretion elicited by splanchnic nerve stimulation or by Ach is consistent with non–exocytotic, multivesicular release on cation exchange basis. Uvnäs B, et al. **Acta Physiol Scand** 1985 Mar;123(3):249–59

Effects of pregnancy and magnesium sulfate infusion on blood pressure and plasma catecholamines. Lee MI, et al. **Am J Perinatol** 1985 Oct; 2(4):325–7

Co–release of neuropeptide Y and catecholamines during physical exercise in man. Lundberg JM, et al. **Biochem Biophys Res Commun** 1985 Nov 27;133(1):30–6

Calcium–independent desensitization of rises in intracellular free Ca2+ concentration and catecholamine release in cultured adrenal chromaffin cells. Sasakawa N, et al. **Biochem Biophys Res Commun** 1985 Nov 27; 133(1):147–53

Relation of substance P to catecholamine metabolism and stress. Oehme P. **Biomed Biochim Acta** 1985;44(10):1401–9 (36 ref.)

The synthesis and metabolism of catecholamines in the spinal cord of the rat after acute and chronic transections. Commissiong JW. **Brain Res** 1985 Nov 11;347(1):104–11

Differential ontogeny of three putative catecholamine cell types in the postnatal rat retina. Foster GA, et al. **Brain Res** 1985 Oct; 354(2):187–96

Autoradiography of high affinity uptake of catecholamines by primary astrocyte cultures. Semenoff D, et al. **Brain Res** 1985 Nov 25; 348(1):125–36

Plasma catecholamines in the lamprey: intrinsic cardiovascular messengers? Dashow L, et al. **Comp Biochem Physiol [C]** 1985; 82(1):119–22

Plasma catecholamines and erythrocyte swelling following capture stress in a marine teleost fish. Ling N, et al. **Comp Biochem Physiol [C]** 1985; 82(1):231–4

Evidence for gamma–aminobutyric acid modulation of ovarian hormonal effects on luteinizing hormone secretion and hypothalamic catecholamine activity in the female rat. Adler BA, et al. **Endocrinology** 1986 Jan;118(1):91–7

Endocrinological effects of intrathecal morphine. Sebel PS, et al. **Eur J Anaesthesiol** 1985 Sep;2(3):291–6

Long–term application of some catecholamines elevates levels of other catecholamines in rats. Porta S, et al. **Exp Pathol** 1985;28(3):181–6

Effects of protease inhibitors and calmodulin inhibitors on Ca2+ influx and catecholamine secretion in isolated bovine adrenal medullary cells. Nishibe S, et al. **Gen Pharmacol** 1985;16(5):455–62

Blood sugar in relation to endocrine hormones during hemorrhagic shock in dogs. Malliwah JA, et al. **Hiroshima J Med Sci** 1985 Sep; 34(3):281–90

Effect of hydrocortisone on catecholamines evoked cardiovascular responses. Parle MK, et al. **Indian J Exp Biol** 1985 Aug; 23(8):437–40

Modulation of oxytocin evoked uterine responses with phosphodiesterase active agents and catecholamines. Singh M, et al. **Indian J Exp Biol** 1985 Aug;23(8):441–6

Fat cell adrenoceptors: inter– and intraspecific differences and hormone regulation. Lafontan M, et al. **Int J Obes** 1985;9 Suppl 1:117–27 (58 ref.)

Effects of L–dopa supplementation on concentrations of brain catechols, dopamine receptor binding and the incidence of pale, soft and exudative meat in stress–susceptible pigs. Erlander MG, et al. **J Anim Sci** 1985 Oct;61(4):914–23

Reconstitution of catecholamine–stimulated adenylate cyclase activity using three purified proteins. May DC, et al. **J Biol Chem** 1985 Dec 15;260(29):15829–33

Ascorbic acid and catecholamine release from digitonin–treated chromaffin cells. Morita K, et al. **J Biol Chem** 1985 Dec 5; 260(28):15112–6

Estimation of adrenal catecholamines by elevated–temperature liquid chromatography with amperometric detection. Gagner JP, et al. **J Chromatogr** 1985 Aug 9;342(2):363–9

High–performance liquid chromatographic assay of free norepinephrine, epinephrine, dopamine, vanillylmandelic acid and homovanillic acid. Gerlo E, et al. **J Chromatogr** 1985 Sep 13;343(1):9–20

Estimation of catecholamines by ion–exchange chromatography on Asahipak ES–502C using glycylglycine as the post–derivatizing agent. Seki T, et al. **J Chromatogr** 1985 Sep 20;332:9–13

Distribution of central cholinergic neurons in the baboon (Papio papio). II. A topographic atlas correlated with catecholamine neurons. Satoh K, et al. **J Comp Neurol** 1985 Jun 8;236(2):215–33

Colocalization of neuropeptide Y immunoreactivity in brainstem catecholaminergic neurons that project to the paraventricular nucleus of the hypothalamus. Sawchenko PE, et al. **J Comp Neurol** 1985 Nov 8;241(2):138–53

Synthesis and utilization of catecholamines in the rat superior cervical ganglion following changes in the nerve impulse flow. Anden NE, et al. **J Neural Transm** 1985;64(2):81–92

Nerve growth factor and dexamethasone modulate synthesis and storage of catecholamines in cultured rat adrenal medullary cells: dependence on postnatal age. Müller TH, et al. **J Neurochem** 1986 Feb; 46(2):516–24

Involvement of peripheral and central catecholamine systems in neural–immune interactions. Livnat S, et al. **J Neuroimmunol** 1985 Nov; 10(1):5–30 (123 ref.)

An in vivo steady–state method for the determination of catecholamine biosynthesis in the rat brain using high–performance liquid chromatography with electrochemical detection. Harris PE, et al. **J Neurosci Methods** 1985 Sep;14(4):221–32

The pharmacological characterization of 3,4–dihydroxyphenylimino–2–imidazolidine (DPI) as a potent mixed alpha 1/alpha 2–adrenoceptor agonist rather than as a dopamine receptor agonist. van Oene JC, et al. **J Pharm Pharmacol** 1985 Nov; 37(11):844–7

Dihydropyridine BAY K 8644 enables reduction of Ca concentration to induce catecholamine secretion from the perfused cat adrenal. Sorimachi M, et al. **Jpn J Physiol** 1985;35(5):871–4

Determination of catecholamines in tissue and body fluids using microbore HPLC with amperometric detection. Durkin TA, et al. **Life Sci** 1985 Nov 11;37(19):1803–10

Determination of the endogenous and evoked release of catecholamines from the hypothalamus and caudate nucleus of the conscious and unrestrained rat. Ruwe WD, et al. **Life Sci** 1985 Nov 11; 37(19):1749–56

Plasma catecholamine measurements in resting and stressed conscious rats, using high performance liquid chromatography with electrochemical detection. Siri FM, et al. **Life Sci** 1985 Nov 18;37(20):1923–31

Effects of prostaglandin E1 on adrenal medulla chromaffin cells: model for studies of catecholamine release. Hariri NI, et al. **Methods Find Exp Clin Pharmacol** 1985 Jun;7(6):297–302

Atrial natriuretic factor, catecholamines, and natriuresis [letter] Racz K, et al. **N Engl J Med** 1986 Jan 30;314(5):321–2

Electrophysiological and neurochemical correlates of the neurotoxic effects of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) on central catecholamine neurons in the mouse. Jonsson G, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):1–6

Cysteamine effects on monoamines, dopamine–beta–hydroxylase and the hypothalamic–pituitary axis. Terry LC, et al. **Neuroendocrinology** 1985 Dec;41(6):467–75

Adrenal release of catecholamines and Met–enkephalin before and after stress as measured by a novel in vivo dialysis method in the rat. Jarry H, et al. **Neurosci Lett** 1985 Oct 10;60(3):273–8

The prefrontal 'cortex' in the pigeon catecholamine histofluorescence. Divac I, et al. **Neuroscience** 1985 Jul;15(3):677–82

Diffusion coefficients of neurotransmitters and their metabolites in brain extracellular fluid space. Rice ME, et al. **Neuroscience** 1985 Jul;

15(3):891-902

Organization of LHRH cells: differential apposition of neurotensin, substance P and catecholamine axons. Hoffman GE. **Peptides (Fayetteville)** 1985 May-Jun;6(3):439-61

Autoxidation of catechol(amine)s. Schüsler-van Hees MT, et al. **Pharm Weekbl [Sci]** 1985 Dec 13;7(6):245-51

Operantly conditioned running: effects on brain catecholamine concentrations and receptor densities in the rat. de Castro JM, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):495-500

Genes for neurotransmitter synthesis, storage and release. Joh TH. **Prog Clin Biol Res** 1985;192:423-9

The effect of pindolol on exercise-induced increase in plasma vasoactive prostanoids and catecholamines in healthy men. Laustiola K, et al. **Prostaglandins Leukotrienes Med** 1985 Nov;20(2):111-20

Catecholamines in different areas of brain during the ovulatory cycle in the hen and their relationship to egg traits. Moudgal RP, et al. **Zentralbl Veterinarmed [A]** 1985 Sep;32(8):573-80

[Studies on the feedback regulation of pulsatile luteinizing hormone secretion. II. Role of the catecholaminergic system in estrogen-induced suppression of the frequency of pulsatile LH secretion in ovariectomized rats] Tadokoro Y. **Nippon Naibunpi Gakkai Zasshi** 1985 Jul 20; 61(7):765-74 (Eng. Abstr.) **(Jpn)**

[The subnucleus gelatinosus of the nucleus tractus solitarii is a catecholaminergic nucleus--immunohistochemical and ultrastructural studies in human fetuses] Takahashi H. **No To Shinkei** 1985 Aug; 37(8):815-24 (Eng. Abstr.) **(Jpn)**

[Electrochemical detection method] Iriyama K, et al. **Seikagaku** 1985 Jul; 57(7):607-9 **(Jpn)**

[Effect of intraoral surgical trauma on the catecholamine depletion rate in the brain and adrenal medulla in rats] Kim KW. **Taehan Chikkwa Uisa Hyophoe Chi** 1985 Jul;23(7):603-16 **(Kor)**

[Effect of antidepressants on the balance of biogenic amines and their metabolites in the rat brain] Kamysheva VA, et al. **Farmakol Toksikol** 1985 Sep-Oct;48(5):22-4 (Eng. Abstr.) **(Rus)**

[Comparative analysis of concentrations of corticosteroids and catecholamines in the urine of persons in different vocationals] Smirnov KM, et al. **Fiziol Cheloveka** 1985 Sep-Oct;11(5):834-8 **(Rus)**

[Catecholamine metabolism in persons exposed to dithiocarbamates] Kaskevich LM. **Gig Tr Prof Zabol** 1985 Oct;(10):50-1 **(Rus)**

[Catecholamine metabolism in a high-altitude environment] Davydova NA, et al. **Kosm Biol Aviakosm Med** 1985 Jul-Aug;19(4):60-3 (Eng. Abstr.) **(Rus)**

[Determination of blood catecholamines by high performance liquid chromatography using electrochemical detection] Larskii EG, et al. **Lab Delo** 1985;(9):519-22 (Eng. Abstr.) **(Rus)**

[Interrelations between monoamines and luliberin in the synaptosomes of the medio-basal hypothalamus and its separate structures] Babichev VN, et al. **Probl Endokrinol (Mosk)** 1985 Sep-Oct;31(5):36-41 (Eng. Abstr.) **(Rus)**

[Cytoreceptors in the molecular mechanisms of hormone action] Rozen VB. **Probl Endokrinol (Mosk)** 1985 Sep-Oct;31(5):21-6 (Eng. Abstr.) **(Rus)**

CHILD BEHAVIOR DISORDERS

Effective management with lithium of a persistent, post-traumatic hypomania in a 10-year-old child. Joshi P, et al. **J Dev Behav Pediatr** 1985 Dec;6(6):352-4

CHILD DEVELOPMENT DISORDERS

Longisectional interaction structure analysis (LISA) in psychopharmacology and developmental psychopathology. Lienert GA, et al. **Neuropsychobiology** 1985;14(1):27-34

CHLORDIAZEPOXIDE

Imipramine and chlordiazepoxide in depressive and anxiety disorders. II. Efficacy in anxious outpatients. Kahn RJ, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):79-85

Imipramine and chlordiazepoxide in depressive and anxiety disorders. I. Efficacy in depressed outpatients. Lipman RS, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):68-77

Benzodiazepine receptors modulate circulating plasma vasopressin concentration. Wible JH Jr, et al. **Brain Res** 1985 Dec 16; 359(1-2):368-70

Chlordiazepoxide and morphine reduce pressor response to brain stimulation in awake rats. Brandão ML, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):1069-71

The effects of clozapine on shuttle-box avoidance responding in rats: comparisons with haloperidol and chlordiazepoxide. Sanger DJ. **Pharmacol Biochem Behav** 1985 Aug;23(2):231-6

Involvement of the N4-oxide group in the phototoxicity of chlordiazepoxide in the rat. Bakri A, et al. **Photodermatol** 1985 Aug; 2(4):205-12

Neuropeptide modulation of the behavioral effects of drugs. Barrett JE, et al. **Prog Clin Biol Res** 1985;192:37-50

P-CHLOROPHENYLALANINE

Modulation of action of kainic acid on the behavior of rats by p-chlorophenylalanine and by gaba-mimetic drugs. Biochemical correlation between behavior and treatments. Molla-Hosseini C, et al. **J Pharmacol** 1985 Jul-Sep;16(3):299-312

Biochemical and behavioral changes in rats after prolonged treatment with desipramine: interaction with p-chlorophenylalanine. Brunello N, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):20-2

Evidence of norepinephrine-mediated suppression of para-chlorophenylalanine-induced muricidal behavior. Pucilowski O, et al. **Pharmacol Res Commun** 1985 Oct;17(10):983-9

CHLORPROMAZINE

Determination of chlorpromazine and its sulphoxide in pharmaceutical dosage forms by third-order derivative ultraviolet spectroscopy. Fasanmade AA, et al. **Analyst** 1985 Sep;110(9):1117-24

Construction of ion-selective electrodes for chlorpromazine, amitriptyline, propantheline and meperidine: analytical study and application to pharmaceutical analysis. Mitsana-Papazoglou A, et al. **Analyst** 1985 Sep; 110(9):1091-4

Effects of chlorpromazine and the antidepressant drugs amitriptyline, clomipramine and mianserin on the Ca-depleted rat uterus. Villar A, et al. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):264-71

Effects of psychotropic drugs on thermal responses to radiofrequency radiation. Jauchem JR, et al. **Aviat Space Environ Med** 1985 Dec; 56(12):1183-8

Kinetic study of the transient phase of a second-order chemical reaction coupled to an enzymic step: application to the oxidation of chlorpromazine by peroxidase-hydrogen peroxide. Escribano J, et al. **Biochim Biophys Acta** 1985 Oct 18;831(3):313-20

ESR spectral changes induced by chlorpromazine in spin-labeled erythrocyte ghost membranes. Yamaguchi T, et al. **Biochim Biophys Acta** 1985 Nov 7;820(2):157-64

Studies of contents of norepinephrine and 5-hydroxytryptamine in brain--II. Effect of sodium barbitone and chlorpromazine. Rahman TA, et al. **Comp Biochem Physiol [C]** 1985;82(1):159-63

Sex-related hyperthermic response to chlorpromazine in the offspring of rats treated with imipramine. Fujii T, et al. **Dev Pharmacol Ther** 1985;8(6):364-73

Electron microscopic morphometric studies on synaptic vesicles of long-term CPZ-administered rat striatum. Takeichi M. **Folia Psychiatr Neurol Jpn** 1985;39(2):185-91

Neuroleptic drug-induced coagulopathy: mechanism of reaction and duration of effect. Zengotita HE, et al. **J Clin Psychiatry** 1986 Jan; 47(1):35-7

Changes in 3H-spiperone, 3H-WB 4101 and 3H-dihydroalprenolol bindings to brain membranes produced by postnatal pretreatment with chlorpromazine in adult rats. Hayashi T, et al. **Jpn J Pharmacol** 1985 Sep;39(1):45-50

Photo-CIDNP in nucleic acid bases and their nucleotides induced by chlorpromazine and analogs. Marko J, et al. **Photochem Photobiol** 1985 Sep;42(3):213-21

Therapeutic monitoring of chlorpromazine II: Pitfalls in whole blood analysis. McKay G, et al. **Ther Drug Monit** 1985;7(4):472-7

[Dehalogenation and N-dealkylation of chlorpromazine in patients undergoing chronic treatment] Ninci R, et al. **Boll Soc Ital Biol Sper** 1985 Aug 30;61(8):1101-4 (Eng. Abstr.) **(Ita)**

CHOICE BEHAVIOR

[Delayed spatial choice in the monkey with different probabilities of signal presentation] Nikitin VS. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct; 35(5):968-70 **(Rus)**

CLOMIPRAMINE

Response to sequential administration of clomipramine and lithium carbonate in treatment-resistant depression. Schrader GD, et al. **Br J Psychiatry** 1985 Nov;147:573-5

Clomipramine prescribing doctors beware [letter] Links PS, et al. **Can Med Assoc J** 1986 Jan 1;134(1):15

Amineptine in the management of the depressive syndromes. Scarzella L, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(4):429-39

Some effects of chlorimipramine and imipramine on the schedule-controlled behavior of the pigeon. Lamb RJ, et al. **Psychopharmacology (Berlin)** 1985;87(1):7-11

[Plasma levels of clomipramine and its metabolites in hospitalized depressed patients] Debray Q, et al. **Ann Med Psychol (Paris)** 1985 May; 143(5):464-74 **(Fre)**

COCAINE

Impaired pharmacists: seek treatment [letter] **Am J Hosp Pharm** 1985 Oct; 42(10):2142, 2144

Neuroendocrine findings in a chronic cocaine abusers: a preliminary report. Gawin FH, et al. **Br J Psychiatry** 1985 Nov;147:569-73

Topics in the chemistry of cocaine. Schlesinger HL. **Bull Narc** 1985 Jan-Mar;37(1):63-78

The role of food deprivation in the maintenance and reinstatement of cocaine-seeking behavior in rats. Carroll ME. **Drug Alcohol Depend** 1985 Nov;16(2):95-109

Cocaine: an overview of current issues. Grabowski J, et al. **Int J Addict** 1985 Jun-Jul;20(6-7):1065-88 (86 ref.)

Bromocriptine treatment for cocaine abuse: the dopamine depletion hypothesis. Dackis CA, et al. **Int J Psychiatry Med** 1985-86; 15(2):125-35

Enhanced interpretation of nonverbal cues in male cocaine abusers. Giannini AJ, et al. **Int J Psychiatry Med** 1985-86;15(1):41-5

The urinary excretion of cocaine and metabolites in humans: a kinetic analysis of published data. Ambre J. **J Anal Toxicol** 1985 Nov-Dec; 9(6):241-5

Use of DB-1 capillary columns in the GC/FID analysis of benzoylecgonine. Falk PM, et al. **J Anal Toxicol** 1985 Nov-Dec; 9(6):273-4

Disposition of cocaine in fatal poisoning in man. Poklis A, et al. **J Anal Toxicol** 1985 Sep-Oct;9(5):227-9

Brain concentrations of cocaine and benzoylecgonine in fatal cases. Spiehler VR, et al. **J Forensic Sci** 1985 Oct;30(4):1003-11

Binding sites for [3H]cocaine in mouse striatum and cerebral cortex have different dissociation kinetics. Reith ME, et al. **J Neurochem** 1986 Jan; 46(1):309-12

Acute tolerance development to the cardiovascular and subjective effects of cocaine. Fischman MW, et al. **J Pharmacol Exp Ther** 1985 Dec; 235(3):677-82

Cocaine in herbal tea [letter] Siegel RK, et al. **JAMA** 1986 Jan 3; 255(1):40

Cocaine use in America: epidemiologic and clinical perspectives. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:1-226

Cocaine use in America: Introduction and overview. Adams EH, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:1-7

Food deprivation produces persistent increases in self-administration behavior during cocaine extinction. Carroll ME. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:125-31

Patterns and consequences of cocaine use. Chitwood DD. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:111-29

Reinforcement and rapid delivery systems: understanding adverse consequences of cocaine. Cohen S. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:151-7

Platelet serotonin transporter in cocaine patients. Dackis CA, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:164-9

Cocaine use in a treatment: population: patterns and diagnostic distinctions. Gawin FH, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:182-92

Parameters of intracranial self-administration of cocaine into the medial prefrontal cortex. Goeders NE, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:132-7

Cocaine abuse: neurochemistry, phenomenology, and treatment. Gold MS, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:130-50

Cocaine use in young adulthood: patterns of use and psychosocial correlates. Kandel DB, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:76-110

Characteristics of cocaine abusers presenting for treatment. Schnoll SH, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:171-81

Characteristics of humans volunteering for a cocaine research project. Schuster CR, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985; 61:158-70

New patterns of cocaine use: changing doses and routes. Siegel RK. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:204-20

Double-blind comparison of desipramine and placebo in withdrawal from cocaine dependence. Tennant FS Jr, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:159-63

The 800-COCAINE helpline: survey of 500 callers. Washton AM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:224-30

Cocaine: treatment perspectives. Wesson DR, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:193-203

New concepts in cocaine addiction: the dopamine depletion hypothesis. Dackis CA, et al. **Neurosci Biobehav Rev** 1985 Fall;9(3):469-77 (83 ref.)

Locomotor effects of cocaine, cocaine congeners, and local anesthetics in mice. Reith ME, et al. **Pharmacol Biochem Behav** 1985 Nov; 23(5):831-6

Cocaine potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys. Thompson DM, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):823-9

One-way generalization of clonidine to the discriminative stimulus produced by cocaine. Wood DM, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):529-33

Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. Zito KA, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):1029-36

Reinforcing stimulus properties of endocoids. Goeders NE, et al. **Prog Clin Biol Res** 1985;192:63-9

Cocaine: effects on acoustic startle and startle elicited electrically from the cochlear nucleus. Harty TP, et al. **Psychopharmacology (Berlin)** 1985; 87(4):396-9

COGNITION

Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. Simons AD, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):43-8

Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. Arnsten AF, et al. **Science** 1985 Dec 13;230(4731):1273-6

COGNITION DISORDERS

Concentrations of glycine and serine in cerebrospinal fluid during disturbed consciousness; a study of the therapeutic effect of thyrotropin-releasing hormone on the consciousness level. Yanai Y, et al. **Eur Neurol** 1986;25(1):19-25

COLOR PERCEPTION

Avfail in color avoidance learning by starlings (Sturnus vulgaris) and red-winged blackbirds (Agelaius phoeniceus). Mason JR, et al. **J Comp Psychol** 1985 Dec;99(4):403-10

COMPULSIVE BEHAVIOR

Obsessive-compulsive symptoms following stimulants [letter] Koizumi HM. **Biol Psychiatry** 1985 Dec;20(12):1332-3

CONDITIONING (PSYCHOLOGY)

The conditioned place preference paradigm in rats: effect of bupropion. Ortmann R. **Life Sci** 1985 Nov 25;37(21):2021-7

Behavioral effects and benzodiazepine antagonist activity of Ro 15-1788 (flumazepil) in pigeons. Witkin JM, et al. **Life Sci** 1985 Oct 28; 37(17):1587-95

Neuropeptide modulation of the behavioral effects of drugs. Barrett JE, et al. **Prog Clin Biol Res** 1985;192:37-50

Some effects of chlorimipramine and imipramine on the schedule-controlled behavior of the pigeon. Lamb RJ, et al. **Psychopharmacology (Berlin)** 1985;87(1):7-11

CONDITIONING, CLASSICAL

Pharmacological manipulations of the nucleus accumbens: effects on classically conditioned responses and locomotor activity in the cat. Wilson WJ, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(3-4):91-105

A comment on 'coyote control and taste aversion'. Burns RJ, et al. **Appetite** 1985 Sep;6(3):276-81

Coyote control and taste aversion: a predation problem or a people problem? Ellins SR. **Appetite** 1985 Sep;6(3):272-5

Research on forms of conditioned avoidance in coyotes. Lehner PN, et al. **Appetite** 1985 Sep;6(3):265-7

Coyote control and taste aversion. Quick DL, et al. **Appetite** 1985 Sep; 6(3):253-64

Brief comments on 'coyote control and taste aversion'. Wade DA. **Appetite** 1985 Sep;6(3):268-71

Avfail in color avoidance learning by starlings (Sturnus vulgaris) and red-winged blackbirds (Agelaius phoeniceus). Mason JR, et al. **J Comp Psychol** 1985 Dec;99(4):403-10

The effects of pimozide on the establishment of conditioned reinforcement as a function of the amount of conditioning. Hoffman DC, et al. **Psychopharmacology (Berlin)** 1985;87(4):454-60

Extinguishing conditioned inhibition in flavour-aversion learning: effects of repeated testing and extinction of the excitatory element. Best MR, et al. **Q J Exp Psychol [B]** 1985 Nov;37(4):359-78

[Influence of intracaudate injection of muscimol on the conditioning performance and EEG in rabbits] Huang YY, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Jun;6(2):77-8 (Eng. Abstr.)**(Chi)**

[Conditioned reactions of hippocampal neurons during amphetamine poisoning and its counteraction with haloperidol] Zhavoronkova LA, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):957-63 (Eng. Abstr.) **(Rus)**

CONDITIONING, OPERANT

A comparison of peripheral and central effects of CCK8 on water-reinforced operant responding. Cohen SL, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):229-38

Stressor invoked exacerbation of amphetamine-elicited perseveration. Anisman H, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):173-83

Operantly conditioned running: effects on brain catecholamine concentrations and receptor densities in the rat. de Castro JM, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):495-500

Effects of d-amphetamine and of beta-phenylethylamine on fixed interval responding maintained by self-regulated lateral hypothalamic stimulation in rats. Greenshaw AJ, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):519-23

Effects of pesticides and drugs on working memory in rats: continuous delayed response. Heise GA, et al. **Pharmacol Biochem Behav** 1985 Oct; 23(4):591-8

Methamphetamine, physostigmine, atropine and mecamylamine: effects on force lever performance. Preston KL, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):781-8

Pyrazoloquinoline benzodiazepine receptor ligands: effects on schedule-controlled behavior in dogs. Shannon HE, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):317-23

Delta-9-tetrahydrocannabinol potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys. Thompson DM, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):1051-7

Cocaine potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys. Thompson DM, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):823-9

ACTH1-24 effects on d-amphetamine self-administration and the dynamics of brain dopamine in rats. Leccese AP, et al. **Prog Clin Biol Res** 1985;192:71-81

Effect of the experimental antidepressant AHR-9377 on performance during differential reinforcement of low response rate. O'Donnell JM, et al. **Psychopharmacology (Berlin)** 1985;87(3):283-5

The effects of atropine, benactyzine, and physostigmine on a repeated acquisition baseline in monkeys. Penetar DM. **Psychopharmacology (Berlin)** 1985;87(1):69-76

The effect of peripheral noradrenaline depletion on responding on a schedule of differential reinforcement of low rates of response (DRL). Salmon P, et al. **Psychopharmacology (Berlin)** 1985;87(1):77-80

CONSCIOUSNESS

Neurochemical regulation of the states of alertness. Gaillard JM. **Ann Clin Res** 1985;17(5):175-84 (59 ref.)

CORTICOSTERONE

Corticosterone: narrow range required for normal body and thymus weight and ACTH. Akana SF, et al. **Am J Physiol** 1985 Nov; 249(5 Pt 2):R527-32

Corticosteroids and plasma restitution after hemorrhage and hypothalamic lesions. Bealer SL. **Am J Physiol** 1986 Jan;250(1 Pt 2):R18-23

Alpha 2-noradrenergic feeding rhythm in paraventricular nucleus: relation to corticosterone. Bhakthavatsalam P, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 2):R83-8

Interaction of light and corticosterone on food intake and brown adipose tissue of the rat. Fukushima M, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 2):R753-7

Interaction of prolactin with adrenal hormones in blood pressure regulation in rats. Mills DE, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 1):E614-8

The effect of catabolic doses of corticosterone on heat production in the growing rat. Coyer P, et al. **Br J Nutr** 1985 May;53(3):491-9

Effect of dietary factors on the responses of chicks to corticosterone injections. Bartov I. **Br Poult Sci** 1985 Oct;26(4):473-81

Reduced-5-hydroxytryptamine-dependent behavior in rats following chronic corticosterone treatment. Dickinson SL, et al. **Brain Res** 1985 Oct 14;345(1):10-8

Glucocorticoid toxicity in the hippocampus: temporal aspects of neuronal vulnerability. Sapolsky RM. **Brain Res** 1985 Dec 16;359(1-2):300-5

A complex noncoordinate regulation of alpha-lactalbumin and 25 K beta-casein by corticosterone, prolactin, and insulin in long term cultures of normal rat mammary cells. Ray DB, et al. **Endocrinology** 1986 Jan;118(1):393-407

Stimulation of corticosterone production by atrial natriuretic polypeptide in hypophysectomized rats. Nakamura M, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):285-6

Glucocorticoid hormones inhibit DNA synthesis in glial cells cultured in chemically defined medium. Kniss DA, et al. **Exp Cell Res** 1985 Nov;161(1):29-40

Acute changes in plasma steroids and agonistic behavior in male Japanese quail. Ramenofsky M. **Gen Comp Endocrinol** 1985 Oct;60(1):116-28

The effect of exposure to 40 degrees on the heat production and the serum concentrations of triiodothyronine, thyroxine, and corticosterone in immature domestic fowl. Williamson RA, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):178-86

Distribution of 18-hydroxycorticosterone between red blood cells and plasma. Zager PG, et al. **J Clin Endocrinol Metab** 1986 Jan; 62(1):84-9

Effect of atrial peptides on aldosterone production. Atarashi K, et al. **J Clin Invest** 1985 Nov;76(5):1807-11

The significance of receptor physiology for corticosterone-induced cleft palate in A/J mice. Brown KS, et al. **J Craniofac Genet Dev Biol [Suppl]** 1985;1:299-304

Vasopressin secretion as a possible target of the gamma-aminobutyric acid-mediated component of the corticosteroid feedback effect. Acs Z, et al. **J Endocrinol** 1985 Dec;107(3):303-7

Participation of the nucleus reticularis gigantocellularis in the morphine-induced elevation of plasma corticosterone in rats. Kishioka S, et al. **Jpn J Pharmacol** 1985 Jul;38(3):334-6

The effects of the acute administration of phencyclidine hydrochloride (PCP) on the release of corticosterone, growth hormone and prolactin in the rat. Pechnick RN, et al. **Life Sci** 1986 Jan 20;38(3):291-6

Dietary tyrosine suppresses the rise in plasma corticosterone following acute stress in rats. Reinstein DK, et al. **Life Sci** 1985 Dec 9; 37(23):2157-63

Serotonergic stimulation of prolactin and corticosterone secretion is mediated by different pathways from the mediobasal hypothalamus. Van de Kar LD, et al. **Neuroendocrinology** 1985 Nov;41(5):380-4

Changes induced by corticosterone and adrenalectomy in synaptosomal and platelet uptake and binding of 5-HT. The relationship to [3H]imipramine binding. Lee PH, et al. **Neuropharmacology** 1985 Nov; 24(11):1043-50

Plasma norepinephrine, epinephrine and corticosterone stress responses to restraint in individual male and female rats, and their correlations. Livezey GT, et al. **Neurosci Lett** 1985 Nov 20;62(1):51-6

The effects of putative anxiolytic compounds (PK 8165, PK 9084 and tracazolate) on the rat corticosterone response. File SE, et al. **Physiol Behav** 1985 Oct;35(4):583-6

Flavor, forced choice and deprivation affect corticosterone selection by the adrenalectomized rat. Willer VK, et al. **Physiol Behav** 1985 Jul; 35(1):53-9

Serum corticosterone levels in embryos, newly hatched, and young turkey poults. Wentworth BC, et al. **Poult Sci** 1985 Nov;64(11):2195-201

The role of prostaglandins in aldosterone and corticosterone secretion by isolated perfused rat zona glomerulosa cells. Hindawi RK, et al. **Prostaglandins Leukotrienes Med** 1985 Nov;20(2):121-8

Structure-activity studies with ACTH/alpha-MSH fragments on corticosteroid secretion of isolated zona glomerulosa and fasciculata cells. Szalay KS, et al. **Regul Pept** 1985 Jul;11(3):187-92

CORTICOTROPIN

ACTH 4-9 analogue (Org 2766) in depressed elderly patients. I. Effect on depressed mood. Frederiksen SO, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):341-8

ACTH 4-9 analogue (Org 2766) in depressed elderly patients. II. Effect on memory and vigilance. Frederiksen SO, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):349-57

Corticosterone: narrow range required for normal body and thymus weight and ACTH. Akana SF, et al. **Am J Physiol** 1985 Nov; 249(5 Pt 2):R527-32

Endocrine correlates of susceptibility to motion sickness. Kohl RL. **Aviat Space Environ Med** 1985 Dec;56(12):1158-65

The influence of tetracosactide and adrenal steroids on renal kallikrein activity and urinary kallikrein excretion in rats. Marin-Grez M. **Biochem Pharmacol** 1985 Nov 15;34(22):4013-7

Involvement of protein kinase C in the regulation of adrenocorticotropin release from rat anterior pituitary cells. Abou-Samra AB, et al. **Endocrinology** 1986 Jan;118(1):212-7

Corticotropin-releasing factor stimulates the release of adrenocorticotropin from domestic fowl pituitary cells. Carsia RV, et al. **Endocrinology** 1986 Jan;118(1):143-8

Inhibitory effect of adrenocorticotropin on corticotropin- releasing factor release from rat hypothalamus in vitro. Suda T, et al. **Endocrinology** 1986 Jan;118(1):459-61

Proopiomelanocortin-derived peptides in testicular interstitial fluid: characterization and changes in secretion after human chorionic gonadotropin or luteinizing hormone-releasing hormone analog treatment. Valenca MM, et al. **Endocrinology** 1986 Jan;118(1):32-7

Somatostatin stimulates ACTH release in brown trout (Salmo trutta L.). Langhorne P. **Gen Comp Endocrinol** 1986 Jan;61(1):71-5

Dexamethasone suppresses cortisol but not ACTH and beta-endorphin plasma concentration in healthy man. Lypka A, et al. **Horm Metab Res** 1985 Oct;17(10):547

Effect of dopamine on ACTH-induced glucocorticoid secretion in rat adrenal suspended cells. Matsuki M, et al. **Horm Metab Res** 1985 Aug; 17(8):429-31

Effect of ovine corticotropin releasing factor and arginine vasopressin on ACTH and aldosterone secretion in sheep. Redekopp C, et al. **Horm Metab Res** 1985 Aug;17(8):428-9

Distinct behavior of beta-endorphin and corticotropin toward leucine aminopeptidase action. Li CH, et al. **Int J Pept Protein Res** 1985 Aug; 26(2):113-7

Effects of ACTH and prednisone on mood: incidence and time of onset. Cameron OG, et al. **Int J Psychiatry Med** 1985-86;15(3):213-23

Dermorphin reduces the metyrapone-evoked release of adrenocorticotropin, beta-endorphin, and beta-lipotropin in man. Degli Uberti EC, et al. **J Clin Endocrinol Metab** 1985 Dec;61(6):1018-22

The responses of plasma adrenocorticotropin and cortisol to corticotropin-releasing hormone (CRH) and cerebrospinal fluid immunoreactive CRH in anorexia nervosa patients. Hotta M, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):319-24

Regulation of beta-endorphin and ACTH in brain by estradiol. Wardlaw SL, et al. **Life Sci** 1985 Nov 18;37(20):1941-7

Response of ACTH and cortisol to corticotropin-releasing hormone in anorexia nervosa [letter] Cavagnini F, et al. **N Engl J Med** 1986 Jan 16;314(3):184-5

Corticotropin-releasing activity of the renin-angiotensin system peptides in rat and in man. Gaillard RC, et al. **Neuroendocrinology** 1985 Dec; 41(6):511-7

Intravenous application of ovine and human corticotropin releasing factor (CRF): ACTH, cortisol and CRF levels. Stalla GK, et al. **Neuroendocrinology** 1986;42(1):1-5

ACTH neuromodulation of the developing motor system and neonatal learning in the rat. Acker GR, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 2:41-9

Influence of CCK and bombesin on ACTH and cortisol secretion in the conscious dog. Thomas RM, et al. **Peptides (Fayetteville)** 1985 Jul-Aug; 6(4):703-7

ACTH 1-24-induced potentiation of norepinephrine contractile responses in aortic strips from spontaneously hypertensive (SH) and normotensive (WKY) rats. Vergona RA, et al. **Peptides (Fayetteville)** 1985 Jul-Aug; 6(4):581-4

Hormone secretagogues increase cytosolic calcium by increasing cAMP in corticotropin-secreting cells. Luini A, et al. **Proc Natl Acad Sci USA** 1985 Dec;82(23):8034-8

Corticotropin-releasing factor-induced adrenocorticotropin hormone release and synthesis is blocked by incorporation of the inhibitor of cyclic AMP-dependent protein kinase into anterior pituitary tumor cells by liposomes. Reisine T, et al. **Proc Natl Acad Sci USA** 1985 Dec; 82(23):8261-5

ACTH1-24 effects on d-amphetamine self-administration and the dynamics of brain dopamine in rats. Leccese AP, et al. **Prog Clin Biol Res** 1985;192:71-81

Analysis of the dual mechanism of ACTH release by arginine vasopressin and its analogs in conscious rats. Mormède P, et al. **Regul Pept** 1985 Nov 7;12(3):175-84

Structure-activity studies with ACTH/alpha-MSH fragments on corticosteroid secretion of isolated zona glomerulosa and fasciculata cells. Szalay KS, et al. **Regul Pept** 1985 Jul;11(3):187-92

[Effects of cigarette smoking on endocrine function in man] Yao M, et al. **Masui** 1985 Aug;34(8):1105-14 (Eng. Abstr.) **(Jpn)**

[The study of opioid peptides in the normal menstrual cycle, pregnancy and labor] Takayama S, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Sep;37(9):1813-9 (Eng. Abstr.) **(Jpn)**

CORTICOTROPIN RELEASING HORMONE

Immunocytochemical observations of corticotropin-releasing-factor-containing neurons in the rat hypothalamus with special reference to neuronal communication. Shioda S, et al. **Acta Anat (Basel)** 1985;124(1-2):58-64

Binding sites for corticotropin releasing factor in sensory areas of the rat hindbrain and spinal cord. Skofitsch G, et al. **Brain Res Bull** 1985 Nov;15(5):519-22

Changes in pituitary responses to synthetic ovine corticotrophin releasing factor in fetal sheep. Norman LJ, et al. **Can J Physiol Pharmacol** 1985 Nov;63(11):1398-403

Corticotropin-releasing factor stimulates the release of adrenocorticotropin from domestic fowl pituitary cells. Carsia RV, et al. **Endocrinology** 1986 Jan;118(1):143-8

Glucocorticoid modulation of corticotropin-releasing factor desensitization in cultured rat anterior pituitary cells. Ceda GP, et al. **Endocrinology** 1986 Jan;118(1):58-62

Involvement of corticotropin-releasing factor and somatostatin in stress-induced inhibition of growth hormone secretion in the rat. Rivier C, et al. **Endocrinology** 1985 Dec;117(6):2478-82

Inhibitory effect of adrenocorticotropin on corticotropin- releasing factor release from rat hypothalamus in vitro. Suda T, et al. **Endocrinology** 1986 Jan;118(1):459-61

Cloning and sequence analysis of cDNA for rat corticotropin-releasing factor precursor. Jingami H, et al. **FEBS Lett** 1985 Oct 21; 191(1):63-6

The hypothalamo-hypophysial system in acipenseridae. X. Corticoliberin-like immunoreactivity in the hypothalamus and hypophysis of Acipenser ruthenus L. Belenky MA, et al. **Gen Comp Endocrinol** 1985 Oct;60(1):20-6

Effect of ovine corticotropin releasing factor and arginine vasopressin on ACTH and aldosterone secretion in sheep. Redekopp C, et al. **Horm Metab Res** 1985 Aug;17(8):428-9

Solid phase synthesis of ovine corticotropin releasing factor. Morell JL, et al. **Int J Pept Protein Res** 1985 Jul;26(1):49-54

The responses of plasma adrenocorticotropin and cortisol to corticotropin-releasing hormone (CRH) and cerebrospinal fluid immunoreactive CRH in anorexia nervosa patients. Hotta M, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):319-24

Development of the hypothalamic-pituitary-axis in the ovine fetus: ontogeny of action of ovine corticotropin-releasing factor. MacIsaac RJ, et al. **J Dev Physiol** 1985 Oct;7(5):329-38

Corticotropin-releasing factor in plasma of depressed patients and controls [letter] Charlton BG, et al. **Lancet** 1986 Jan 18;1(8473):161-2

Dexamethasone suppresses pituitary-adrenal but not behavioral effects of centrally administered CRF. Britton DR, et al. **Life Sci** 1986 Jan 20;38(3):211-6

Combined administration of human corticotropin-releasing factor and lysine vasopressin induces cortisol escape from dexamethasone suppression in healthy subjects. von Bardeleben U, et al. **Life Sci** 1985 Oct 28;37(17):1613-8

Response of ACTH and cortisol to corticotropin-releasing hormone in anorexia nervosa [letter] Cavagnini F, et al. **N Engl J Med** 1986 Jan 16;314(3):184-5

Functional corticotropin releasing factor receptors in the primate peripheral sympathetic nervous system. Udelsman R, et al. **Nature** 1986 Jan 9-15;319(6049):147-50

Corticotropin-releasing activity of the renin-angiotensin system peptides in rat and in man. Gaillard RC, et al. **Neuroendocrinology** 1985 Dec; 41(6):511-7

Involvement of hypothalamic somatostatin in the suppression of growth hormone secretion by central corticotropin-releasing factor in conscious male rats. Katakami H, et al. **Neuroendocrinology** 1985 Nov; 41(5):390-3

Release of pro-opiomelanocortin-derived peptides from the pars intermedia and pars distalis of the rat pituitary: effect of corticotrophin-releasing factor and somatostatin. Kraicer J, et al. **Neuroendocrinology** 1985 Nov;41(5):363-73

Intravenous application of ovine and human corticotropin releasing factor (CRF): ACTH, cortisol and CRF levels. Stalla GK, et al. **Neuroendocrinology** 1986;42(1):1-5

CRF immunoreactive peptides in the human hypophysis: a cautionary note. Beny JL, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):661-7

Behavioral investigation of the coexistence of substance P, corticotropin releasing factor, and acetylcholinesterase in lateral dorsal tegmental neurons projecting to the medial frontal cortex of the rat. Crawley JN, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):891-901

Effects of corticotropin releasing factor on locomotor activity in hypophysectomized rats. Eaves M, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):923-6

Relationship of CRF-immunostained cells and magnocellular neurons in the paraventricular nucleus of rat hypothalamus. Piekut DT, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):873-82

Effects of intravenous and intraventricular injection of antisera directed against corticotropin-releasing factor on the secretion of anterior pituitary hormones. Ono N, et al. **Proc Natl Acad Sci USA** 1985 Nov; 82(22):7787-90

Isolation and amino acid sequence of corticotropin-releasing factor from pig hypothalami. Patthy M, et al. **Proc Natl Acad Sci USA** 1985 Dec; 82(24):8762-6

Corticotropin-releasing factor-induced adrenocorticotropin hormone release and synthesis is blocked by incorporation of the inhibitor of cyclic AMP-dependent protein kinase into anterior pituitary tumor cells by liposomes. Reisine T, et al. **Proc Natl Acad Sci USA** 1985 Dec; 82(23):8261-5

The physiology of corticotropin-releasing factor (CRF). Raux-Demay MC, et al. **Reprod Nutr Dev** 1985;25(5):931-43 (67 ref.)

[Coexpression of immunoreactivity with an anti-corticoliberin immune serum and immunoreactivity with an anti-vasopressin immune serum in human hypothalamic neurons] Clavequin MC, et al. **Ann Endocrinol (Paris)** 1985;46(1):64-6 (Eng. Abstr.) **(Fre)**

[Corticotropin-releasing hormone] Emeric de Sauval E. **Medicina (B Aires)** 1984;44(4):422-9 **(Spa)**

DANSYL COMPOUNDS

Mitochondrial nicotinamide nucleotide transhydrogenase: inhibition by ethoxyformic anhydride, dansyl chloride, and pyridoxal phosphate. Yamaguchi M, et al. **Arch Biochem Biophys** 1985 Nov 15; 243(1):20-7

Ca2+-specific fluorescence changes in N-dansylaminoethyl-labelled oncomodulin. Mutus B, et al. **Can J Biochem Cell Biol** 1985 Sep; 63(9):998-1002

Measurement of neutral sugars in glycoproteins as dansyl derivatives by automated high-performance liquid chromatography. Eggert FM, et al. **J Chromatogr** 1985 Sep 27;333(1):123-31

[Determination of adenine nucleotides by thin-layer chromatography combined with the dansylation reaction] Tkachenko AG, et al. **Prikl Biokhim Mikrobiol** 1985 Jul-Aug;21(4):553-7 (Eng. Abstr.) **(Rus)**

DELUSIONS

AIDS and homosexual panic [letter] Rapaport M, et al. **Am J Psychiatry** 1985 Dec;142(12):1516

Delusional hypochondriasis, depression, and amoxapine [letter] Tollefson G. **Am J Psychiatry** 1985 Dec;142(12):1518-9

Depression, drugs, and delusions. Howarth BG, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1145-7

DEPRESSION

A double-blind evaluation of trazodone in the treatment of depression in the elderly. Ather SA, et al. **Br J Clin Pract** 1985 May; 39(5):192-9

Pharmacological strategies in depression. Katona CL, et al. **Br J Hosp Med** 1985 Sep;34(3):168-71

Lithium potentiation of imipramine in treatment resistant depression [letter] Roy A, et al. **Br J Psychiatry** 1985 Nov;147:582-3

Response to sequential administration of clomipramine and lithium carbonate in treatment-resistant depression. Schrader GD, et al. **Br J Psychiatry** 1985 Nov;147:573-5

Plasma immunoglobulins in depressed and lithium-treated patients [letter] Wood K, et al. **Br J Psychiatry** 1985 Nov;147:581-2

Use of specific serotonin uptake inhibitors as antidepressants. Lemberger L, et al. **Clin Neuropharmacol** 1985;8(4):299-317 (142 ref.)

The tolerance and antidepressive activity of fluvoxamine as a single dose compared to a twice daily dose. Siddiqui UA, et al. **Curr Med Res Opin** 1985;9(10):681-90

Psychostimulant treatment of depressive disorders secondary to medical illness. Woods SW, et al. **J Clin Psychiatry** 1986 Jan;47(1):12-5

Tyrosine for the treatment of depression. Gelenberg AJ, et al. **Nutr Health** 1984;3(3):163-73 (44 ref.)

Benzodiazepines in the control of anxiety-induced depression. Fairhurst MM. **S Afr Med J** 1985 Oct 26;Suppl:29

[Controlled trial of amitriptyline in a group of patients with so-called functional pseudorheumatic pain (letter)] Limon J, et al. **Presse Med** 1985 Nov 30;14(41):2107 **(Fre)**

DEPRESSIVE DISORDER

A double blind study in out-patients with primary non-agitated depression treated with imipramine in combination with placebo, diazepam or dixyrazine. Feet PO, et al. **Acta Psychiatr Scand** 1985 Oct; 72(4):334-40

ACTH 4-9 analogue (Org 2766) in depressed elderly patients. II. Effect on memory and vigilance. Frederiksen SO, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):349-57

ACTH 4-9 analogue (Org 2766) in depressed elderly patients. I. Effect on depressed mood. Frederiksen SO, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):341-8

Tricyclic blood levels [letter] Boyer WT. **Am J Psychiatry** 1985 Nov; 142(11):1388

ECT versus tricyclic antidepressants [letter] Fogel BS. **Am J Psychiatry** 1986 Jan;143(1):121-2

Using MMPI lithium response scales [letter] Lane JB. **Am J Psychiatry** 1985 Nov;142(11):1388-9

Dysthymia and attention deficit disorder in adults [letter] Mattes JA. **Am J Psychiatry** 1986 Jan;143(1):114-5

Antidepressant effects of carbamazepine. Post RM, et al. **Am J Psychiatry** 1986 Jan;143(1):29-34

Continuation drug therapy for major depressive episodes: how long should it be maintained? Prien RF, et al. **Am J Psychiatry** 1986 Jan; 143(1):18-23

Delusional hypochondriasis, depression, and amoxapine [letter] Tollefson G. **Am J Psychiatry** 1985 Dec;142(12):1518-9

Depression, drugs, and delusions. Howarth BG, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1145-7

Imipramine and chlordiazepoxide in depressive and anxiety disorders. I. Efficacy in depressed outpatients. Lipman RS, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):68-77

The outcome of antidepressant use in the medically ill. Popkin MK, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1160-3

Exaggerated orthostatic responsivity of plasma norepinephrine in depression. Rudorfer MV, et al. **Arch Gen Psychiatry** 1985 Dec; 42(12):1186-92

Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. Simons AD, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):43-8

Treatment outcome validation of DSM-III depressive subtypes. Clinical usefulness in outpatients with mild to moderate depression. Stewart JW, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1148-53

Prescribing hints for the treatment of anxiety and depression. Horgan D. **Aust Fam Physician** 1985 Sep;14(9):872-5

Platelet 3H-imipramine binding in depressed elderly patients. Schneider LS, et al. **Biol Psychiatry** 1985 Nov;20(11):1234-7

Drug treatment of bipolar depression and mania. Cookson JC. **Br J Hosp Med** 1985 Sep;34(3):172-5 (92 ref.)

Adrenergic receptors in depression. Effects of electroconvulsive therapy. Cooper SJ, et al. **Br J Psychiatry** 1985 Jul;147:23-9

Lithium in severe depression [letter] Fraser AA, et al. **Br J Psychiatry** 1985 Sep;147:324

A double-blind out-patient trial of indalpine vs mianserin. Naylor GJ, et al. **Br J Psychiatry** 1985 Sep;147:306-9

L-5HTP in depression resistant to re-uptake inhibitors. An open comparative study with tranylcypromine. Nolen WA, et al. **Br J Psychiatry** 1985 Jul;147:16-22

The effect of desipramine upon melatonin and cortisol secretion in depressed and normal subjects. Thompson C, et al. **Br J Psychiatry** 1985 Oct;147:389-93

Liquid chromatographic determination of inhibition of monoamine oxidase activity in platelet rich plasma of depressed patients treated with phenelzine. Gupta RN, et al. **Clin Chim Acta** 1985 Oct 31; 152(1-2):63-9

Nomifensine: an antidepressant with a difference? Ereshefsky L. **Clin Pharm** 1985 Nov-Dec;4(6):673-4

A controlled trial of amitriptyline and cianopramine in major depression. Mellsop GW, et al. **Clin Ther** 1985;7(6):699-703 (8 ref.)

A double-blind trial comparing mianserin and maprotiline in depressed inpatients. Palha AP, et al. **Clin Ther** 1985;7(5):584-92

Depression in the intensive care unit. Bronheim HE, et al. **Crit Care Med** 1985 Nov;13(11):985-8

Self-rating data as a selecting factor in clinical trials of psychotropic drugs. Baumann U, et al. **Eur Arch Psychiatry Neurol Sci** 1985; 235(2):65-70

Current treatment of depression. Bowden CL. **Hosp Community Psychiatry** 1985 Nov;36(11):1192-200

Evaluation of long-term use of antidepressant medication. Risse SC, et al. **Hosp Community Psychiatry** 1985 Nov;36(11):1215-6

Effects of ACTH and prednisone on mood: incidence and time of onset. Cameron OG, et al. **Int J Psychiatry Med** 1985-86;15(3):213-23

Methylphenidate for medical in-patients. Fisch RZ. **Int J Psychiatry Med** 1985-86;15(1):75-9

Empirical study on an inpatient psychogeriatric unit: biological treatment in patients with depressive illness. Meyers BS, et al. **Int J Psychiatry Med** 1985-86;15(2):111-24

Peripheral adrenoceptors and serotonin receptors in depression. Changes associated with response to treatment with trazodone or amitriptyline. Healy D, et al. **J Affective Disord** 1985 Nov;9(3):285-96

Plasma tyrosine/neutral amino acid ratio correlated with clinical response to nortriptyline in endogenously depressed patients. Møller SE, et al. **J Affective Disord** 1985 Nov;9(3):223-9

Measurement of reinforcement in depression: a pilot study. Hughes JR, et al. **J Behav Ther Exp Psychiatry** 1985 Sep;16(3):231-6

Clinical significance, evaluation, and management of secondary depression in schizophrenia. Becker RE, et al. **J Clin Psychiatry** 1985 Nov; 46(11 Pt 2):26-32

Are antidepressant trials too short? A case report. Eisenberg J, et al. **J Clin Psychiatry** 1986 Jan;47(1):38-9

Treatment of depression in outpatients: a controlled comparison of the onset of action of amoxapine and maprotiline. Fabre LF. **J Clin Psychiatry** 1985 Dec;46(12):521-4

Simultaneous panic and depressive disorder: response to antidepressant treatments. Grunhaus L, et al. **J Clin Psychiatry** 1986 Jan;47(1):4-7

Methylphenidate in mild depression: a double-blind controlled trial. Mattes JA. **J Clin Psychiatry** 1985 Dec;46(12):525-7

Acute response to methylphenidate as a predictor of outcome of treatment with TCAs in the elderly. Spar JA, et al. **J Clin Psychiatry** 1985 Nov; 46(11):466-9

Psychostimulant treatment of depressive disorders secondary to medical illness. Woods SW, et al. **J Clin Psychiatry** 1986 Jan;47(1):12-5

The ethological approach to the assessment of depressive disorders. Fossi L, et al. **J Nerv Ment Dis** 1984 Jun;172(6):332-41

Sulfate and glucuronide conjugates of 3-methoxy-4-hydroxyphenylglycol (MHPG) in urine of depressed patients: central and peripheral influences. Peyrin L, et al. **J Neural Transm** 1985;63(3-4):255-69

Platelet alpha 2-adrenoceptors in major depression: relationship with urinary 4-hydroxy-3-methoxyphenylglycol and age at onset. Sacchetti E, et al. **J Psychiatr Res** 1985;19(4):579-86

Influence of personality on response to monoamine oxidase inhibitors and tricyclic antidepressants. Shawcross CR, et al. **J Psychiatr Res** 1985; 19(4):557-62

Corticotropin-releasing factor in plasma of depressed patients and controls [letter] Charlton BG, et al. **Lancet** 1986 Jan 18;1(8473):161-2

Depression and the general practitioner. Carney MW, et al. **Practitioner** 1985 Nov;229(1409):1017-25

CSF somatostatin in affective illness and normal volunteers. Rubinow DR, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(4):393-400

Amineptine in the management of the depressive syndromes. Scarzella L, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(4):429-39

The efficiency of ECT: II. Correlation of specific treatment variables to response rate in unilateral ECT. Rich CL, et al. **Psychiatry Res** 1985 Oct;16(2):147-54

Cerebrospinal fluid monoamine and monoamine metabolite concentrations in melancholia. Roy A, et al. **Psychiatry Res** 1985 Aug;15(4):281-92

A comparison between the growth hormone responses to amphetamine and clonidine [letter] Siever LJ, et al. **Psychiatry Res** 1985 Sep; 16(1):79-82

Variation in human platelet 3H-imipramine binding. Tang SW, et al. **Psychiatry Res** 1985 Oct;16(2):141-6

Lower 3H-imipramine binding in platelets from untreated depressed patients compared to healthy controls. Wägner A, et al. **Psychiatry Res** 1985 Oct;16(2):131-9

Effect of lysine vasopressin in depressed patients on mood and 24-hour rhythm of growth hormone, cortisol, melatonin and prolactin. Zohar J, et al. **Psychoneuroendocrinology** 1985;10(3):273-9

Specificity and nonspecificity--a major problem in biologically oriented psychopathology. Heimann H. **Psychopathology** 1985;18(2-3):82-7

MHPG excretion in endogenous depression: relationship to clinical state and the effects of ECT. Joseph MH, et al. **Psychopharmacology (Berlin)** 1985;87(4):442-8

Combined use of TCAs and MAOIs [letter] Stewart JW. **Psychosomatics** 1985 Nov;26(11):879

[Lithium prophylaxis, o.k., but for how long?] Slooff CJ, et al. **Ned Tijdschr Geneeskd** 1985 Sep 7;129(36):1729-33 (Eng. Abstr.) **(Dut)**

[Depression, anxiety and neurotic disorders] Wilmotte J. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):469-79 (Eng. Abstr.) **(Fre)**

[New proposals for the development of the concepts of neurotic anxiety, major depression and panic attack] Xhenseval B. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):480-508 (68 ref.) (Eng. Abstr.) **(Fre)**

[Plasma levels of clomipramine and its metabolites in hospitalized depressed patients] Debray Q, et al. **Ann Med Psychol (Paris)** 1985 May;143(5):464-74 **(Fre)**

[Correlation between serum levels of amitriptyline and the Hamilton scale of depression using high-pressure liquid chromatography] Cruz Igartúa A, et al. **Bol Asoc Med PR** 1985 Sep;77(9):375-80 **(Spa)**

[Relation of blood levels of amoxapine and its active metabolites to its pharmacologic response and toxicity] Calvo MB, et al. **Med Clin (Barc)** 1985 Sep 14;85(7):269-72 (Eng. Abstr.) **(Spa)**

DEPTH PERCEPTION

Haloperidol blocks amphetamine induced recovery of binocular depth perception after bilateral visual cortex ablation in cat. Hovda DA, et al. **Proc West Pharmacol Soc** 1985;28:209-11

DESIPRAMINE

Selective antidepressants and cerebrospinal fluid. Lack of specificity on norepinephrine and serotonin metabolites. Potter WZ, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1171-7

Obsessive-compulsive disorder and serotonin: is there a connection? Insel TR, et al. **Biol Psychiatry** 1985 Nov;20(11):1174-88

The effect of desipramine upon melatonin and cortisol secretion in depressed and normal subjects. Thompson C, et al. **Br J Psychiatry** 1985 Oct;147:389-93

Modification of behavioral response to intra-hippocampal injections of noradrenaline and adrenoceptor agonists by chronic treatment with desipramine and citalopram: functional aspects of adaptive receptor changes. Płaźnik A, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):245-52

Are antidepressant trials too short? A case report. Eisenberg J, et al. **J Clin Psychiatry** 1986 Jan;47(1):38-9

Double-blind comparison of desipramine and placebo in withdrawal from cocaine dependence. Tennant FS Jr, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:159-63

Biochemical and behavioral changes in rats after prolonged treatment with desipramine: interaction with p-chlorophenylalanine. Brunello N, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):20-2

Chronic dosage of imipramine in animal experiment: concentrations of imipramine and desipramine in the rat brain after various modes of dosage. Melzacka M, et al. **Pol J Pharmacol Pharm** 1985 Jul-Aug;37(4):525-32

Mesolimbic noradrenaline but not dopamine is responsible for organization of rat behavior in the forced swim test and an anti-immobilizing effect of desipramine. Płaźnik A, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):347-57

Effects of some antidepressant drugs on apomorphine concentration in the central nervous system of rats and apomorphine-induced stereotypy. Rurak A, et al. **Pol J Pharmacol Pharm** 1985 Jul-Aug;37(4):509-15

DESOXYCORTICOSTERONE

The hypertensinogenic activity of 19-nor-deoxycorticosterone in the adrenalectomized spontaneously hypertensive rat. Gorsline J, et al. **J Steroid Biochem** 1985 Oct;23(4):535-6

Intrahypothalamic effects of progestin agonists on estrous behavior and progestin receptor binding. Glaser JH, et al. **Physiol Behav** 1985 Jun;34(6):871-7

DEXTROAMPHETAMINE

Obsessive-compulsive symptoms following stimulants [letter] Koizumi HM. **Biol Psychiatry** 1985 Dec;20(12):1332-3

Modulation of terminal excitability of mesolimbic dopaminergic neurons by D-amphetamine and haloperidol. Mereu G, et al. **Brain Res** 1985 Dec 16;359(1-2):88-96

Individual differences in non-regulatory ingestive behavior and catecholamine systems. Mittleman G, et al. **Brain Res** 1985 Nov 25;348(1):112-7

Analysis of dopamine D1 and D2 receptor involvement in d- and l-amphetamine-induced anorexia in rats. Gilbert DB, et al. **Brain Res Bull** 1985 Oct;15(4):385-9

Chronic administration of D-amphetamine increases [3H]spiroperidol binding in cat brain. Trulson ME, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):267-70

Salbutamol, d-amphetamine and d-fenfluramine reduce sucrose intake in freely fed rats by acting on different neurochemical mechanisms. Borsini F, et al. **Int J Obes** 1985;9(4):277-83

Psychostimulant treatment of depressive disorders secondary to medical illness. Woods SW, et al. **J Clin Psychiatry** 1986 Jan;47(1):12-5

Iron deficiency induces reversal of dopamine dependent circadian cycles: differential response to d-amphetamine and TRH. Youdim MB, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):851-5

Effects of d-amphetamine and of beta-phenylethylamine on fixed interval responding maintained by self-regulated lateral hypothalamic stimulation in rats. Greenshaw AJ, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):519-23

The role of the midbrain reticular formation in the expression of two opposing nigral denervation syndromes. Vaccarino FJ, et al. **Physiol Behav** 1985 Nov;35(5):749-52

ACTH1-24 effects on d-amphetamine self-administration and the dynamics of brain dopamine in rats. Leccese AP, et al. **Prog Clin Biol Res** 1985;192:71-81

Different pattern of association of beta-endorphin and cortisol responses to dextroamphetamine in postmenopausal women and young men. Halbreich U, et al. **Psychiatry Res** 1985 Sep;16(1):11-9

Lithium attenuates the activation-euphoria but not the psychosis induced by d-amphetamine in schizophrenia. van Kammen DP, et al. **Psychopharmacology (Berlin)** 1985;87(1):111-5

Effects of L-tyrosine on brain monoamines in rats given intravenous amphetamine. Smith DG, et al. **Subst Alcohol Actions Misuse** 1984-85;5(6):293-8

DIAZEPAM

Comparison of paracetamol and aminophenazone plus diazepam suppositories for anxiety and pain relief after tonsillectomy in children. Lindgren L, et al. **Acta Anaesthesiol Scand** 1985 Oct;29(7):679-82

Myorelaxant effect of diazepam. Interactions with neuromuscular blocking agents and cholinergic drugs. Wali FA. **Acta Anaesthesiol Scand** 1985 Nov;29(8):785-9

Early treatment response in anxious outpatients treated with diazepam. Downing RW, et al. **Acta Psychiatr Scand** 1985 Dec;72(6):522-8

A double blind study in out-patients with primary non-agitated depression treated with imipramine in combination with placebo, diazepam or dixyrazine. Feet PO, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):334-40

The influence of diazepam on the pharmacokinetics of intravenous and epidural bupivacaine in the rhesus monkey. Thompson GA, et al. **Anesth Analg** 1986 Feb;65(2):151-5

Physostigmine: an antidote for excessive central nervous system depression or paradoxical rage reactions resulting from intravenous diazepam. Jastak JT. **Anesth Prog** 1985 May-Jun;32(3):87-92

Effect of diazepam on drug absorption and gastric emptying in man. Adelhøj B, et al. **Br J Anaesth** 1985 Nov;57(11):1107-9

The effects of diazepam on the auditory brain stem responses. Adams DA, et al. **Br J Audiol** 1985 Nov;19(4):277-80

Specific changes in local cerebral glucose utilization in the rat brain induced by acute and chronic diazepam. Ableitner A, et al. **Brain Res** 1985 Dec 16;359(1-2):49-56

Severe withdrawal syndrome after substitution of a short-acting benzodiazepine for a long-acting benzodiazepine. Bond WS, et al. **Drug Intell Clin Pharm** 1985 Oct;19(10):742-4

Famotidine, a new H2-receptor antagonist, does not affect hepatic elimination of diazepam or tubular secretion of procainamide. Klotz U, et al. **Eur J Clin Pharmacol** 1985;28(6):671-5

Development of tolerance to the anticonvulsant effect of diazepam in amygdala-kindled rats. Löscher W, et al. **Exp Neurol** 1985 Nov;90(2):373-84

Omeprazole inhibits oxidative drug metabolism. Studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. Gugler R, et al. **Gastroenterology** 1985 Dec;89(6):1235-41

The effect of diazepam on body temperature change in humans during cold exposure. Martin SM. **J Clin Pharmacol** 1985 Nov-Dec;25(8):611-3

Six-week trial with diazepam: some clinical observations. Rickels K, et al. **J Clin Psychiatry** 1985 Nov;46(11):470-4

Modification of the inotropic effect of digoxin by diazepam in rat left atria. Castillo-Ferrando JR, et al. **J Pharm Pharmacol** 1985 Nov;37(11):828-9

Differential diazepam-antagonist effects of the benzodiazepine receptor ligand CGS 9895 in rodents. Katzman NJ, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):589-95

Imaging of [11C]-labelled Ro 15-1788 binding to benzodiazepine receptors in the human brain by positron emission tomography. Persson A, et al. **J Psychiatr Res** 1985;19(4):609-22

Nimodipine's interactions with other drugs: II. Diazepam. Draski LJ, et al. **Life Sci** 1985 Dec 2;37(22):2123-8

Attenuating effect of diazepam on stress-induced increases in noradrenaline turnover in specific brain regions of rats: antagonism by Ro 15-1788. Ida Y, et al. **Life Sci** 1985 Dec 30;37(26):2491-8

Effects of diazepam at the neuromuscular junction. Wali FA. **Life Sci** 1985 Oct 28;37(17):1559-61 (19 ref.)

The provision of diazepam to psychiatric patients [letter] Hammett E. **Milit Med** 1985 Nov;150(11):625

Dose effect and preference comparison of diazepam and oxazepam. Griffiths RR, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 55:97-8

Effect of short-term swimming stress and diazepam on 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) levels in the caudate nucleus: an in vivo voltammetric study. Ikeda M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct; 331(1):23-6

Non-benzodiazepine anxiolytics: potential activity of phenylpiperazines without 3H-diazepam displacing action. Lloyd KG, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):645-52

Comparison of buspirone and diazepam in generalized anxiety disorder. Jacobson AF, et al. **Pharmacotherapy** 1985 Sep-Oct;5(5):290-6

Conditioned suppression of sexual behavior in stallions and reversal with diazepam. McDonnell SM, et al. **Physiol Behav** 1985 Jun;34(6):951-6

On the brain endocoid for benzodiazepine recognition sites. Guidotti A, et al. **Prog Clin Biol Res** 1985;192:477-84

Tolerance to the benzodiazepine diazepam in an animal model of anxiolytic activity. Stephens DN, et al. **Psychopharmacology (Berlin)** 1985;87(3):322-7

Is delay of reward mediated by shock-avoidance behavior a critical target for anti-punishment effects of diazepam in rats? Thiébot MH, et al. **Psychopharmacology (Berlin)** 1985;87(4):473-9

Intra-arterial diazepam. A report of 2 cases. Schulenburg CE, et al. **S Afr Med J** 1985 Dec 7;68(12):891-2

Social effects of diazepam use: a longitudinal field study. Caplan RD, et al. **Soc Sci Med** 1985;21(8):887-98

[Physostigmine: an antidote in diazepam poisoning] Pedersen JE. **Ugeskr Laeger** 1985 Nov 4;147(45):3586-7 (Eng. Abstr.) **(Dan)**

[Functional synergism of beta-adrenomimetics and seduxen during action on the uterine contractile function in an experiment] Gersamiia TV, et al. **Akush Ginekol (Mosk)** 1985 Aug;(8):65-6 **(Rus)**

[Effect of diazepam, meprobamate and amizyl on the emotional reactions of the rabbit to hypothalamic stimulation] Davituliani DS, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):952-6 (Eng. Abstr.) **(Rus)**

DIBENZAZEPINES

Effects of haloperidol and low dose clozapine on the acetylcholine turnover rate in rat forebrain structures. Bluth R, et al. **Biomed Biochim Acta** 1985;44(10):1531-9

A double-blind out-patient trial of indalpine vs mianserin. Naylor GJ, et al. **Br J Psychiatry** 1985 Sep;147:306-9

Possible mechanism for mianserin induced neutropenia associated with saturable elimination kinetics. O'Donnell JL, et al. **Br Med J [Clin Res]** 1985 Nov 16;291(6506):1375-6

A double-blind trial comparing mianserin and maprotiline in depressed inpatients. Palha AP, et al. **Clin Ther** 1985;7(5):584-92

Octopamine receptors in the molluscan aortic bulb: effects of clozapine and chlordimeform. Dougan DF, et al. **Comp Biochem Physiol [C]** 1985; 82(1):193-7

Metapramine overdose: report of two cases and analytical determinations. Rouquette C, et al. **J Anal Toxicol** 1985 Nov-Dec;9(6):275-7

The effect of phenothiazine and dibenzazepine pretreatment on the metabolism of methamphetamine in rats. Mori M, et al. **J Pharm Pharmacol** 1985 Nov;37(11):819-20

Neutropenia and mianserin [letter] Forgan-Smith J, et al. **Med J Aust** 1985 Oct 28;143(9):398

Differential effects of thioridazine, clozapine and metoclopramide on the induction of adrenomedullary enzymes by apomorphine. Ekker M, et al. **Neuropharmacology** 1985 Nov;24(11):1063-6

The effects of clozapine on shuttle-box avoidance responding in rats: comparisons with haloperidol and chlordiazepoxide. Sanger DJ. **Pharmacol Biochem Behav** 1985 Aug;23(2):231-6

DIBENZOTHIEPINS

Prolonged inhibition of striatal dopamine receptor sites by isofloxythepin. Lau YS, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):25-31

Flumezapine and zotepine: 5-hydroxytryptamine antagonism not involved in the lack of synergism of these antipsychotic drugs with amfonelic acid in rats. Fuller RW, et al. **J Pharm Pharmacol** 1985 Oct; 37(10):755-6

DIBENZOXAZEPINES

Delusional hypochondriasis, depression, and amoxapine [letter] Tollefson G. **Am J Psychiatry** 1985 Dec;142(12):1518-9

How effective is loxapine? [letter] Tuason VB, et al. **Am J Psychiatry** 1986 Jan;143(1):116-7

Effect of loxapine and amoxapine on oxidative metabolism of rat brain 'in vitro'. Velasco Martin A, et al. **Arch Farmacol Toxicol** 1985 Aug; 11(2):117-25

Treatment of depression in outpatients: a controlled comparison of the onset of action of amoxapine and maprotiline. Fabre LF. **J Clin Psychiatry** 1985 Dec;46(12):521-4

Amoxapine overdose [letter] Weaver KE. **J Clin Psychiatry** 1985 Dec; 46(12):545

Dopamine receptor binding of a novel dibenzodioxazocine derivative, EGYT-2509. Gyüre K, et al. **Pol J Pharmacol Pharm** 1985 May-Jun; 37(3):253-61

[Relation of blood levels of amoxapine and its active metabolites to its pharmacologic response and toxicity] Calvo MB, et al. **Med Clin (Barc)** 1985 Sep 14;85(7):269-72 (Eng. Abstr.) **(Spa)**

DIETHYLAMINES

[Determining secondary aliphatic amines in the air using the dithiocarbamate formation test] Iakimova VP, et al. **Gig Tr Prof Zabol** 1985 Oct;(10):55-6 **(Rus)**

DISCRIMINATION (PSYCHOLOGY)

Mechanistic studies on DOM as a discriminative stimulus. Glennon RA, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):937-41

Amphetamine-haloperidol discrimination: effects of chronic drug treatment. Haenlein M, et al. **Pharmacol Biochem Behav** 1985 Dec; 23(6):949-52

Discriminative stimulus properties and brain distribution of phencyclidine in rats following administration by injection and smoke inhalation. Wessinger WD, et al. **Pharmacol Biochem Behav** 1985 Oct; 23(4):607-12

One-way generalization of clonidine to the discriminative stimulus produced by cocaine. Wood DM, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):529-33

DISCRIMINATION LEARNING

Alternation behavior, spatial discrimination, and reversal disturbances following 6-hydroxydopamine lesions in the nucleus accumbens of the rat. Taghzouti K, et al. **Behav Neural Biol** 1985 Nov;44(3):354-63

N-Ethyl-17(R,S)-methyl-(6aR,10aR)-delta 8-tetrahydrocannabinol-18-oic amide. Brain pharmacokinetics in mice, triglyceride/phospholipid partitioning and generalization to the discriminative stimulus properties of delta 9-THC in rats. Franke I, et al. **Biochem Pharmacol** 1985 Nov 15;34(22):3983-6

Discriminative stimulus properties of valproic acid in the pigeon. Picker M, et al. **Psychopharmacology (Berlin)** 1985;87(4):449-53

DOPA

A pulse radiolysis investigation of the oxidation of the melanin precursors 3,4-dihydroxyphenylalanine (dopa) and the cysteinyldopas. Thompson A, et al. **Biochim Biophys Acta** 1985 Nov 22;843(1-2):49-57

gamma-L-Glutamyl-L-dopa is a dopamine pro-drug, relatively specific for the kidney in normal subjects. Worth DP, et al. **Clin Sci** 1985 Aug; 69(2):207-14

New synthesis of fluorine-18-labeled 6-fluoro-L-dopa by cleaving the carbon-silicon bond with fluorine. Diksic M, et al. **J Nucl Med** 1985 Nov;26(11):1314-8

Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. Breese GR, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):287-95

DOPAMINE

Autoradiography of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): uptake in the monoaminergic pathways and in melanin containing tissues. Lydén A, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Aug;57(2):130-5

Effect of rate of hemorrhage on sympathoadrenal catecholamine release in cats. Bereiter DA, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 1):E69-75

Mania, clonidine, and dopamine [letter] Shen WW. **Am J Psychiatry** 1986 Jan;143(1):127

Extractive acylation and mass spectrometric assay of 3-methoxytyramine, normetanephrine, and metanephrine in cerebrospinal fluid. Beck O, et al. **Anal Biochem** 1985 Sep;149(2):492-500

A genetic analysis of stereotypy in the mouse: dopaminergic plasticity following chronic stress. Cabib S, et al. **Behav Neural Biol** 1985 Sep;

44(2):239-48

Alternation behavior, spatial discrimination, and reversal disturbances following 6-hydroxydopamine lesions in the nucleus accumbens of the rat. Taghzouti K, et al. **Behav Neural Biol** 1985 Nov;44(3):354-63

Persistent depletion of striatal dopamine in mice by 1-methyl-4-(2-thienyl)-1,2,3,6-tetrahydropyridine (MTTP). Fuller RW, et al. **Biochem Pharmacol** 1986 Jan 15;35(2):143-4

Effect of phosphatase inhibition of in vitro dopamine sulfation and 3'-phosphoadenosine-5'-phosphosulfate catabolism in human brain. Whittemore RM, et al. **Biochem Pharmacol** 1985 Nov 1; 34(21):3853-6

Quantitation of a mass action of dopaminergic neurones regulating temporal damping of linear electrocortical waves. Wright JJ, et al. **Biol Cybern** 1985;52(5):281-90

Excitatory neuronal responses to dopamine in the cerebral cortex: involvement of D2 but not D1 dopamine receptors. Bradshaw CM, et al. **Br J Pharmacol** 1985 Oct;86(2):483-90

Prevention of dopaminergic toxicity of MPTP in mice by phenylethylamine, a specific substrate of type B monoamine oxidase. Melamed E, et al. **Br J Pharmacol** 1985 Nov;86(3):529-31

Dopaminergic modulation of sensory responses of striatal neurons: single unit studies. Abercrombie ED, et al. **Brain Res** 1985 Dec 9; 358(1-2):27-33

Modulation of the endogenous acetylcholine release from rat striatal slices. Alberch J, et al. **Brain Res** 1985 Nov 4;346(2):353-6

In vitro dopamine biosynthesis in the median eminence of rat hypothalamic slices: involvement of voltage-dependent Ca2+ channels. Arita J, et al. **Brain Res** 1985 Nov 18;347(2):299-305

Strain differences in pituitary prolactin content: relationship to number of hypothalamic dopamine neurons. Baker H, et al. **Brain Res** 1985 Dec 9;358(1-2):16-26

Topographical dopamine and serotonin distribution and turnover in rat striatum. Beal MF, et al. **Brain Res** 1985 Dec 9;358(1-2):10-5

Modification of electroretinograms in dopamine-depleted retinas. Citron MC, et al. **Brain Res** 1985 Oct 14;345(1):186-91

Growth hormone-releasing factor modifies dopaminergic but not serotonergic activity in the arcuate nucleus of hypothalamus in the rat, as recorded in vivo by differential pulse voltammetry. Crespi F, et al. **Brain Res** 1985 Dec 2;348(2):367-70

Differences between the release of radiolabelled and endogenous dopamine from superfused rat brain slices: effects of depolarizing stimuli, amphetamine and synthesis inhibition. Herdon H, et al. **Brain Res** 1985 Dec 2;348(2):309-20

Increase of dopamine turnover in bilateral striata after unilateral injection of haloperidol into substantia nigra of unrestrained rats. Ishii K, et al. **Brain Res** 1985 Dec 16;359(1-2):260-6

Stimulation of retinal dopamine biosynthesis in vivo by exogenous tetrahydrobiopterin: relationship to tyrosine hydroxylase activation. Iuvone PM, et al. **Brain Res** 1985 Dec 16;359(1-2):392-6

Behavioral and neurochemical effect of daily injection with neurotensin into the ventral tegmental area. Kalivas PW, et al. **Brain Res** 1985 Dec 9;358(1-2):70-6

Modulation of dopaminergic activity in the nucleus accumbens following facilitation or blockade of the dopaminergic transmission in the amygdala: a study by in vivo differential pulse voltammetry. Louilot A, et al. **Brain Res** 1985 Oct 28;346(1):141-5

Dopamine inhibition of neurotensin-induced increase in Ca2+ influx into rat pituitary cells. Memo M, et al. **Brain Res** 1985 Nov 18; 347(2):253-7

Dopamine decreases cell excitability in rat striatal neurons by pre- and postsynaptic mechanisms. Mercuri N, et al. **Brain Res** 1985 Dec 9; 358(1-2):110-21

Modulation of terminal excitability of mesolimbic dopaminergic neurons by D-amphetamine and haloperidol. Mereu G, et al. **Brain Res** 1985 Dec 16;359(1-2):88-96

Correlation between adenosine triphosphate levels, dopamine release and electrical activity in the carotid body: support for the metabolic hypothesis of chemoreception. Obeso A, et al. **Brain Res** 1985 Nov 25;348(1):64-8

Dopaminergic regulation of GABA release from the intact goldfish retina. O'Brien DR, et al. **Brain Res** 1985 Dec 23;360(1-2):41-50

Effects of water deprivation and administration of hypertonic saline on dopamine concentrations in posterior pituitary and vasopressin release in rats. Oki Y, et al. **Brain Res** 1985 Nov 25;348(1):9-14

Presynaptic inhibition of dopamine synthesis in rat striatum: effects of chronic dopamine depletion and receptor blockade. Reches A, et al. **Brain Res** 1985 Nov 18;347(2):346-9

Enduring enhancement in frontal cortex dopamine utilization in an animal model of amphetamine psychosis. Robinson TE, et al. **Brain Res** 1985 Sep 23;343(2):374-7

Homocysteine prevents apomorphine-induced decreases in dopamine metabolites. Saller CF, et al. **Brain Res** 1985 Dec 23;360(1-2):407-8

GABA axons in synaptic contact with dopamine neurons in the substantia nigra: double immunocytochemistry with biotin-peroxidase and protein A-colloidal gold. van den Pol AN, et al. **Brain Res** 1985 Nov 25; 348(1):146-54

Dopamine-dependent contralateral circling induced by neurotensin applied unilaterally to the ventral tegmental area in rats. Holmes LJ, et al. **Brain Res Bull** 1985 Nov;15(5):537-8

Dopamine-stimulated parathyroid hormone release in vitro: further evidence for a two-pool model of parathyroid hormone secretion. Hanley DA, et al. **Can J Physiol Pharmacol** 1985 Sep;63(9):1139-44

Radioenzymatic microassay for simultaneous estimations of dopamine, norepinephrine, and epinephrine in plasma, urine, and tissues. Hussain MN, et al. **Clin Chem** 1985 Nov;31(11):1861-4

Effect of low-dose dopamine infusion on basal and stimulated TSH and prolactin concentrations in man. Connell JM, et al. **Clin Endocrinol (Oxf)** 1985 Aug;23(2):185-92

The role of plasma osmolality, angiotensin II and dopamine in vasopressin release in man. Morton JJ, et al. **Clin Endocrinol (Oxf)** 1985 Aug; 23(2):129-38

Epinephrine, norepinephrine and dopamine concentrations in amphibian brain. Cooney MM, et al. **Comp Biochem Physiol** [C] 1985; 82(2):395-7

The effects of adrenalectomy on the ontogenesis of brain: noradrenaline and dopamine content. Leret ML, et al. **Comp Biochem Physiol** [C] 1985;82(2):475-7

Dopamine: a prolactin-inhibiting hormone. Ben-Jonathan N. **Endocr Rev** 1985 Fall;6(4):564-89 (281 ref.)

Does endogenous dopamine modulate human sympathetic activity through DA2 receptors? Mannelli M, et al. **Eur J Clin Pharmacol** 1985; 29(2):159-64

Prenatal exposure of rats to antidepressants enhances agonist affinity of brain dopamine receptors and dopamine-mediated behaviour. De Ceballos ML, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):257-62

17 beta-Estradiol at a physiological dose acutely increases dopamine turnover in rat brain. Di Paolo T, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):197-203

Phencyclidine binding sites in the nucleus accumbens and phencyclidine-induced hyperactivity are decreased following lesions of the mesolimbic dopamine system. French ED, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):1-9

Prevention of MPTP-induced neurotoxicity by AGN-1133 and AGN-1135, selective inhibitors of monoamine oxidase-B. Heikkila RE, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):313-7

The effect of dopamine upon oxidative metabolism of brown fat adipocytes. Maxwell G, et al. **Eur J Pharmacol** 1985 Oct 22; 116(3):293-7

Dopamine but not norepinephrine or serotonin uptake inhibitors protect mice against neurotoxicity of MPTP. Melamed E, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):179-81

Dopaminergic inhibition of the action of vasopressin on the cortical collecting tubule. Muto S, et al. **Eur J Pharmacol** 1985 Aug 27; 114(3):393-7

Stimulation of D-2 dopamine receptors in rat mesocortical areas inhibits the release of [3H]dopamine. Plantje JF, et al. **Eur J Pharmacol** 1985 Aug 27;114(3):401-2

Hyper-reactivity to amphetamine in rats with dopaminergic grafts. Herman JP, et al. **Exp Brain Res** 1985;60(3):521-6

Influence of cerebroventricular injection of dopamine on plasma prolactin and LH levels of postlaying and broody turkey hens. Hargis BM, et al. **Gen Comp Endocrinol** 1986 Jan;61(1):142-7

A biochemical study of cholinergic-dopaminergic interactions in the central nervous system. De Souza H, et al. **Gen Pharmacol** 1985; 16(5):533-6

The effects of estradiol and progesterone on the concentration of striatal dopamine and tyramine in ovariectomized mice. Yeung SC, et al. **Gen Pharmacol** 1985;16(5):517-9

Effect of dopamine on ACTH-induced glucocorticoid secretion in rat adrenal suspended cells. Matsuki M, et al. **Horm Metab Res** 1985 Aug; 17(8):429-31

Involvement of hypothalamic dopamine in the regulation of prolactin secretion. Reymond MJ, et al. **Horm Res** 1985;22(3):142-52 (76 ref.)

Bromocriptine treatment for cocaine abuse: the dopamine depletion hypothesis. Dackis CA, et al. **Int J Psychiatry Med** 1985-86; 15(2):125-35

Effects of chemical sympathectomy on dopamine and noradrenaline content of the dog gastrointestinal tract. Esplugues JV, et al. **J Auton Pharmacol** 1985 Sep;5(3):189-95

Hydroxyl radical attack on dopamine. Slivka A, et al. **J Biol Chem** 1985 Dec 15;260(29):15466-72

Calcium permeability changes and neurotransmitter release in cultured brain neurons. II. Temporal analysis of neurotransmitter release. Yarom M, et al. **J Biol Chem** 1985 Dec 25;260(30):16294-302

Determination of dopamine-3- and 4-O-sulphate in human plasma and urine by anion-exchange high-performance liquid chromatography with fluorimetric detection. Yamamoto T, et al. **J Chromatogr** 1985 Aug 9; 342(2):261-7

Increased dopaminergic inhibition of prolactin in the hypoprolactinaemic IPL nude rat. Cohen H, et al. **J Endocrinol** 1985 Dec;107(3):325-9

Dopamine decreases release of luteinizing hormone releasing hormone from superfused rat mediobasal hypothalamus. Tasaka K, et al.

J Endocrinol Invest 1985 Aug;8(4):373-6

Circadian regulation of retinomotor movements. I. Interaction of melatonin and dopamine in the control of cone length. Pierce ME, et al. **J Gen Physiol** 1985 Nov;86(5):671-89

3-Phenyl-1-indanamines. Potential antidepressant activity and potent inhibition of dopamine, norepinephrine, and serotonin uptake. Bøgesø KP, et al. **J Med Chem** 1985 Dec;28(12):1817-28

Comparative chronic effects of buspirone or neuroleptics on rat brain dopaminergic neurotransmission. McMillen BA. **J Neural Transm** 1985; 64(1):1-12

Detection of 5-S-cysteinyldopamine in human brain. Rosengren E, et al. **J Neural Transm** 1985;63(3-4):247-53

N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine increases acetylcholine and decreases dopamine in mouse striatum: both responses are blocked by anticholinergic drugs. Hadjiconstantinou M, et al. **J Neurochem** 1985 Dec;45(6):1957-9

Dopamine metabolites in rat cisternal cerebrospinal fluid: major contribution from extrastriatal dopamine neurones. Hutson PH, et al. **J Neurochem** 1986 Jan;46(1):186-90

Synthesis of gamma-glutamyldopamine and other peptidoamines in the nervous system of Aplysia californica. McCaman MW, et al. **J Neurochem** 1985 Dec;45(6):1828-35

Presynaptic dopamine autoreceptors control tyrosine hydroxylase activation in depolarized striatal dopaminergic terminals. el Mestikawy S, et al. **J Neurochem** 1986 Jan;46(1):12-22

Deprenyl protects dopamine neurons from the neurotoxic effect of 1-methyl-4-phenylpyridinium ion. Mytilineou C, et al. **J Neurochem** 1985 Dec;45(6):1951-3

Interactions between vasoactive intestinal peptide and dopamine in the rabbit retina: stimulation of a common adenylate cyclase. Pachter JA, et al. **J Neurochem** 1986 Jan;46(1):257-64

Chronic use of intracerebral dialysis for the in vivo measurement of 3,4-dihydroxyphenylethylamine and its metabolite 3,4-dihydroxyphenylacetic acid. Westerink BH, et al. **J Neurochem** 1986 Jan;46(1):181-5

Acute effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on dopamine metabolism in mouse and rat striatum. Pileblad E, et al. **J Pharm Pharmacol** 1985 Oct;37(10):707-11

Direct evidence for brain-specific release of dopamine from a redox delivery system. Simpkins JW, et al. **J Pharm Sci** 1985 Oct; 74(10):1033-6

Rapid tolerance to neuroleptic-induced stimulation of dopamine release in freely moving rats. Di Chiara G, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):487-94

Adrenergic and dopaminergic control of the canine paw microcirculation. Endean ED, et al. **J Surg Res** 1986 Jan;40(1):49-54

Dopamine and isoproterenol in imipramine intoxication in the dog. Sangster B, et al. **J Toxicol Clin Toxicol** 1985;23(4-6):407-20

Peripheral origin of plasma dopamine. Yoneda S, et al. **Jpn Circ J** 1985 Sep;49(9):1028-34

The inotropic effects of dopamine and its precursor levodopa on isolated human ventricular myocardium. Brown L, et al. **Klin Wochenschr** 1985 Nov 4;63(21):1117-23

Plasma and brain catecholamines in experimental uremia: acute and chronic studies. Ali F, et al. **Life Sci** 1985 Nov 11;37(19):1757-64

A comparison between dopamine-stimulated adenylate cyclase and 3H-SCH 23390 binding in rat striatum. Andersen PH, et al. **Life Sci** 1985 Nov 25;37(21):1971-83

Effects of L-dopa and L-tyrosine on release of free and conjugated dopamine, homovanillic acid and dihydroxyphenylacetic acid from slices of rat striatum. Tyce GM, et al. **Life Sci** 1985 Dec 23; 37(25):2439-48

The dopaminergic innervation of the intermediate lobe and of the neural lobe of the pituitary gland. Holzbauer M, et al. **Med Biol** 1985; 63(3):97-116 (131 ref.)

1-methyl-4-phenylpyridine is neurotoxic to the nigrostriatal dopamine pathway. Bradbury AJ, et al. **Nature** 1986 Jan 2-8;319(6048):56-7

Is inhibition of striatal synaptosomal tyrosine hydroxylation by dopamine agonists a measure of dopamine autoreceptor function? Fowler CJ, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):12-9

Striatal dopamine and motor activity changes observed shortly after lithium administration. Otero Losada ME, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Sep;330(3):169-74

Acute restraint stress decreases dopamine synthesis and turnover in the median eminence: a model for the study of the inhibitory neuronal influences on tuberoinfundibular dopaminergic neurons. Demarest KT, et al. **Neuroendocrinology** 1985 Nov;41(5):437-44

Acute restraint stress decreases tuberoinfundibular dopaminergic neuronal activity: evidence for a differential response in male versus female rats. Demarest KT, et al. **Neuroendocrinology** 1985 Dec;41(6):504-10

Absence of inhibitory dopaminergic control of the rabbit pituitary gland intermediate lobe. Schimchowitsch S, et al. **Neuroendocrinology** 1986; 42(1):71-4

Mesolimbic dopamine lesions produce an augmented behavioral response to enkephalin. Kalivas PW, et al. **Neuropharmacology** 1985 Oct; 24(10):931-6

Cathinone affects dopamine and 5-hydroxytryptamine neurons in vivo as measured by changes in metabolites and synthesis in four forebrain regions in the rat. Nielsen JA. **Neuropharmacology** 1985 Sep; 24(9):845-52

The discriminant dopamine antagonist property of benzamides is observed at various times after their systemic or intracerebroventricular administration. Protais P, et al. **Neuropharmacology** 1985 Sep; 24(9):861-7

Drug-induced field potential changes in dopaminergic target areas after electrical stimulation of the rat mesencephalon. Dimpfel W. **Neuropsychobiology** 1985;14(1):42-52

Interactions between neuropeptides and dopamine neurons in the ventromedial mesencephalon. Kalivas PW. **Neurosci Biobehav Rev** 1985 Winter;9(4):573-87 (216 ref.)

Dopamine and thermoregulation: an evaluation with special reference to dopaminergic pathways. Lee TF, et al. **Neurosci Biobehav Rev** 1985 Winter;9(4):589-98

Effects of neurotoxic and mechanical lesions of the mesostriatal dopamine pathway on striatal polyamine levels in the rat: modulation by chronic ganglioside GM1 treatment. Agnati LF, et al. **Neurosci Lett** 1985 Nov 11;61(3):339-44

Tyrosine availability determines stimulus-evoked dopamine release from rat striatal slices. Milner JD, et al. **Neurosci Lett** 1985 Aug 30; 59(2):215-20

Kindling of dopaminergic pathways modifies the effect of substantia nigra lesions on rotational behaviour. Mintz M, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):7-11

Dopamine uptake blockers protect against the dopamine depleting effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the mouse striatum. Ricaurte GA, et al. **Neurosci Lett** 1985 Sep 6;59(3):259-64

Ascorbic acid does not modulate stimulated dopamine release: in vivo voltammetric data in the rat. Stamford JA, et al. **Neurosci Lett** 1985 Oct 10;60(3):357-62

Changes in catecholamine concentrations in the hypothalamus and region of the midbrain raphe in male and female rats during postnatal development. Stanley HF, et al. **Neurosci Lett** 1985 Nov 20; 62(1):75-80

Evidence for species differences between rats and gerbils in striatal dopamine content and dopamine metabolism. Upchurch M. **Neurosci Lett** 1985 Aug 30;59(2):159-63

Effects of dopamine superfusion on the activity of rabbit carotid chemoreceptors in vitro. Leitner LM, et al. **Neuroscience** 1985 Oct; 16(2):431-8

Responses of rat pallidum cells to cortex stimulation and effects of altered dopaminergic activity. Toan DL, et al. **Neuroscience** 1985 Jul; 15(3):683-94

Regulation of biosynthesis and release of pars intermedia peptides in Rana ridibunda: dopamine affects both acetylation and release of alpha-MSH. Jenks BG, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):913-21

Food-related stimuli increase the ratio of 3,4-dihydroxyphenylacetic acid to dopamine in the hypothalamus. Simansky KJ, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):253-8

Phencyclidine-induced dopamine-dependent behaviors in chronic haloperidol-treated rats. Yamaguchi K, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):803-9

Dopaminergic behavior in frontal decorticated rats. Itoh S, et al. **Physiol Behav** 1985 Jul;35(1):109-12

Effects of dopamine agonists on hypothalamic defensive attack in cats. Maeda H, et al. **Physiol Behav** 1985 Jul;35(1):89-92

Hungarian and Polish Pharmacological Societies. 7th joint symposium: Dopamine. Zakopane 12-15 September 1984, Poland. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):227-443

Dopaminergic inhibition of sympathetic activity in the cat. Doda M, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):397-404

Effect of dopamine on the transmembrane potentials of guinea-pig heart preparations. Kecskemeti V, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):411-9

Depolarisation-evoked release of dopamine and histamine from brain tissue and studies on presynaptic dopamine-histamine interaction. Nowak JZ. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):359-81 (111 ref.)

Mesolimbic noradrenaline but not dopamine is responsible for organization of rat behavior in the forced swim test and an anti-immobilizing effect of desipramine. Plaźnik A, et al. **Pol J Pharmacol Pharm** 1985 May-Jun; 37(3):347-57

Stimulation of hippocampal dopaminergic receptors: behavioral and electrophysiological effects. Smiałowski A. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):333-45

Taurine and its derivatives alter brain dopamine metabolism similarly to GABA in mice and rats. Ahtee L, et al. **Prog Clin Biol Res** 1985; 179:331-41

Behavioral evidence for cholecystokinin modulation of dopamine in the mesolimbic pathway. Crawley JH. **Prog Clin Biol Res** 1985; 192:131-8

Substance P modulation of the mesolimbic dopamine system. Kalivas P. **Prog Clin Biol Res** 1985;192:403-8

ACTH1-24 effects on d-amphetamine self-administration and the dynamics of brain dopamine in rats. Leccese AP, et al. **Prog Clin Biol Res** 1985;192:71-81

Cholecystokinin-dopamine receptor interactions as studied with cholecystokinin receptor antagonists. Murphy RB. **Prog Clin Biol Res** 1985;192:105-13

Electrophysiological effects of cholecystokinin: central dopaminergic systems. Wang RY, et al. **Prog Clin Biol Res** 1985;192:95-103

Cerebrospinal fluid monoamine and monoamine metabolite concentrations in melancholia. Roy A, et al. **Psychiatry Res** 1985 Aug;15(4):281-92

The effects of pimozide on the establishment of conditioned reinforcement as a function of the amount of conditioning. Hoffman DC, et al. **Psychopharmacology (Berlin)** 1985;87(4):454-60

Neurotensin effect on calcium transport and dopamine release in rat striatum. Battaini F, et al. **Regul Pept [Suppl]** 1985;4:188-90

Failure of branched-chain amino acids to affect synaptosomal uptake of norepinephrine and dopamine. Cobert BJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Dec;50(3):455-8

[Adrenaline, noradrenaline and dopamine excretion and anxiety levels in surgical patients] Barham O, et al. **Arch Psychol (Frankf)** 1985; 137(4):291-5 (Eng. Abstr.) **(Ger)**

[Effect of ibopamine on the renal functional response to extracellular volume expansion in man] Agnoli GC, et al. **Cardiologia** 1985 Feb; 30(2):129-37 (Eng. Abstr.) **(Ita)**

[Strain gauge plethysmography in the evaluation of the effect of acute administration of ibopamine on the peripheral circulation of normal subjects] Longhini C, et al. **Cardiologia** 1982 Dec;27(12):1189-95 (Eng. Abstr.) **(Ita)**

[Effects of ibopamine on the peripheral circulation of normal subjects after protracted administration] Musacci GF, et al. **Cardiologia** 1982 Dec;27(12):1171-5 (Eng. Abstr.) **(Ita)**

[Antagonism of sulpiride to the action of ibopamine at the level of peripheral circulation] Musacci GF, et al. **Cardiologia** 1932 Dec; 27(12):1163-9 (Eng. Abstr.) **(Ita)**

[The effects of dopamine on the release of immunoreactive beta-endorphin-like peptide from the dispersed cells of the rat neurointermediate lobe] Furuki Y, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jul 20;61(7):744-52 (Eng. Abstr.) **(Jpn)**

[Dopamine, its regulation of hormone secretion and its clinical significance] Yoshimura M. **Rinsho Byori** 1985 May;33(5):509-12 **(Jpn)**

[Distribution of thyrotropin releasing hormone in the mouse brain and effects of various amines--immunohistochemical study] Senda Y, et al. **Rinsho Shinkeigaku** 1985 Aug;25(8):973-81 (Eng. Abstr.) **(Jpn)**

[Effect of dopamine and dopamine mimetics on Na, K-ATPase of corpus striatum synaptosomes] Komissarov IV, et al. **Biull Eksp Biol Med** 1985 Oct;100(10):400-3 (Eng. Abstr.) **(Rus)**

[Role of cyclic AMP in the action of dopamine on the spontaneous and glutamate-induced activity of neostriatal neurons in the rat] Godukhin OV, et al. **Neirofiziologiia** 1985;17(5):614-9 (Eng. Abstr.) **(Rus)**

DOPAMINE BETA-HYDROXYLASE

Effects of calcium and limited proteolysis on membrane-bound and releasable dopamine beta-hydroxylase in adrenomedullary catecholamine granules. Helle KB, et al. **Acta Physiol Scand** 1985 Nov; 125(3):423-7

Fumarate is the cause of the apparent ping-pong kinetics of dopamine beta-hydroxylase. Palatini P. **Biochem Int** 1985 Oct;11(4):565-72

Inhibition of the retrograde axonal transport of dopamine-beta-hydroxylase antibodies by the calcium ionophore A23187. Lees GJ. **Brain Res** 1985 Oct 14;345(1):62-7

Sympathoadrenal activity and plasma glucose effects on plasma dopamine-beta-hydroxylase levels in rats. Muñoz JA, et al. **Clin Chim Acta** 1985 Nov 15;152(3):243-52

Segregation analysis of dopamine-beta-hydroxylase (DBH) and catechol-O-methyltransferase (COMT): identification of major locus and polygenic components. Goldin LR. **Genet Epidemiol** 1985; 2(3):317-25

Distribution of dopamine-beta-hydroxylase-like immunoreactivity in the rat pineal organ. Schröder H, et al. **Histochemistry** 1985; 83(4):375-80

Differential roles of raphe nuclei in the regulation of dopamine beta-hydroxylase in the adrenal gland of the rat. Lima L, et al. **J Neurochem** 1986 Jan;46(1):317-20

Plasma norepinephrine, epinephrine, and dopamine beta-hydroxylase activity during exercise in man. Péronnet F, et al. **Med Sci Sports Exerc** 1985 Dec;17(6):683-8

Cell nuclear accumulation of estrogen receptors in rat brain and pituitary gland after treatment with a dopamine-beta-hydroxylase inhibitor. Blaustein JD. **Neuroendocrinology**, 1986;42(1):44-50

Cysteamine effects on monoamines, dopamine-beta-hydroxylase and the hypothalamic-pituitary axis. Terry LC, et al. **Neuroendocrinology** 1985 Dec;41(6):467-75

Genes for neurotransmitter synthesis, storage and release. Joh TH. **Prog Clin Biol Res** 1985;192:423-9

DOXEPIN

Excretion of doxepin and N-desmethyldoxepin in human milk. Kemp J, et al. **Br J Clin Pharmacol** 1985 Nov;20(5):497-9

DRUG SCREENING

Distress vocalization in rat pups. A simple screening method for anxiolytic drugs. Gardner CR. **J Pharmacol Methods** 1985 Nov;14(3):181-7

ELECTROCONVULSIVE THERAPY

ECT versus tricyclic antidepressants [letter] Fogel BS. **Am J Psychiatry** 1986 Jan;143(1):121-2

Adrenergic receptors in depression. Effects of electroconvulsive therapy. Cooper SJ, et al. **Br J Psychiatry** 1985 Jul;147:23-9

Empirical study on an inpatient psychogeriatric unit: biological treatment in patients with depressive illness. Meyers BS, et al. **Int J Psychiatry Med** 1985-86;15(2):111-24

Noninvasive assessment of electroconvulsive-induced changes in cardiac function. Mulgaokar GD, et al. **J Clin Psychiatry** 1985 Nov; 46(11):479-82

The efficiency of ECT: II. Correlation of specific treatment variables to response rate in unilateral ECT. Rich CL, et al. **Psychiatry Res** 1985 Oct;16(2):147-54

MHPG excretion in endogenous depression: relationship to clinical state and the effects of ECT. Joseph MH, et al. **Psychopharmacology (Berlin)** 1985;87(4):442-8

ELECTROENCEPHALOGRAPHY

A study of the mediator spectrum of delta-9 tetrahydrocanabinol effects on cerebral bioelectric activity. Machula AI, et al. **Drug Alcohol Depend** 1985 Aug;15(4):383-8

Sleep and electroencephalography: points of interest and points of controversy. Guilleminault C, et al. **J Clin Neurophysiol** 1984 Jul; 1(3):275-91 (115 ref.)

The effects of entorhinal cortex lesions on type 1 and type 2 theta. Montoya CP, et al. **Physiol Behav** 1985 Jul;35(1):121-6

Effect of propranolol on brain electrical activity during hyperbaric oxygenation in the rat. Torbati D. **Undersea Biomed Res** 1985 Dec; 12(4):423-9

[Influence of intracaudate injection of muscimol on the conditioning performance and EEG in rabbits] Huang YY, et al. **Chung Kuo Yao Li Hsueh Pao** 1985 Jun;6(2):77-8 (Eng. Abstr.) **(Chi)**

[The activating effect of MCI-2016 (bifemelane hydrochloride) on EEG in cats] Egawa M, et al. **No To Shinkei** 1985 Aug;37(8):759-65 (Eng. Abstr.) **(Jpn)**

[Effects of phenobarbital on EEG and sensory evoked potentials in normal cat brain] Takaya M, et al. **No To Shinkei** 1985 Aug;37(8):785-90 (Eng. Abstr.) **(Jpn)**

[Importance of superslow activity of brain structures to the stability of engrams and the effects of neurotropic substances] Lapina IA. **Vestn Akad Med Nauk SSSR** 1985;(9):38-40 (Eng. Abstr.) **(Rus)**

[Relation between the dynamics of EEG indices after a single dose of the tranquilizer phenazepam and its efficacy during a course of treatment of patients with borderline neuropsychological disorders] Uvarova LG, et al. **Zh Nevropatol Psikhiatr** 1985;85(11):1701-9 (Eng. Abstr.) **(Rus)**

ELECTROLYTES

Characterization of a Na : K : 2C1 cotransport system in the apical membrane of a renal epithelial cell line (LLC-PK1). Brown CD, et al. **J Membr Biol** 1985;87(2):131-9

Endocrine control of renal handling of solutes and water in vertebrates. Nishimura H. **Renal Physiol** 1985;8(4-5):279-300 (125 ref.)

EMOTIONS

[Effect of diazepam, meprobamate and amizyl on the emotional reactions of the rabbit to hypothalamic stimulation] Davituliani DS, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):952-6 (Eng. Abstr.) **(Rus)**

ENDORPHINS

Sex-dependent effects of neonatally administered morphiceptin and D-ala-D-leu-enkephalin on maze learning in rats. de Avila A, et al. **Behav Neural Biol** 1985 Nov;44(3):393-402

Action of (D-Pro4)-beta-casomorphin1-5 on processes of synaptic transmission. Kammerer E, et al. **Biomed Biochim Acta** 1985; 44(9):1379-87

Biosynthesis of beta-endorphin in pancreatic islets of neonatal Wistar rats. Niendorf WR, et al. **Biomed Biochim Acta** 1985;44(9):K51-4

Effects of beta-casomorphin on dentate hippocampal field potentials in freely moving rats. Reymann KG, et al. **Biomed Biochim Acta** 1985; 44(5):749-54

The interaction of endogenous opiates with autonomic circulatory control in the dog. Caffrey JL, et al. **Circ Shock** 1985;17(3):233-42

The effects of acclimation temperature on pituitary and plasma beta-endorphin in rats at 32.5 degrees C. Gwosdow AR, et al. **Comp Biochem Physiol [C]** 1985;82(2):269-72

Gastroduodenal bicarbonate secretion in mucosal protection. Possible role of vasoactive intestinal peptide and opiates. Flemström G, et al. **Dig Dis Sci** 1985 Nov;30(11 Suppl):63S-68S

gamma-Endorphin-generating endopeptidase: distribution in body tissues and cellular localization in rat testis. Lebouille JL, et al. **Endocrinology** 1986 Jan;118(1):372-6

gamma-Aminobutyric acid inhibits beta-endorphin secretion from the anterior pituitary but not the neurointermediate lobe in the rat. Petraglia F, et al. **Endocrinology** 1986 Jan;118(1):360-6

Proopiomelanocortin-derived peptides in testicular interstitial fluid: characterization and changes in secretion after human chorionic gonadotropin or luteinizing hormone-releasing hormone analog treatment. Valenca MM, et al. **Endocrinology** 1986 Jan;118(1):32-7

Beta-endorphin and met-enkephalin in peritoneal and ovarian follicular fluids of fertile and postmenopausal women. Petraglia F, et al. **Fertil Steril** 1985 Nov;44(5):615-21

Occurrence of beta-endorphin-like immunoreactivity in the brain of the teleost, Boops boops. Vallarino M. **Gen Comp Endocrinol** 1985 Oct;60(1):63-9

Effects of chronically elevated intake of sweet solutions on sexual behavior of male rats. Lieblich I, et al. **Horm Behav** 1985 Sep;19(3):278-91

Dexamethasone suppresses cortisol but not ACTH and beta-endorphin plasma concentration in healthy man. Lypka A, et al. **Horm Metab Res** 1985 Oct;17(10):547

Influence of beta-endorphin on phytohemagglutinin-induced lymphocyte proliferation and on the expression of mononuclear cell surface antigens in vitro. Puppo F, et al. **Immunopharmacology** 1985 Oct;10(2):119-25

Studies on opioid receptor selectivity of beta-endorphin antagonists. Hammonds RG Jr, et al. **Int J Pept Protein Res** 1985 Aug;26(2):118-20

Distinct behavior of beta-endorphin and corticotropin toward leucine aminopeptidase action. Li CH, et al. **Int J Pept Protein Res** 1985 Aug;26(2):113-7

Comparison of the effect of insulin hypoglycemia and clonidine on secretion of growth hormone, cortisol and beta-endorphin in children and adolescents. Gil-Ad I, et al. **Isr J Med Sci** 1985 Nov;21(11):912-4

Dermorphin reduces the metyrapone-evoked release of adrenocorticotropin, beta-endorphin, and beta-lipotropin in man. Degli Uberti EC, et al. **J Clin Endocrinol Metab** 1985 Dec;61(6):1018-22

Time of origin of opioid peptide-containing neurons in the rat hypothalamus. Khachaturian H, et al. **J Comp Neurol** 1985 Jun 22;236(4):538-46

Endogenous opioid peptides and hypothalamic neuroendocrine neurones. Bicknell RJ. **J Endocrinol** 1985 Dec;107(3):437-46 (100 ref.)

Endogenous opioids and related peptides: from molecular biology to clinical medicine. The Sir Henry Dale lecture for 1985. Imura H, et al. **J Endocrinol** 1985 Nov;107(2):147-57

Effect of alpha-endorphin on the antigen-induced primary antibody response of human blood B cells in vitro. Heijnen CJ, et al. **J Immunol** 1986 Jan;136(1):213-6

Synthesis and activity profiles of novel cyclic opioid peptide monomers and dimers. Schiller PW, et al. **J Med Chem** 1985 Dec;28(12):1766-71

Purification of peptides derived from proenkephalin A on Bio-Rex 70. Wilson SP. **J Neurosci Methods** 1985 Oct-Nov;15(2):155-63

Regulation of beta-endorphin and ACTH in brain by estradiol. Wardlaw SL, et al. **Life Sci** 1985 Nov 18;37(20):1941-7

Menopausal syndrome: plasma levels of beta-endorphin in post-menopausal women measured by a specific radioimmunoassay. Aleem FA, et al. **Maturitas** 1985 Nov;7(4):329-34

Has morphine a physiological function in the animal kingdom? [news] Kosterlitz HW. **Nature** 1985 Oct 24-30;317(6039):671-2

Effect of indolamines on beta-endorphin release by rat anterior pituitary cells. Abou Samra AB, et al. **Neuroendocrinology** 1985 Dec;41(6):490-3

A subset of beta-endorphin- or dynorphin-containing neurons in the medial basal hypothalamus accumulates estradiol. Morrell JI, et al. **Neuroendocrinology** 1985 Nov;41(5):417-26

Metabolic profiling of opioid peptides in tooth pulp by HPLC and radioreceptor assay. Desiderio DM, et al. **Neuropeptides** 1985 Sep;6(5):463-9

Depletion of noradrenaline in the hypothalamus reduces the febrile responses induced by prostaglandin E2, thyrotropin-releasing hormone and beta-endorphin in rats. Lin MT, et al. **Neuropharmacology** 1985 Nov;24(11):1039-42

Opioid activity of pro-enkephalin-derived peptides in mouse vas deferens and guinea pig ileum. Sánchez-Blázquez P, et al. **Neurosci Lett** 1985 Nov 11;61(3):267-71

Contrast medium cause the apparent increase in beta-endorphin levels in human CSF following brain stimulation [letter] Akil H, et al. **Pain** 1985 Nov;23(3):301-4

Characterization of opioid peptides from maternal and fetal sheep adrenal glands. Dunlap CE 3d, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):483-9

Mediation by gonadal steroids of plasma beta-endorphin and LH in castrated female and male rats. Forman LJ, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):835-9

Acetylation of alpha MSH and beta-endorphin by rat neurointermediate pituitary secretory granule-associated acetyltransferase. Gibson TR, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):615-20

Experimental dissociation of food intake and plasma beta-endorphin following 2-deoxy-D-glucose in rats. Lowy MT, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):569-73

Continuous social defeat induces an increase of endogenous opioids in discrete brain areas of the mongolian gerbil. Raab A, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):387-91

Demonstration of beta-casomorphin immunoreactive materials in in vitro digests of bovine milk and in small intestine contents after bovine milk ingestion in adult humans. Svedberg J, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):825-30

Effect of oral contraceptives on the rat brain and pituitary opioid peptides. Tejwani GA, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):555-61

Degradation of alpha and beta neo-endorphin by rat brain membrane peptidases. Ulrich C, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):475-82

Des-Tyr1-gamma-endorphin (DT gamma E) and des-enkephalin-gamma-endorphin (DE gamma E): plasma profile and brain uptake after systemic administration in the rat. Verhoef JC, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):467-74

Endocoids. Proceedings of an International Symposium. Fort Worth, Texas, May 23-26, 1984. **Prog Clin Biol Res** 1985;192:1-541

Brain endocoid identification as a strategy for the development of a new generation of psychoactive drugs. Costa E. **Prog Clin Biol Res** 1985;192:29-36

Identification and secretion of gamma-endorphin and beta-endorphin-like peptides from the neurointermediate pituitary of the rat. Dorsa DM, et al. **Prog Clin Biol Res** 1985;192:285-92

Behavioral effects of cholecystokinin and its related peptides in rats. Itoh S, et al. **Prog Clin Biol Res** 1985;192:139-45

Opiate receptor mediated effects of IFN-alpha and lymphocyte derived endorphin-like peptides. Smith EM, et al. **Prog Clin Biol Res** 1985;192:259-64

Behavioral effects of non-opioid fragments of beta-endorphin. van Ree JM, et al. **Prog Clin Biol Res** 1985;192:277-84

Different pattern of association of beta-endorphin and cortisol responses to dextroamphetamine in postmenopausal women and young men. Halbreich U, et al. **Psychiatry Res** 1985 Sep;16(1):11-9

Demonstration of a beta-casomorphin immunoreactive material in the plasma of newborn calves after milk intake. Umbach M, et al. **Regul Pept** 1985 Nov 7;12(3):223-30

Effect of a beta-casomorphin analog on ion transport in rabbit ileum: evidence for a cholinergic mediation. Hautefeuille M, et al. **Regul Pept [Suppl]** 1985;4:219-20

Recent developments in the bioassay of opioids. Kosterlitz HW, et al. **Regul Pept [Suppl]** 1985;4:1-7

Changes of plasma beta-endorphin like immunoreactivity induced by aging. Laorden ML, et al. **Rev Esp Fisiol** 1985 Sep;41(3):357-8

[Biosynthesis of endogenous opiates] Haubold G. **Med Monatsschr Pharm** 1985 Oct;8(10):301-3 (Eng. Abstr.) **(Ger)**

[The effects of dopamine on the release of immunoreactive beta-endorphin-like peptide from the dispersed cells of the rat neurointermediate lobe] Furuki Y, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jul 20;61(7):744-52 (Eng. Abstr.) **(Jpn)**

[The study of opioid peptides in the normal menstrual cycle, pregnancy and labor] Takayama S, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Sep;37(9):1813-9 (Eng. Abstr.) **(Jpn)**

[The immunologic and enkephalin-endorphin systems] Chmielarczyk W, et al. **Pol Tyg Lek** 1985 Sep 8;40(36):1027-30 (60 ref.) **(Pol)**

[Beta-endorphin-like immunoreactivity of the blood plasma of hamadryas baboons and its changes] Golanov EV, et al. **Biull Eksp Biol Med** 1985 Dec;100(12):677-9 (Eng. Abstr.) **(Rus)**

[Levels of 5-HIAA and beta-endorphin in CSF after intrathecal morphine] González Navarro A, et al. **Arch Neurobiol (Madr)** 1985 Jul-Aug;48(4):211-3 (Eng. Abstr.) **(Spa)**

ENKEPHALIN, LEUCINE

Enkephalin degradation by human erythrocytes and hemolysates studied using 1H NMR spectroscopy. Vandenberg JI, et al. **Arch Biochem Biophys** 1985 Nov 1;242(2):515-22

Sex-dependent effects of neonatally administered morphiceptin and D-ala-D-leu-enkephalin on maze learning in rats. de Avila A, et al. **Behav Neural Biol** 1985 Nov;44(3):393-402

Hydrolysis of leucine enkephalin in the nasal cavity of the rat--a possible factor in the low bioavailability of nasally administered peptides. Hussain A, et al. **Biochem Biophys Res Commun** 1985 Dec 31;133(3):923-8

Opioid peptides in rat islets of Langerhans. Immunoreactive met- and leu-enkephalins and BAM-22P. Timmers KI, et al. **Diabetes** 1986 Jan;

35(1):52-7

Leucine-enkephalin-like immunoreactive fibers in the medial preoptic area of the rat: their distribution and origin. Yamano M, et al. **Exp Brain Res** 1985;60(3):535-41

Some species differences in cardiovascular responses to intravenously injected leucine-enkephalin. Koyama S, et al. **Experientia** 1985 Nov 15;41(11):1394-6

High-performance liquid chromatographic analysis of pulmonary metabolites of Leu- and Met-enkephalins in isolated perfused rat lung. Crooks PA, et al. **J Pharm Sci** 1985 Sep;74(9):1010-2

Enkephalin binding systems in human plasma. II: Leu-enkephalin serum albumin interaction. De Marco V, et al. **Neurochem Res** 1985 Oct;10(10):1355-69

Mechanisms of leu-enkephalin hydrolysis in human plasma. Roscetti G, et al. **Neurochem Res** 1985 Oct;10(10):1393-404

Regional differences in mu 1-binding of [3H][D-Ala2,D-Leu5]-enkephalin: comparisons of thalamus and cortex in the rat. Goodman RR, et al. **Neurosci Lett** 1985 Aug 30;59(2):155-8

Leucine-enkephalin-like immunoreactive afferent fibers to pudendal motoneurons in the cat. Konishi A, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):109-13

[Effect of enkephalins on morphologic and hormonal manifestations of the stress reaction] Lishmanov IuB, et al. **Patol Fiziol Eksp Ter** 1985 Sep-Oct;(5):14-7 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, METHIONINE

Sex-dependent effects of neonatally administered morphiceptin and D-ala-D-leu-enkephalin on maze learning in rats. de Avila A, et al. **Behav Neural Biol** 1985 Nov;44(3):393-402

Calorimetric and fluorescence characterization of interactions between enkephalins and liposomal and synaptic plasma membranes containing gangliosides. Myers M, et al. **Biochemistry** 1985 Jul 16;24(15):4076-82

Central effects of D-Ala2-met-enkephalinamide on the blood pressure of rats after central chemical sympathectomy or serotoninectomy. Brus R, et al. **Biomed Biochim Acta** 1985;44(5):779-83

Distribution of enkephalin-immunoreactive neurons in the forebrain and upper brainstem of the squirrel monkey. Inagaki S, et al. **Brain Res** 1985 Dec 16;359(1-2):267-80

Interaction between epinephrine, prostaglandin E, and met-enkephalin in the regulation of insulin release in man. Giugliano D, et al. **Diabete Metab** 1985 Oct;11(5):295-302

Opioid peptides in rat islets of Langerhans. Immunoreactive met- and leu-enkephalins and BAM-22P. Timmers KI, et al. **Diabetes** 1986 Jan;35(1):52-7

Beta-endorphin and met-enkephalin in peritoneal and ovarian follicular fluids of fertile and postmenopausal women. Petraglia F, et al. **Fertil Steril** 1985 Nov;44(5):615-21

Photoreactive enkephalin analogue: [D-Ala2, p-N3-Phe4-Met5]-enkephalin. Synthesis, purification by high performance liquid chromatography and characterization. Yeung CW. **Int J Pept Protein Res** 1985 Jul;26(1):63-9

High-performance liquid chromatographic analysis of pulmonary metabolites of Leu- and Met-enkephalins in isolated perfused rat lung. Crooks PA, et al. **J Pharm Sci** 1985 Sep;74(9):1010-2

Somatostatin, substance P and [Lys]-vasopressin interfere with the binding of [3H][D-Ala2, Met5]enkephalinamide to rat brain membranes. Maruyame M. **Jpn J Pharmacol** 1985 Aug;38(4):445-7

Mesolimbic dopamine lesions produce an augmented behavioral response to enkephalin. Kalivas PW, et al. **Neuropharmacology** 1985 Oct;24(10):931-6

Adrenal release of catecholamines and Met-enkephalin before and after stress as measured by a novel in vivo dialysis method in the rat. Jarry H, et al. **Neurosci Lett** 1985 Oct 10;60(3):273-8

Response of plasma proenkephalin peptide F to exercise. Kraemer W, et al. **Peptides (Fayetteville)** 1985;6 Suppl 2:167-9

Satiety, hunger and regional brain content of cholecystokinin/gastrin and met-enkephalin immunoreactivity in sheep. Scallet AC, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):937-43

Do neuropeptide systems mediate some of the effects of antipsychotic drugs? Bissette G, et al. **Prog Clin Biol Res** 1985;192:349-53

Reinforcing stimulus properties of endocoids. Goeders NE, et al. **Prog Clin Biol Res** 1985;192:63-9

[Met-enkephalin-Arg-Gly-Leu-like immunoreactivity-containing nerve elements in the guinea-pig intestine. An immunohistochemical study using whole mount preparations] Shimosegawa T, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Aug 20;61(8):802-15 (Eng. Abstr.) **(Jpn)**

ENKEPHALINS

NADH-dehydrogenase reaction in combination with immunoperoxidase (PAP) staining for light microscopic observation on the interneuronal relations of the enteric nervous system of the pig. Scheuermann DW, et al. **Acta Anat (Basel)** 1985;124(1-2):31-4

Decreased plasma enkephalins in copper deficiency in man. Bhathena SJ, et al. **Am J Clin Nutr** 1986 Jan;43(1):42-6

Electron microscopic localization of N-terminal proenkephalin (synenkephalin) immunostaining in the guinea pig organ of Corti. Eybalin M, et al. **Brain Res** 1985 Dec 9;358(1-2):354-9

The coexistence of two neuroactive peptides in a subpopulation of retinal amacrine cells. Li HB, et al. **Brain Res** 1985 Oct 14;345(1):176-80

In vitro and in vivo effects of kelatorphan on enkephalin metabolism in rodent brain. Waksman G, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):233-43

High enkephalyl peptide degradation, due to angiotensin-converting enzyme-like activity in human CSF. Lantz I, et al. **FEBS Lett** 1985 Nov 25;193(1):31-4

Delta and mu opiate receptor probes: fluorescent enkephalins with high receptor affinity and specificity. Mihara H, et al. **FEBS Lett** 1985 Nov 25;193(1):35-8

Immunohistochemistry of beta-neoendorphin and dynorphin in the endocrine pancreas of rat and man. Cetin Y. **Histochemistry** 1985;83(4):369-73

Localization of enkephalin-like immunoreactive amacrine cells in the larval tiger salamander retina: a light and electron microscopic study. Watt CB, et al. **J Comp Neurol** 1985 Nov 8;241(2):171-9

Co-localization and characterization of immunoreactive peptides derived from two opioid precursors in guinea pig adrenal glands. Evans CJ, et al. **J Neurosci** 1985 Dec;5(12):3423-7

Reserpine changes the dynamic state of enkephalin stores in rat striatum and adrenal medulla by different mechanisms. Mocchetti I, et al. **J Neurosci** 1985 Dec;5(12):3379-85

Purification of peptides derived from proenkephalin A on Bio-Rex 70. Wilson SP. **J Neurosci Methods** 1985 Oct-Nov;15(2):155-63

Enkephalin-degrading activity in arthropode hemolymphe. Coletti-Previero MA, et al. **Neuropeptides** 1985 Sep;6(5):405-15

Elevated potassium stimulates enkephalin biosynthesis in bovine chromaffin cells. Siegel RE, et al. **Neuropeptides** 1985 Dec;6(6):543-52

Detection of preprocholecystokinin and preproenkephalin A mRNAs in rat brain by hybridization histochemistry using complementary RNA probes. Siegel RE, et al. **Neuropeptides** 1985 Dec;6(6):573-80

Isolation and characterization of an enkephalin-hydrolyzing dipeptidyl-aminopeptidase from calf-brain striatum. van Buuren KJ, et al. **Neuropeptides** 1985 Sep;6(5):381-9

Localization of peptides in nerve terminals in the paracervical ganglion of the rat by light and electron microscopic immunohistochemistry: enkephalin and atrial natriuretic factor. Papka RE, et al. **Neurosci Lett** 1985 Nov 11;61(3):285-90

Distribution of human leumorphin-like immunoreactivity in the monkey spinal cord revealed by immunocytochemistry. Uda K, et al. **Neurosci Lett** 1985 Nov 20;62(1):39-44

Steady state levels of pro-dynorphin-related end products in the striatum and substantia nigra of the adult rhesus monkey. Dores RM, et al. **Peptides (Fayetteville)** 1985;6 Suppl 2:143-8

Prodynorphin peptide immunocytochemistry in rhesus monkey brain. Khachaturian H, et al. **Peptides (Fayetteville)** 1985;6 Suppl 2:155-66

Expression of preproenkephalin-like mRNA and its peptide products in mammalian testis and ovary. Kilpatrick DL, et al. **Proc Natl Acad Sci USA** 1985 Nov;82(21):7467-9

Depolarization regulates adrenal preproenkephalin mRNA. LaGamma EF, et al. **Proc Natl Acad Sci USA** 1985 Dec;82(23):8252-5

[Molecular structures of preproenkephalins and nicotinic acetylcholine receptor] Noda M. **Seikagaku** 1985 Jun;57(6):447-71 (100 ref.) **(Jpn)**

[Cytochemical research on the effect of a synthetic enkephalin analog on the protein content and enzyme activity of neurons] Gershtein LM, et al. **Tsitologiia** 1985 Sep;27(9):1059-63 (Eng. Abstr.) **(Rus)**

ENURESIS

Maprotiline in nocturnal enuresis [letter] Gillman MA, et al. **J Clin Psychiatry** 1985 Dec;46(12):546

Successful treatment of nocturnal enuresis: a practical approach. Maizels M, et al. **Primary Care** 1985 Dec;12(4):621-35 (45 ref.)

Terodiline in children with diurnal enuresis. Elmér M. **Scand J Urol Nephrol [Suppl]** 1984;87:59-61

[Sydnocarb as the method of choice in persistent enuresis? Findings after 2 years of administration] Simlová M, et al. **Cesk Psychiatr** 1985 Oct;81(5):312-3 (Eng. Abstr.) **(Cze)**

EPHEDRINE

Determination of sodium, ephedrine and procaine in pharmaceuticals by capillary isotachophoresis. Fanali S, et al. **J Chromatogr** 1985 Aug 23;330(2):436-8

Cardiovascular teratogenicity of ephedrine in chick embryos. Nishikawa T, et al. **Toxicol Lett** 1985 Dec;29(1):59-63

[Bronchomotor effects of (-) ephedrine, (+/-) ephedrine and (+) pseudoephedrine in guinea pigs] Floch A, et al. **Ann Pharm Fr** 1985;43(1):31-8 (Eng. Abstr.) **(Fre)**

[Development of reverse tolerance to the ambulation-increasing effect of ephedrine after repeated administration in mice] Hirabayashi M, et al. **Yakubutsu Seishin Kodo** 1985 Sep;5(3):231-41 (Eng. Abstr.) **(Jpn)**

EPINEPHRINE

Comparison of adrenaline and phenylephrine in out-of-hospital cardiopulmonary resuscitation. A double-blind study. Silfvast T, et al. **Acta Anaesthesiol Scand** 1985 Aug;29(6):610-3

Anxiety and epinephrine in multiparous women in labor: relationship to duration of labor and fetal heart rate pattern. Lederman RP, et al. **Am J Obstet Gynecol** 1985 Dec 15;153(8):870-7

Potentiation of hemorrhage-evoked catecholamine release by prior blood loss in cats. Bereiter DA, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 1):E18-23

Effect of rate of hemorrhage on sympathoadrenal catecholamine release in cats. Bereiter DA, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 1):E69-75

Interaction of prolactin with adrenal hormones in blood pressure regulation in rats. Mills DE, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 1):E614-8

Extractive acylation and mass spectrometric assay of 3-methoxytyramine, normetanephrine, and metanephrine in cerebrospinal fluid. Beck O, et al. **Anal Biochem** 1985 Sep;149(2):492-500

Endocrine correlates of susceptibility to motion sickness. Kohl RL. **Aviat Space Environ Med** 1985 Dec;56(12):1158-65

Age-related memory deficits in rats and mice: enhancement with peripheral injections of epinephrine. Sternberg DB, et al. **Behav Neural Biol** 1985 Sep;44(2):213-20

Epinephrine facilitation of appetitive learning: attenuation with adrenergic receptor antagonists. Sternberg DB, et al. **Behav Neural Biol** 1985 Nov; 44(3):447-53

Epinephrine decreases low density lipoprotein processing and lipid synthesis in cultured human fibroblasts. Mazière C, et al. **Biochem Biophys Res Commun** 1985 Dec 31;133(3):958-63

Evidence for adrenergic control of transcellular calcium distribution in liver. Hill CE, et al. **Biochem J** 1985 Sep 15;230(3):733-7

Studies on the activation of rat liver pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase by adrenaline and glucagon. Role of increases in intramitochondrial Ca2+ concentration. McCormack JG. **Biochem J** 1985 Nov 1;231(3):597-608

Immunohistochemical and biochemical study on the development of the noradrenaline- and adrenaline-storing cells of the adrenal medulla of the rat. Verhofstad AA, et al. **Cell Tissue Res** 1985;242(2):233-43

Radioenzymatic microassay for simultaneous estimations of dopamine, norepinephrine, and epinephrine in plasma, urine, and tissues. Hussain MN, et al. **Clin Chem** 1985 Nov;31(11):1861-4

Simultaneous determination of epinephrine and norepinephrine in urine by derivative synchronous fluorescence spectroscopy. Valcárcel M, et al. **Clin Chem** 1985 Nov;31(11):1790-4

Effects of exogenous catecholamines and exercise on plasma magnesium concentrations. Joborn H, et al. **Clin Endocrinol (Oxf)** 1985 Sep; 23(3):219-26

The effect of adrenaline upon cardiovascular and metabolic functions in man. Fellows IW, et al. **Clin Sci** 1985 Aug;69(2):215-22

The distribution of catecholamines between platelets and plasma in normal human subjects. Smith CC, et al. **Clin Sci** 1985 Jul;69(1):1-6

Comparison of basal metabolic activities and hormonal sensitivities between mesenteric and epididymal adipocytes. Tshuchimoto M, et al. **Comp Biochem Physiol** [A] 1985;82(2):377-83

Epinephrine, norepinephrine and dopamine concentrations in amphibian brain. Cooney MM, et al. **Comp Biochem Physiol** [C] 1985; 82(2):395-7

Epinephrine lowers subcutaneous wound oxygen tension. Jensen JA, et al. **Curr Surg** 1985 Nov-Dec;42(6):472-4

Interaction between epinephrine, prostaglandin E, and met-enkephalin in the regulation of insulin release in man. Giugliano D, et al. **Diabete Metab** 1985 Oct;11(5):295-302

Release of catecholamines follows suckling or electrical stimulation of mammary nerve in lactating rats. Clapp C, et al. **Endocrinology** 1985 Dec;117(6):2498-504

Alpha 2-adrenoceptor coupling to adenylate cyclase in adrenaline insensitive human platelets. Swart SS, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):113-9

Effect of ascorbic acid and adrenergic receptor blockers on adrenaline induced in vitro follicular atresia in white Leghorn hens. Moudgal RP, et al. **Indian J Exp Biol** 1985 Jun;23(6):343-4

Age-related augmentation of plasma catecholamines during dynamic exercise in healthy males. Fleg JL, et al. **J Appl Physiol** 1985 Oct; 59(4):1033-9

Stimulation of 1,2-diacylglycerol accumulation in hepatocytes by vasopressin, epinephrine, and angiotensin II. Bocckino SB, et al. **J Biol Chem** 1985 Nov 15;260(26):14201-7

Phorbol esters inhibit alpha 1-adrenergic effects and decrease the affinity of liver cell alpha 1-adrenergic receptors for (-)-epinephrine. Corvera S, et al. **J Biol Chem** 1986 Jan 15;261(2):520-6

Inhibitors of Na+/H+ exchange block stimulus-provoked arachidonic acid release in human platelets. Selective effects on platelet activation by epinephrine, ADP, and lower concentrations of thrombin. Sweatt JD, et al. **J Biol Chem** 1985 Oct 25;260(24):12910-9

Fluid temperature and volume dependence of the dissociated plasma epinephrine and norepinephrine response to drinking. Puddey IB, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):438-40

Ontogeny of phenylethanolamine N-methyltransferase- and tyrosine hydroxylase-like immunoreactivity in presumptive adrenaline neurones of the foetal rat central nervous system. Foster GA, et al. **J Comp Neurol** 1985 Jun 15;236(3):348-81

Epinephrine decreases the potassium requirements of hamster sperm capacitation: furosemide blocks the effect of epinephrine. Bize I, et al. **J Exp Zool** 1985 Aug;235(2):261-7

Adrenergic responses of the cardiovascular system of the eel, Anguilla australis, in vivo. Hipkins SF. **J Exp Zool** 1985 Jul;235(1):7-20

Peripheral origin of plasma dopamine. Yoneda S, et al. **Jpn Circ J** 1985 Sep;49(9):1028-34

Alpha-methyladrenaline: a possible active metabolite of alpha-methyldopa in the rat brain. Himeno A, et al. **Jpn J Pharmacol** 1985 Sep;39(1):91-8

Plasma and brain catecholamines in experimental uremia: acute and chronic studies. Ali F, et al. **Life Sci** 1985 Nov 11;37(19):1757-64

Plasma norepinephrine, epinephrine, and dopamine beta-hydroxylase activity during exercise in man. Péronnet F, et al. **Med Sci Sports Exerc** 1985 Dec;17(6):683-8

Mechanism of epinephrine's glycogenolytic effect in isolated canine hepatocytes. Steiner KE, et al. **Metabolism** 1985 Nov;34(11):1020-3

Epinephrine-stimulated maintained rubidium efflux from guinea pig hepatocytes may involve alpha 1- and alpha 2-adrenoceptors. Henley JM. **Mol Pharmacol** 1985 Nov;28(5):431-5

Platelet-aggregation response to single or paired aggregating stimuli after low-dose aspirin [letter] Cerletti C, et al. **N Engl J Med** 1986 Jan 30; 314(5):316-8

Reduction of central epinephrine concentrations is consistent with the continued occurrence of ovulation in rats treated with an inhibitor (LY 134046) of phenylethanolamine N-methyltransferase. Sheaves R, et al. **Neuroendocrinology** 1985 Nov;41(5):432-6

Plasma norepinephrine, epinephrine and corticosterone stress responses to restraint in individual male and female rats, and their correlations. Livezey GT, et al. **Neurosci Lett** 1985 Nov 20;62(1):51-6

Partial liver denervations dissociate the inhibitory effects of pancreatic glucagon and epinephrine on feeding. MacIsaac L, et al. **Physiol Behav** 1985 Aug;35(2):233-7

Management of Vipera berus adder bite. Jones TI, et al. **Practitioner** 1985 Nov;229(1409):956-8

Psychoneuroendocrine stress responses and mood as related to the menstrual cycle. Collins A, et al. **Psychosom Med** 1985 Nov-Dec; 47(6):512-27

Adrenaline, emotional arousal and memory. Christianson SA, et al. **Scand J Psychol** 1985;26(3):237-48

Effects of adrenaline infusion on platelet number, volume and release reaction. Lande K, et al. **Thromb Haemost** 1985 Aug 30;54(2):450-3

Studies of alpha 2-adrenergic receptors of intact and functional washed human platelets by binding of 3H-dihydroergocryptine and 3H-yohimbine--correlation of 3H-yohimbine binding with the potentiation by adrenaline of ADP-induced aggregation. Lanza F, et al. **Thromb Haemost** 1985 Aug 30;54(2):402-8

[Adrenaline, noradrenaline and dopamine excretion and anxiety levels in surgical patients] Barham O, et al. **Arch Psychol (Frankf)** 1985; 137(4):291-5 (Eng. Abstr.) **(Ger)**

[The influence of pipemidic acid on epinephrine and collagen induced platelet aggregation in vitro] Reuter HD, et al. **Arzneimittelforschung** 1985;35(8):1326-9 (Eng. Abstr.) **(Ger)**

[Effects of repeated injections of epinephrine on lipolysis in rats] Shibata H. **Jikken Dobutsu** 1985 Jul;34(3):315-8 (Eng. Abstr.) **(Jpn)**

[Receptors on the platelet membrane] Watanabe K, et al. **Rinsho Byori** 1985 Jul;33(7):726-33 (22 ref.) **(Jpn)**

[Excretion of catecholamines in relation to personality types A and B] Zaleska T, et al. **Pol Tyg Lek** 1985 Jul 15;40(28):781-3 (Eng. Abstr.) **(Pol)**

[Catecholamine content in the adrenals of rats developing under hypokinesia and muscle training] Abzalov RA. **Biol Nauki** 1985; (10):55-8 (Eng. Abstr.) **(Rus)**

[Analysis of the factors determining the change in cardiac output during administration of catecholamines] Osadchii LI, et al. **Biull Eksp Biol Med** 1985 Oct;100(10):387-90 (Eng. Abstr.) **(Rus)**

ESCAPE REACTION

A stimulatory effect of intraaccumbens injections of noradrenaline on the behavior of rats in the forced swim test. Płaźnik A, et al. **Psychopharmacology (Berlin)** 1985;87(1):119-23

Attenuated response to nomifensine in rats during a swim test following lesion of the habenula complex. Thornton EW, et al. **Psychopharmacology (Berlin)** 1985;87(1):81-5

[Pharmaco-ethological analysis of agonistic behavior between resident and intruder mice: effects of adrenergic beta-blockers] Yoshimura H, et al. **Yakubutsu Seishin Kodo** 1985 Sep;5(3):223-9 (Eng. Abstr.) **(Jpn)**

ESTRADIOL

The depressing (negative) effect of oestradiol benzoate on the in vitro secretion of LH and FSH by the pituitary gland of the LRH-pretreated long-term ovariectomized rat changes into the augmentative (positive) effect after discontinuation of the LRH-pretreatment. Schuiling GA, et al. **Acta Endocrinol (Copenh)** 1985 Nov;110(3):329-37

Uterine changes on removal of submaxillary glands in rats (histological changes/uterine peroxidase/blood estradiol level). Bhattacharyya J, et al. **Biochem Biophys Res Commun** 1985 Dec 17;133(2):462-7

Effect of alterations in pulsatile luteinizing hormone release on ovarian follicular atresia and steroid secretion on diestrus 1 in the rat estrous cycle. Devorshak-Harvey E, et al. **Biol Reprod** 1985 Aug;33(1):103-11

Does the seasonal increase in estradiol negative feedback prevent luteinizing hormone surges in anestrous ewes by suppressing hypothalamic gonadotropin-releasing hormone pulse frequency? Legan SJ, et al. **Biol Reprod** 1985 Aug;33(1):117-31

Simultaneous measurement of luteinizing hormone-releasing hormone and luteinizing hormone during estradiol-induced luteinizing hormone surges in the ovariectomized ewe. Schillo KK, et al. **Biol Reprod** 1985 Oct;33(3):644-52

Rostral hypothalamic microinfusions of 5,7 dihydroxytryptamine produce anatomically and neurochemically selective depletions of hippocampal serotonin and increase the influence of estrogen and food deprivation on locomotor activity. Waldbillig RJ, et al. **Brain Res** 1985 Nov 11;347(1):149-53

Evidence for gamma-aminobutyric acid modulation of ovarian hormonal effects on luteinizing hormone secretion and hypothalamic catecholamine activity in the female rat. Adler BA, et al. **Endocrinology** 1986 Jan;118(1):91-7

Regulation of pituitary gonadotropin-releasing hormone (GnRH) receptors by pulsatile GnRH in female rats: effects of estradiol and prolactin. Duncan JA, et al. **Endocrinology** 1986 Jan;118(1):320-7

17 beta-Estradiol at a physiological dose acutely increases dopamine turnover in rat brain. Di Paolo T, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):197-203

The effects of estradiol and progesterone on the concentration of striatal dopamine and tyramine in ovariectomized mice. Yeung SC, et al. **Gen Pharmacol** 1985;16(5):517-9

Estrogen uptake capacity of individual pituitary cell types from male and female rats one, fourteen and fifty days after castration. Smith PF, et al. **Horm Metab Res** 1985 Nov;17(11):583-7

Steroid and thyroid hormone profiles following a single injection of partly purified salmon gonadotropin or GnRH analogues in male and female sea lamprey. Sower SA, et al. **J Exp Zool** 1985 Sep;235(3):403-8

Stimulation of hypothalamic LHRH levels and release by gonadal steroids. Kalra PS. **J Steroid Biochem** 1985 Nov;23(5B):725-31

Regulation of beta-endorphin and ACTH in brain by estradiol. Wardlaw SL, et al. **Life Sci** 1985 Nov 18;37(20):1941-7

Luteinizing hormone releasing hormone enhances proceptivity in a primate. Kendrick KM, et al. **Neuroendocrinology** 1985 Dec;41(6):449-53

Estrogen exposure affects the post-ovariectomy increases in both LH and FSH release in female rats. Matt DW, et al. **Neuroendocrinology** 1986;42(1):21-7

A subset of beta-endorphin- or dynorphin-containing neurons in the medial basal hypothalamus accumulates estradiol. Morrell JI, et al. **Neuroendocrinology** 1985 Nov;41(5):417-26

[Hormonal response following the use of gonadotropin-releasing hormone, estradiol and gestil in sheep] Batzhargalin E. **Vet Med Nauki** 1985;22(9):60-6 (Eng. Abstr.) **(Bul)**

[Studies on the feedback regulation of pulsatile luteinizing hormone secretion. II. Role of the catecholaminergic system in estrogen-induced suppression of the frequency of pulsatile LH secretion in ovariectomized rats] Tadokoro Y. **Nippon Naibunpi Gakkai Zasshi** 1985 Jul 20;61(7):765-74 (Eng. Abstr.) **(Jpn)**

[Direct and indirect hormonal effects on the function of the adenohypophysis] Fedotov VP. **Probl Endokrinol (Mosk)** 1985 Sep-Oct;31(5):27-30 (Eng. Abstr.) **(Rus)**

EUPHORIA

Lithium attenuates the activation-euphoria but not the psychosis induced by d-amphetamine in schizophrenia. van Kammen DP, et al. **Psychopharmacology (Berlin)** 1985;87(1):111-5

EXPLORATORY BEHAVIOR

Effect of domperidone on apomorphine inhibition of the copulatory response and exploratory behaviour in the female rat. Sietnieks A, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Sep;57(3):160-5

Does the benzodiazepine antagonist Ro 15-1788 reverse the actions of picrotoxin and pentylenetetrazole on social and exploratory behaviour? File SE, et al. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):272-9

SKF 38393 and apomorphine modify locomotion and exploration in rats placed on a holeboard by separate actions at dopamine D-1 and D-2 receptors. Fletcher GH, et al. **Eur J Pharmacol** 1985 Nov 19;117(3):381-5

Effect of an atypical barbiturate, the 2-allophanyl-2-allyl-4-valerolactone (valofan), on exploratory behaviour and brain serotonin concentrations in mice. Traversa U, et al. **J Pharmacol** 1985 Jul-Sep;16(3):279-90

EXTINCTION (PSYCHOLOGY)

Extinguishing conditioned inhibition in flavour-aversion learning: effects of repeated testing and extinction of the excitatory element. Best MR, et al. **Q J Exp Psychol [B]** 1985 Nov;37(4):359-78

FEAR

AIDS and homosexual panic [letter] Rapaport M, et al. **Am J Psychiatry** 1985 Dec;142(12):1516

Calcium channel blockers in the treatment of panic disorder [letter] Goldstein JA. **J Clin Psychiatry** 1985 Dec;46(12):546

Simultaneous panic and depressive disorder: response to antidepressant treatments. Grunhaus L, et al. **J Clin Psychiatry** 1986 Jan;47(1):4-7

Fear-enhanced acoustic startle is not attenuated by acute or chronic imipramine treatment in rats. Cassella JV, et al. **Psychopharmacology (Berlin)** 1985;87(3):278-82

[New proposals for the development of the concepts of neurotic anxiety, major depression and panic attack] Xhenseval B. **Acta Psychiatr Belg** 1985 Jul-Aug;85(4):480-508 (68 ref.) (Eng. Abstr.) **(Fre)**

[Panic attacks in adolescents] Dugas M, et al. **Presse Med** 1985 Nov 9;14(38):1951-4 (Eng. Abstr.) **(Fre)**

FENFLURAMINE

Serotonergic regulation of prolactin and growth hormone secretion in man. Lewis DA, et al. **Acta Endocrinol (Copenh)** 1985 Oct;110(2):152-7

Pharmacokinetics of fenfluramine and norfenfluramine in volunteers given D- and DL-fenfluramine for 15 days. Caccia S, et al. **Eur J Clin Pharmacol** 1985;29(2):221-4

Salbutamol, d-amphetamine and d-fenfluramine reduce sucrose intake in freely fed rats by acting on different neurochemical mechanisms. Borsini F, et al. **Int J Obes** 1985;9(4):277-83

Fenfluramine therapy for autism [letter] Pranzatelli MR, et al. **J Autism Dev Disord** 1985 Dec;15(4):439-41

Down-regulation of [3H]5-hydroxytryptamine binding sites in chick embryo brain by monoamine oxidase inhibitors or fenfluramine and potentiation by d,l-5-hydroxytryptophan. Soblosky JS, et al. **J Neurochem** 1985 Dec;45(6):1923-31

Effects of initial body weight on anorexia and tolerance to fenfluramine in rats. Carlton J, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):551-4

Effect of fenfluramine on GDP-binding to brown adipose tissue mitochondria. Lupien JR, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):509-11

FK 33-824

Interaction between epinephrine, prostaglandin E, and met-enkephalin in the regulation of insulin release in man. Giugliano D, et al. **Diabete Metab** 1985 Oct;11(5):295-302

FLUPHENAZINE

Combination alprazolam-neuroleptic treatment of the positive and negative symptoms of schizophrenia. Wolkowitz OM, et al. **Am J Psychiatry** 1986 Jan;143(1):85-7

Neuroleptic drug-induced coagulopathy: mechanism of reaction and duration of effect. Zengotita HE, et al. **J Clin Psychiatry** 1986 Jan;47(1):35-7

Plasma levels of neuroleptic in patients receiving depot fluphenazine. Cohen BM, et al. **J Clin Psychopharmacol** 1985 Dec;5(6):328-32

Prolixin group. Can nursing intervention groups lower recidivism? Selander JM, et al. **J Psychosoc Nurs Ment Health Serv** 1985 Nov;23(11):16-20

Characteristics of D-1 dopamine receptors labelled by [3H]fluphenazine in homogenates of rat neostriatum. Cincotta M, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):85-9

Depot fluphenazine and plasma prolactin. Gift T, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):407-12

Early unwanted effects of fluphenazine esters related to plasma fluphenazine concentrations in schizophrenic patients. Altamura AC, et al. **Psychopharmacology (Berlin)** 1985;87(1):30-3

Plasma levels of fluphenazine during fluphenazine decanoate treatment in schizophrenia. Chang SS, et al. **Psychopharmacology (Berlin)** 1985;87(1):55-8

FLURAZEPAM

Anticonvulsant and convulsant properties of flurazepam. Kalichman MW.

Neuropharmacology 1985 Nov;24(11):1127-30

FOOD DEPRIVATION

Influence of hormones and undernutrition on brain development in newborn rats. Pascual-Leone AM, et al. **Biol Neonate** 1985; 48(4):228-36

The role of food deprivation in the maintenance and reinstatement of cocaine-seeking behavior in rats. Carroll ME. **Drug Alcohol Depend** 1985 Nov;16(2):95-109

Food deprivation produces persistent increases in self-administration behavior during cocaine extinction. Carroll ME. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:125-31

FSH

Regulation of gonadotrophin secretion in male mice from birth to adulthood. Response to LRH injection, castration and testosterone replacement therapy. Jean-Faucher C, et al. **Acta Endocrinol (Copenh)** 1985 Oct;110(2):193-9

The depressing (negative) effect of oestradiol benzoate on the in vitro secretion of LH and FSH by the pituitary gland of the LRH-pretreated long-term ovariectomized rat changes into the augmentative (positive) effect after discontinuation of the LRH-pretreatment. Schuiling GA, et al. **Acta Endocrinol (Copenh)** 1985 Nov;110(3):329-37

Follicle-stimulating hormone within and secreted from anterior pituitaries of female golden hamsters during the estrous cycle and after ovariectomy. Cameron JL, et al. **Biol Reprod** 1985 Aug;33(1):132-9

Postcastration rise in plasma gonadotropins is blocked by a luteinizing hormone-releasing hormone antagonist. Condon TP, et al. **Biol Reprod** 1985 Oct;33(3):715-21

Active immunization of gilts against gonadotropin-releasing hormone: effects on secretion of gonadotropins, reproductive function, and responses to agonists of gonadotropin-releasing hormone. Esbenshade KL, et al. **Biol Reprod** 1985 Oct;33(3):569-77

Cholinergic inhibition of follicle-stimulating hormone-induced progestin production by cultured rat granulosa cells. Kasson BG, et al. **Biol Reprod** 1985 Dec;33(5):1158-67

Effects of intermittent pulsatile infusion of luteinizing hormone-releasing hormone on dihydrotestosterone-suppressed gonadotropin secretion in castrate rams. Schanbacher BD. **Biol Reprod** 1985 Oct;33(3):603-11

Muscarinic cholinergic mediation of LHRH-induced LH and FSH secretion in normal men. Chiodera P, et al. **Clin Endocrinol (Oxf)** 1985 Oct;23(4):361-6

Dose-related changes in LH bioactivity with intranasal GnRH agonist administration. Chiang RS, et al. **Contraception** 1985 Oct; 32(4):347-57

Effects of gonadectomy and steroid treatment on plasma gonadotropins and the response of superfused pituitaries to gonadotropin-releasing hormone in the turtle Sternotherus odoratus. Licht P, et al. **Gen Comp Endocrinol** 1985 Dec;60(3):441-9

Suppression of plasma gonadotropins and testosterone in adult male monkeys (Macaca fascicularis) by a potent inhibitory analog of gonadotropin-releasing hormone. Adams LA, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):58-63

Individual variations in FSH release after a GnRH challenge and relationship with semen output in young bulls. Abdel Malak G, et al. **J Reprod Fertil** 1985 Nov;75(2):345-50

Central effects of an antagonist and an antiserum to substance P on serum gonadotropin and prolactin secretion. Dees WL, et al. **Life Sci** 1985 Oct 28;37(17):1627-31

Inhibition of gonadotropin secretion induced by cholecystokinin implants in the medial preoptic area by the dopamine receptor blocker, pimozide, in the rat. Hashimoto R, et al. **Neuroendocrinology** 1986;42(1):32-7

Estrogen exposure affects the post-ovariectomy increases in both LH and FSH release in female rats. Matt DW, et al. **Neuroendocrinology** 1986;42(1):21-7

GABA

Inhibitory effect of GABA on phrenic discharge activity of rabbit through microinjection into nucleus tractus solitarii. Huang CJ, et al. **Acta Acad Med Wuhan** 1985;5(3):147-52

GABA inhibits inhalation anaesthetic-induced membrane fluidization: a spin label study in synaptic and phospholipid membranes. Rosenberg PH, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Sep;57(3):154-9

GABA-mediated baroreceptor inhibition of reticulospinal neurons. Sun MK, et al. **Am J Physiol** 1985 Dec;249(6 Pt 2):R672-80

Inhibitory amino acid effects upon cortical evoked potentials. Rossi ST, et al. **An Acad Bras Cienc** 1985 Mar;57(1):111-3

Neurons and terminals in the retrohippocampal region in the rat's brain identified by anti-gamma-aminobutyric acid and anti-glutamic acid decarboxylase immunocytochemistry. Köhler C, et al. **Anat Embryol (Berl)** 1985;173(1):35-44

Neurotoxic insecticides inhibit GABA-dependent chloride uptake by mouse brain vesicles. Bloomquist JR, et al. **Biochem Biophys Res Commun** 1985 Nov 27;133(1):37-43

Possible involvement of K+-conductance in the action of gamma-aminobutyric acid in the guinea-pig hippocampus. Inoue M, et al. **Br J Pharmacol** 1985 Oct;86(2):515-24

Identification of extrasynaptic binding sites for [3H]GABA in peripheral nerve. Barolet AW, et al. **Brain Res** 1985 Dec 9;358(1-2):104-9

Mushroom body feedback interneurones in the honeybee show GABA-like immunoreactivity. Bicker G, et al. **Brain Res** 1985 Dec 23;360(1-2):394-7

Evaluation of the electrophysiological consequences of GABA removal from the synaptic cleft by Na+ ion transport-coupled neuronal uptake. Cupello A, et al. **Brain Res** 1985 Dec 9;358(1-2):364-6

GABA-immunoreactive neurons in the rat dorsal lateral geniculate nucleus: light microscopical observations. Gabbott PL, et al. **Brain Res** 1985 Oct 28;346(1):171-5

Colocalization of [3H]muscimol and antisera to GABA and glutamic acid decarboxylase within the same neurons in monkey retina. Hendrickson A, et al. **Brain Res** 1985 Dec 2;348(2):391-6

Postnatal development of GABA- and glycine-mediated inhibition of feline retinal ganglion cells in the area centralis. Ikeda H, et al. **Brain Res** 1985 Nov;355(1):1-17

Contralateral circling behavior induced by intranigral microinjections of taurine and GABA in rats. Kamata K, et al. **Brain Res** 1985 Sep 23; 343(2):275-82

Local stimulation induced GABAergic response in rat striatal slice preparations: intracellular recordings on QX-314 injected neurons. Kita T, et al. **Brain Res** 1985 Dec 23;360(1-2):304-10

Localization of gamma-aminobutyric acid and glutamic acid decarboxylase in rhesus monkey retina. Nishimura Y, et al. **Brain Res** 1985 Dec 16;359(1-2):351-5

Dopaminergic regulation of GABA release from the intact goldfish retina. O'Brien DR, et al. **Brain Res** 1985 Dec 23;360(1-2):41-50

Folic acid has a disinhibitory action in the rat hippocampal slice preparation. Otis LC, et al. **Brain Res** 1985 Nov 4;346(2):281-6

Responses to gamma-aminobutyric acid applied to cell bodies and dendrites of rat visual cortical neurons. Scharfman HE, et al. **Brain Res** 1985 Dec 9;358(1-2):385-9

GABA axons in synaptic contact with dopamine neurons in the substantia nigra: double immunocytochemistry with biotin-peroxidase and protein A-colloidal gold. van den Pol AN, et al. **Brain Res** 1985 Nov 25; 348(1):146-54

Selectivity of the uptake of glutamate and GABA in two morphologically distinct insect neuromuscular synapses. van Marle J, et al. **Brain Res** 1985 Nov 25;348(1):107-11

Projection of olfactory bulb efferents to layer I GABAergic neurons in the entorhinal area. Combination of anterograde degeneration and immunoelectron microscopy in rat. Wouterlood FG, et al. **Brain Res** 1985 Sep 23;343(2):283-96

Localization in the brain of the inhibition by GABA of luteinizing hormone release that follows orchidectomy in rats. Donoso AO. **Braz J Med Biol Res** 1985;18(1):97-100

Studies of the role of gamma-aminobutyric acid in the hypothalamic control of feed intake in sheep. Girard CL, et al. **Can J Physiol Pharmacol** 1985 Oct;63(10):1297-301

Spontaneous and GABA-induced single channel currents in cultured murine spinal cord neurons. Mathers DA. **Can J Physiol Pharmacol** 1985 Oct;63(10):1228-33

Interactions of gamma-aminobutyric acid (GABA), pentobarbital, and homopantothenic acid (HOPA) on internally perfused frog sensory neurons. Akaike N, et al. **Cell Mol Neurobiol** 1985 Sep;5(3):245-55

Benzodiazepine binding sites in rat submaxillary gland: absence of markers of GABA system. Pérez C, et al. **Comp Biochem Physiol [C]** 1985; 82(2):451-6

Development of a high-affinity GABA uptake system in embryonic amphibian spinal neurons. Lamborghini JE, et al. **Dev Biol** 1985 Nov; 112(1):167-76

Evidence for gamma-aminobutyric acid modulation of ovarian hormonal effects on luteinizing hormone secretion and hypothalamic catecholamine activity in the female rat. Adler BA, et al. **Endocrinology** 1986 Jan;118(1):91-7

Endocrine modulation of gamma-aminobutyric acidergic innervation in the rat fallopian tube. Celotti F, et al. **Endocrinology** 1986 Jan; 118(1):334-9

gamma-Aminobutyric acid inhibits beta-endorphin secretion from the anterior pituitary but not the neurointermediate lobe in the rat. Petraglia F, et al. **Endocrinology** 1986 Jan;118(1):360-6

GABAergic regulation of melanocyte-stimulating hormone secretion from the pars intermedia of Xenopus laevis: immunocytochemical and physiological evidence. Verburg-van Kemenade BM, et al. **Endocrinology** 1986 Jan;118(1):260-7

Regulation of [35S]t-butylbicyclophosphorothionate binding sites in rat brain by GABA, pyrethroid and barbiturate. Seifert J, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):191-8

Involvement of bicuculline-insensitive receptors in the hypothermic effect of GABA and its agonists. Serrano JS, et al. **Gen Pharmacol** 1985; 16(5):505-8

Effect of anticonvulsants, centazolone and centpropazine, on gamma amino butyric acid metabolism in mouse brain. Tripathi LM, et al. **Indian J Exp Biol** 1985 Aug;23(8):452-5

Kinetic studies of ox-liver glutamate dehydrogenase oxidative deamination of two glutamate analogues, L-threo-gamma-methylglutamate and L-alpha-amino-gamma-nitraminobutyrate, in the presence of the allosteric effector ADP. Hornby DP, et al. **Int J Biochem** 1985; 17(7):851-4

The medullary cardiovascular effects of imidazolines and some GABA analogues: a review. Bousquet P, et al. **J Auton Nerv Syst** 1985 Nov; 14(3):263-70 (39 ref.)

Selective retrograde labeling with D-[3H]-aspartate in afferents to the mammalian superior colliculus. Matute C, et al. **J Comp Neurol** 1985 Nov 1;241(1):34-49

Vasopressin secretion as a possible target of the gamma-aminobutyric acid-mediated component of the corticosteroid feedback effect. Acs Z, et al. **J Endocrinol** 1985 Dec;107(3):303-7

GABA agonists. Resolution, absolute stereochemistry, and enantioselectivity of (S)-(+)- and (R)-(-)-dihydromuscimol. Krogsgaard-Larsen P, et al. **J Med Chem** 1985 Nov;28(11):1612-7

Synthesis of alkyl-substituted arecoline derivatives as gamma-aminobutyric acid uptake inhibitors. Müller-Uri C, et al. **J Med Chem** 1986 Jan;29(1):125-32

Effect of adrenalectomy on gamma-aminobutyric acid concentrations in the central nervous system. David S, et al. **J Neurochem** 1986 Jan; 46(1):161-5

Induced release of gamma-aminobutyric acid by a carrier-mediated, high-affinity uptake of L-glutamate in cultured chick retina cells. do Nascimento JL, et al. **J Neurochem** 1985 Dec;45(6):1820-7

Distribution of gamma-aminobutyric acid and glutamate decarboxylase in the layers of rat oviduct. Murashima YL, et al. **J Neurochem** 1986 Jan;46(1):166-72

Development of the gamma-aminobutyric acid neurotransmitter system in the rat cerebral cortex during repeated administration of the GABA-transaminase inhibitor ethanolamine O-sulphate. Sykes CC, et al. **J Neurochem** 1986 Jan;46(1):213-7

Pharmacological properties of gamma-aminobutyric acid-, glutamate-, and aspartate-induced depolarizations in cultured astrocytes. Kettenmann H, et al. **J Neurosci** 1985 Dec;5(12):3295-301

Dual ultrastructural localization of two neurotransmitter-related antigens: colloidal gold-labeled neurophysin-immunoreactive supraoptic neurons receive peroxidase-labeled glutamate decarboxylase- or gold-labeled GABA-immunoreactive synapses. van den Pol AN. **J Neurosci** 1985 Nov;5(11):2940-54

Modulation of action of kainic acid on the behavior of rats by p-chlorophenylalanine and by gaba-mimetic drugs. Biochemical correlation between behavior and treatments. Molla-Hosseini C, et al. **J Pharmacol** 1985 Jul-Sep;16(3):299-312

Noradrenergic modulation of cortical acetylcholine release is both direct and gamma-aminobutyric acid-mediated. Beani L, et al. **J Pharmacol Exp Ther** 1986 Jan;236(1):230-6

Gamma-aminobutyric acid uptake and the termination of inhibitory synaptic potentials in the rat hippocampal slice. Dingledine R, et al. **J Physiol (Lond)** 1985 Sep;366:387-409

GABA, depressants and chloride ions affect the rate of dissociation of 35S-t-butylbicyclophosphorothionate binding. Maksay G, et al. **Life Sci** 1985 Dec 9;37(23):2173-80

gamma-Aminobutyric acid in peripheral tissues. Tanaka C. **Life Sci** 1985 Dec 16;37(24):2221-35 (115 ref.)

Potentiation of Na+-dependent uptake of gamma-aminobutyric acid in mouse brain particles by buffer-mediated proton removal. Roberts E, et al. **Neurochem Res** 1985 Aug;10(8):1025-46

Numerical estimation of gamma-aminobutyric acid (GABA)-containing neurons in three thalamic nuclei of the cat: direct GABA immunocytochemistry. Madarasz M, et al. **Neurosci Lett** 1985 Oct 24; 61(1-2):73-8

Pentobarbital promotes bursts of gamma-aminobutyric acid-activated single channel currents in cultured mouse central neurons. Mathers DA. **Neurosci Lett** 1985 Sep 30;60(2):121-6

Studies on the depression of gamma-aminobutyric acid potentials by phloridzin in cat dorsal root ganglion cells in vitro. Stevens DR, et al. **Neurosci Lett** 1985 Sep 30;60(2):115-9

Immunohistochemical localization of GABAergic cells in the developing human dorsal lateral geniculate nucleus. Wadhwa S, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):97-101

Factors controlling the release of GABA from goldfish retinal horizontal cells. Yazulla S. **Neurosci Res [Suppl]** 1985;2:S147-65

gamma-Aminobutyrate sensitivity does not change during long-term potentiation in rat hippocampal slices. Scharfman HE, et al. **Neuroscience** 1985 Jul;15(3):695-702

Excitatory transmitter release induced by high concentrations of gamma-aminobutyric acid (GABA) in crayfish neuromuscular junctions. Finger W. **Pflugers Arch** 1985 Oct;405(3):265-73

Elicitation of conspecific attack or defense in the male rat by intraventricular injection of a GABA agonist or antagonist. Depaulis A, et al. **Physiol Behav** 1985 Sep;35(3):447-53

Avoidance of GABA-containing diets by olfactory bulbectomized rats. Tews JK, et al. **Physiol Behav** 1985 Jun;34(6):983-6

Taurine and its derivatives alter brain dopamine metabolism similarly to GABA in mice and rats. Ahtee L, et al. **Prog Clin Biol Res** 1985; 179:331-41

Gamma-aminobutyric acid and chloride channels: regulation by neuropeptides. Guidotti A, et al. **Regul Pept [Suppl]** 1985;4:172-81

The content and release of endogenous GABA in isolated horizontal cells of the goldfish retina. Ayoub GS, et al. **Vision Res** 1985; 25(9):1187-93

[Concentrations of free and bound 4-aminobutyric acid in human serum: reference values] Uhlhaas S, et al. **J Clin Chem Clin Biochem** 1985 Sep; 23(9):525-8 (Eng. Abstr.) **(Ger)**

[Structuro-functional organization of intracortical inhibition] Batuev AS. **Fiziol Zh** 1985 Sep-Oct;31(5):530-8 (Eng. Abstr.) **(Rus)**

GALVANIC SKIN RESPONSE

Skin conductance reaction (SCR)-habituation test, a tool to detect anxiolytic activity. Its justification by the correlation between SCR-habituation test activities and specific binding potencies in benzodiazepines. Marcy R, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):387-91

GENERALIZATION, STIMULUS

Effects of preexposure flavor concentration on conditioned aversion and neophobia. Gilley DW, et al. **Behav Neural Biol** 1985 Nov; 44(3):503-8

N-Ethyl-17(R,S)-methyl-(6aR,10aR)-delta 8-tetrahydrocannabinol-18-oic amide. Brain pharmacokinetics in mice, triglyceride/phospholipid partitioning and generalization to the discriminative stimulus properties of delta 9-THC in rats. Franke I, et al. **Biochem Pharmacol** 1985 Nov 15;34(22):3983-6

One-way generalization of clonidine to the discriminative stimulus produced by cocaine. Wood DM, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):529-33

GLUCURONIDASE

Cellulose and pectin alter intestinal beta-glucuronidase (EC 3.2.1.31) in the rat. Lindop R, et al. **Br J Nutr** 1985 Jul;54(1):21-6

Phorbol myristate acetate enhances human polymorphonuclear neutrophil release of granular enzymes but inhibits chemokinesis. Hoult JR, et al. **Br J Pharmacol** 1985 Nov;86(3):533-7

The use of gene fusions to study the expression of uidR, a negative regulatory gene of Escherichia coli K-12. Blanco C, et al. **Gene** 1985; 36(1-2):159-67

Properties of rat and mouse beta-glucuronidase mRNA and cDNA, including evidence for sequence polymorphism and genetic regulation of mRNA levels. Watson G, et al. **Gene** 1985;36(1-2):15-25

Egasyn, a protein which determines the subcellular distribution of beta-glucuronidase, has esterase activity. Medda S, et al. **J Biol Chem** 1985 Dec 15;260(29):15802-8

GONADOTROPINS, PITUITARY

Gonadotrophin release and meat consumption in vegetarian women. Hill PB, et al. **Am J Clin Nutr** 1986 Jan;43(1):37-41

[The effects of bromocriptine on the pulsatile pattern and the circadian profile of gonadotropins and testosterone secretion in normal adult men] Aisaka K, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jun 20; 61(6):701-9 (Eng. Abstr.) **(Jpn)**

GUANETHIDINE

Effects of guanethidine and phenethylguanidine on the frog neuromuscular junction. Enomoto K, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):187-96

HABITUATION (PSYCHOPHYSIOLOGY)

Depletion of brain serotonin by 5,7-dihydroxytryptamine alters the response to amphetamine and the habituation of locomotor activity in rats. Gately PF, et al. **Psychopharmacology (Berlin)** 1985;87(4):400-5

HALOPERIDOL

Effect of carbamazepine on neuroleptic plasma levels and efficacy [letter] Fast DK, et al. **Am J Psychiatry** 1986 Jan;143(1):117-8

Treatment of intractable hiccups with intramuscular haloperidol. Ives TJ, et al. **Am J Psychiatry** 1985 Nov;142(11):1368-9

Differential effects of haloperidol decanoate, a long-acting neuroleptic, in behavioral and biochemical tests. Oka M, et al. **Arch Int Pharmacodyn Ther** 1985 Oct;277(2):289-302

Effects of psychotropic drugs on thermal responses to radiofrequency radiation. Jauchem JR, et al. **Aviat Space Environ Med** 1985 Dec; 56(12):1183-8

Antisera raised against the drug haloperidol. Juszczak R, et al. **Biochem Pharmacol** 1985 Nov 15;34(22):3959-63

Effects of haloperidol and low dose clozapine on the acetylcholine turnover rate in rat forebrain structures. Bluth R, et al. **Biomed Biochim Acta** 1985;44(10):1531-9

Sulpiride and haloperidol in schizophrenia: a double-blind cross-over study of therapeutic effect, side effects and plasma concentrations. Gerlach J, et al. **Br J Psychiatry** 1985 Sep;147:283-8

Synaptic rearrangements in medial prefrontal cortex of haloperidol-treated rats. Benes FM, et al. **Brain Res** 1985 Nov 25; 348(1):15-20

Increase of dopamine turnover in bilateral striata after unilateral injection of haloperidol into substantia nigra of unrestrained rats. Ishii K, et al. **Brain Res** 1985 Dec 16;359(1-2):260-6

Modulation of terminal excitability of mesolimbic dopaminergic neurons by D-amphetamine and haloperidol. Mereu G, et al. **Brain Res** 1985 Dec 16;359(1-2):88-96

Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. arap Mengech HN, et al. **East Afr Med J** 1984 Jun;61(6):435-8

Haloperidol-induced suppression of carotid chemoreception in vitro. Nolan WF, et al. **J Appl Physiol** 1985 Sep;59(3):814-20

Treatment of phenylcyclohexylpyrrolidine (PHP) psychosis with haloperidol. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1985; 23(2-3):185-9

Comparative evaluation of the behavioural consequences of prenatal and early postnatal exposure to haloperidol in rats. Cuomo V, et al. **Neurobehav Toxicol Teratol** 1985 Sep-Oct;7(5):489-92

The effect of dopamine receptor agonist treatment on haloperidol-induced supersensitivity in mice. Fayle P, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):715-20

Amphetamine-haloperidol discrimination: effects of chronic drug treatment. Haenlein M, et al. **Pharmacol Biochem Behav** 1985 Dec; 23(6):949-52

Relative effectiveness of pimozide, haloperidol and trifluoperazine on self-stimulation rate-intensity functions. Lynch MR, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):777-80

The effects of clozapine on shuttle-box avoidance responding in rats: comparisons with haloperidol and chlordiazepoxide. Sanger DJ. **Pharmacol Biochem Behav** 1985 Aug;23(2):231-6

Phencyclidine-induced dopamine-dependent behaviors in chronic haloperidol-treated rats. Yamaguchi K, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):803-9

Haloperidol blocks amphetamine induced recovery of binocular depth perception after bilateral visual cortex ablation in cat. Hovda DA, et al. **Proc West Pharmacol Soc** 1985;28:209-11

Neuropeptide modulation of the behavioral effects of drugs. Barrett JE, et al. **Prog Clin Biol Res** 1985;192:37-50

Haloperidol and thyroid-binding globulin [letter] Lawlor BA, et al. **South Med J** 1985 Dec;78(12):1525

[Determination of blood haloperidol levels by radioimmunoassay--a methodological study] Zhou DF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Jun; 18(3):155-7 (Eng. Abstr.) **(Chi)**

[Conditioned reactions of hippocampal neurons during amphetamine poisoning and its counteraction with haloperidol] Zhavoronkova LA, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):957-63 (Eng. Abstr.) **(Rus)**

HEXOBARBITAL

Selected ion monitoring analysis of pseudoracemic hexobarbital and its major metabolites in blood and urine of rats. van der Graaff M, et al. **Biomed Mass Spectrom** 1985 Sep;12(9):464-9

Direct effect of carbon monoxide on hexobarbital metabolism in the isolated perfused liver in the absence of hemoglobin. Takano T, et al. **J Toxicol Environ Health** 1985;15(6):847-54

HISTAMINE

Increased permeability of microcarrier-cultured endothelial monolayers in response to histamine and thrombin. A model for the in vitro study of increased vasopermeability. Killackey JJ, et al. **Am J Pathol** 1986 Jan;122(1):50-61

Accumulation of inositol phosphates and cyclic AMP in guinea-pig cerebral cortical preparations. Effects of norepinephrine, histamine, carbamylcholine and 2-chloroadenosine. Hollingsworth EB, et al. **Biochim Biophys Acta** 1985 Nov 20;847(2):207-16

Experimental allergic orchitis in mice. II. Association of disease susceptibility with the locus controlling Bordetella pertussis-induced sensitivity to histamine. Teuscher C. **Immunogenetics** 1985; 22(5):417-25

Effect of Rumex nepalensis extracts on histamine, acetylcholine and carbachol evoked responses on isolated guinea pig ileum, frog rectus abdominis muscle, rabbit heart and blood pressure of dog. Aggarwal P, et al. **Indian J Exp Biol** 1985 Aug;23(8):447-51

Effect of leukotrienes, 12-HETE, histamine, bradykinin, and 5-hydroxytryptamine on in vivo rabbit cerebral arteriolar diameter. Kamitani T, et al. **J Cereb Blood Flow Metab** 1985 Dec;5(4):554-9

Highly sensitive high-performance liquid chromatographic technique for the simultaneous measurement of histamine, 1-methylhistamine and other biogenic amines. Devalia JL, et al. **J Chromatogr** 1985 Oct 11; 343(2):407-12

Analysis of cheese for histamine, tyramine, tryptamine, histidine, tyrosine, and tryptophane. Chang SF, et al. **J Dairy Sci** 1985 Nov; 68(11):2840-6

Phencyclidine and the dynamics of mouse brain histamine. Itoh Y, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):788-92

The effects of histamine and some related compounds on conditioned avoidance response in rats. Tasaka K, et al. **Life Sci** 1985 Nov 25; 37(21):2005-14

Changes in body temperature after administration of acetylcholine, histamine, morphine, prostaglandins and related agents: II. Clark WG, et al. **Neurosci Biobehav Rev** 1985 Fall;9(3):479-552 (741 ref.)

Involvement of brain histamine in delta 9-tetrahydrocannabinol tolerance and withdrawal. Verberne AJ, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):153-9

Histamine and serotonin independently elicit drinking in the rat. Kraly FS, et al. **Physiol Behav** 1985 Jun;34(6):963-7

Depolarisation-evoked release of dopamine and histamine from brain tissue and studies on presynaptic dopamine-histamine interaction. Nowak JZ. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):359-81 (111 ref.)

[Effects of serotonin (5HT) and histamine on the pulmonary circulation with particular reference to arterial and venous segment resistance--comparison between an experimental study and model circuit analysis] Yamashita H, et al. **Nippon Kyobu Shikkan Gakkai Zasshi** 1985 Jul;23(7):767-75 (Eng. Abstr.) **(Jpn)**

[Effect of histamine on motor and vascular effects on the small intestine induced by acetylcholine] Lavrova ZS, et al. **Fiziol Zh SSSR** 1985 Sep; 71(9):1156-63 (Eng. Abstr.) **(Rus)**

[Functional activity of serotonin- and histaminergic systems in humans during long-term antiorthostatic hypokinesia] Davydova NA, et al. **Kosm Biol Aviakosm Med** 1985 Sep-Oct;19(5):27-30 (Eng. Abstr.) **(Rus)**

HOMOVANILLIC ACID

Selective antidepressants and cerebrospinal fluid. Lack of specificity on norepinephrine and serotonin metabolites. Potter WZ, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1171-7

Homovanillic acid, vanillylmandelic acid and 5-hydroxyindole-3-acetic acid are undetectable in urine of the muskrat. Yoshioka M, et al. **Chem Pharm Bull (Tokyo)** 1985 May;33(5):2145-8

Fusaric acid-induced elevation of homovanillic acid in the CSF as an index of brain noradrenaline synthesis. Elghozi JL, et al. **Eur J Pharmacol** 1985 Nov 19;117(3):363-7

Determination of homovanillic acid in human plasma by high-performance liquid chromatography with electrochemical detection. Yoshida A, et al. **J Chromatogr** 1985 Sep 13;343(1):155-9

Effects of L-dopa and L-tyrosine on release of free and conjugated dopamine, homovanillic acid and dihydroxyphenylacetic acid from slices of rat striatum. Tyce GM, et al. **Life Sci** 1985 Dec 23; 37(25):2439-48

Brain ventricular size and CSF monoamine metabolites in an adolescent inpatient population. Jennings WS Jr, et al. **Psychiatry Res** 1985 Oct; 16(2):87-94

Dexamethasone increases plasma HVA but not MHPG in normal humans. Wolkowitz OM, et al. **Psychiatry Res** 1985 Oct;16(2):101-9

HUNGER

Satiety, hunger and regional brain content of cholecystokinin/gastrin and met-enkephalin immunoreactivity in sheep. Scallet AC, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):937-43

[Neuromediator sensitivity of neurons of the reticular formation and orbital cortex in hungry and satiated rabbits] Borisova EV. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):907-13 (Eng. Abstr.) **(Rus)**

HYDANTOINS

Mephenytoin hydroxylation polymorphism: characterization of the enzymatic deficiency in liver microsomes of poor metabolizers phenotyped in vivo. Meier UT, et al. **Clin Pharmacol Ther** 1985 Nov; 38(5):488-94

High-performance liquid chromatographic support for the baseline separation of all phenylthiohydantoin amino acids. Kruggel WG, et al. **J Chromatogr** 1985 Aug 9;342(2):376-9

[Ultrastructural changes in Mycobacterium rubrum cells exposed to sulfochloranthine] Poglazova MN, et al. **Mikrobiologiia** 1985 Jul-Aug; 54(4):628-33 (Eng. Abstr.) **(Rus)**

HYDRAZINES

Spin trapping of a free radical intermediate formed during microsomal metabolism of hydrazine. Noda A, et al. **Biochem Biophys Res Commun** 1985 Dec 31;133(3):1086-91

Dopaminergic drugs improve human visual contrast sensitivity. Domenici L, et al. **Hum Neurobiol** 1985;4(3):195-7

Internalization and delivery to lysosomes of hydrazide horseradish peroxidase, a covalent membrane probe. Storrie B, et al. **J Histochem Cytochem** 1985 Nov;33(11):1145-52

Increased life expectancy resulting from addition of L-deprenyl to Madopar treatment in Parkinson's disease: a longterm study. Birkmayer W, et al. **J Neural Transm** 1985;64(2):113-27

Pharmacokinetics of the toxic hydrazino metabolites formed from isoniazid in humans. Lauterburg BH, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):566-70

HYDROXYBUTYRATES

Use of alcohol oxidase to measure the methanol produced during the hydrolysis of D- and L-methyl-3-hydroxybutyric acid. Herzberg GR, et al. **Anal Biochem** 1985 Sep;149(2):354-7

Mitochondrial alterations in embryos exposed to B-hydroxybutyrate in whole embryo culture. Horton WE Jr, et al. **Anat Rec** 1985 Sep; 213(1):94-101

Effects of insulin on the metabolism of acetate, beta-hydroxybutyrate and triglycerides by the bovine mammary gland. Laarveld B, et al. **Comp Biochem Physiol [B]** 1985;82(2):265-7

Mathematical model for determining the effects of intracytoplasmic inclusions on volume and density of microorganisms. Mas J, et al. **J Bacteriol** 1985 Nov;164(2):749-56

Gammahydroxybutyric acid: central biochemical and behavioral effects in neonatal rats. Hedner T, et al. **Pharmacol Biochem Behav** 1985 Aug; 23(2):185-9

HYDROXYDOPAMINES

Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. II: The striatum of the rat is heterogeneously organized for rotational behaviour. Herrera-Marschitz M, et al. **Acta Physiol Scand** 1985 Nov; 125(3):529-35

Rotational behaviour elicited by intracerebral injections of apomorphine and pergolide in 6-hydroxy-dopamine-lesioned rats. I: Comparison between systemic and intrastriatal injections. Herrera-Marschitz M, et al. **Acta Physiol Scand** 1985 Nov;125(3):519-27

Effects of morphine on sprouting of locus coeruleus fibers in the neonatal rat. Bardo MT, et al. **Brain Res** 1985 Oct;354(2):161-8

Separation of the motor consequences from other actions of unilateral 6-hydroxydopamine lesions in the nigrostriatal neurones of rat brain. Hamilton MH, et al. **Brain Res** 1985 Dec 2;348(2):220-8

Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. Breese GR, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):287-95

Effects of chronic dietary lithium on behavioral indices of dopamine denervation supersensitivity in the rat. Swerdlow NR, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):324-9

Bilateral lesions of the striatum induced with 6-hydroxydopamine abolish apomorphine-induced yawning in rats. Dourish CT, et al. **Neuropharmacology** 1985 Nov;24(11):1051-5

Effects of 6-OHDA lesions of the central medial nucleus accumbens on rat intravenous morphine self-administration. Smith JE, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):843-9

Intraventricular 6-hydroxydopamine increases thyrotropin-releasing hormone (TRH) content in regions of rat brain. Engber TM, et al. **Regul Pept** 1985 Sep;12(1):51-7

HYDROXYINDOLEACETIC ACID

Selective antidepressants and cerebrospinal fluid. Lack of specificity on norepinephrine and serotonin metabolites. Potter WZ, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1171-7

Anterior cerebellar vermal stimulation: effect on behavior and basal forebrain neurochemistry in rat. Albert TJ, et al. **Biol Psychiatry** 1985 Dec;20(12):1267-76

Homovanillic acid, vanillylmandelic acid and 5-hydroxyindole-3-acetic acid are undetectable in urine of the muskrat. Yoshioka M, et al. **Chem Pharm Bull (Tokyo)** 1985 May;33(5):2145-8

Analytical considerations for quantitative determination of serotonin and its metabolically related products in biological matrices. Mailman RB, et al. **Clin Chem** 1985 Nov;31(11):1849-54

Effects of saltwater adaptation on serotonin metabolite concentrations in the cerebrospinal fluid of rainbow trout (Salmo gairdneri). Mazeaud MM, et al. **Comp Biochem Physiol [C]** 1985;82(1):109-13

Effect of short-term swimming stress and diazepam on 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) levels in the caudate nucleus: an in vivo voltammetric study. Ikeda M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct; 331(1):23-6

Brain ventricular size and CSF monoamine metabolites in an adolescent inpatient population. Jennings WS Jr, et al. **Psychiatry Res** 1985 Oct; 16(2):87-94

[Effect of prolonged interaction of mice with aggressive and submissive types of behavior on the concentration of serotonin, 5-hydroxyindoleacetic acid and noradrenalin in the brain] Kudriavtseva NN, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):879-83 (Eng. Abstr.) **(Rus)**

[Levels of 5-HIAA and beta-endorphin in CSF after intrathecal morphine] González Navarro A, et al. **Arch Neurobiol (Madr)** 1985 Jul-Aug;48(4):211-5 (Eng. Abstr.) **(Spa)**

HYDROXYTRYPTOPHAN

Anterior cerebellar vermal stimulation: effect on behavior and basal forebrain neurochemistry in rat. Albert TJ, et al. **Biol Psychiatry** 1985 Dec;20(12):1267-76

Modulation of 5-hydroxytryptamine-induced head-twitch response by drugs acting at GABA and related receptors. Handley SL, et al. **Br J Pharmacol** 1985 Sep;86(1):297-303

L-5HTP in depression resistant to re-uptake inhibitors. An open comparative study with tranylcypromine. Nolen WA, et al. **Br J Psychiatry** 1985 Jul;147:16-22

Analytical considerations for quantitative determination of serotonin and its metabolically related products in biological matrices. Mailman RB, et al. **Clin Chem** 1985 Nov;31(11):1849-54

Peripheral serotonin2 receptor blockade does not inhibit 5-hydroxytryptophan-induced aldosterone stimulation. Shenker Y, et al. **J Clin Endocrinol Metab** 1985 Dec;61(6):1201-4

Down-regulation of [3H]5-hydroxytryptamine binding sites in chick embryo brain by monoamine oxidase inhibitors or fenfluramine and potentiation by d,l-5-hydroxytryptophan. Soblosky JS, et al. **J Neurochem** 1985 Dec;45(6):1923-31

HYDROXYZINE

Possible potentiation by hydroxyzine of metoclopramide's undesirable side effects [letter] Fouilladieu JL, et al. **Anesth Analg** 1985 Dec; 64(12):1227-8

HYPOCHONDRIASIS

Delusional hypochondriasis, depression, and amoxapine [letter] Tollefson G. **Am J Psychiatry** 1985 Dec;142(12):1518-9

IMIPRAMINE

A double blind study in out-patients with primary non-agitated depression treated with imipramine in combination with placebo, diazepam or dixyrazine. Feet PO, et al. **Acta Psychiatr Scand** 1985 Oct; 72(4):334-40

No purging, no binge eating: a mechanism for imipramine's action in bulimia? [letter] Claman JM, et al. **Am J Psychiatry** 1985 Dec; 142(12):1515-6

Hyperpyrexia following psychotropic drug overdose. Peebles-Brown AE. **Anaesthesia** 1985 Nov;40(11):1097-9

Imipramine for the treatment of fibrositis: a therapeutic trial. Wysenbeek AJ, et al. **Ann Rheum Dis** 1985 Nov;44(11):752-3

Imipramine and chlordiazepoxide in depressive and anxiety disorders. II. Efficacy in anxious outpatients. Kahn RJ, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):79-85

Imipramine and chlordiazepoxide in depressive and anxiety disorders. I. Efficacy in depressed outpatients. Lipman RS, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):68-77

Platelet 3H-imipramine binding in depressed elderly patients. Schneider LS, et al. **Biol Psychiatry** 1985 Nov;20(11):1234-7

Unchanged platelet 3H-imipramine binding in normal subjects after imipramine administration. Suranyi-Cadotte BE, et al. **Biol Psychiatry** 1985 Nov;20(11):1240-3

Lithium potentiation of imipramine in treatment resistant depression [letter] Roy A, et al. **Br J Psychiatry** 1985 Nov;147:582-3

A controlled trial of amitriptyline and cianopramine in major depression. Mellsop GW, et al. **Clin Ther** 1985;7(6):699-703 (8 ref.)

Sex-related hyperthermic response to chlorpromazine in the offspring of rats treated with imipramine. Fujii T, et al. **Dev Pharmacol Ther** 1985;8(6):364-73

Cooperativity in inhibition of coupled and uncoupled respiration in rat liver and brain mitochondria by imipramine. Rajan RR, et al. **Indian J Biochem Biophys** 1985 Apr;22(2):71-7

Effect of imipramine hydrochloride on cardiac conduction system. Sabherwal U, et al. **Indian J Med Res** 1985 Oct;82:353-8

Tritiated imipramine binding to platelets in manic subjects. Lewis DA, et al. **J Affective Disord** 1985 Nov;9(3):207-11

Possible artefacts in imipramine binding assays [letter] Whitaker PM.

J Neurochem 1985 Dec;45(6):1960

Effect of phenobarbitone on the distribution and elimination of imipramine in rats. Lin TH, et al. **J Pharm Pharmacol** 1985 Oct;37(10):735-8

Dopamine and isoproterenol in imipramine intoxication in the dog. Sangster B, et al. **J Toxicol Clin Toxicol** 1985;23(4-6):407-20

Changes induced by corticosterone and adrenalectomy in synaptosomal and platelet uptake and binding of 5-HT. The relationship to [3H]imipramine binding. Lee PH, et al. **Neuropharmacology** 1985 Nov; 24(11):1043-50

Chronic dosage of imipramine in animal experiment: concentrations of imipramine and desipramine in the rat brain after various modes of dosage. Melzacka M, et al. **Pol J Pharmacol Pharm** 1985 Jul-Aug; 37(4):525-32

Characterization of endogenous inhibitors of [3H]-imipramine binding and [3H]-serotonin uptake from rat serum. Angel I, et al. **Prog Clin Biol Res** 1985;192:457-64

Characterization of the endocoid for imipramine recognition sites. Barbaccia ML, et al. **Prog Clin Biol Res** 1985;192:431-40

5-methoxytryptoline and close analogs as candidates for the endogenous ligand of the 3H-imipramine recognition site. Langer SZ, et al. **Prog Clin Biol Res** 1985;192:441-55

Demonstration of an imipramine endacoid in rat brain. Rehavi M, et al. **Prog Clin Biol Res** 1985;192:465-72

Cardiovascular peripheric effects of a new tricyclic antidepressant, cianopramine (Ro 11-2465) in dogs. Cicardo VH, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):381-6

Variation in human platelet 3H-imipramine binding. Tang SW, et al. **Psychiatry Res** 1985 Oct;16(2):141-6

Lower 3H-imipramine binding in platelets from untreated depressed patients compared to healthy controls. Wägner A, et al. **Psychiatry Res** 1985 Oct;16(2):131-9

Fear-enhanced acoustic startle is not attenuated by acute or chronic imipramine treatment in rats. Cassella JV, et al. **Psychopharmacology (Berlin)** 1985;87(3):278-82

Some effects of chlorimipramine and imipramine on the schedule-controlled behavior of the pigeon. Lamb RJ, et al. **Psychopharmacology (Berlin)** 1985;87(1):7-11

IMPRINTING (PSYCHOLOGY)

Neurochemical studies on imprinting behavior in chick and duckling. Takamatsu K, et al. **Neurochem Res** 1985 Oct;10(10):1371-91

INHIBITION (PSYCHOLOGY)

Extinguishing conditioned inhibition in flavour-aversion learning: effects of repeated testing and extinction of the excitatory element. Best MR, et al. **Q J Exp Psychol [B]** 1985 Nov;37(4):359-78

LEARNING

Electrolytic, but not 5,7-dihydroxytryptamine, lesions of the nucleus medianus raphe impair acquisition of a radial maze task. Asin KE, et al. **Behav Neural Biol** 1985 Nov;44(3):415-24

Sex-dependent effects of neonatally administered morphiceptin and D-ala-D-leu-enkephalin on maze learning in rats. de Avila A, et al. **Behav Neural Biol** 1985 Nov;44(3):393-402

Post-training brain catecholamine levels: lack of response to water-motivated training. Gold PE, et al. **Behav Neural Biol** 1985 Nov; 44(3):425-33

Epinephrine facilitation of appetitive learning: attenuation with adrenergic receptor antagonists. Sternberg DB, et al. **Behav Neural Biol** 1985 Nov; 44(3):447-53

On-demand platform improves accuracy of the Morris water maze procedure. Burešová O, et al. **J Neurosci Methods** 1985 Oct; 15(1):63-72

ACTH neuromodulation of the developing motor system and neonatal learning in the rat. Acker GR, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 2:41-9

[Memory--2. Neurophysiologic studies of learning] Tsukahara N. **Nippon Rinsho** 1985 Jul;43(7):1314-20 (20 ref.) **(Jpn)**

[Memory--4. Physiological and biochemical studies in memory and learning] Yamamoto C. **Nippon Rinsho** 1985 Jul;43(7):1332-5 **(Jpn)**

LEVODOPA

The effect of an increased ratio of carbidopa to levodopa on the pharmacokinetics of levodopa. Kaakkola S, et al. **Acta Neurol Scand** 1985 Oct;72(4):385-91

Sinemet 'abusers'. Nausieda PA. **Clin Neuropharmacol** 1985;8(4):318-27

Effect of L-dopa with and without inhibition of extra cerebral dopa decarboxylase on gastric acid secretion and gastrin release in man. Caldara R, et al. **Gut** 1985 Oct;26(10):1014-7

Dopaminergic drugs improve human visual contrast sensitivity. Domenici L, et al. **Hum Neurobiol** 1985;4(3):195-7

L-dopa in the treatment of negative schizophrenic symptoms: a single-subject experimental study. Kay SR, et al. **Int J Psychiatry Med** 1985-86;15(3):293-8

Effects of L-dopa supplementation on concentrations of brain catechols, dopamine receptor binding and the incidence of pale, soft and exudative meat in stress-susceptible pigs. Erlander MG, et al. **J Anim Sci** 1985 Oct;61(4):914-23

Copper(II) and nickel(II) ternary complexes of L-dopa and related compounds. Kiss T, et al. **J Inorg Biochem** 1985 Dec;25(4):247-59

Increased life expectancy resulting from addition of L-deprenyl to Madopar treatment in Parkinson's disease: a longterm study. Birkmayer W, et al. **J Neural Transm** 1985;64(2):113-27

The inotropic effects of dopamine and its precursor levodopa on isolated human ventricular myocardium. Brown L, et al. **Klin Wochenschr** 1985 Nov 4;63(21):1117-23

Effects of L-dopa and L-tyrosine on release of free and conjugated dopamine, homovanillic acid and dihydroxyphenylacetic acid from slices of rat striatum. Tyce GM, et al. **Life Sci** 1985 Dec 23; 37(25):2439-48

LH

Regulation of gonadotrophin secretion in male mice from birth to adulthood. Response to LRH injection, castration and testosterone replacement therapy. Jean-Faucher C, et al. **Acta Endocrinol (Copenh)** 1985 Oct;110(2):193-9

The depressing (negative) effect of oestradiol benzoate on the in vitro secretion of LH and FSH by the pituitary gland of the LRH-pretreated long-term ovariectomized rat changes into the augmentative (positive) effect after discontinuation of the LRH-pretreatment. Schuiling GA, et al. **Acta Endocrinol (Copenh)** 1985 Nov;110(3):329-37

GnRH-stimulated LH release from rat anterior pituitary cells in culture: refractoriness and recovery. Jinnah HA, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 1):E619-25

cAMP augmentation of secretagogue-induced luteinizing hormone secretion. Turgeon JL, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 1):E62-8

Effects of calmodulin and lipoxygenase inhibitors on LH (lutropin)- and LHRH (luliberin)-agonist-stimulated steroidogenesis in rat Leydig cells. Sullivan MH, et al. **Biochem J** 1985 Nov 15;232(1):55-9

The role of endogenous gonadotropin-releasing hormone in the control of luteinizing hormone and testosterone secretion in the juvenile male monkey, Macaca fascicularis. Cameron JL, et al. **Biol Reprod** 1985 Aug; 33(1):147-56

Postcastration rise in plasma gonadotropins is blocked by a luteinizing hormone-releasing hormone antagonist. Condon TP, et al. **Biol Reprod** 1985 Oct;33(3):715-21

Effect of alterations in pulsatile luteinizing hormone release on ovarian follicular atresia and steroid secretion on diestrus 1 in the rat estrous cycle. Devorshak-Harvey E, et al. **Biol Reprod** 1985 Aug; 33(1):103-11

Active immunization of gilts against gonadotropin-releasing hormone: effects on secretion of gonadotropins, reproductive function, and responses to agonists of gonadotropin-releasing hormone. Esbenshade KL, et al. **Biol Reprod** 1985 Oct;33(3):569-77

Serotonergic influences on pituitary gland and hypothalamic induction of prolactin and luteinizing hormone release in the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Biol Reprod** 1985 Dec; 33(5):1064-72

Does the seasonal increase in estradiol negative feedback prevent luteinizing hormone surges in anestrous ewes by suppressing hypothalamic gonadotropin-releasing hormone pulse frequency? Legan SJ, et al. **Biol Reprod** 1985 Aug;33(1):117-31

Effects of intermittent pulsatile infusion of luteinizing hormone-releasing hormone on dihydrotestosterone-suppressed gonadotropin secretion in castrate rams. Schanbacher BD. **Biol Reprod** 1985 Oct;33(3):603-11

Simultaneous measurement of luteinizing hormone-releasing hormone and luteinizing hormone during estradiol-induced luteinizing hormone surges in the ovariectomized ewe. Schillo KK, et al. **Biol Reprod** 1985 Oct;33(3):644-52

Changes of the release of luteinizing hormone (LH) on the day of proestrus after lesions or stimulation of the raphe nuclei in rats. Morello H, et al. **Brain Res** 1985 Dec 23;360(1-2):311-7

Electrochemical stimulation of plasma LH and hypothalamic norepinephrine concentrations at short- and long-term intervals after hypothalamic knife cuts. Phelps CP, et al. **Brain Res** 1985 Nov 18; 347(2):328-35

The role of endogenous serotonin in phasic LH release. Meyer DC, et al. **Brain Res Bull** 1985 Sep;15(3):283-6

Localization in the brain of the inhibition by GABA of luteinizing hormone release that follows orchidectomy in rats. Donoso AO. **Braz J Med Biol Res** 1985;18(1):97-100

Cellular mechanisms of acute estrogen negative feedback on LH secretion: pituitary responsiveness to LHRH and estradiol receptor kinetics in the pituitary, preoptic hypothalamic area, and the caudal hypothalamic area of the rat brain. Johnston CA, et al. **Braz J Med Biol Res** 1985; 18(1):125-30

Muscarinic cholinergic mediation of LHRH-induced LH and FSH secretion in normal men. Chiodera P, et al. **Clin Endocrinol (Oxf)** 1985

Oct;23(4):361-6

Dose-related changes in LH bioactivity with intranasal GnRH agonist administration. Chiang RS, et al. **Contraception** 1985 Oct; 32(4):347-57

Evidence for gamma-aminobutyric acid modulation of ovarian hormonal effects on luteinizing hormone secretion and hypothalamic catecholamine activity in the female rat. Adler BA, et al. **Endocrinology** 1986 Jan;118(1):91-7

Developmental changes in the positive feedback effect of estrogen on luteinizing hormone release in ovariectomized female rhesus monkeys. Terasawa E. **Endocrinology** 1985 Dec;117(6):2490-7

Influence of cerebroventricular injection of dopamine on plasma prolactin and LH levels of postlaying and broody turkey hens. Hargis BM, et al. **Gen Comp Endocrinol** 1986 Jan;61(1):142-7

Effects of gonadectomy and steroid treatment on plasma gonadotropins and the response of superfused pituitaries to gonadotropin-releasing hormone in the turtle Sternotherus odoratus. Licht P, et al. **Gen Comp Endocrinol** 1985 Dec;60(3):441-9

Suppression of plasma gonadotropins and testosterone in adult male monkeys (Macaca fascicularis) by a potent inhibitory analog of gonadotropin-releasing hormone. Adams LA, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):58-63

Dopamine decreases release of luteinizing hormone releasing hormone from superfused rat mediobasal hypothalamus. Tasaka K, et al. **J Endocrinol Invest** 1985 Aug;8(4):373-6

Hormonal responses to gonadotrophin releasing hormone during testicular development in male African green monkeys. Brady AG, et al. **J Med Primatol** 1985;14(6):293-304

Fetal Leydig cell culture--an in vitro system for the study of trophic hormone and GnRH receptors and actions. Dufau ML, et al. **J Steroid Biochem** 1985 Nov;23(5B):743-55 (84 ref.)

Mechanism of action of gonadotropin releasing hormone: role of lipoxygenase products of arachidonic acid in luteinizing hormone release. Naor Z, et al. **J Steroid Biochem** 1985 Nov;23(5B):711-7

Luteinizing hormone releasing activity of [Gln8]-LHRH and [His5, Trp7, Tyr8]-LHRH in the cockerel, in vivo and in vitro. Chou HF, et al. **Life Sci** 1985 Dec 30;37(26):2459-65

Central effects of an antagonist and an antiserum to substance P on serum gonadotropin and prolactin secretion. Dees WL, et al. **Life Sci** 1985 Oct 28;37(17):1627-31

Inhibition of gonadotropin secretion induced by cholecystokinin implants in the medial preoptic area by the dopamine receptor blocker, pimozide, in the rat. Hashimoto R, et al. **Neuroendocrinology** 1986;42(1):32-7

Estrogen exposure affects the post-ovariectomy increases in both LH and FSH release in female rats. Matt DW, et al. **Neuroendocrinology** 1986;42(1):21-7

Neural signals for oxytocin and LH release. Dyer RG. **Oxf Rev Reprod Biol** 1985;7:223-60 (104 ref.)

Mediation by gonadal steroids of plasma beta-endorphin and LH in castrated female and male rats. Forman LJ, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):835-9

Effects of in vivo pretreatment with D-Trp-6-LH-RH on prolactin and LH secretion by pituitary glands in vitro. Torres-Aleman I, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):993-5

[Studies on the feedback regulation of pulsatile luteinizing hormone secretion. II. Role of the catecholaminergic system in estrogen-induced suppression of the frequency of pulsatile LH secretion in ovariectomized rats] Tadokoro Y. **Nippon Naibunpi Gakkai Zasshi** 1985 Jul 20; 61(7):765-74 (Eng. Abstr.) **(Jpn)**

LH-FSH RELEASING HORMONE

Regulation of gonadotrophin secretion in male mice from birth to adulthood. Response to LRH injection, castration and testosterone replacement therapy. Jean-Faucher C, et al. **Acta Endocrinol (Copenh)** 1985 Oct;110(2):193-9

The depressing (negative) effect of oestradiol benzoate on the in vitro secretion of LH and FSH by the pituitary gland of the LRH-pretreated long-term ovariectomized rat changes into the augmentative (positive) effect after discontinuation of the LRH-pretreatment. Schuiling GA, et al. **Acta Endocrinol (Copenh)** 1985 Nov;110(3):329-37

GnRH-stimulated LH release from rat anterior pituitary cells in culture: refractoriness and recovery. Jinnah HA, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 1):E619-25

Possible vascular effects of an LH-RH agonist on the peripheral circulation of the rat testes. Habenicht UF, et al. **Andrologia** 1985 Sep-Oct;17(5):440-3

Changes in LHRH in human maternal plasma during pregnancy. Kawamura Y, et al. **Asia Oceania J Obstet Gynaecol** 1985 Sep; 11(3):437-40

Gonadotropin releasing hormone activation is mediated by dimerization of occupied receptors. Hazum E, et al. **Biochem Biophys Res Commun** 1985 Dec 17;133(2):449-56

Calcium-independent phosphatidylinositol response in gonadotropin-releasing-hormone-stimulated pituitary cells. Naor Z, et al. **Biochem J** 1985 Oct 1;231(1):19-23

Postcastration rise in plasma gonadotropins is blocked by a luteinizing hormone-releasing hormone antagonist. Condon TP, et al. **Biol Reprod** 1985 Oct;33(3):715-21

Active immunization of gilts against gonadotropin-releasing hormone: effects on secretion of gonadotropins, reproductive function, and responses to agonists of gonadotropin-releasing hormone. Esbenshade KL, et al. **Biol Reprod** 1985 Oct;33(3):569-77

Effects of intermittent pulsatile infusion of luteinizing hormone-releasing hormone on dihydrotestosterone-suppressed gonadotropin secretion in castrate rams. Schanbacher BD. **Biol Reprod** 1985 Oct;33(3):603-11

Simultaneous measurement of luteinizing hormone-releasing hormone and luteinizing hormone during estradiol-induced luteinizing hormone surges in the ovariectomized ewe. Schillo KK, et al. **Biol Reprod** 1985 Oct;33(3):644-52

Cellular mechanisms of acute estrogen negative feedback on LH secretion: pituitary responsiveness to LHRH and estradiol receptor kinetics in the pituitary, preoptic hypothalamic area, and the caudal hypothalamic area of the rat brain. Johnston CA, et al. **Braz J Med Biol Res** 1985; 18(1):125-30

Inhibition of testosterone production with ketoconazole alone and in combination with a gonadotropin releasing hormone analogue in the rat. English HF, et al. **Cancer Res** 1986 Jan;46(1):38-42

Ependymoneuronal specializations between LHRH fibers and cells of the cerebroventricular system. Kozlowski GP, et al. **Cell Tissue Res** 1985; 242(2):301-11

Muscarinic cholinergic mediation of LHRH-induced LH and FSH secretion in normal men. Chiodera P, et al. **Clin Endocrinol (Oxf)** 1985 Oct;23(4):361-6

Dose-related changes in LH bioactivity with intranasal GnRH agonist administration. Chiang RS, et al. **Contraception** 1985 Oct; 32(4):347-57

Species differences in the sensitivity to a GnRH antagonist. Limonta P, et al. **Contraception** 1985 Jul;32(1):75-85

Regulation of pituitary gonadotropin-releasing hormone (GnRH) receptors by pulsatile GnRH in female rats: effects of estradiol and prolactin. Duncan JA, et al. **Endocrinology** 1986 Jan;118(1):320-7

Proopiomelanocortin-derived peptides in testicular interstitial fluid: characterization and changes in secretion after human chorionic gonadotropin or luteinizing hormone-releasing hormone analog treatment. Valenca MM, et al. **Endocrinology** 1986 Jan;118(1):32-7

Alternative indications for pulsatile gonadotropin-releasing hormone therapy in infertile women. Phansey SA, et al. **Fertil Steril** 1985 Nov; 44(5):589-94

Immunoreactive gonadotropin-releasing hormone-like material in the brain and the pituitary gland during the periovulatory period in the brown trout (Salmo trutta L.): relationships with the plasma and pituitary gonadotropin. Breton B, et al. **Gen Comp Endocrinol** 1986 Jan; 61(1):109-19

In vitro study of the direct ovarian effects of gonadotropin-releasing hormone (GnRH) in the frogs, Rana pipiens and Rana catesbeiana. Hubbard GM, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):154-61

Projections of luteinizing hormone-releasing hormone and vasotocin fibers to the anterior part of the preoptic nucleus in the toad, Bufo japonicus. Jokura Y, et al. **Gen Comp Endocrinol** 1985 Dec; 60(3):390-7

Effect of mammalian luteinizing hormone-releasing hormone on plasma testosterone in male alligators, with observations on the nature of alligator hypothalamic gonadotropin-releasing hormone. Lance VA, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):138-43

In vivo and in vitro responses to gonadotropin releasing hormone in the turtle, Chrysemys picta, in relation to sex and reproductive stage. Licht P, et al. **Gen Comp Endocrinol** 1985 Oct;60(1):75-85

Stress-induced inhibition of reproduction: evidence of suppressed secretion of LH-RH in an amphibian. Moore FL, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):252-8

Topical absorption of gonadotropin-releasing hormone (GnRH) in goldfish. Sherwood NM, et al. **Gen Comp Endocrinol** 1986 Jan; 61(1):13-9

Effects of dibutyryl cyclic AMP and gonadotropin-releasing hormone added prior to filter sterilization of the media and variation in oxygen partial pressure on output of human chorionic gonadotropin from term placental explants. Haning RV Jr, et al. **Gynecol Obstet Invest** 1985; 20(2):74-7

Luteinizing hormone-releasing hormone facilitates the display of sexual behavior in male voles (Microtus canicaudus). Boyd SK, et al. **Horm Behav** 1985 Sep;19(3):252-64

Studies of a controlled-release microcapsule formulation of an LH-RH agonist (D-Trp-6-LH-RH) in the rhesus monkey menstrual cycle. Asch RH, et al. **Int J Fertil** 1985;30(2):19-26

Suppression of plasma gonadotropins and testosterone in adult male monkeys (Macaca fascicularis) by a potent inhibitory analog of gonadotropin-releasing hormone. Adams LA, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):58-63

Characterization of a gonadotropin-releasing hormone receptor site in term placenta and chorionic villi. Iwashita M, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):127-33

Administration of low dose pulsatile gonadotropin-releasing hormone

(GnRH) to GnRH-deficient men regulates free alpha-subunit secretion. Spratt DI, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):102-8

In-vivo activity of the LH-releasing hormone pulse generator in castrated and intact male rats. Dluzen DE, et al. **J Endocrinol** 1985 Dec; 107(3):331-40

LRFD6a has a dose-related stimulatory or inhibitory effect on the ovary in normal luteal phase women. Barnea ER, et al. **J Endocrinol Invest** 1985 Aug;8(4):297-302

Dopamine decreases release of luteinizing hormone releasing hormone from superfused rat mediobasal hypothalamus. Tasaka K, et al. **J Endocrinol Invest** 1985 Aug;8(4):373-6

Steroid and thyroid hormone profiles following a single injection of partly purified salmon gonadotropin or GnRH analogues in male and female sea lamprey. Sower SA, et al. **J Exp Zool** 1985 Sep;235(3):403-8

Luteinizing hormone releasing hormone (LHRH): I. A new ovulation-inducing agent. Rojanasakul A, et al. **J Med Assoc Thai** 1985 Oct;68(10):528-33

Ovulation induction and pregnancy in women with hypothalamic amenorrhea treated with intermittent gonadotropin-releasing hormone. Corenblum B, et al. **J Reprod Med** 1985 Oct;30(10):736-40

Potentiation of GnRH response by clomiphene citrate. Goerzen J, et al. **J Reprod Med** 1985 Oct;30(10):749-52

Unexplained infertility and its treatment with intermittent GnRH application. Bohnet HG. **J Steroid Biochem** 1985 Nov;23(5B):863-5

Molecular mechanism of gonadotropin releasing hormone action. Conn PM, et al. **J Steroid Biochem** 1985 Nov;23(5B):703-10

Pregnancy interfering action of LHRH and anti-LHRH. Das C, et al. **J Steroid Biochem** 1985 Nov;23(5B):803-6

Fetal Leydig cell culture--an in vitro system for the study of trophic hormone and GnRH receptors and actions. Dufau ML, et al. **J Steroid Biochem** 1985 Nov;23(5B):743-55 (84 ref.)

Gonadotropin-releasing hormone as a paracrine hormone and neurotransmitter in extra-pituitary sites. Hsueh AJ, et al. **J Steroid Biochem** 1985 Nov;23(5B):757-64

Effect of LHRH agonists and antagonists in male and female bonnet monkeys (Macaca radiata). Jagannadha Rao A, et al. **J Steroid Biochem** 1985 Nov;23(5B):807-9

Stimulation of hypothalamic LHRH levels and release by gonadal steroids. Kalra PS. **J Steroid Biochem** 1985 Nov;23(5B):725-31

In the central role of GnRH in the regulation of reproductive functions: mechanism of action and practical results. Keri G, et al. **J Steroid Biochem** 1985 Nov;23(5B):719-23 (9 ref.)

Gonadotropin-releasing hormone as a modulator of ovarian function. Knecht M, et al. **J Steroid Biochem** 1985 Nov;23(5B):771-8 (61 ref.)

Antigonadotropic actions of GnRH agonist on ovarian cells in vivo and in vitro. Maruo T, et al. **J Steroid Biochem** 1985 Nov;23(5B):765-70

Mechanism of action of gonadotropin releasing hormone: role of lipoxygenase products of arachidonic acid in luteinizing hormone release. Naor Z, et al. **J Steroid Biochem** 1985 Nov;23(5B):711-7

Gonadotropin releasing hormone analogs for female contraception by inhibition of ovulation. Nillius SJ. **J Steroid Biochem** 1985 Nov; 23(5B):849-54

Inhibition of sex-steroid hormone induced ornithine decarboxylase and poly(A)-polymerase activities by a GnRH agonist in the rat kidney. Prasad MS, et al. **J Steroid Biochem** 1985 Nov;23(5B):793-4

Direct inhibitory actions of GnRH on accessory reproductive organs of rat. Reddy PR, et al. **J Steroid Biochem** 1985 Nov;23(5B):819-22

The dominant role of amide group at C-terminus for recognition by antibody in primates against gonadotropin releasing hormone. Singh V, et al. **J Steroid Biochem** 1985 Nov;23(5B):801-2

Hormonal effects of GnRH agonist in the human male: an approach to male contraception using combined androgen and GnRH agonist treatment. Swerdloff RS, et al. **J Steroid Biochem** 1985 Nov; 23(5B):855-61

Immunobiology of gonadotropin-releasing hormone. Talwar GP. **J Steroid Biochem** 1985 Nov;23(5B):795-800 (37 ref.)

Species differences in the sensitivity to GnRH analogs. Thau RB, et al. **J Steroid Biochem** 1985 Nov;23(5B):811-7

Comparisons of the potential utility of LHRH agonists and antagonists for fertility control. Vickery BH. **J Steroid Biochem** 1985 Nov; 23(5B):779-91 (83 ref.)

Recent developments in female contraception: LHRH. Vijayan E. **J Steroid Biochem** 1985 Nov;23(5B):827-31

Luteinizing hormone releasing activity of [Gln8]-LHRH and [His5, Trp7, Tyr8]-LHRH in the cockerel, in vivo and in vitro. Chou HF, et al. **Life Sci** 1985 Dec 30;37(26):2459-65

Sexually dimorphic age-related changes in the distribution of immunoreactive luteinizing hormone releasing hormone in the platyfish. Schreibman MP, et al. **Mech Ageing Dev** 1985 Dec;33(1):29-37

The isolation and measurement of luteinizing hormone-releasing hormone (LHRH) from the rat testis. Hedger MP, et al. **Mol Cell Endocrinol** 1985 Sep;42(2):163-74

Effects of castration and maturational age of male rats on the process of copper-stimulated release of luteinizing hormone releasing hormone from median eminence explants: evidence that androgens increase the affinity of the copper-interactive sites for copper. Colombani-Vidal M, et al. **Neuroendocrinology** 1985 Dec;41(6):454-61

Luteinizing hormone releasing hormone enhances proceptivity in a primate. Kendrick KM, et al. **Neuroendocrinology** 1985 Dec; 41(6):449-53

FSH- and LH-releasing activity in the hypothalamus of female hamsters during proestrus and estrus: effects of arcuate nucleus lesions. Lamperti AA. **Neuroendocrinology** 1985 Nov;41(5):374-9

Neural signals for oxytocin and LH release. Dyer RG. **Oxf Rev Reprod Biol** 1985;7:223-60 (104 ref.)

Organization of LHRH cells: differential apposition of neurotensin, substance P and catecholamine axons. Hoffman GE. **Peptides (Fayetteville)** 1985 May-Jun;6(3):439-61

Multiple molecular forms of gonadotropin-releasing hormone in teleost fish brain. King JA, et al. **Peptides (Fayetteville)** 1985 Jul-Aug; 6(4):689-94

Neuronal responsiveness to gonadotropin-releasing hormone and its correlation with sexual receptivity in the rat. Rothfeld JM, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):603-8

LH-RH antagonist inhibits gonadal steroid secretion in vitro. Spona J, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):379-82

Effects of in vivo pretreatment with D-Trp-6-LH-RH on prolactin and LH secretion by pituitary glands in vitro. Torres-Alemán I, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):993-5

Isolation of the gene and hypothalamic cDNA for the common precursor of gonadotropin-releasing hormone and prolactin release-inhibiting factor in human and rat. Adelman JP, et al. **Proc Natl Acad Sci USA** 1986 Jan;83(1):179-83

Characterization of pituitary calcium-activated, phospholipid-dependent protein kinase: redistribution by gonadotropin-releasing hormone. Naor Z, et al. **Proc Natl Acad Sci USA** 1985 Dec;82(23):8203-7

Inhibition of gonadotropin-induced granulosa cell differentiation by activation of protein kinase C. Shinohara O, et al. **Proc Natl Acad Sci USA** 1985 Dec;82(24):8518-22

Manipulation of the hypothalamo-pituitary gonadal axis in the juvenile rainbow trout: influence of pituitary transplantation and LHRH analogue treatment. Weil C, et al. **Reprod Nutr Dev** 1985; 25(5):895-907

[Peptidergic transmission and late slow EPSP in sympathetic ganglion cells] Jiang ZG. **Sneng Li Ko Hsueh Chin Chan** 1984 Oct; 15(4):301-5 **(Chi)**

[Ovulation induction using synthetic LHRH] de Plunkett T. **Soins Gynecol Obstet Pueric Pediatr** 1985 Jun-Jul;(49-50):21-4 **(Fre)**

[Treatment of sex behavior disorders with LH-RH superagonists (letter)] Allolio B, et al. **Dtsch Med Wochenschr** 1985 Dec 13;110(50):1952 **(Ger)**

[Metabolism of progesterone in fetal membranes. The effect of sex steroids and gonadotropin-releasing hormone on progesterone metabolism in fetal membranes] Hori D, et al. **Igaku Kenkyu** 1985 Jul;55(2):97-102 (Eng. Abstr.) **(Jpn)**

[Study on the direct inhibitory action of luteinizing hormone-releasing hormone on the steroidogenesis of cultured human corpus luteum cells] Okamoto S. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Oct; 37(10):2107-16 (Eng. Abstr.) **(Jpn)**

[Interrelations between monoamines and luliberin in the synaptosomes of the medio-basal hypothalamus and its separate structures] Babichev VN, et al. **Probl Endokrinol (Mosk)** 1985 Sep-Oct;31(5):36-41 (Eng. Abstr.) **(Rus)**

LIPOTROPIN

Dermorphin reduces the metyrapone-evoked release of adrenocorticotropin, beta-endorphin, and beta-lipotropin in man. Degli Uberti EC, et al. **J Clin Endocrinol Metab** 1985 Dec;61(6):1018-22

[The study of opioid peptides in the normal menstrual cycle, pregnancy and labor] Takayama S, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Sep;37(9):1813-9 (Eng. Abstr.) **(Jpn)**

LITHIUM

Diurnal variations in serum lithium and renal lithium clearance in rats given lithium as a single small dose or as multiple high doses. Olesen OV, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Sep;57(3):171-5

Lithium and hair texture. McCreadie RG, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):387-8

Lithium and bulimia: the role of the dopaminergic and opiatergic systems [letter] Gillman MA, et al. **Am J Psychiatry** 1985 Dec; 142(12):1522-3

Using MMPI lithium response scales [letter] Lane JB. **Am J Psychiatry** 1985 Nov;142(11):1388-9

A comment on 'coyote control and taste aversion'. Burns RJ, et al. **Appetite** 1985 Sep;6(3):276-81

Coyote control and taste aversion: a predation problem or a people problem? Ellins SR. **Appetite** 1985 Sep;6(3):272-5

Research on forms of conditioned avoidance in coyotes. Lehner PN, et al. **Appetite** 1985 Sep;6(3):265-7

Coyote control and taste aversion. Quick DL, et al. **Appetite** 1985 Sep; 6(3):253-64

Brief comments on 'coyote control and taste aversion'. Wade DA. **Appetite** 1985 Sep;6(3):268-71

Lithium and RBC water permeability [letter] Ballast CL, et al. **Biol Psychiatry** 1985 Dec;20(12):1336-7

NMR chemistry analysis of red blood cell constituents in normal subjects and lithium-treated psychiatric patients. Domino EF, et al. **Biol Psychiatry** 1985 Dec;20(12):1277-83

Does lithium stabilize muscarinic receptors? [letter] Lerer B, et al. **Biol Psychiatry** 1985 Nov;20(11):1247-50

Interhelical effects on the low-frequency modes and phase transitions of Li- and Na-DNA. Demarco C, et al. **Biopolymers** 1985 Nov; 24(11):2035-40

Lithium in severe depression [letter] Fraser AA, et al. **Br J Psychiatry** 1985 Sep;147:324

Social support and long-term lithium outcome. O'Connell RA, et al. **Br J Psychiatry** 1985 Sep;147:272-5

Lithium potentiation of imipramine in treatment resistant depression [letter] Roy A, et al. **Br J Psychiatry** 1985 Nov;147:582-3

Response to sequential administration of clomipramine and lithium carbonate in treatment-resistant depression. Schrader GD, et al. **Br J Psychiatry** 1985 Nov;147:573-5

Plasma immunoglobulins in depressed and lithium-treated patients [letter] Wood K, et al. **Br J Psychiatry** 1985 Nov;147:581-2

Behavioural structure and mechanisms of anorexia: calibration of natural and abnormal inhibition of eating. Blundell JE, et al. **Brain Res Bull** 1985 Oct;15(4):371-6

Lithium effects on selected circadian rhythms in rats. McEachron DL, et al. **Brain Res Bull** 1985 Sep;15(3):347-50

Thermodynamic characterization of the partially denatured states of ribonuclease A in calcium chloride and lithium chloride. Ahmad F. **Can J Biochem Cell Biol** 1985 Oct;63(10):1058-63

Effect of fluoride, lithium or strontium on acid production by pelleted human dental plaque (short communication). Eisenberg AD, et al **Caries Res** 1985;19(5):454-7

Li as exogenous marker for urine volume determinations [letter] Larsen CE. **Clin Chem** 1986 Jan;32(1 Pt 1):222

Lithium suppresses hibernation in the Turkish hamster. Giedke H, et al. **Experientia** 1985 Nov 15;41(11):1391-2

Effect of long term lithium therapy on red blood cell choline transport in neutropenic patients. Falezza G, et al. **Haematologica (Pavia)** 1985 May-Jun;70(3):202-4

Production of LiF:Ti thermoluminescence dosimeter material. Aypar A, et al. **Int J Appl Radiat Isot** 1985 Jul;36(7):566-8

Lithium and impairment of renal concentrating ability. Miller AL, et al. **J Affective Disord** 1985 Sep;9(2):115-9

Lithium-carbamazepine versus lithium-neuroleptic prophylaxis in bipolar illness. Shukla S, et al. **J Affective Disord** 1985 Nov;9(3):219-22

Coupling of Li+ distribution to the plasma membrane potential of rat cortical synaptosomes. Schmalzing G. **J Biol Chem** 1986 Jan 15; 261(2):650-6

Mixed bipolar disorder responsive to lithium and clonazepam [letter] Adler LW. **J Clin Psychiatry** 1986 Jan;47(1):49-50

Lithium carbonate and the 'cycloid spectrum' [letter] Novae A. **J Clin Psychiatry** 1985 Nov;46(11):504-5

Failure of sulindac to increase serum lithium levels. Ragheb MA, et al. **J Clin Psychiatry** 1986 Jan;47(1):33-4

Ordinary conditions for indefinite continuation of lithium therapy [letter] Sandifer MG. **J Clin Psychiatry** 1985 Nov;46(11):505

Effective management with lithium of a persistent, post-traumatic hypomania in a 10-year-old child. Joshi P, et al. **J Dev Behav Pediatr** 1985 Dec;6(6):352-4

Resolution of the competitive inhibitory effects of lithium and AMPPNP on the beat frequency of ATP-reactivated, demembranated, sea urchin sperm flagella. Pate EF et al. **J Muscle Res Cell Motil** 1985 Aug; 6(4):507-12

Effects of chronic dietary lithium on behavioral indices of dopamine denervation supersensitivity in the rat. Swerdlow NR et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):324-9

Reduction of temperature and lithium poisoning [letter] Follézou JY, et al. **N Engl J Med** 1985 Dec 19;313(25):1609

Striatal dopamine and motor activity changes observed shortly after lithium administration. Otero Losada ME, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Sep;330(3):169-74

Membranes, methylation and lithium responsive psychoses. Hitzemann R, et al. **Nutr Health** 1984;3(3):153-62

Lithium perhydroantamanide complex (2:1): exposure of the peptide backbone in the analog of antamanide with antitoxic impotency. Karle IL. **Proc Natl Acad Sci USA** 1985 Nov;82(21):7155-9

Prophylaxis and the lithium ratio in bipolar patients. Yassa R, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):423-8

Lithium attenuates the activation-euphoria but not the psychosis induced by d-amphetamine in schizophrenia. van Kammen DP, et al. **Psychopharmacology (Berlin)** 1985;87(1):111-5

Reduction of specific arginine-vasopressin binding sites of renal medulla membranes in lithium treated rats. Mitsui T, et al. **Res Commun Chem Pathol Pharmacol** 1985 Nov;50(2):201-8

[Lithium intoxication--report of 10 cases] Wang SY, et al. **Taiwan I Hsueh Hui Tsa Chih** 1985 Aug;84(8):960-8 (Eng. Abstr.) **(Chi)**

[Prophylactic efficacy of lithium in recurrent bipolar affective disorders] Yang YY, et al. **Taiwan I Hsueh Hui Tsa Chih** 1985 Jun; 84(6):722-6 (Eng. Abstr.) **(Chi)**

[Experience with lithiotherapy in psychoses in childhood and adolescence] Kadlecová B, et al. **Cesk Psychiatr** 1985 Oct;81(5):339-44 (Eng. Abstr.) **(Cze)**

[Lithium prophylaxis, o.k., but for how long?] Slooff CJ, et al. **Ned Tijdschr Geneeskd** 1985 Sep 7;129(36):1729-33 (Eng. Abstr.) **(Dut)**

[Effect of lithium, carbamazepine, ca-valproate and diazepam on changes in social isolation-induced behavior in mice] Oehler J, et al. **Biomed Biochim Acta** 1985;44(10):1523-30 (Eng. Abstr.) **(Ger)**

[Effect of immunomodulators on the production of interleukin 2] Skotnicki AB. **Przegl Lek** 1985;42(7):573-9 (Eng. Abstr.) **(Pol)**

[Lithium in the human body] Fleishman DG, et al. **Fiziol Cheloveka** 1985 Nov-Dec;11(6):1020-5 **(Rus)**

[The renin-angiotensin-aldosterone axis in patients treated with lithium carbonate] Lucas A, et al. **Med Clin (Barc)** 1985 Nov 16; 85(16):647-9 (Eng. Abstr.) **(Spa)**

LORAZEPAM

Beta-blockers and psychic stress: a double-blind, placebo-controlled study of bopindolol vs lorazepam and butalbital in surgical patients. Chierichetti SM, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Sep; 23(9):510-4

Lorazepam use and catatonic syndrome [letter] Peterson GN. **J Clin Psychopharmacol** 1985 Dec;5(6):359-60

MANIC DISORDER

Mania, clonidine, and dopamine [letter] Shen WW. **Am J Psychiatry** 1986 Jan;143(1):127

Drug treatment of bipolar depression and mania. Cookson JC. **Br J Hosp Med** 1985 Sep;34(3):172-5 (92 ref.)

Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. arap Mengech HN, et al. **East Afr Med J** 1984 Jun;61(6):435-8

Tritiated imipramine binding to platelets in manic subjects. Lewis DA, et al. **J Affective Disord** 1985 Nov;9(3):207-11

Effective management with lithium of a persistent, post-traumatic hypomania in a 10-year-old child. Joshi P, et al. **J Dev Behav Pediatr** 1985 Dec;6(6):352-4

Treatment of mania using a calcium antagonist--preliminary trial. Caillard V. **Neuropsychobiology** 1985;14(1):23-6

MATERNAL BEHAVIOR

The importance of olfactory bulb noradrenalin for maternal recognition in sheep. Pissonnier D, et al. **Physiol Behav** 1985 Sep;35(3):361-3

MEMORY

ACTH 4-9 analogue (Org 2766) in depressed elderly patients. II. Effect on memory and vigilance. Frederiksen SO, et al. **Acta Psychiatr Scand** 1985 Oct;72(4):349-57

Age-related memory deficits in rats and mice: enhancement with peripheral injections of epinephrine. Sternberg DB, et al. **Behav Neural Biol** 1985 Sep;44(2):213-20

Epinephrine facilitation of appetitive learning: attenuation with adrenergic receptor antagonists. Sternberg DB, et al. **Behav Neural Biol** 1985 Nov; 44(3):447-53

Defective responsiveness of adenylate cyclase to forskolin in the Drosophila memory mutant rutabaga. Dudai Y, et al. **J Neurogenet** 1985 Dec;2(6):365-80

On-demand platform improves accuracy of the Morris water maze procedure. Burešova O, et al. **J Neurosci Methods** 1985 Oct; 15(1):63-72

Is cholinergic activity of the caudate nucleus involved in memory? Prado-Alcala RA. **Life Sci** 1985 Dec 9;37(23):2135-42 (61 ref.)

Effects of pesticides and drugs on working memory in rats: continuous delayed response. Heise GA, et al. **Pharmacol Biochem Behav** 1985 Oct; 23(4):591-8

Effects of pesticides and drugs on working memory in rats: continuous non-match. Heise GA, et al. **Pharmacol Biochem Behav** 1985 Oct; 23(4):599-605

Chronic administration of sulbutiamine improves long term memory formation in mice: possible cholinergic mediation. Micheau J, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):195-8

Adrenalectomy fails to alter radial maze performance of rats at retention intervals of 24 hours or less. Yongue BG, et al. **Physiol Behav** 1985 Oct;35(4):651-4

Comparative effects of cholinergic drugs and lesions of nucleus basalis or fimbria-fornix on delayed matching in rats. Dunnett SB. **Psychopharmacology (Berlin)** 1985;87(3):357-63

Adrenaline, emotional arousal and memory. Christianson SA, et al. **Scand J Psychol** 1985;26(3):237–48

[Memory--4. Physiological and biochemical studies in memory and learning] Yamamoto C. **Nippon Rinsho** 1985 Jul;43(7):1332–5 **(Jpn)**

[Importance of superslow activity of brain structures to the stability of engrams and the effects of neurotropic substances] Lapina IA. **Vestn Akad Med Nauk SSSR** 1985;(9):38–40 (Eng. Abstr.) **(Rus)**

[Delayed spatial choice in the monkey with different probabilities of signal presentation] Nikitin VS. **Zh Vyssh Nerv Deiat** 1985 Sep–Oct; 35(5):968–70 **(Rus)**

MENTAL DISORDERS

Attitude change concerning right to refuse treatment: the impact of experience. Binder RL, et al. **Am J Psychiatry** 1985 Nov; 142(11):1362–5

Demographic predictors of the use of injectable versus oral antipsychotic medications in outpatients. Price N, et al. **Am J Psychiatry** 1985 Dec; 142(12):1491–2

Prevention of drug abuse by promoting mental health among school students. Gazmuri-Plaza C, et al. **Bull Narc** 1985 Apr–Sep; 37(2–3):107–12

Psychiatrists and their prescribing practices. Falk WE, et al. **Compr Psychiatry** 1985 Nov–Dec;26(6):548–53

Psychotropic medication use in chronically mentally ill females [letter] Batey SR, et al. **Drug Intell Clin Pharm** 1985 Nov;19(11):844–5

Psychological considerations in the use of psychotropic drugs with women patients. Mogul KM. **Hosp Community Psychiatry** 1985 Oct; 36(10):1080–5

Carbamazepine treatment of a patient with Klüver–Bucy syndrome. Stewart JT. **J Clin Psychiatry** 1985 Nov;46(11):496–7

Imaging of [11C]-labelled Ro 15–1788 binding to benzodiazepine receptors in the human brain by positron emission tomography. Persson A, et al. **J Psychiatr Res** 1985;19(4):609–22

The provision of diazepam to psychiatric patients [letter] Hammett E. **Milit Med** 1985 Nov;150(11):625

Longisectional interaction structure analysis (LISA) in psychopharmacology and developmental psychopathology. Lienert GA, et al. **Neuropsychobiology** 1985;14(1):27–34

Problems in the development of neuropeptides as psychotherapeutic drugs. Manberg PJ. **Prog Clin Biol Res** 1985;192:343–8

Brain ventricular size and CSF monoamine metabolites in an adolescent inpatient population. Jennings WS Jr, et al. **Psychiatry Res** 1985 Oct; 16(2):87–94

Computer-assisted review of antipsychotics on acute care units. Molnar G, et al. **QRB** 1985 Sep;11(9):271–4

[Neuroleptics in psychogeriatrics. A proposal for a more rational prescription policy] Willekens-Bogaers MA, et al. **Tijdschr Gerontol Geriatr** 1985 Oct;16(5):179–89 (Eng. Abstr.) **(Dut)**

[The use of psychoactive drugs] Huttunen MO. **Duodecim** 1985; 101(17):1698–711 (82 ref.) **(Fin)**

[The future of biological psychiatry] Linnoila M. **Duodecim** 1985; 101(17):1732–7 **(Fin)**

[Results of psychiatric treatment] Lönnqvist J. **Duodecim** 1985; 101(17):1676–85 **(Fin)**

[Driving fitness. Decrement caused by psychiatric disease and psychopharmaceuticals] Ahlheim C. **Med Monatsschr Pharm** 1985 Oct; 8(10):304–5 **(Ger)**

MENTAL PROCESSES

Control of the human functional state. Medvedev VI, et al. **Hum Physiol** 1984 Sep–Oct;10(5):353–61

MEPROBAMATE

Treatment of meprobamate overdose with repeated oral doses of activated charcoal. Hassan E. **Ann Emerg Med** 1986 Jan;15(1):73–6

Effect of tranquilizers on the total acetylcholine content and acetylcholinesterase activity in the brain tissue of Arvicanthis niloticus. Fathi MM, et al. **Comp Biochem Physiol** [C] 1985;82(2):467–74

[Effect of diazepam, meprobamate and amizyl on the emotional reactions of the rabbit to hypothalamic stimulation] Davituliani DS, et al. **Zh Vyssh Nerv Deiat** 1985 Sep–Oct;35(5):952–6 (Eng. Abstr.) **(Rus)**

METHYLPHENIDATE

Dysthymia and attention deficit disorder in adults [letter] Mattes JA. **Am J Psychiatry** 1986 Jan;143(1):114–5

Obsessive–compulsive symptoms following stimulants [letter] Koizumi HM. **Biol Psychiatry** 1985 Dec;20(12):1332–3

Effect of methylphenidate pretreatment on the behavioral and biochemical responses to amphetamine. Kolta MG, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):279–82

Methylphenidate for medical in-patients. Fisch RZ. **Int J Psychiatry Med** 1985–86;15(1):75–9

A developmental dose–response analysis of the effects of methylphenidate on the peer interactions of attention deficit disordered boys. Cunningham CE, et al. **J Child Psychol Psychiatry** 1985 Nov; 26(6):955–71

Gas chromatographic–mass spectrometric analysis of methylphenidate and p–hydroxymethylphenidate using deuterated internal standards. Patrick KS, et al. **J Chromatogr** 1985 Oct 11;343(2):329–38

Methylphenidate in mild depression: a double-blind controlled trial. Mattes JA. **J Clin Psychiatry** 1985 Dec;46(12):525–7

Acute response to methylphenidate as a predictor of outcome of treatment with TCAs in the elderly. Spar JA, et al. **J Clin Psychiatry** 1985 Nov; 46(11):466–9

Psychostimulant treatment of depressive disorders secondary to medical illness. Woods SW, et al. **J Clin Psychiatry** 1986 Jan;47(1):12–5

Attention deficit disorder with hyperactivity: differential effects of methylphenidate on impulsivity. Rapport MD, et al. **Pediatrics** 1985 Dec;76(6):938–43

Neuropharmacology of methylphenidate and a neural substrate for childhood hyperactivity. Gualtieri CT, et al. **Psychiatr Clin North Am** 1985 Dec;8(4):875–92

METHYPRYLON

Pharmacokinetics of methyprylon following a single oral dose. Gwilt PR, et al. **J Pharm Sci** 1985 Sep;74(9):1001–3

METHYSERGIDE

Methysergide and spinal inhibition from electrical stimulation in the periaqueductal grey. Foong FW, et al. **Eur J Pharmacol** 1985 Oct 22; 116(3):239–48

Peripheral serotonin2 receptor blockade does not inhibit 5–hydroxytryptophan–induced aldosterone stimulation. Shenker Y, et al. **J Clin Endocrinol Metab** 1985 Dec;61(6):1201–4

MMPI

Using MMPI lithium response scales [letter] Lane JB. **Am J Psychiatry** 1985 Nov;142(11):1388–9

MOTION PERCEPTION

High thresholds for movement perception in schizophrenia may indicate abnormal extraneous noise levels of central vestibular activity. Wertheim AH, et al. **Biol Psychiatry** 1985 Nov;20(11):1197–210

MOTOR ACTIVITY

Pharmacological manipulations of the nucleus accumbens: effects on classically conditioned responses and locomotor activity in the cat. Wilson WJ, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(3–4):91–105

Effect of a novel environment on locomotor hyperactivity of rats induced by apomorphine in the nucleus accumbens. Morgenstern R, et al. **Biomed Biochim Acta** 1985;44(10):1517–22

The effects of methyl beta-carboline–3–carboxylate on social interaction and locomotor activity when microinjected into the nucleus raphe dorsalis of the rat. Hindley SW, et al. **Br J Pharmacol** 1985 Nov; 86(3):753–61

Separation of the motor consequences from other actions of unilateral 6–hydroxydopamine lesions in the nigrostriatal neurones of rat brain. Hamilton MH, et al. **Brain Res** 1985 Dec 2;348(2):220–8

Contralateral circling behavior induced by intranigral microinjections of taurine and GABA in rats. Kamata K, et al. **Brain Res** 1985 Sep 23; 343(2):275–82

Rostral hypothalamic microinfusions of 5,7 dihydroxytryptamine produce anatomically and neurochemically selective depletions of hippocampal serotonin and increase the influence of estrogen and food deprivation on locomotor activity. Waldbillig RJ, et al. **Brain Res** 1985 Nov 11; 347(1):149–53

Behavioral, autonomic and motor effects of neuroleptic drugs in cats: motor impairment and aggression. Beleslin DB, et al. **Brain Res Bull** 1985 Sep;15(3):353–6

Dopamine-dependent contralateral circling induced by neurotensin applied unilaterally to the ventral tegmental area in rats. Holmes LJ, et al. **Brain Res Bull** 1985 Nov;15(5):537–8

Differential effects of chronic lead intoxication on circadian rhythm of ambulatory activity and on regional brain norepinephrine levels in rats. Shafiq-ur-Rehman, et al. **Bull Environ Contam Toxicol** 1986 Jan; 36(1):81–91

Suppression of PCP-induced behavioral arousal in the rat by yohimbine pretreatment. Byron K, et al. **Eur J Pharmacol** 1985 Nov 5; 117(2):271–3

Phospholipid liposomes potentiate the inhibitory effect of antidepressant drugs on immobility of rats in a despair test (constrained swim). Drago F, et al. **Eur J Pharmacol** 1985 Sep 24;115(2–3):179–84

SKF 38393 and apomorphine modify locomotion and exploration in rats placed on a holeboard by separate actions at dopamine D-1 and D-2 receptors. Fletcher GH, et al. **Eur J Pharmacol** 1985 Nov 19; 117(3):381–5

best copy available

MOTOR ACTIVITY

Phencyclidine binding sites in the nucleus accumbens and phencyclidine-induced hyperactivity are decreased following lesions of the mesolimbic dopamine system. French ED, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):1-9

Prazosin: effect on psychomotor-stimulant cues and locomotor activity in mice. Snoddy AM, et al. **Eur J Pharmacol** 1985 Oct 22; 116(3):221-8

Glucocorticoids facilitate the retention of acquired immobility during forced swimming. Veldhuis HD, et al. **Eur J Pharmacol** 1985 Sep 24; 115(2-3):211-7

Quantitative differences in the pharmacological effects of (+)- and (-)-cathinone. Gugelmann R, et al. **Experientia** 1985 Dec 15; 41(12):1568-71

Carbon dioxide production by individual mice as an index of behavioral and metabolic activity. Bushnell PJ, et al. **Fundam Appl Toxicol** 1985 Oct;5(5):962-70

Analysis of the long-lasting antagonistic effect of caerulein on amphetamine hyperactivity in rats. Matsubara K, et al. **Jpn J Pharmacol** 1985 Aug;38(4):381-90

Transient responses of heart rate, arterial pressure, and head movement at the beginning of eating in awake cats. Matsukawa K, et al. **Jpn J Physiol** 1985;35(4):599-611

Biochemical and behavioral changes in rats after prolonged treatment with desipramine: interaction with p-chlorophenylalanine. Brunello N, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):20-2

Bromocriptine potentiates the behavioural effects of directly and indirectly acting dopamine receptor agonists in mice. Jenkins OF, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):7-11

Striatal dopamine and motor activity changes observeo shortly after lithium administration. Otero Losada ME, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Sep;330(3):169-74

Mesolimbic dopamine lesions produce an augmented behavioral response to enkephalin. Kalivas PW, et al. **Neuropharmacology** 1985 Oct; 24(10):931-6

Effects of drugs on neurotransmitter release: experiments in vivo and in vitro. Tapia R. **Neurosci Biobehav Rev** 1985 Fall;9(3):391-7 (64 ref.)

Kindling of dopaminergic pathways modifies the effect of substantia nigra lesions on rotational behaviour. Mintz M, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):7-11

ACTH neuromodulation of the developing motor system and neonatal learning in the rat. Acker GR, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 2:41-9

Behavioral investigation of the coexistence of substance P, corticotropin releasing factor, and acetylcholinesterase in lateral dorsal tegmental neurons projecting to the medial frontal cortex of the rat. Crawley JN, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):891-901

Effects of corticotropin releasing factor on locomotor activity in hypophysectomized rats. Eaves M, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):923-6

Different effects of apomorphine on climbing behavior and locomotor activity in three strains of mice. Cabib S, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):555-7

Operantly conditioned running: effects on brain catecholamine concentrations and receptor densities in the rat. de Castro JM, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):495-500

Locomotor effects of cocaine, cocaine congeners, and local anesthetics in mice. Reith ME, et al. **Pharmacol Biochem Behav** 1985 Nov; 23(5):831-6

The effects of thyrotropin releasing hormone on rats with lesions of the mesolimbic and nigrostriatal dopamine systems. Andrews JS, et al. **Physiol Behav** 1985 Jul;35(1):93-7

Mapping of contraversive and ipsiversive circling responses to ventral tegmental and substantia nigra electrical stimulation. Gratton A, et al. **Physiol Behav** 1985 Jul;35(1):61-5

The role of the midbrain reticular formation in the expression of two opposing nigral denervation syndromes. Vaccarino FJ, et al. **Physiol Behav** 1985 Nov;35(5):749-52

Behavioral evidence for cholecystokinin modulation of dopamine in the mesolimbic pathway. Crawley JH. **Prog Clin Biol Res** 1985; 192:131-8

Behavioral effects of cholecystokinin and its related peptides in rats. Itoh S, et al. **Prog Clin Biol Res** 1985;192:139-45

Effects of cholecystokinin and vasoactive intestinal peptide on locomotion and rearing in neofrontal decorticated rats. Katsuura G, et al. **Prog Clin Biol Res** 1985;192:147-50

Depletion of brain serotonin by 5,7-dihydroxytryptamine alters the response to amphetamine and the habituation of locomotor activity in rats. Gately PF, et al. **Psychopharmacology (Berlin)** 1985;87(4):400-5

A stimulatory effect of intraaccumbens injections of noradrenaline on the behavior of rats in the forced swim test. Plaznik A, et al. **Psychopharmacology (Berlin)** 1985;87(1):119-23

Comparison of motor activity measured by two different methods: optical and inductive systems. Diez-Noguera A, et al. **Rev Esp Fisiol** 1985 Sep;41(3):281-5

Partial insomnia, hyperactivity and hyperdipsia induced by repeated administration of toluene in rats: their relation to brain monoamine metabolism. Arito H, et al. **Toxicology** 1985 Oct;37(1-2):99-110

[Effect of hypobaric hypoxia on motor behavior in rats] Bucher U, et al. **Biomed Biochim Acta** 1985;44(7-8):1163-70 (Eng. Abstr.) **(Ger)**

[Effect of desaminoocta-pancreozymin on the locomotor activity of rats] Treptow K, et al. **Biomed Biochim Acta** 1985;44(10):1541-7 (Eng. Abstr.) **(Ger)**

[Development of reverse tolerance to the ambulation-increasing effect of ephedrine after repeated administration in mice] Hirabayashi M, et al. **Yakubutsu Seishin Kodo** 1985 Sep;5(3):231-41 (Eng. Abstr.) **(Jpn)**

MSH

GABAergic regulation of melanocyte-stimulating hormone secretion from the pars intermedia of Xenopus laevis: immunocytochemical and physiological evidence. Verburg-van Kemenade BM, et al. **Endocrinology** 1986 Jan;118(1):260-7

TRH analogue with C-terminal thioamide group. Synthesis, receptor binding, TSH-releasing activity and alpha-MSH-releasing activity. Kruszynski M, et al. **Experientia** 1985 Dec 15;41(12):1576-7

Absence of inhibitory dopaminergic control of the rabbit pituitary gland intermediate lobe. Schimchowitsch S, et al. **Neuroendocrinology** 1986; 42(1):71-4

Acetylation of alpha MSH and beta-endorphin by rat neurointermediate pituitary secretory granule-associated acetyltransferase. Gibson TR, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):615-20

Regulation of biosynthesis and release of pars intermedia peptides in Rana ridibunda: dopamine affects both acetylation and release of alpha-MSH. Jenks BG, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):913-21

Structure-activity studies with ACTH/alpha-MSH fragments on corticosteroid secretion of isolated zona glomerulosa and fasciculata cells. Szalay KS, et al. **Regul Pept** 1985 Jul;11(3):187-92

NEUROREGULATORS

Pharmacological manipulations of the nucleus accumbens: effects on classically conditioned responses and locomotor activity in the cat. Wilson WJ, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(3-4):91-105

Neurotransmitter release by certain neuropeptides in the chicken retina. Bauer B, et al. **Acta Ophthalmol (Copenh)** 1985 Oct;63(5):581-7

Neurochemical regulation of the states of alertness. Gaillard JM. **Ann Clin Res** 1985;17(5):175-84 (59 ref.)

Development of sympathetic neurones in vivo: an investigation of the possible role of glucocorticosteroids in regulating transmitter type. Hill CE, et al. **Aust J Exp Biol Med Sci** 1985 Aug;63 (Pt 4):439-49

Polyamines appear to be second messengers in mediating Ca2+ fluxes and neurotransmitter release in potassium-depolarized synaptosomes. Iqbal Z, et al. **Biochem Biophys Res Commun** 1985 Dec 17; 133(2):563-73

Is there feedback regulation of neurotransmitter release by autoreceptors? Kalsner S. **Biochem Pharmacol** 1985 Dec 1;34(23):4085-97 (86 ref.)

Muscarinic receptors discriminated by pirenzepine are involved in the regulation of neurotransmitter release in rat nucleus accumbens. de Belleroche J, et al. **Br J Pharmacol** 1985 Oct;86(2):505-8

Neurochemical aspects of the Rett syndrome. Riederer P, et al. **Brain Dev** 1985;7(3):351-60

The role of putative excitatory amino acid neurotransmitters in the initiation of locomotion in the lamprey spinal cord. II. The effects of amino acid uptake inhibitors. Brodin L, et al. **Brain Res** 1985 Dec 23; 360(1-2):149-58

The role of putative excitatory amino acid neurotransmitters in the initiation of locomotion in the lamprey spinal cord. I. The effects of excitatory amino acid antagonists. Brodin L, et al. **Brain Res** 1985 Dec 23;360(1-2):139-48

Possible excitatory amino acid afferents to nucleus raphe dorsalis of the rat investigated with retrograde wheat germ agglutinin and D-[3H]aspartate tracing. Kalen P, et al. **Brain Res** 1985 Dec 23; 360(1-2):285-97

Estrogen effects on neuronal responsiveness to electrical and neurotransmitter stimulation: an in vitro study on the ventromedial nucleus of the hypothalamus. Kow LM, et al. **Brain Res** 1985 Nov 11;347(1):1-10

In vivo voltammetry: promise and perspective. Stamford JA. **Brain Res** 1985 Oct;357(2):119-35 (135 ref.)

Actions of feeding-relevant agents on hypothalamic glucose-responsive neurons in vitro. Kow LM, et al. **Brain Res Bull** 1985 Nov; 15(5):509-13

Neurotransmitters in the intestine of the Atlantic cod, Gadus morhua. Jensen J, et al. **Comp Biochem Physiol [C]** 1985;82(1):81-9

Transmitter expression and morphological development of embryonic medullary and mesencephalic raphe neurones after transplantation to the adult rat central nervous system. I. Grafts to the spinal cord. Foster GA, et al. **Exp Brain Res** 1985;60(3):427-44

Calcium diffusion models and transmitter release in neurons. Zucker RS. **Fed Proc** 1985 Dec;44(15):2950-2

Effects of putative neurotransmitters on release of prolactin from pituitary glands of the domestic fowl co-incubated with hypothalamic tissue. Hall TR, et al. **Gen Pharmacol** 1985;16(5):483-8

Cardiac calcium channels and their control by neurotransmitters and drugs. Trautwein W, et al. **J Am Coll Cardiol** 1985 Dec; 6(6):1409-16

Membrane retrieval by macropinocytosis in presynaptic terminals during transmitter release in cat sympathetic ganglia in situ. Kadota T, et al. **J Electron Microsc (Tokyo)** 1982;31(1):73-80

Endogenous opioids and related peptides: from molecular biology to clinical medicine. The Sir Henry Dale lecture for 1985. Imura H, et al. **J Endocrinol** 1985 Nov;107(2):147-57

A role for transglutaminase in neurotransmitter release by rat brain synaptosomes. Pastuszko A, et al. **J Neurochem** 1986 Feb; 46(2):499-508

Kainic acid differentially affects the synaptosomal release of endogenous and exogenous amino acidic neurotransmitters. Poli A, et al. **J Neurochem** 1985 Dec;45(6):1677-86

Mapping of transmitter-specific connections: simultaneous demonstration of anterograde degeneration and changes in the immunostaining pattern induced by lesions. Záborszky L, et al. **J Neurosci Methods** 1985 Sep; 14(4):255-66

Coexistence of high-affinity uptake mechanisms for putative neurotransmitter molecules in chick embryo retinal neurons in purified culture. Pessin M, et al. **J Neurosci Res** 1985;14(3):317-28

Adrenergic neurohumoral influences on FFA release from bone marrow adipose tissue. Tran MA, et al. **J Pharmacol** 1985 Apr-Jun; 16(2):171-9

Calcium entry and transmitter release at voltage-clamped nerve terminals of squid. Augustine GJ, et al. **J Physiol (Lond)** 1985 Oct;367:163-81

Neostigmine increases the size of subunits composing the quantum of transmitter release at mouse neuromuscular junction. Carlson CG, et al. **J Physiol (Lond)** 1985 Oct;367:489-502

Gonadotropin-releasing hormone as a paracrine hormone and neurotransmitter in extra-pituitary sites. Hsueh AJ, et al. **J Steroid Biochem** 1985 Nov;23(5B):757-64

Assessment of some transmitter actions in rat cerebellar slices. Flint RS, et al. **Life Sci** 1986 Jan 20;38(3):233-9

Phorbol ester, an activator of protein kinase C, enhances calcium-dependent release of sympathetic neurotransmitter. Wakade AR, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct; 331(1):122-4

Indices of neurotransmitter synthesis and release in aging sympathetic nervous system. Partanen M, et al. **Neurobiol Aging** 1985 Fall; 6(3):227-32

Properties of the uptake and release of neurotransmitter glutamate in cerebral cortical tissue of guinea pigs. Takagaki G, et al. **Neurochem Res** 1985 Aug;10(8):1059-69

Modification of the anticonvulsant activity of 2-amino-5-phosphonovalerate by agents affecting different neurotransmitter systems. Czuczwar SJ, et al. **Neuropharmacology** 1985 Oct;24(10):965-8

Basic and clinical aspects of adenosinergic neuromodulation. Marangos PJ, et al. **Neurosci Biobehav Rev** 1985 Fall;9(3):421-30 (135 ref.)

Effects of drugs on neurotransmitter release: experiments in vivo and in vitro. Tapia R. **Neurosci Biobehav Rev** 1985 Fall;9(3):391-7 (64 ref.)

Peptidergic efferents from the intercalated nuclei of the amygdala to the parabrachial nucleus in the rat. Moga MM, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):13-8

Differential regulation of peptide and catecholamine characters in cultured sympathetic neurons. Kessler JA. **Neuroscience** 1985 Jul;15(3):827-39

Diffusion coefficients of neurotransmitters and their metabolites in brain extracellular fluid space. Rice ME, et al. **Neuroscience** 1985 Jul; 15(3):891-902

ACTH neuromodulation of the developing motor system and neonatal learning in the rat. Acker GR, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 2:41-9

Substance K and substance P differentially modulate mesolimbic and mesocortical systems. Deutch AY, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 2:113-22

Excitatory transmitter release induced by high concentrations of gamma-aminobutyric acid (GABA) in crayfish neuromuscular junctions. Finger W. **Pflugers Arch** 1985 Oct;405(3):265-73

Effects of Anemonia sulcata toxin II on presynaptic currents and evoked transmitter release at neuromuscular junctions of the mouse. Molgó J, et al. **Pflugers Arch** 1985 Dec;405(4):349-53

Studies on brain monoamine neurotransmitters in mice after prenatal exposure to barbiturate. Yanai J, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):215-9

Neurotransmitter effects on body temperature are modified with increasing age. Ferguson AV, et al. **Physiol Behav** 1985 Jun; 34(6):977-81

Effects of lipid peroxidation on neurotransmitters uptake by rat synaptosomes. Dabrowiecki Z, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):325-31

Developmental neurochemistry: pharmacology and toxicology. Johnston MV. **Proc West Pharmacol Soc** 1985;28:311-3

Neurochemical relation between excitatory and inhibitory amino acids in hippocampus. Baba A, et al. **Prog Clin Biol Res** 1985;179:271-9

Pharmacological evidence for taurine as an inhibitory neurotransmitter in the cerebellum. Sakai Y, et al. **Prog Clin Biol Res** 1985; 179:313-9 (15 ref.)

Possible involvement of calmodulin in modulatory role of taurine in rat cerebral beta-adrenergic neurons. Segawa T, et al. **Prog Clin Biol Res** 1985;179:321-30

Distribution of non-opioid peptides in the mammalian CNS: relationship to monoamine neurotransmitter systems. Westlund KN. **Prog Clin Biol Res** 1985;192:395-402

Immunocytochemical and physiological identification of taurine neurons in the mammalian CNS. Wu JY, et al. **Prog Clin Biol Res** 1985; 179:261-70

Taurine on hippocampal slices: comparison to GABA and glycine, and antagonism by 4-aminopyridine. Zeise M. **Prog Clin Biol Res** 1985; 179:281-7

Neurotransmitters and their role in pulmonary physiology. Richardson J. **Recent Results Cancer Res** 1985;99:29-33

Neuromodulation of the cardiac vagus: comparison of neuropeptide Y and related peptides. Kilborn MJ, et al. **Regul Pept** 1985 Oct; 12(2):155-61

Effects of oxytocin and vasopressin in the central and in the autonomic nervous system. Interactions with other presumptive neurotransmitters. Dreifuss JJ, et al. **Regul Pept [Suppl]** 1985;4:165-71

[Circadian rhythm of central monoamine neurotransmitters in mammals] Ye WL. **Sheng Li Ko Hsueh Chin Chan** 1984 Oct;15(4):316-20 **(Chi)**

[The future of biological psychiatry] Linnoila M. **Duodecim** 1985; 101(17):1732-7 **(Fin)**

[Trivastal] Benoit P, et al. **Soins** 1985 Oct;(463):I-II **(Fre)**

[Possibilities in the treatment of schizophrenia based on biochemical findings] Nagashi M. **Seishin Shinkeigaku Zasshi** 1985;87(7):435-43 **(Jpn)**

[Continuity and change in chemical mediation] Haulică I. **Rev Med Chir Soc Med Nat Iasi** 1984 Apr-Jun;88(2):233-8 (21 ref.) **(Rum)**

[Effect of neuroregulators on the synaptic activity of the hippocampus] Skrebitskii VG. **Usp Fiziol Nauk** 1985 Oct-Dec;16(4):35-48 (58 ref.) **(Rus)**

[Neuromediator mechanisms of regulating immune reactions in schizophrenics] Aliev NA. **Zh Nevropatol Psikhiatr** 1985; 85(9):1382-5 (Eng. Abstr.) **(Rus)**

[Neuromediator sensitivity of neurons of the reticular formation and orbital cortex in hungry and satiated rabbits] Borisova EV. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):907-13 (Eng. Abstr.) **(Rus)**

NEUROTENSIN

The effect of nephrectomy and ureter ligation on plasma neurotensin-like immunoreactivity levels in the conscious rat. Theodorsson-Norheim E, et al. **Acta Physiol Scand** 1985 Mar;123(3):269-72

Dexamethasone reduces fat-induced release of neurotensin in the rat. Theodorsson-Norheim E, et al. **Acta Physiol Scand** 1985 Mar; 123(3):331-3

Neurotensin-like immunoreactivity and neurotensin receptors in the rat hypothalamus and in the neurointermediate lobe of the pituitary gland. Goedert M, et al. **Brain Res** 1985 Dec 9;358(1-2):59-69

Behavioral and neurochemical effect of daily injection with neurotensin into the ventral tegmental area. Kalivas PW, et al. **Brain Res** 1985 Dec 9;358(1-2):70-6

The coexistence of two neuroactive peptides in a subpopulation of retinal amacrine cells. Li HB, et al. **Brain Res** 1985 Oct 14;345(1):176-80

Dopamine inhibition of neurotensin-induced increase in Ca2+ influx into rat pituitary cells. Memo M, et al. **Brain Res** 1985 Nov 18; 347(2):253-7

Characterization and autoradiographic distribution of neurotensin binding sites in the human brain. Sarrieau A, et al. **Brain Res** 1985 Dec 2; 348(2):375-80

Suppression of norepinephrine-elicited feeding by neurotensin: evidence for behavioral, anatomical and pharmacological specificity. Stanley BG, et al. **Brain Res** 1985 Sep 23;343(2):297-304

Dopamine-dependent contralateral circling induced by neurotensin applied unilaterally to the ventral tegmental area in rats. Holmes LJ, et al. **Brain Res Bull** 1985 Nov;15(5):537-8

The inhibitory effect of neurotensin on the motor activity of rabbit ileum: dependence on the ionic environment. Holzer P, et al. **Eur J Pharmacol** 1985 Nov 19;117(3):329-35

Neurotensin increases colonic motility. Thor K, et al. **Gastroenterology** 1986 Jan;90(1):27-31

Pupillary effects of neurotensin: structure-activity relationships. Hernandez DE, et al. **Neuropeptides** 1985 Dec;6(6):561-8

The chronotropic action of neurotensin in the guinea pig isolated heart. Bachelard H, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):841-5

Organization of LHRH cells: differential apposition of neurotensin, substance P and catecholamine axons. Hoffman GE. **Peptides (Fayetteville)** 1985 May-Jun;6(3):439-61

The effects of neurotensin on gastrointestinal motility in rodents. Ayres EA, et al. **Proc West Pharmacol Soc** 1985;28:153-5

Actions and interactions of neurotensin on preoptic anterior hypothalamic neurons in vitro. Baldino F Jr, et al. **Prog Clin Biol Res** 1985; 192:409-21

Neuropeptide modulation of the behavioral effects of drugs. Barrett JE, et al. **Prog Clin Biol Res** 1985;192:37-50

Do neuropeptide systems mediate some of the effects of antipsychotic drugs? Bissette G, et al. **Prog Clin Biol Res** 1985;192:349-53

Characterization of the metabolism of substance P and neurotensin by human angiotensin I converting enzyme and 'enkephalinase'. Skidgel RA. **Prog Clin Biol Res** 1985;192:371-8

Release and degradation of neurotensin during perfusion of rat small intestine with lipid. Ferris CF, et al. **Regul Pept** 1985 Oct; 12(2):101-11

Neurotensin effect on calcium transport and dopamine release in rat striatum. Battaini F, et al. **Regul Pept [Suppl]** 1985;4:188-90

NEUROTIC DISORDERS

[Alprazolam vs. oxazepam in the treatment of anxious-neurotic patients] Pöldinger W. **Schweiz Rundsch Med Prax** 1985 Oct 29; 74(44):1199-203 (Eng. Abstr.) **(Ger)**

[Relation between the dynamics of EEG indices after a single dose of the tranquilizer phenazepam and its efficacy during a course of treatment of patients with borderline neuropsychological disorders] Uvarova LG, et al. **Zh Nevropatol Psikhiatr** 1985;85(11):1701-9 (Eng. Abstr.) **(Rus)**

NITRAZEPAM

Polarographic assay of nitrazepam formulations. Mishra AK, et al. **Analyst** 1985 Sep;110(9):1105-9

The effect of repeated doses of temazepam and nitrazepam on human psychomotor performance. Tedeschi G, et al. **Br J Clin Pharmacol** 1985 Oct;20(4):361-7

Age, sex, and nitrazepam kinetics: relation to antipyrine disposition. Greenblatt DJ, et al. **Clin Pharmacol Ther** 1985 Dec;38(6):697-703

NOMIFENSINE

Nomifensine for emotional incontinence in the elderly. Sandyk R, et al. **Clin Neuropharmacol** 1985;8(4):377-8

Nomifensine: an antidepressant with a difference? Ereshefsky L. **Clin Pharm** 1985 Nov-Dec;4(6):673-4

Trouble with nomifensine. **Drug Ther Bull** 1985 Dec 16;23(25):98-100

Dopaminergic drugs improve human visual contrast sensitivity. Domenici L, et al. **Hum Neurobiol** 1985;4(3):195-7

New nomifensine derivatives: synthesis and evaluation of central effects. Pozzo-Balbi T, et al. **Pharmazie** 1985 Aug;40(8):579-80

The responsiveness of the endogenous inhibitor of cAMP-dependent protein kinase to apomorphine in rat striatum after prolonged treatment with nomifensin. Szmigielski A, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):285-93

Attenuated response to nomifensine in rats during a swim test following lesion of the habenula complex. Thornton EW, et al. **Psychopharmacology (Berlin)** 1985;87(1):81-5

NOREPINEPHRINE

Identification of an alpha-adrenoceptor binding inhibitor: possible implications in diabetes mellitus. Wider MD, et al. **Acta Diabetol Lat** 1985 Jul-Sep;22(3):263-9

Effect of rate of hemorrhage on sympathoadrenal catecholamine release in cats. Bereiter DA, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 1):E69-75

Potentiation of hemorrhage-evoked catecholamine release by prior blood loss in cats. Bereiter DA, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 1):E18-23

Alpha 2-noradrenergic feeding rhythm in paraventricular nucleus: relation to corticosterone. Bhakthavatsalam P, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 2):R83-8

Interaction of prolactin with adrenal hormones in blood pressure regulation in rats. Mills DE, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 1):E614-8

CSF noradrenaline and schizophrenia [letter] Kemali D, et al. **Am J Psychiatry** 1986 Jan;143(1):126-7

Exaggerated orthostatic responsivity of plasma norepinephrine in depression. Rudorfer MV, et al. **Arch Gen Psychiatry** 1985 Dec; 42(12):1186-92

Gabapentin decreases monoamine release without affecting acetylcholine release in the brain. Schlicker E, et al. **Arzneimittelforschung** 1985; 35(9):1347-9

Plasma norepinephrine, blood pressure and heart rate response to graded change in body position. Fiorica V, et al. **Aviat Space Environ Med** 1985 Dec;56(12):1166-71

Endocrine correlates of susceptibility to motion sickness. Kohl RL. **Aviat Space Environ Med** 1985 Dec;56(12):1158-65

Fatty acids and the control of adipocyte glycerolphosphate acyltransferase by noradrenaline [letter] Saggerson D, et al. **Biochem J** 1985 Oct 15; 231(2):495-6

Regulation of lipolysis during pregnancy and lactation in sheep. Response to noradrenaline and adenosine. Vernon RG, et al. **Biochem J** 1985 Sep 15;230(3):651-6

Accumulation of inositol phosphates and cyclic AMP in guinea-pig cerebral cortical preparations. Effects of norepinephrine, histamine, carbamylcholine and 2-chloroadenosine. Hollingsworth EB, et al. **Biochim Biophys Acta** 1985 Nov 20;847(2):207-16

Contributions of noradrenergic neurones of the locus coeruleus to the temporal damping of linear electrocortical waves. Wright JJ, et al. **Biol Cybern** 1985;52(6):351-6

The functional importance of cerebral noradrenergic processes for the activating action of nootropic drugs in the behavioural despair test in mice. Schmidt J. **Biomed Biochim Acta** 1985;44(5):755-61

Cold exposure or chronic noradrenaline treatment induces an increase in the calmodulin-like immunoreactivity of brown adipose tissue of rats. Mory G. **Biosci Rep** 1985 Aug;5(8):659-65

Mobilization of extracellularly bound Ca2+ during high K+ and norepinephrine stimulation of the rabbit aorta. Lodge NJ, et al. **Blood Vessels** 1985;22(5):234-43

Cholinesterase activity and exposure time to acetylcholine as factors influencing the muscarinic inhibition of [3H]-noradrenaline overflow from guinea-pig isolated atria. Fuder H, et al. **Br J Pharmacol** 1985 Dec;86(4):905-14

Dietary and pharmacological alterations in endogenous angiotensin II: effect on noradrenaline pressor responsiveness in the rat. Jones DR, et al. **Br J Pharmacol** 1985 Dec;86(4):889-97

Opposing alpha- and beta-adrenergic mechanisms mediate dose-dependent actions of noradrenaline on supraoptic vasopressin neurones in vivo. Day TA, et al. **Brain Res** 1985 Dec 9; 358(1-2):171-9

The action of norepinephrine in the dentate gyrus: beta-mediated facilitation of evoked potentials in vitro. Lacaille JC, et al. **Brain Res** 1985 Dec 9;358(1-2):210-20

Noradrenergic changes and memory loss in aged mice. Leslie FM, et al. **Brain Res** 1985 Dec 16;359(1-2):292-9

Clonidine and cortical plasticity: possible evidence for noradrenergic involvement. Nelson SB, et al. **Brain Res** 1985 Nov;355(1):39-50

Electrochemical stimulation of plasma LH and hypothalamic norepinephrine concentrations at short- and long-term intervals after hypothalamic knife cuts. Phelps CP, et al. **Brain Res** 1985 Nov 18; 347(2):328-35

Effect of phenytoin on [3H]norepinephrine release from synaptosomes. Pincus JH, et al. **Brain Res** 1985 Dec 2;348(2):387-90

Suppression of norepinephrine-elicited feeding by neurotensin: evidence for behavioral, anatomical and pharmacological specificity. Stanley BG, et al. **Brain Res** 1985 Sep 23;343(2):297-304

The effect of high-frequency electrical stimulation and norepinephrine on cyclic AMP levels in normal versus norepinephrine-depleted rat hippocampal slices. Stanton PK, et al. **Brain Res** 1985 Dec 9; 358(1-2):343-8

Sympathetic neurons grown in culture generate ATP by glycolysis: correlation between ATP content and [3H]norepinephrine uptake and storage. Wakade AR, et al. **Brain Res** 1985 Dec 16; 359(1-2):397-401

Effect of ventral noradrenergic bundle transection and locus coeruleus lesions on urinary 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) excretion in the rat. Weise VK, et al. **Brain Res** 1985 Dec 16;359(1-2):239-45

Efferent projections from the paraventricular nucleus mediating alpha 2-noradrenergic feeding. Weiss GF, et al. **Brain Res** 1985 Nov 18; 347(2):225-38

Tonic activity of medial preoptic norepinephrine mechanism for body temperature maintenance in sleeping and awake rats. Datta S, et al. **Brain Res Bull** 1985 Nov;15(5):447-51

Feeding behavior elicited by electrical stimulation of the lateral hypothalamic area in the rat: role of the adrenergic pathways and receptors. Homrich JG, et al. **Braz J Med Biol Res** 1985; 18(1):15-27

Differential effects of chronic lead intoxication on circadian rhythm of ambulatory activity and on regional brain norepinephrine levels in rats. Shafiq-ur-Rehman, et al. **Bull Environ Contam Toxicol** 1986 Jan; 36(1):81-91

The relationship between the thermogenic response of brown adipose tissue and age during noradrenaline infusion in the young rabbit. Harris WH, et al. **Can J Physiol Pharmacol** 1985 Oct;63(10):1215-20

Effects of (+/-)-sotalol, (+/-)-propranolol, and (-)-propranolol on norepinephrine release upon hepatic nerve stimulation in the dog liver in vivo. Yamaguchi N. **Can J Physiol Pharmacol** 1985 Nov; 63(11):1423-8

Comparative distribution of neuropeptide tyrosine-, vasoactive intestinal polypeptide-, substance P-immunoreactive, acetylcholinesterase-positive and noradrenergic nerves in the reproductive tract of the female rat. Papka RE, et al. **Cell Tissue Res** 1985;242(3):475-90

Immunohistochemical and biochemical study on the development of the noradrenaline- and adrenaline-storing cells of the adrenal medulla of the rat. Verhofstad AA, et al. **Cell Tissue Res** 1985;242(2):233-43

Correlation between refractory periods and activation-recovery intervals from electrograms: effects of rate and adrenergic interventions. Millar CK, et al. **Circulation** 1985 Dec;72(6):1372-9

Enhancement by norepinephrine of automaticity in sheep cardiac Purkinje fibers exposed to hypoxic glucose-free Tyrode's solution: a role for alpha-adrenoceptors? Mugelli A, et al. **Circulation** 1986 Jan; 73(1):180-8

Simultaneous determination of epinephrine and norepinephrine in urine by derivative synchronous fluorescence spectroscopy. Valcárcel M, et al. **Clin Chem** 1985 Nov;31(11):1790-4

Effects of exogenous catecholamines and exercise on plasma magnesium concentrations. Joborn H, et al. **Clin Endocrinol (Oxf)** 1985 Sep; 23(3):219-26

The distribution of catecholamines between platelets and plasma in normal human subjects. Smith CC, et al. **Clin Sci** 1985 Jul;69(1):1-6

Studies of contents of norepinephrine and 5-hydroxytryptamine in brain--I. Normal and cold exposure. Aly MS, et al. **Comp Biochem Physiol** [C] 1985;82(1):155-8

Epinephrine, norepinephrine and dopamine concentrations in amphibian brain. Cooney MM, et al. **Comp Biochem Physiol** [C] 1985; 82(2):395-7

The effects of adrenalectomy on the ontogenesis of brain: noradrenaline and dopamine content. Leret ML, et al. **Comp Biochem Physiol** [C] 1985;82(2):475-7

Studies of contents of norepinephrine and 5-hydroxytryptamine in brain--II. Effect of sodium barbitone and chlorpromazine. Rahman TA, et al. **Comp Biochem Physiol** [C] 1985;82(1):159-63

Release of catecholamines follows suckling or electrical stimulation of mammary nerve in lactating rats. Clapp C, et al. **Endocrinology** 1985 Dec;117(6):2498-504

Fusaric acid-induced elevation of homovanillic acid in the CSF as an index of brain noradrenaline synthesis. Elghozi JL, et al. **Eur J Pharmacol** 1985 Nov 19;117(3):363-7

Pharmacological characterization and regional distribution of alpha-noradrenergic binding sites of rat spinal cord. Giron LT Jr, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):285-90

Dopamine but not norepinephrine or serotonin uptake inhibitors protect mice against neurotoxicity of MPTP. Melamed E, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):179-81

Modification of behavioral response to intra-hippocampal injections of noradrenaline and adrenoceptor agonists by chronic treatment with desipramine and citalopram: functional aspects of adaptive receptor changes. Plaźnik A, et al. **Eur J Pharmacol** 1985 Nov 5; 117(2):245-52

Clonidine inhibits central noradrenergic neurons in unanesthetized cats. Reiner PB. **Eur J Pharmacol** 1985 Sep 24;115(2-3):249-57

Interaction of norepinephrine and superior cervical ganglion input in the rat pineal body. Reyes-Vazquez C, et al. **Exp Neurol** 1985 Dec; 90(3):522-8

Blockade of the pressor response to angiotensins I and II in the bullfrog, Rana catesbeiana. Harper RA, et al. **Gen Comp Endocrinol** 1985 Nov; 60(2):227-35

Interference of pentobarbital and thiopental with the vascular contraction and noradrenaline release in human cerebral arteries. Sánchez-Ferrer CF, et al. **Gen Pharmacol** 1985;16(5):469-73

Effect of aging on the response of the cerebral cortex to noradrenergic denervation. Harik SI, et al. **Gerontology** 1985;31(5):285-92

Neuropeptide Y (NPY)-like immunoreactivity in guinea pig uterus is reduced during pregnancy in parallel with noradrenergic nerves. Fried G, et al. **Histochemistry** 1985;83(5):437-42

Age-related augmentation of plasma catecholamines during dynamic exercise in healthy males. Fleg JL, et al. **J Appl Physiol** 1985 Oct; 59(4):1033-9

Effect of head-down tilt on basal plasma norepinephrine and renin activity in humans. Goldsmith SR, et al. **J Appl Physiol** 1985 Oct; 59(4):1068-71

Noradrenergic projections to the spinal cord and their role in cardiovascular control. Coote JH. **J Auton Nerv Syst** 1985 Nov; 14(3):255-62 (55 ref.)

Calcium and norepinephrine levels of rat salivary glands after terbutaline, dobutamine or isoproterenol. Schneyer CA. **J Auton Nerv Syst** 1985 Oct;14(2):191-200

Effects of chemical sympathectomy on dopamine and noradrenaline content of the dog gastrointestinal tract. Esplugues JV, et al. **J Auton Pharmacol** 1985 Sep;5(3):189-95

Irreversible inactivation of the beta-adrenoreceptor by a partial agonist. Evidence for selective loss of the agonist high affinity binding sites. Baker SP, et al. **J Biol Chem** 1985 Dec 15;260(29):15820-8

Insulin receptors and insulin modulation of norepinephrine uptake in neuronal cultures from rat brain. Boyd FT Jr, et al. **J Biol Chem** 1985 Dec 15;260(29):15880-4

Enhancement of norepinephrine biosynthesis by ascorbic acid in cultured bovine chromaffin cells. Levine M, et al. **J Biol Chem** 1985 Oct 25; 260(24):12942-7

Ascorbic acid regulation of norepinephrine biosynthesis in isolated chromaffin granules from bovine adrenal medulla. Levine M, et al. **J Biol Chem** 1985 Dec 15;260(29):15598-603

Regioselectivity of catechol O-methyltransferase. The effect of pH on the site of O-methylation of fluorinated norepinephrines. Thakker DR, et al. **J Biol Chem** 1986 Jan 5;261(1):178-84

Modification of the vasoconstrictor effects of noradrenaline and serotonin by the selective calcium antagonist PY 108-068 in the peripheral circulation of anesthetized cats. Hof RP, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 6:S53-60

Prejunctional alpha 2-adrenoceptors and norepinephrine release in the forearm of normal humans. Kiowski W, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 6:S144-8

Fluid temperature and volume dependence of the dissociated plasma epinephrine and norepinephrine response to drinking. Puddey IB, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):438-40

3-Phenyl-1-indanamines. Potential antidepressant activity and potent inhibition of dopamine, norepinephrine, and serotonin uptake. Bøgesø KP, et al. **J Med Chem** 1985 Dec;28(12):1817-28

Correlation of rates of calcium entry and release of endogenous norepinephrine in rat brain region synaptosomes. Daniell LC, et al. **J Neurochem** 1986 Jan;46(1):249-56

Neuroimmunomodulatory interactions of norepinephrine and serotonin. Walker RF, et al. **J Neuroimmunol** 1985 Nov;10(1):41-58 (91 ref.)

Noradrenergic modulation of cortical acetylcholine release is both direct and gamma-aminobutyric acid-mediated. Beani L, et al. **J Pharmacol Exp Ther** 1986 Jan;236(1):230-6

Measurement of thermodynamic parameters for norepinephrine contraction of isolated rabbit thoracic aorta. Raffa RB, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):596-600

A simplified liquid chromatography and electrochemical detection method for measurement of plasma noradrenaline. Brent PJ, et al. **J Pharmacol Methods** 1985 Nov;14(3):243-8

Noradrenaline and functional plasticity in kitten visual cortex: a re-examination. Adrien J, et al. **J Physiol (Lond)** 1985 Oct; 367:73-98

Direct observations of responses of mesenteric microcirculation of the rat to circulating noradrenaline. Hébert MT, et al. **J Physiol (Lond)** 1985 Nov;368:393-407

Presynaptic regulation by ACh of the NE mediated responses in the rat vas deferens. Miranda HF, et al. **J Recept Res** 1985;5(4):231-43

Acute increase of noradrenaline on vascular resistance in the corpus luteum of the pseudopregnant rat. Selstam G, et al. **J Reprod Fertil** 1985 Nov;75(2):351-6

Peripheral origin of plasma dopamine. Yoneda S, et al. **Jpn Circ J** 1985 Sep;49(9):1028-34

Plasma and brain catecholamines in experimental uremia: acute and chronic studies. Ali F, et al. **Life Sci** 1985 Nov 11;37(19):1757-64

Hepatic adrenoceptors involved in the glycogenolytic response to exogenous (-)-norepinephrine in the dog liver in vivo. Garceau D, et al. **Life Sci** 1985 Nov 25;37(21):1963-70

Attenuating effect of diazepam on stress-induced increases in noradrenaline turnover in specific brain regions of rats: antagonism by Ro 15-1788. Ida Y, et al. **Life Sci** 1985 Dec 30;37(26):2491-8

The calcium channel activator, Bay K 8644, enhances K+-evoked efflux of acetylcholine and noradrenaline from rat brain slices. Middlemiss DN. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):114-6

Depletion of noradrenaline in the hypothalamus reduces the febrile responses induced by prostaglandin E2, thyrotropin-releasing hormone and beta-endorphin in rats. Lin MT, et al. **Neuropharmacology** 1985 Nov;24(11):1039-42

The regulation of noradrenaline synthesis in central nerve terminals by autoreceptors and heteroreceptors in rat. Birch PJ, et al. **Neurosci Lett** 1985 Aug 30;59(2):197-202

Plasma norepinephrine, epinephrine and corticosterone stress responses to restraint in individual male and female rats, and their correlations. Livezey GT, et al. **Neurosci Lett** 1985 Nov 20;62(1):51-6

Norepinephrine depolarizes lateral horn cells of neonatal rat spinal cord in vitro. Ma RC, et al. **Neurosci Lett** 1985 Sep 30;60(2):163-8

Effects of noradrenaline on some potassium currents in CA1 neurones in rat hippocampal slices. Sah P, et al. **Neurosci Lett** 1985 Oct 10; 60(3):295-300

Noradrenaline mediates slow excitatory synaptic potentials in rat dorsal raphe neurons in vitro. Yoshimura M, et al. **Neurosci Lett** 1985 Nov 11;61(3):305-10

Presynaptic autoinhibition during rest and sodium-pump inhibition in isolated rat portal vein preparation. Török TL, et al. **Neuroscience** 1985 Oct;16(2):439-49

Cardiovascular effects of neuropeptide Y in the nucleus tractus solitarius of rats: relationship with noradrenaline and vasopressin. Carter DA, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):421-5

ACTH 1-24-induced potentiation of norepinephrine contractile responses in aortic strips from spontaneously hypertensive (SH) and normotensive (WKY) rats. Vergona RA, et al. **Peptides (Fayetteville)** 1985 Jul-Aug; 6(4):581-4

Evidence of norepinephrine-mediated suppression of para-chlorophenylalanine-induced muricidal behavior. Pucilowski O, et al. **Pharmacol Res Commun** 1985 Oct;17(10):983-9

The effects of isolation, grouping and aggressive interactions on indole- and catecholamine levels and apparent turnover in the hypothalamus and midbrain of the male golden hamster. Payne AP, et al. **Physiol Behav** 1985 Jun;34(6):911-6

The importance of olfactory bulb noradrenalin for maternal recognition in sheep. Pissonnier D, et al. **Physiol Behav** 1985 Sep;35(3):361-3

Role of hypothalamic norepinephrine in control of meal patterns. Shor-Posner G, et al. **Physiol Behav** 1985 Aug;35(2):209-14

Mesolimbic noradrenaline but not dopamine is responsible for organization of rat behavior in the forced swim test and an anti-immobilizing effect of desipramine. Płaźnik A, et al. **Pol J Pharmacol Pharm** 1985 May-Jun; 37(3):347-57

Vasoactive intestinal polypeptide acts synergistically with norepinephrine to depress spontaneous discharge rate in cerebral cortical neurons. Ferron A, et al. **Proc Natl Acad Sci USA** 1985 Dec;82(24):8810-2

External Ca-independent release of norepinephrine by sympathomimetics and its role in negative feedback modulation. Vizi ES, et al. **Proc Natl Acad Sci USA** 1985 Dec;82(24):8775-9

Effects of dietary lipids on cardiovascular parameters in the conscious rat and adrenergic responses in isolated perfused organ systems. Dixon WR, et al. **Proc West Pharmacol Soc** 1985;28:19-22

Antagonism between norepinephrine and the Ca++ channel blockers nifedipine and verapamil in isolated guinea pig ventricle. Woods JP, et al. **Proc West Pharmacol Soc** 1985;28:11-4

The effects of L-threo-dihydroxyphenylserine on norepinephrine metabolism in rat brain. Semba J, et al. **Psychiatry Res** 1985 Aug; 15(4):319-26

Clinical studies of the effect of (+) and (-)-oxaprotiline upon noradrenaline uptake. Checkley SA, et al. **Psychopharmacology (Berlin)** 1985;87(1):116-8

A stimulatory effect of intraaccumbens injections of noradrenaline on the behavior of rats in the forced swim test. Płaźnik A, et al. **Psychopharmacology (Berlin)** 1985;87(1):119-23

Effects of carbamazepine on noradrenergic mechanisms in affectively ill patients. Post RM, et al. **Psychopharmacology (Berlin)** 1985; 87(1):59-63

The effect of peripheral noradrenaline depletion on responding on a schedule of differential reinforcement of low rates of response (DRL). Salmon P, et al. **Psychopharmacology (Berlin)** 1985;87(1):77-80

Psychoneuroendocrine stress responses and mood as related to the menstrual cycle. Collins A, et al. **Psychosom Med** 1985 Nov-Dec; 47(6):512-27

Galanin potentiates electrical stimulation and exogenous norepinephrine-induced contractions in the rat vas deferens. Ohhashi T, et al. **Regul Pept** 1985 Oct;12(2):163-71

Failure of branched-chain amino acids to affect synaptosomal uptake of norepinephrine and dopamine. Cobert BJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Dec;50(3):455-8

Effects of L-tyrosine on brain monoamines in rats given intravenous amphetamine. Smith DG, et al. **Subst Alcohol Actions Misuse** 1984-85; 5(6):293-8

[Adrenaline, noradrenaline and dopamine excretion and anxiety levels in surgical patients] Barham O, et al. **Arch Psychol (Frankf)** 1985; 137(4):291-5 (Eng. Abstr.) **(Ger)**

[Concentrations of external noradrenergic axonal networks in the area of type-III neuronal aggregates and dense capillary networks of the external submucosal plexus (Schabadasch's) in the pig small intestine] Stach W, et al. **Z Mikrosk Anat Forsch** 1985;99(4):617-26 (Eng. Abstr.) **(Ger)**

[Effects of colchicine on the actions of ADH, norepinephrine and forskolin on skin permeability of the frog] Svelto M, et al. **Boll Soc Ital Biol Sper** 1985 Jul 30;61(7):989-93 (Eng. Abstr.) **(Ita)**

[Excretion of catecholamines in relation to personality types A and B] Zaleska T, et al. **Pol Tyg Lek** 1985 Jul 15;40(28):781-3 (Eng. Abstr.) **(Pol)**

[Catecholamine content in the adrenals of rats developing under hypokinesia and muscle training] Abzalov RA. **Biol Nauki** 1985; (10):55-8 (Eng. Abstr.) **(Rus)**

[Analysis of the factors determining the change in cardiac output during administration of catecholamines] Osadchii LI, et al. **Biull Eksp Biol Med** 1985 Oct;100(10):387-90 (Eng. Abstr.) **(Rus)**

[Effect of prolonged interaction of mice with aggressive and submissive types of behavior on the concentration of serotonin, 5-hydroxyindoleacetic acid and noradrenalin in the brain] Kudriavtseva NN, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):879-83 (Eng. Abstr.) **(Rus)**

NORMETANEPHRINE

Extractive acylation and mass spectrometric assay of 3-methoxytyramine, normetanephrine, and metanephrine in cerebrospinal fluid. Beck O, et al. **Anal Biochem** 1985 Sep;149(2):492-500

NORTRIPTYLINE

Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. Simons AD, et al. **Arch Gen Psychiatry** 1986 Jan;43(1):43-8

CSF and plasma levels of nortriptyline and its 10-hydroxy metabolite. Nordin C, et al. **Br J Clin Pharmacol** 1985 Oct;20(4):411-3

Nortriptyline in attention deficit disorder [letter] Saul RC. **Clin Neuropharmacol** 1985;8(4):382-3

Plasma tyrosine/neutral amino acid ratio correlated with clinical response to nortriptyline in endogenously depressed patients. Møller SE, et al. **J Affective Disord** 1985 Nov;9(3):223-9

Extremely rapid hydroxylation of debrisoquine: a case report with implication for treatment with nortriptyline and other tricyclic antidepressants. Bertilsson L, et al. **Ther Drug Monit** 1985; 7(4):478-80

OBSESSIVE-COMPULSIVE DISORDER

Treatment outlines for the management of obsessive-compulsive disorders. The Quality Assurance Project. **Aust NZ J Psychiatry** 1985 Sep;19(3):240-53

Obsessive-compulsive disorder and serotonin: is there a connection? Insel TR, et al. **Biol Psychiatry** 1985 Nov;20(11):1174-88

Drug treatment of obsessive-compulsive disorder. Lelliott PT, et al. **Drugs** 1986 Jan;31(1):75-80

A comparison between the growth hormone responses to amphetamine and clonidine [letter] Siever LJ, et al. **Psychiatry Res** 1985 Sep; 16(1):79-82

OPIPRAMOL

Correlation between the rate of dissolution and absorption of opipramol from solid oral forms. Kanarkowski R, et al. **Mater Med Pol** 1985 Apr-Jun;17(2):85-7

ORGANIC MENTAL DISORDERS

Neurochemical aspects of the Rett syndrome. Riederer P, et al. **Brain Dev** 1985;7(3):351-60

Double-blind trial of suloctidil versus placebo in moderate to severe mental deterioration. Baro F, et al. **Pharmatherapeutica** 1985; 4(6):399-404

ORGANIC MENTAL DISORDERS, PSYCHOTIC

Treatment of mania using a calcium antagonist--preliminary trial. Caillard V. **Neuropsychobiology** 1985;14(1):23-6

OXAZEPAM

Severe withdrawal syndrome after substitution of a short-acting benzodiazepine for a long-acting benzodiazepine. Bond WS, et al. **Drug Intell Clin Pharm** 1985 Oct;19(10):742-4

Application of derivative-differential UV spectrophotometry for the determination of oxazepam or phenobarbitone in the presence of dipyridamole. el-Yazbi FA, et al. **J Pharm Belg** 1985 Jul-Aug; 40(4):244-8

Dose effect and preference comparison of diazepam and oxazepam. Griffiths RR, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984; 55:97-8

[Alprazolam vs. oxazepam in the treatment of anxious-neurotic patients] Pöldinger W. **Schweiz Rundsch Med Prax** 1985 Oct 29; 74(44):1199-203 (Eng. Abstr.) **(Ger)**

PARASYMPATHOMIMETICS

Myorelaxant effect of diazepam. Interactions with neuromuscular blocking agents and cholinergic drugs. Wali FA. **Acta Anaesthesiol Scand** 1985 Nov;29(8):785-9

Regulation of cerebrovascular gamma-glutamyltranspeptidase by adrenergic and cholinergic agonists. Grammas P, et al. **Biochem Pharmacol** 1985 Dec 1;34(23):4177-9

Cholinergic inhibition of follicle-stimulating hormone-induced progestin production by cultured rat granulosa cells. Kasson BG, et al. **Biol Reprod** 1985 Dec;33(5):1158-67

Cholinergic influences on the EMG oesophageal activity in the pigeon. Fileccia R, et al. **Boll Soc Ital Biol Sper** 1985 Sep 30;61(9):1357-63

The electrogenesis mechanism of hyperpolarizations induced by muscarinic agonists in hamster submandibular ganglion cells. Suzuki T, et al. **Bull Tokyo Dent Coll** 1985 Aug;26(3):153-7

A biochemical study of cholinergic-dopaminergic interactions in the central nervous system. De Souza H, et al. **Gen Pharmacol** 1985; 16(5):533-6

Characterization of cholinoreceptors in the rat urinary bladder by the use of agonists and antagonists of the cholinergic system. Adami M, et al. **J Auton Pharmacol** 1985 Sep;5(3):197-205

Distribution of central cholinergic neurons in the baboon (Papio papio). I. General morphology. Satoh K, et al. **J Comp Neurol** 1985 Jun 8; 236(2):197-214

Augmentation of cholinergic-mediated amylase release by forskolin in mouse parotid gland. Watson EL, et al. **Life Sci** 1985 Dec 30; 37(26):2531-7

Cholinergic and VIPergic effects on thyroid hormone secretion in the mouse. Ahrén B. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):585-9

The influence of neuropharmaca on the nasal glands. Preliminary report. Klaassen AB, et al. **Rhinology** 1985 Sep;23(3):191-4

[Possibilities of regulating uterine contractile function with adrenergic and cholinergic agents in an experiment] Pankratova VV, et al. **Akush Ginekol (Mosk)** 1985 Aug;(8):62-3 **(Rus)**

[Effect of M-cholinomimetics on nociceptive stimulation in the spinal cord] Nemirovskiĭ AIu. **Farmakol Toksikol** 1985 Sep-Oct;48(5):36-9 (Eng. Abstr.) **(Rus)**

PARGYLINE

Chronic clorgyline and pargyline increase apomorphine-induced stereotypy in the rat. Campbell IC, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):921-5

PENTOBARBITAL

Pentobarbital suppresses basal and reflexive pancreatic polypeptide release in dogs. Taborsky GJ Jr, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 1):E577-83

The effect of pentobarbital on lidocaine toxicity and brainstem concentration. Mack RE Jr, et al. **Anesth Prog** 1985 Jul-Aug; 32(4):147-50

Interactions of gamma-aminobutyric acid (GABA), pentobarbital, and homopantothenic acid (HOPA) on internally perfused frog sensory neurons. Akaike N, et al. **Cell Mol Neurobiol** 1985 Sep;5(3):245-55

Interference of pentobarbital and thiopental with the vascular contraction and noradrenaline release in human cerebral arteries. Sánchez-Ferrer CF, et al. **Gen Pharmacol** 1985;16(5):469-73

Immediate effects of procaine and pentobarbital on placodal and non-placodal head ectoderm of the chick embryo in vitro. Rowlett KA, et al. **J Anat** 1985 Mar;140 (Pt 2):181-8

Determination of thiopental and pentobarbital in plasma using high-performance liquid chromatography. Houdret N, et al. **J Chromatogr** 1985 Oct 11;343(2):437-42

Intraseptal microinjections of substance P and analogs potentiate pentobarbital-induced narcosis and depression of hippocampal cholinergic activity. Zucker JR, et al. **J Pharmacol Exp Ther** 1985 Nov; 235(2):398-401

Influence of several bacterial and viral vaccines on hepatic drug metabolism in mice. Descotes J, et al. **Methods Find Exp Clin Pharmacol** 1985 Sep;7(9):481-3

Experimental assessment of the relative abuse liability of triazolam and pentobarbital. Roache JD, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:106-10

Pentobarbital promotes bursts of gamma-aminobutyric acid-activated single channel currents in cultured mouse central neurons. Mathers DA. **Neurosci Lett** 1985 Sep 30;60(2):121-6

The prolonging effect of N,N'-diallylpentobarbital on the drug-induced sleep and motor incoordination. Yamamoto I, et al. **Res Commun Chem Pathol Pharmacol** 1985 Nov;50(2):209-19

Hemodialysis clearance of pentobarbital during continuous infusion. Wermeling D, et al. **Ther Drug Monit** 1985;7(4):485-7

PEPTIDES

Turns in peptides and proteins. Rose GD, et al. **Adv Protein Chem** 1985; 37:1-109 (383 ref.)

Actions of polypeptides at the neuromuscular junction. Wali FA. **Agents Actions** 1985 Sep;16(6):558-66

Reactions of nitrogen dioxide in aqueous model systems: oxidation of tyrosine units in peptides and proteins. Prütz WA, et al. **Arch Biochem Biophys** 1985 Nov 15;243(1):125-34

Hydrolysis of leucine enkephalin in the nasal cavity of the rat--a possible factor in the low bioavailability of nasally administered peptides. Hussain A, et al. **Biochem Biophys Res Commun** 1985 Dec 31;133(3):923-8

Progress in chronophysiology of peptide hormones with emphasis on clinical application of analogues. Angeli A, et al. **Chronobiologia** 1985 Jul-Sep;12(3):293-304

Peptide YY: metabolism and effect on pancreatic secretion in dogs. Pappas TN, et al. **Gastroenterology** 1985 Dec;89(6):1387-92

Plasma glucagon-immunoreactive components in early life in dogs. Ghiglione M, et al. **Horm Metab Res** 1985 Aug;17(8):387-90

Synthesis of peptide labelled with p-iodophenylalanine which corresponds to the first amphipathic region of apolipoprotein C-I. Harding DR, et al. **Int J Pept Protein Res** 1985 Aug;26(2):208-13

Current contributions of peptide synthesis to studies on brain-gut-skin triangle peptides. Yajima H, et al. **Int J Pept Protein Res** 1985 Oct; 26(4):337-61 (208 ref.)

The distribution of somatostatin-like immunoreactivity in the monkey hippocampal formation. Bakst I, et al. **J Comp Neurol** 1985 Jun 22; 236(4):423-42

Distribution of certain peptide-containing nerve fibres and endocrine cells in the gastrointestinal mucosa in five mammalian species. Keast JR, et al. **J Comp Neurol** 1985 Jun 15;236(3):403-22

Segmental distribution of peptide- and 5HT-like immunoreactivity in nerve terminals and fibers of the thoracolumbar sympathetic nuclei of the cat. Krukoff TL, et al. **J Comp Neurol** 1985 Oct 1; 240(1):103-16

Segmental distribution of peptide-like immunoreactivity in cell bodies of the thoracolumbar sympathetic nuclei of the cat. Krukoff TL, et al. **J Comp Neurol** 1985 Oct 1;240(1):90-102

Regeneration of peptide-containing retinofugal axons into the optic tectum with reappearance of a substance P-containing lamina. Kuljis RO, et al. **J Comp Neurol** 1985 Oct 1;240(1):1-15

Co-localization and characterization of immunoreactive peptides derived from two opioid precursors in guinea pig adrenal glands. Evans CJ, et al. **J Neurosci** 1985 Dec;5(12):3423-7

Release of pro-opiomelanocortin-derived peptides from the pars intermedia and pars distalis of the rat pituitary: effect of corticotrophin-releasing factor and somatostatin. Kraicer J, et al. **Neuroendocrinology** 1985 Nov;41(5):363-73

Aging and the blood-brain barrier: changes in the carrier-mediated transport of peptides in rats. Banks WA, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):171-5

Peptidergic efferents from the intercalated nuclei of the amygdala to the parabrachial nucleus in the rat. Moga MM, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):13-8

Peptides and feeding. Morley JE, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 2:181-92 (183 ref.)

Further evidence that peptide histidine isoleucine (PHI) may function as a prolactin releasing factor in rats. Ohta H, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):709-12

Serotonin and co-localized peptides: effects on spinal motoneuron excitability. White SR. **Peptides (Fayetteville)** 1985;6 Suppl 2:123-7

Cloning and sequence analysis of cDNA encoding urotensin I precursor. Ishida I, et al. **Proc Natl Acad Sci USA** 1986 Jan;83(2):308-12

Involvement of peptide histidine isoleucine (PHI) in prolactin secretion induced by serotonin in rats. Tojo K, et al. **Proc Soc Exp Biol Med** 1985 Dec;180(3):558-61

Peptide hormones and their possible functions in the normal and abnormal lung. Becker KL. **Recent Results Cancer Res** 1985;99:17-28

Occurrence and distribution of regulatory peptides in the respiratory tract. Polak JM, et al. **Recent Results Cancer Res** 1985;99:1-16

Effect of regulatory polypeptides on the substance P stimulated lower esophageal sphincter pressure in pigs. Aggestrup S. **Regul Pept** 1985 Sep;12(1):1-7

The subcellular distribution of peptides immunoreactive for the amino-terminal of pro-cholecystokinin in rat brain. Allard LR, et al. **Regul Pept** 1985 Sep;12(1):59-66

Galanin potentiates electrical stimulation and exogenous norepinephrine-induced contractions in the rat vas deferens. Ohhashi T, et al. **Regul Pept** 1985 Oct;12(2):163-71

Vasoactive intestinal peptide effects on GH3 pituitary tumor cells: high affinity binding, affinity labeling, and adenylate cyclase stimulation. Comparison with peptide histidine isoleucine and growth hormone-releasing factor. Wood CL, et al. **Regul Pept** 1985 Nov 7; 12(3):237-48

Peptide and amino acid electropharmacology of cultured mammalian central neurons and clonal pituitary cells. Barker JL, et al. **Regul Pept [Suppl]** 1985;4:14-22

Some ionic mechanisms of slow peptidergic neuronal excitation. Brown DA, et al. **Regul Pept [Suppl]** 1985;4:157-64

[The influence of viscosity-increasing pharmaceutic aids on the liberation of the peptide gonadotropin releasing hormone (GnRH) in solution] Lorenz D, et al. **Pharmazie** 1985 Sep;40(9):631-7 (Eng. Abstr.) **(Ger)**

[Determination of the secondary structure of proteins from circular dichroism spectra. IV. Contribution of aromatic amino acid residues into circular dichroism spectra of proteins in the peptide region] Bolotina IA, et al. **Mol Biol (Mosk)** 1985 Sep-Oct;19(5):1409-21 (Eng. Abstr.) **(Rus)**

[Regulatory mediators of the bone marrow--myelopeptides] Petrov RV, et al. **Vestn Akad Med Nauk SSSR** 1985;(8):58-62 (Eng. Abstr.) **(Rus)**

PERPHENAZINE

Perphenazine decanoate in sesame oil vs. perphenazine enanthate in sesame oil: a comparative study of pharmacokinetic properties and some clinical implications. Knudsen P, et al. **Acta Psychiatr Scand [Suppl]** 1985; 322:11-4

Perphenazine decanoate vs. perphenazine enanthate: efficacy and side effects in a 6 week double-blind, comparative study of 50 drug monitored psychotic patients. Knudsen P, et al. **Acta Psychiatr Scand [Suppl]** 1985;322:15-28

Pharmacokinetic implications of different oil vehicles used in depot neuroleptic treatment. Knudsen P, et al. **Acta Psychiatr Scand [Suppl]** 1985;322:7-10

Therapeutic advantages of monitoring plasma concentrations of perphenazine in clinical practice. Hansen LB, et al.

Psychopharmacology (Berlin) 1985;87(1):16-9

PERSONALITY DISORDERS

Treatment outlines for the management of obsessive-compulsive disorders. The Quality Assurance Project. **Aust NZ J Psychiatry** 1985 Sep;19(3):240-53

Personality diagnosis and illness diagnosis. Brown JH, et al. **Can J Psychiatry** 1985 Oct;30(6):428-33

PHENCYCLIDINE

The effect of the acetylcholine transport blocker 2-(4-phenylpiperidino) cyclohexanol (AH5183) on the subcellular storage and release of acetylcholine in mouse brain. Carroll PT. **Brain Res** 1985 Dec 9; 358(1-2):200-9

Effects of 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (AH5183) on rat cortical synaptosome choline uptake, acetylcholine storage and release. Otero DH, et al. **Brain Res** 1985 Dec 16; 359(1-2):208-14

Suppression of PCP-induced behavioral arousal in the rat by yohimbine pretreatment. Byron K, et al. **Eur J Pharmacol** 1985 Nov 5; 117(2):271-3

Phencyclidine binding sites in the nucleus accumbens and phencyclidine-induced hyperactivity are decreased following lesions of the mesolimbic dopamine system. French ED, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):1-9

Inhibition of phencyclidine percutaneous absorption by parenterally administered hypertonic saline. Bailey DN, et al. **J Anal Toxicol** 1985 Nov-Dec;9(6):267-8

Effect of phencyclidine on the metabolism of individual brain proteins. Koul O, et al. **J Neurochem** 1986 Feb;46(2):470-4

Phencyclidine and the dynamics of mouse brain histamine. Itoh Y, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):788-92

Treatment of phenylcyclohexylpyrrolidine (PHP) psychosis with haloperidol. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1985; 23(2-3):185-9

The effects of the acute administration of phencyclidine hydrochloride (PCP) on the release of corticosterone, growth hormone and prolactin in the rat. Pechnick RN, et al. **Life Sci** 1986 Jan 20;38(3):291-6

Phencyclidine increases the affinity of dihydropyridine calcium channel antagonist binding in rat brain. Bolger GT, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Sep;330(3):227-34

Ketamine and phencyclidine cause a voltage-dependent block of responses to L-aspartic acid. Honey CR, et al. **Neurosci Lett** 1985 Oct 24; 61(1-2):135-9

Differences between calcium channel inhibitors in their effects on phencyclidine-induced behavioral stimulation in mice. Grebb JA, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):613-8

The effects of phencyclidine and ketamine on sensory thresholds and reaction times in the baboon. Lukas SE, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):743-7

Delta-9-tetrahydrocannabinol potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys. Thompson DM, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):1051-7

Cocaine potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys. Thompson DM, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):823-9

Discriminative stimulus properties and brain distribution of phencyclidine in rats following administration by injection and smoke inhalation. Wessinger WD, et al. **Pharmacol Biochem Behav** 1985 Oct; 23(4):607-12

Phencyclidine-induced dopamine-dependent behaviors in chronic haloperidol-treated rats. Yamaguchi K, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):803-9

Phencyclidine in low doses selectively blocks a presynaptic voltage-regulated potassium channel in rat brain. Bartschat DK, et al. **Proc Natl Acad Sci USA** 1986 Jan;83(1):189-92

Evidence for an endogenous peptide ligand and antagonist for PCP receptors. Contreras PC, et al. **Prog Clin Biol Res** 1985;192:495-8

Effects of cigarette smoke and 3-methylcholanthrene on the disposition of phencyclidine and its N-ethylamine analogue in the isolated perfused lung of rats. Law FC, et al. **Toxicology** 1985 Dec;37(3-4):275-84

PHENCYCLIDINE ABUSE

Management of PCP intoxication. Price WA, et al. **Am Fam Physician** 1985 Dec;32(6):115-8

Reserpine and phencyclidine-associated psychosis: three case reports. Berlant JL. **J Clin Psychiatry** 1985 Dec;46(12):542-4

PHENELZINE

Liquid chromatographic determination of inhibition of monoamine oxidase activity in platelet rich plasma of depressed patients treated with phenelzine. Gupta RN, et al. **Clin Chim Acta** 1985 Oct 31; 152(1-2):63-9

Switching monoamine oxidase inhibitors. True BL, et al. **Drug Intell Clin Pharm** 1985 Nov;19(11):825-7

Psychosis following phenelzine discontinuation [letter] **J Clin Psychopharmacol** 1985 Dec;5(6):360-1

Metabolism and pharmacokinetics of phenelzine: lack of evidence for acetylation pathway in humans. Robinson DS, et al. **J Clin Psychopharmacol** 1985 Dec;5(6):333-7

Bulimia and monoamine oxidase inhibitors: a predictor study. Hardy BW, et al. **Tex Med** 1985 Oct;81(10):39-42

PHENETHYLAMINES

Stereoselectivity and isoenzyme selectivity of monoamine oxidase inhibitors. Enantiomers of amphetamine, N-methylamphetamine and deprenyl. Robinson JB. **Biochem Pharmacol** 1985 Dec 1; 34(23):4105-8

[14C]-beta-phenethylamine, its distribution after administration by various routes to cats, and the effects of monoamine oxidase inhibitors. Garcha G, et al. **Br J Pharmacol** 1985 Dec;86(4):877-88

Prevention of dopaminergic toxicity of MPTP in mice by phenylethylamine, a specific substrate of type B monoamine oxidase. Melamed E, et al. **Br J Pharmacol** 1985 Nov;86(3):529-31

The enantiomers of SK&F 83566, a new selective D-1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D-2 agonist RU 24213. Molloy AG, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):183-6

Increased life expectancy resulting from addition of L-deprenyl to Madopar treatment in Parkinson's disease: a longterm study. Birkmayer W, et al. **J Neural Transm** 1985;64(2):113-27

Effects of deuterium substitution on the catabolism of beta-phenylethylamine: an in vivo study. Dyck LE, et al. **J Neurochem** 1986 Feb;46(2):399-404

Deprenyl protects dopamine neurons from the neurotoxic effect of 1-methyl-4-phenylpyridinium ion. Mytilineou C, et al. **J Neurochem** 1985 Dec;45(6):1951-3

Effects of d-amphetamine and of beta-phenylethylamine on fixed interval responding maintained by self-regulated lateral hypothalamic stimulation in rats. Greenshaw AJ, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):519-23

Projection of an endocoid involved with schizophrenic reaction. Proctor CD, et al. **Prog Clin Biol Res** 1985;192:387-93

Effects of the putative D-1 antagonist SCH 23390 on stereotyped behaviour induced by the D-2 agonist RU24213. Pugh MT, et al. **Psychopharmacology (Berlin)** 1985;87(3):308-12

A rapid and sensitive procedure for the simultaneous analysis of beta-phenylethylamine and tranylcypromine in rat brain using trichloroacetylation and gas chromatography. Baker GB, et al. **Res Commun Chem Pathol Pharmacol** 1985 Sep;49(3):471-4

PHENOBARBITAL

Demonstration of H2O2 production in vivo during aminopyrine metabolism and phenobarbital induction. Premereur N, et al. **Arch Int Physiol Biochim** 1985 Sep;93(3):241-8

Initial rate of sodium taurocholate uptake in isolated elutriated hepatocytes from untreated and phenobarbital-treated rats. Willson RA, et al. **Biochem Pharmacol** 1985 Dec 15;34(24):4257-62

Characterization of testosterone 16 alpha-hydroxylase (I-P-450(16) alpha) induced by phenobarbital in mice. Devore K, et al. **Biochemistry** 1985 Sep 24;24(20):5632-7

Prenatal versus neonatal long-term effect of phenobarbital on mouse microsomal drug-oxidizing system. Yanai J, et al. **Biol Neonate** 1985; 48(5):269-73

Modulation of asialoglycoprotein receptor levels in rat liver by phenobarbital treatment. Evarts RP, et al. **Carcinogenesis** 1985 Dec; 6(12):1767-73

Free concentration of carbamazepine and carbamazepine-10,11-epoxide in children and adults. Influence of age and phenobarbitone co-medication. Riva R, et al. **Clin Pharmacokinet** 1985 Nov-Dec; 10(6):524-31

Neonatal population pharmacokinetics of phenobarbital derived from routine clinical data. Grasela TH Jr, et al. **Dev Pharmacol Ther** 1985; 8(6):374-83

Distribution of phenobarbital in whole blood during pregnancy and perinatally--an in vitro study. Wallin A, et al. **Eur J Clin Pharmacol** 1985;29(2):187-91

The structure of phenobarbital-inducible rat liver cytochrome P-450 isoenzyme PB-4. Production and characterization of site-specific antibodies. Frey AB, et al. **J Biol Chem** 1985 Dec 5; 260(28):15253-65

Effect of phenobarbital on adult rat liver cells treated with 3'-methyl-4-dimethylaminoazobenzene in primary culture. Miyazaki M, et al. **J Cancer Res Clin Oncol** 1985;110(3):191-5

High-performance liquid chromatographic analysis of 1-(beta-D-glucopyranosyl)phenobarbital in urine. Bhargava VO, et al. **J Chromatogr** 1985 Sep 13;343(1):219-23

Application of derivative-differential UV spectrophotometry for the determination of oxazepam or phenobarbitone in the presence of dipyridamole. el-Yazbi FA, et al. **J Pharm Belg** 1985 Jul-Aug; 40(4):244-8

Effect of phenobarbitone on the pharmacokinetics and tissue levels of amiodarone in the rat. Fruncillo RJ, et al. **J Pharm Pharmacol** 1985 Oct;37(10):729-31

Effect of phenobarbitone on the distribution and elimination of imipramine in rats. Lin TH, et al. **J Pharm Pharmacol** 1985 Oct;37(10):735-8

Cytochrome P-450 isoenzyme content and monooxygenase activities in rat liver: effect of ontogenesis and pretreatment by phenobarbital and 3-methylcholanthrene. Cresteil T, et al. **J Pharmacol Exp Ther** 1986 Jan;236(1):269-76

Barbiturates reduce human cerebral glucose metabolism. Theodore WH, et al. **Neurology** 1986 Jan;36(1):60-4

Benznidazole and nifurtimox nitroreductase activity in liver microsomes from male rats preinduced with phenobarbital or 3-methylcholanthrene. Aguilar EG, et al. **Res Commun Chem Pathol Pharmacol** 1985 Dec; 50(3):443-6

Effects of anticonvulsant drugs on brain cultures from chick embryos: a comparison with cultures from embryos treated in ovo. Sedowofia SK, et al. **Teratogenesis Carcinog Mutagen** 1985;5(3):205-17

Effect of pretreatment with cimeticine or phenobarbital on lipoperoxidation in carbon tetrachloride- and trichloroethylene-dosed rats. Cluet JL, et al. **Toxicology** 1986 Jan;38(1):91-102

[Pharmacokinetics of prednisone after oral administration in children with renal grafts. Changes induced by phenobarbital and renal insufficiency] Perignon F, et al. **Arch Fr Pediatr** 1985 Aug-Sep;42 Suppl 1:639-44 (Eng. Abstr.) **(Fre)**

[Modification of the saccharide structures of orosomuccid in rats stimulated by treatment with phenobarbital] Monnet D, et al. **C R Acad Sci [III]** 1985;301(5):151-6 (Eng. Abstr.) **(Fre)**

[Neonatal jaundice and enzyme induction therapy] Mizutani M, et al. **Nippon Rinsho** 1985 Aug;43(8):1763-71 **(Jpn)**

[Effects of phenobarbital on EEG and sensory evoked potentials in normal cat brain] Takaya M, et al. **No To Shinkei** 1985 Aug;37(8):785-90 (Eng. Abstr.) **(Jpn)**

[Induction of cytochrome P-450 forms in liver microsomes of rats in the early neonatal period after administration of phenobarbital and 3-methylcholanthrene] Guliaeva LF, et al. **Biokhimiia** 1985 Nov; 50(11):1817-24 (Eng. Abstr.) **(Rus)**

[Effect of phenobarbital and Benzonal on succinate and alpha-ketoglutarate oxidation by rat brain mitochondria] Khazanov VA, et al. **Biull Eksp Biol Med** 1985 Dec;100(12):692-4 (Eng. Abstr.) **(Rus)**

[Action of phenobarbital on bacterial luciferase of Photobacterium fischeri] Danilov VS. **Mikrobiologiia** 1985 Jul-Aug;54(4):587-91 (Eng. Abstr.) **(Rus)**

PHENOTHIAZINE TRANQUILIZERS

Radiosensitizing and radioprotective effects of phenothiazines. Maniar HS, et al. **Indian J Exp Biol** 1985 Feb;23(2):100-2

The effect of phenothiazine and dibenzazepine pretreatment on the metabolism of methamphetamine in rats. Mori M, et al. **J Pharm Pharmacol** 1985 Nov;37(11):819-20

PHENOTHIAZINES

A double blind study in out-patients with primary non-agitated depression treated with imipramine in combination with placebo, diazepam or dixyrazine. Feet PO, et al. **Acta Psychiatr Scand** 1985 Oct; 72(4):334-40

Inhibitory effect of phenothiazine derivatives on bone in vivo and osteoblastic cells in vitro. Komoda T, et al. **Biochem Pharmacol** 1985 Nov 1;34(21):3885-9

Electrophysiological effects of ethmozine in perfused rabbit hearts. Dresel PE, et al. **Can J Physiol Pharmacol** 1985 Nov;63(11):1418-22

Effects of the diethylamino analog of ethmozin (ethacizin) upon sympathetic and parasympathetic efferent activity to the canine heart. Hageman GR, et al. **J Pharmacol Exp Ther** 1986 Jan;236(1):75-9

Sensitive high performance liquid chromatographic analysis of ethmozin in plasma. Poirier JM. **Ther Drug Monit** 1985;7(4):439-41

[Comparative analysis of the action of 2 calmodulin inhibitors on the contractile function of the isolated heart] Kapel'ko VI, et al. **Fiziol Zh SSSR** 1985 Sep;71(9):1095-100 (Eng. Abstr.) **(Rus)**

PHENOXYBENZAMINE

The use of two alpha blocking agents, phenoxybenzamine and phentolamine, in ointment and injection form to improve skin flap survival in rats. Goshen J, et al. **Ann Plast Surg** 1985 Nov; 15(5):431-5

Functional involvement of vasopressin in the maintenance of systemic arterial blood pressures after phenoxybenzamine or phentolamine administration: studies in Long-Evans and Brattleboro rats. Winn MJ, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):500-5

The effect of phenoxybenzamine on histamine H1-receptor binding sites in dog frontal cortex membranes. Cook DA, et al. **Proc West Pharmacol Soc** 1985;28:213-5

PHENYLALANINE

Evolutionary implications of features of aromatic amino acid biosynthesis in the genus Acinetobacter. Byng GS, et al. **Arch Microbiol** 1985 Nov; 143(2):122-9

Synthesis of peptide labelled with p-iodophenylalanine which corresponds to the first amphipathic region of apolipoprotein C-I. Harding DR, et al. **Int J Pept Protein Res** 1985 Aug;26(2):208-13

Treatment of attention deficit disorder with DL-phenylalanine. Wood DR, et al. **Psychiatry Res** 1985 Sep;16(1):21-6

PHENYLPROPANOLAMINE

Are antihistamine-decongestants of value in the treatment of acute otitis media in children? Schnore SK, et al. **J Fam Pract** 1986 Jan; 22(1):39-43

PHENYTOIN

Phenytoin and acute mountain sickness on Mount Everest. Wohns RN, et al. **Am J Med** 1986 Jan;80(1):32-6

Effect of phenytoin on [3H]norepinephrine release from synaptosomes. Pincus JH, et al. **Brain Res** 1985 Dec 2;348(2):387-90

Frequency-dependent effects of phenytoin on frog junctional transmission: presynaptic mechanisms. Yaari Y, et al. **Brain Res** 1985 Oct 14;345(1):102-10

Enzyme immunochromatographic assay of phenytoin in capillary and venous blood compared with fluorescence polarization immunoassay of plasma from epileptic patients. Haidukewych D, et al. **Clin Chem** 1986 Jan;32(1 Pt 1):204

Free thyroxin and free triiodothyronine as measured by equilibrium dialysis and analog radioimmunoassay in serum of patients taking phenytoin and carbamazepine. Liewendahl K, et al. **Clin Chem** 1985 Dec;31(12):1993-6

On the interaction between phenytoin and digoxin. Rameis H. **Eur J Clin Pharmacol** 1985;29(1):49-53

Degeneration of granule cells following chronic phenytoin administration: an electron microscopic investigation of the mouse cerebellum. Volk B, et al. **Exp Neurol** 1986 Jan;91(1):60-70

Omeprazole inhibits oxidative drug metabolism. Studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. Gugler R, et al. **Gastroenterology** 1985 Dec;89(6):1235-41

The effect of phenytoin in vitro on normal human mononuclear cells and on human lymphoblastoid B cell lines of different Ig isotype specificities. Wangel AG, et al. **Immunobiology** 1985 Sep; 170(3):232-8

Urinary dihydrodiol metabolites of phenytoin: high-performance liquid chromatographic assay of diastereomeric composition. Maguire JH, et al. **J Chromatogr** 1985 Aug 9;342(2):323-32

Genetic variation in spontaneous and diphenylhydantoin-induced craniofacial malformations in mice. Brown KS, et al. **J Craniofac Genet Dev Biol [Suppl]** 1985;1:305-12

On the mechanism by which phenytoin blocks post-tetanic potentiation at the frog neuromuscular junction. Selzer ME, et al. **J Neurosci** 1985 Nov;5(11):2894-9

Alterations in tissue trace element and ascorbic acid metabolism in phenytoin-fed rats and mice. Dubick MA, et al. **J Nutr** 1985 Nov; 115(11):1481-7

Interaction of phenytoin and inflammation induces gingival overgrowth in rats. do Nascimento A, et al. **J Periodont Res** 1985 Jul; 20(4):386-91

Effects of phenytoin on field bursts of rat hippocampal slices in low-calcium solutions. Snow RW, et al. **Neuropharmacology** 1985 Sep; 24(9):915-7

The in vivo biosynthesis of embryonic proteins after maternal administration of phenytoin in the mouse. Hicks HE, et al. **Proc Soc Exp Biol Med** 1985 Dec;180(3):483-7

Effect of amiodarone on the pharmacokinetics of phenytoin, quinidine, and lidocaine in the rat. Fruncillo RJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Dec;50(3):451-4

Effects of anticonvulsant drugs on brain cultures from chick embryos: a comparison with cultures from embryos treated in ovo. Sedowofia SK, et al. **Teratogenesis Carcinog Mutagen** 1985;5(3):205-17

A new approach to establishing individualized maintenance doses of phenytoin. Bachmann K, et al. **Ther Drug Monit** 1985;7(4):391-400

[Unjustified exclusion of donor kidneys after phenytoin treatment? (letter)] Oldenkott P, et al. **Dtsch Med Wochenschr** 1985 Nov 22; 110(47):1834-5 **(Ger)**

[Gingival hyperplasia and diphenylhydantoin] Barone GP, et al. **Parodontol Stomatol (Nuova)** 1984 Sep-Dec;23(3 Suppl 3):149-55**(Ita)**

[Comparison of i-PiT, TDX and EMIT measurement of serum phenytoin and digoxin levels] Koizumi F, et al. **Rinsho Byori** 1985 Jul; 33(7):761-70 (29 ref.) **(Jpn)**

PHOBIC DISORDERS

Predicting treatment preferences for agoraphobia. Norton GR, et al. **Behav Res Ther** 1985;23(6):699-701

PHYSOSTIGMINE

Physostigmine: an antidote for excessive central nervous system depression or paradoxical rage reactions resulting from intravenous diazepam. Jastak JT. **Anesth Prog** 1985 May-Jun;32(3):87-92

Physostigmine as an antidote for poisoning by combination of thioridazine and trihexyphenidyl. Beilin B, et al. **Br J Clin Pract** 1985 Oct; 39(10):400-1

Acetylcholinesterase inhibition by eserine: rate constants of reaction. Part II. Brufani M, et al. **Ital J Biochem** 1985 Sep-Oct;34(5):328-40

Comparative effects of scopolamine and atropine in preventing cholinesterase inhibitor induced lethality. Janowsky DS, et al. **Milit Med** 1985 Dec;150(12):693-5

The reversible cholinesterase inhibitor physostigmine has channel-blocking and agonist effects on the acetylcholine receptor-ion channel complex. Shaw KP, et al. **Mol Pharmacol** 1985 Dec; 28(6):527-38

Bioavailability of oral physostigmine [letter] Whelpton R, et al. **N Engl J Med** 1985 Nov 14;313(20):1293-4

Effect of ambient temperature on thermoregulation in rats following preoptic/anterior hypothalamic injection of physostigmine. Fehlner KS, et al. **Neuropharmacology** 1985 Oct;24(10):993-7

Facilitation and inhibition of nicotinic transmission by eserine in the sympathetic ganglia of the rabbit. Mo N, et al. **Neuropharmacology** 1985 Nov;24(11):1093-101

Methamphetamine, physostigmine, atropine and mecamylamine: effects on force lever performance. Preston KL, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):781-8

Chin rub CRs are elicited by flavors associated with apomorphine, scopolamine, methscopolamine, physostigmine and neostigmine. Smith RJ, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):583-9

The effects of atropine, benactyzine, and physostigmine on a repeated acquisition baseline in monkeys. Penetar DM. **Psychopharmacology (Berlin)** 1985;87(1):69-76

[Physostigmine: an antidote in diazepam poisoning] Pedersen JE. **Ugeskr Laeger** 1985 Nov 4;147(45):3586-7 (Eng. Abstr.) **(Dan)**

PILOCARPINE

Effects of pilocarpine treatment and of electrical stimulation of the vagus nerve on the rat parathyroid gland, with special reference to the alteration of storage granules. Setoguti T, et al. **Acta Anat (Basel)** 1985; 124(1-2):16-25

Concentration-dependent precorneal loss of pilocarpine in rabbit eyes. Urtti A, et al. **Acta Ophthalmol (Copenh)** 1985 Oct;63(5):502-6

Pilocarpine concentrations in aqueous humor following single drop application. I. Effect of soft contact lenses. Ellis PP, et al. **Curr Eye Res** 1985 Oct;4(10):1041-7

gamma-Glutamyltranspeptidase activity of rat submandibular gland after pilocarpine stimulation. Isacsson G, et al. **Swed Dent J** 1985; 9(4):171-4

PITUITARY HORMONE RELEASING HORMONES

The role of endogenous gonadotropin-releasing hormone in the control of luteinizing hormone and testosterone secretion in the juvenile male monkey, Macaca fascicularis. Cameron JL, et al. **Biol Reprod** 1985 Aug; 33(1):147-56

Active immunization of gilts against gonadotropin-releasing hormone: effects on secretion of gonadotropins, reproductive function, and responses to agonists of gonadotropin-releasing hormone. Esbenshade KL, et al. **Biol Reprod** 1985 Oct;33(3):569-77

Does the seasonal increase in estradiol negative feedback prevent luteinizing hormone surges in anestrous ewes by suppressing hypothalamic gonadotropin-releasing hormone pulse frequency? Legan SJ, et al. **Biol Reprod** 1985 Aug;33(1):117-31

The influence of hGRF, CRF, TRH and LHRH on SRIF release from median eminence fragments. Aguila MC, et al. **Brain Res** 1985 Nov 25;348(1):180-2

Second meeting of the European Neuroendocrine Association. Hypophysiotropic peptides in basic and clinical neuroendocrinology. Milan, October 15-17, 1985. Abstracts. **J Endocrinol Invest** 1985; 8 Suppl 3:1-233

Hormonal responses to gonadotrophin releasing hormone during testicular development in male African green monkeys. Brady AG, et al. **J Med Primatol** 1985;14(6):293-304

Individual variations in FSH release after a GnRH challenge and relationship with semen output in young bulls. Abdel Malak G, et al. **J Reprod Fertil** 1985 Nov;75(2):345-50

Hormone responses to exogenous GnRH pulses in post-partum dairy cows. Peters AR, et al. **J Reprod Fertil** 1985 Nov;75(2):557-65

Influence of passive immunization against GnRH on pregnancy and parturition in the tammar wallaby, Macropus eugenii. Short RV, et al. **J Reprod Fertil** 1985 Nov;75(2):567-75

Increase in brain and pituitary radioimmunoassayable gonadotropin releasing hormone (GnRH) in the European silver eel treated with sexual steroid or human chorionic gonadotropin. Dufour S, et al. **Neuropeptides** 1985 Dec;6(6):495-502

Effects of gonadotropin-releasing hormone on the release of luteinizing hormone and follicle-stimulating hormone from bovine anterior pituitary cell cultures. Braun U, et al. **Zentralbl Veterinarmed [A]** 1985 Sep;32(8):594-605

[Hormonal response following the use of gonadotropin-releasing hormone, estradiol and gestil in sheep] Batzhargalin E. **Vet Med Nauki** 1985;22(9):60-6 (Eng. Abstr.) **(Bul)**

[Pregnancy provoked by pulsatile administration of gonadotropin-releasing hormone in 2 women with oligomenorrhea] Gandar R, et al. **Rev Fr Gynecol Obstet** 1985 Jan;80(1):39-41 (Eng. Abstr.) **(Fre)**

[The influence of viscosity-increasing pharmaceutic aids on the liberation of the peptide gonadotropin releasing hormone (GnRH) in solution] Lorenz D, et al. **Pharmazie** 1985 Sep;40(9):631-7 (Eng. Abstr.) **(Ger)**

[The pulsatile administration of releasing hormone (GnRH) for the treatment of hypothalamic amenorrhea] Urdl W, et al. **Wien Klin Wochenschr** 1985 Dec 6;97(23):883-6 (Eng. Abstr.) **(Ger)**

PITUITARY HORMONES

Melanin concentrating hormone (MCH) effects on teleost (Chrysiptera cyanea) melanophores. Oshima N, et al. **J Exp Zool** 1985 Aug; 235(2):175-80

[Dopamine, its regulation of hormone secretion and its clinical significance] Yoshimura M. **Rinsho Byori** 1985 May;33(5):509-12 **(Jpn)**

[Hypophyseal, thyroid and adrenal cortical hormone levels in the blood serum of newborn infants in the early neonatal period] Ametov AS, et al. **Pediatriia** 1985 Sep;(9):20-2 (Eng. Abstr.) **(Rus)**

PITUITARY HORMONES, ANTERIOR

Administration of low dose pulsatile gonadotropin-releasing hormone (GnRH) to GnRH-deficient men regulates free alpha-subunit secretion. Spratt DI, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):102-8

Effects of intravenous and intraventricular injection of antisera directed against corticotropin-releasing factor on the secretion of anterior pituitary hormones. Ono N, et al. **Proc Natl Acad Sci USA** 1985 Nov; 82(22):7787-90

PREDNISONE

Effects of ACTH and prednisone on mood: incidence and time of onset. Cameron OG, et al. **Int J Psychiatry Med** 1985-86;15(3):213-23

[Pharmacokinetics of prednisone after oral administration in children with renal grafts. Changes induced by phenobarbital and renal insufficiency] Perignon F, et al. **Arch Fr Pediatr** 1985 Aug-Sep;42 Suppl 1:639-44 (Eng. Abstr.) **(Fre)**

PROCHLORPERAZINE

Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes [letter] Stevenson JG, et al. **Am J Hosp Pharm** 1985 Dec; 42(12):2651

Attenuation of cyclophosphamide-induced taste aversions in mice by prochlorperazine, delta 9-tetrahydrocannabinol, nabilone and levonantradol. Landauer MR, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):259-66

PROGESTERONE

Evidence for gamma-aminobutyric acid modulation of ovarian hormonal effects on luteinizing hormone secretion and hypothalamic catecholamine activity in the female rat. Adler BA, et al. **Endocrinology** 1986 Jan;118(1):91-7

In vitro study of the direct ovarian effects of gonadotropin-releasing hormone (GnRH) in the frogs, Rana pipiens and Rana catesbeiana. Hubbard GM, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):154-61

The effects of estradiol and progesterone on the concentration of striatal dopamine and tyramine in ovariectomized mice. Yeung SC, et al. **Gen Pharmacol** 1985;16(5):517-9

The effects of steroid hormones and gonadotropins on in vitro placental conversion of pregnenolone to progesterone. Das NP, et al. **J Steroid Biochem** 1985 Oct;23(4):517-22

Effects of cannabinoids on progesterone release in cultures of rat luteal cells. Leung PC, et al. **Life Sci** 1985 Nov 4;37(18):1691-6

Intrahypothalamic effects of progestin agonists on estrous behavior and progestin receptor binding. Glaser JH, et al. **Physiol Behav** 1985 Jun; 34(6):871-7

[Metabolism of progesterone in fetal membranes. The effect of sex steroids and gonadotropin-releasing hormone on progesterone metabolism in fetal membranes] Hori D, et al. **Igaku Kenkyu** 1985 Jul;55(2):97-102 (Eng. Abstr.) **(Jpn)**

[Study on the direct inhibitory action of luteinizing hormone-releasing hormone on the steroidogenesis of cultured human corpus luteum cells] Okamoto S. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Oct; 37(10):2107-16 (Eng. Abstr.) **(Jpn)**

PROLACTIN

Serotonergic regulation of prolactin and growth hormone secretion in man. Lewis DA, et al. **Acta Endocrinol (Copenh)** 1985 Oct; 110(2):152-7

Interaction of prolactin with adrenal hormones in blood pressure regulation in rats. Mills DE, et al. **Am J Physiol** 1985 Dec; 249(6 Pt 1):E614-8

Prolactin involvement in regulation of testicular 5 alpha-reductase activity in the immature rat. Chase DJ, et al. **Biol Reprod** 1985 Oct; 33(3):637-43

Serotonergic influences on pituitary gland and hypothalamic induction of prolactin and luteinizing hormone release in the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Biol Reprod** 1985 Dec; 33(5):1064-72

Neuroendocrine findings in a chronic cocaine abusers: a preliminary report. Gawin FH, et al. **Br J Psychiatry** 1985 Nov;147:569-73

Strain differences in pituitary prolactin content: relationship to number of hypothalamic dopamine neurons. Baker H, et al. **Brain Res** 1985 Dec 9;358(1-2):16-26

Effect of low-dose dopamine infusion on basal and stimulated TSH and prolactin concentrations in man. Connell JM, et al. **Clin Endocrinol (Oxf)** 1985 Aug;23(2):185-92

Dopamine: a prolactin-inhibiting hormone. Ben-Jonathan N. **Endocr Rev** 1985 Fall;6(4):564-89 (281 ref.)

Regulation of pituitary gonadotropin-releasing hormone (GnRH) receptors by pulsatile GnRH in female rats: effects of estradiol and prolactin. Duncan JA, et al. **Endocrinology** 1986 Jan;118(1):320-7

A complex noncoordinate regulation of alpha-lactalbumin and 25 K beta-casein by corticosterone, prolactin, and insulin in long term cultures of normal rat mammary cells. Ray DB, et al. **Endocrinology** 1986 Jan;118(1):393-407

Somatic growth in hypophysectomized pituitary-homografted rats is promoted by prolactin. Drago F, et al. **Experientia** 1985 Nov 15; 41(11):1442-4

Influence of cerebroventricular injection of dopamine on plasma prolactin and LH levels of postlaying and broody turkey hens. Hargis BM, et al. **Gen Comp Endocrinol** 1986 Jan;61(1):142-7

In vivo release of prolactin in Rana ridibunda following an intravenous injection of thyrotropin-releasing hormone. Kühn ER, et al. **Gen Comp Endocrinol** 1985 Oct;60(1):86-9

Effects of putative neurotransmitters on release of prolactin from pituitary glands of the domestic fowl co-incubated with hypothalamic tissue. Hall TR, et al. **Gen Pharmacol** 1985;16(5):483-8

Phospholipid metabolism and prolactin secretion in vitro. Canonico PL, et al. **Horm Res** 1985;22(3):164-71

Involvement of hypothalamic dopamine in the regulation of prolactin secretion. Reymond MJ, et al. **Horm Res** 1985;22(3):142-52 (76 ref.)

Prolactin and calcium metabolism in pregnant ewes. Barlet JP. **J Endocrinol** 1985 Nov;107(2):171-5

Increased dopaminergic inhibition of prolactin in the hypoprolactinaemic IPL nude rat. Cohen H, et al. **J Endocrinol** 1985 Dec;107(3):325-9

Sexual differentiation of prolactin responsiveness to thyrotropin releasing hormone (TRH) in the rat. Effects of postnatal testosterone on adenohypophyseal TRH receptor ontogenesis in male rats. Watanobe H, et al. **J Endocrinol Invest** 1985 Oct;8(5):459-64

Central effects of an antagonist and an antiserum to substance P on serum gonadotropin and prolactin secretion. Dees WL, et al. **Life Sci** 1985 Oct 28;37(17):1627-31

Inhibition of plasma prolactin in the rat by amantadine. Fayez M, et al. **Life Sci** 1985 Nov 18;37(20):1877-80

The effects of the acute administration of phencyclidine hydrochloride (PCP) on the release of corticosterone, growth hormone and prolactin in the rat. Pechnick RN, et al. **Life Sci** 1986 Jan 20;38(3):291-6

Effect of somatostatin on plasma prolactin. Lugari R, et al. **Minerva Endocrinol** 1985 Apr-Jun;10(2):79-82

Analysis by plaque assays of GH and prolactin release from individual cells in cultures of male pituitaries. Evidence for functional heterogeneity within rat mammotrope and somatotrope populations. Boockfor FR, et al. **Neuroendocrinology** 1986;42(1):64-70

Opioid kappa receptors and the secretion of prolactin (PRL) and growth hormone (GH) in the rat. II. GH and PRL release-inhibiting effects of the opioid kappa receptor agonists bremazocine and U-50,488. Krulich L, et al. **Neuroendocrinology** 1986;42(1):82-7

Dopaminergic modulation of the diethylstilbestrol-induced proliferation of the anterior pituitary gland of the Fisher 344 rat. Miyazaki K, et al. **Neuroendocrinology** 1985 Nov;41(5):405-8

Serotonergic stimulation of prolactin and corticosterone secretion is mediated by different pathways from the mediobasal hypothalamus. Van de Kar LD, et al. **Neuroendocrinology** 1985 Nov;41(5):380-4

Further evidence that peptide histidine isoleucine (PHI) may function as a prolactin releasing factor in rats. Ohta H, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):709-12

Effects of in vivo pretreatment with D-Trp-6-LH-RH on prolactin and LH secretion by pituitary glands in vitro. Torres-Alemán I, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):993-5

Involvement of peptide histidine isoleucine (PHI) in prolactin secretion induced by serotonin in rats. Tojo K, et al. **Proc Soc Exp Biol Med** 1985 Dec;180(3):558-61

Depot fluphenazine and plasma prolactin. Gift T, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):407-12

Dexamethasone increases plasma HVA but not MHPG in normal humans. Wolkowitz OM, et al. **Psychiatry Res** 1985 Oct;16(2):101-9

Cellular mechanisms for neurotensin receptor-mediated release of prolactin. Memo M, et al. **Regul Pept [Suppl]** 1985;4:200-2

PROMETHAZINE

Detachable cast pylon technique for rigid dressings on below-knee amputee patients. Bacon R, et al. **Arch Phys Med Rehabil** 1986 Jan; 67(1):56-8

PROPANEDIOLS

Formaldehyde metabolism by Escherichia coli. Carbon and solvent deuterium incorporation into glycerol, 1,2-propanediol, and 1,3-propanediol. Hunter BK, et al. **Biochemistry** 1985 Jul 16; 24(15):4148-55

Human embryo features that influence the success of cryopreservation with the use of 1,2 propanediol. Lassalle B, et al. **Fertil Steril** 1985 Nov;44(5):645-51

Interspecies variability in propylene glycol dinitrate-induced methemoglobin formation. Wyman JF, et al. **Toxicol Appl Pharmacol** 1985 Nov;81(2):203-12

PROPRANOLOL

Lack of effect of propranolol on the steady-state plasma levels of ketanserin. Trenk D, et al. **Arzneimittelforschung** 1985;35(8):1286-8

Study of propranolol binding to human alpha 1-acid glycoprotein by high-performance liquid chromatography. Soltés L, et al. **Biochem Pharmacol** 1985 Dec 15;34(24):4331-4

Contrasts between pindolol and propranolol concentration-response relationships. Carruthers SG, et al. **Br J Clin Pharmacol** 1985 Oct; 20(4):417-20

Interaction between cholinergic and adrenergic synapses of the rat subfornical organ and the thirst-inducing effect of angiotensin II. Saad WA, et al. **Braz J Med Biol Res** 1985;18(1):37-46

Effects of (+/-)-sotalol, (+/-)-propranolol, and (-)-propranolol on norepinephrine release upon hepatic nerve stimulation in the dog liver in vivo. Yamaguchi N. **Can J Physiol Pharmacol** 1985 Nov; 63(11):1423-8

Effects of betaxolol, propranolol, and atenolol on isoproterenol-induced beta-adrenoceptor responses. Riddell JG, et al. **Clin Pharmacol Ther** 1985 Nov;38(5):554-9

Biologic determinants of propranolol disposition: results from 1308 patients in the Beta-Blocker Heart Attack Trial. Walle T, et al. **Clin Pharmacol Ther** 1985 Nov;38(5):509-18

Haemodynamic effects of low and high doses of insulin during beta receptor blockade in dogs. Reikerås O, et al. **Clin Physiol** 1985 Oct; 5(5):455-67

Receptor binding of propranolol is the missing link between plasma concentration kinetics and the effect-time course in man. Wellstein A, et al. **Eur J Clin Pharmacol** 1985;29(2):131-47

Effect of ascorbic acid and adrenergic receptor blockers on adrenaline induced in vitro follicular atresia in white Leghorn hens. Moudgal RP, et al. **Indian J Exp Biol** 1985 Jun;23(6):343-4

Rapid and simultaneous extraction of propranolol, its neutral and basic metabolites from plasma and assay by high-performance liquid chromatography. Harrison PM, et al. **J Chromatogr** 1985 Oct 11; 343(2):349-58

Dose-dependent presystemic elimination of propranolol due to hepatic first-pass metabolism in rats. Iwamoto K, et al. **J Pharm Pharmacol** 1985 Nov;37(11):826-8

Attempts to use cyanide ion to trap imine intermediates in the microsomal N-dealkylation of propranolol: formation of alpha-aminonitriles as artifacts when using ether for extraction. Shetty HU, et al. **J Pharm Sci** 1985 Sep;74(9):968-71

Population study of poor debrisoquine-type metabolizers of propranolol among Japanese. Hayashi M, et al. **Jpn J Ophthalmol** 1985; 29(3):272-81

Kinetics of 1,2-dinitroglycerin following sustained release nitroglycerin: influence of propranolol and metoprolol. Ochs HR, et al. **Klin Wochenschr** 1985 Nov 15;63(22):1170-3

Once-daily propranolol [letter] Dunn JM, et al. **Lancet** 1985 Nov 23; 2(8465):1183

Ventilatory response to carbon dioxide and to isometric muscle contraction after administration of placebo, propranolol, mepindolol and salbutamol. Bosisio E, et al. **Respiration** 1985;48(2):116-21

Effect of propranolol on brain electrical activity during hyperbaric oxygenation in the rat. Torbati D. **Undersea Biomed Res** 1985 Dec; 12(4):423-9

[A population study of the poor metabolizers of the debrisoquine type in Japan] Hayashi M, et al. **Nippon Ganka Gakkai Zasshi** 1985 Aug; 89(8):983-90 (Eng. Abstr.) **(Jpn)**

PROSTAGLANDINS

Racial differences in renin, aldosterone, prostaglandin and kallikrein of normal male subjects. Lijnen P, et al. **Ann Soc Belg Med Trop** 1985 Sep;65(3):293-301

Changes in body temperature after administration of acetylcholine, histamine, morphine, prostaglandins and related agents: II. Clark WG, et al. **Neurosci Biobehav Rev** 1985 Fall;9(3):479-552 (741 ref.)

The role of prostaglandins in aldosterone and corticosterone secretion by isolated perfused rat zona glomerulosa cells. Hindawi RK, et al. **Prostaglandins Leukotrienes Med** 1985 Nov;20(2):121-8

The effect of pindolol on exercise-induced increase in plasma vasoactive prostanoids and catecholamines in healthy men. Laustiola K, et al. **Prostaglandins Leukotrienes Med** 1985 Nov;20(2):111-20

PSYCHIATRY

Attitude change concerning right to refuse treatment: the impact of experience. Binder RL, et al. **Am J Psychiatry** 1985 Nov; 142(11):1362-5

Psychiatrists and their prescribing practices. Falk WE, et al. **Compr Psychiatry** 1985 Nov-Dec;26(6):548-53

PSYCHOLOGICAL TESTS

[Correlation between serum levels of amitriptyline and the Hamilton scale of depression using high-pressure liquid chromatography] Cruz Igartúa A, et al. **Bol Asoc Med PR** 1985 Sep;77(9):375-80 **(Spa)**

PSYCHOLOGY, EXPERIMENTAL

A comparison of different methods of assessing patterns of responding in discrete trial choice procedures. Sahgal A, et al. **Psychopharmacology (Berlin)** 1985;87(3):374-7

PSYCHOMOTOR PERFORMANCE

The effect of repeated doses of temazepam and nitrazepam on human psychomotor performance. Tedeschi G, et al. **Br J Clin Pharmacol** 1985 Oct;20(4):361-7

Effects of chronic benzodiazepine administration on neuropsychological performance. Bornstein RA, et al. **Clin Neuropharmacol** 1985; 8(4):357-61

Effect of beta-blockers on psychomotor performance in normal volunteers. Betts TA, et al. **Eur J Clin Pharmacol** 1985; 28 Suppl:39-49

Beta-blockers and psychometric performance: studies in normal volunteers. McDevitt DG. **Eur J Clin Pharmacol** 1985; 28 Suppl:35-8

Central effects in man of the novel schistosomicidal benzodiazepine meclonazepam. O'Boyle C, et al. **Eur J Clin Pharmacol** 1985; 29(1):105-8

The prolonging effect of N,N'-diallylpentobarbital on the drug-induced sleep and motor incoordination. Yamamoto I, et al. **Res Commun Chem Pathol Pharmacol** 1985 Nov;50(2):209-19

PSYCHOPATHOLOGY

Longisectional interaction structure analysis (LISA) in psychopharmacology and developmental psychopathology. Lienert GA, et al. **Neuropsychobiology** 1985;14(1):27-34

PSYCHOPHARMACOLOGY

Longisectional interaction structure analysis (LISA) in psychopharmacology and developmental psychopathology. Lienert GA, et al. **Neuropsychobiology** 1985;14(1):27-34

A microcomputer-based method for physiologically interpretable measurement of the rewarding efficacy of brain stimulation. Campbell KA, et al. **Physiol Behav** 1985 Sep;35(3):395-403

A comparison of different methods of assessing patterns of responding in discrete trial choice procedures. Sahgal A, et al. **Psychopharmacology (Berlin)** 1985;87(3):374-7

PSYCHOPHYSIOLOGIC DISORDERS

[Veralipride: treatment of climacteric disorders] Stockmann R. **Rev Fr Gynecol Obstet** 1985 Jun;80(6 Pt 2):495-9 **(Fre)**

PSYCHOPHYSIOLOGY

On-demand platform improves accuracy of the Morris water maze procedure. Burešová O, et al. **J Neurosci Methods** 1985 Oct; 15(1):63-72

A microcomputer-based method for physiologically interpretable measurement of the rewarding efficacy of brain stimulation. Campbell KA, et al. **Physiol Behav** 1985 Sep;35(3):395-403

PSYCHOSES, SUBSTANCE-INDUCED

Psychoses associated with bupropion treatment. Golden RN, et al. **Am J Psychiatry** 1985 Dec;142(12):1459-62

Another case of alprazolam withdrawal syndrome [letter] Vital-Herne J, et al. **Am J Psychiatry** 1985 Dec;142(12):1515

Reserpine and phencyclidine-associated psychosis: three case reports. Berlant JL. **J Clin Psychiatry** 1985 Dec;46(12):542-4

Psychosis following phenelzine discontinuation [letter] **J Clin Psychopharmacol** 1985 Dec;5(6):360-1

Treatment of phenylcyclohexylpyrrolidine (PHP) psychosis with haloperidol. Giannini AJ, et al. **J Toxicol Clin Toxicol** 1985; 23(2-3):185-9

Lithium attenuates the activation-euphoria but not the psychosis induced by d-amphetamine in schizophrenia. van Kammen DP, et al. **Psychopharmacology (Berlin)** 1985;87(1):111-5

PSYCHOTHERAPY

Psychotherapy of schizophrenia. What happens to treatment dropouts. Katz HM, et al. **J Nerv Ment Dis** 1984 Jun;172(6):326-31

[Treatment of psychoses] Tirkkonen A. **Duodecim** 1985; 101(17):1686-97 **(Fin)**

[Psychotherapy of psychotic patients] Bender W. **Nervenarzt** 1985 Sep; 56(9):465-71 (Eng. Abstr.) **(Ger)**

PSYCHOTHERAPY, GROUP

Prolixin group. Can nursing intervention groups lower recidivism? Selander JM, et al. **J Psychosoc Nurs Ment Health Serv** 1985 Nov; 23(11):16-20

PSYCHOTIC DISORDERS

Psychotic patients' understanding of informed consent. Irwin M, et al. **Am J Psychiatry** 1985 Nov;142(11):1351-4

Cholinergic processes in blood samples from patients with major psychiatric disorders. Jope RS, et al. **Biol Psychiatry** 1985 Dec; 20(12):1258-66

Rapid tranquilization: the efficacy of oral concentrate. Dubin WR, et al. **J Clin Psychiatry** 1985 Nov;46(11):475-8

Benzodiazepines in the management of psychotic agitation [letter] Modell JG. **J Clin Psychiatry** 1985 Nov;46(11):506

Lithium carbonate and the 'cycloid spectrum' [letter] Novae A. **J Clin Psychiatry** 1985 Nov;46(11):504-5

A clinical assessment of zuclopenthixol dihydrochloride (Clopixol tablets) in the treatment of psychotic illness. Mann BS, et al. **Pharmatherapeutica** 1985;4(6):387-92

[Present status and trends in drug dependence] Jiang ZN. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Jun; 18(3):181-4 (16 ref.) **(Chi)**

[Experience with lithiotherapy in psychoses in childhood and adolescence] Kadlecová B, et al. **Cesk Psychiatr** 1985 Oct;81(5):339-44 (Eng. Abstr.) **(Cze)**

[Lithium prophylaxis, o.k., but for how long?] Slooff CJ, et al. **Ned Tijdschr Geneeskd** 1985 Sep 7;129(36):1729-33 (Eng. Abstr.) **(Dut)**

[Treatment of psychoses] Tirkkonen A. **Duodecim** 1985; 101(17):1686-97 **(Fin)**

[Psychotherapy of psychotic patients] Bender W. **Nervenarzt** 1985 Sep; 56(9):465-71 (Eng. Abstr.) **(Ger)**

[Preventive effect of valproic acid amide in affective diseases] Kłosiewicz L. **Psychiatr Pol** 1985 Jan-Feb;19(1):23-9 (Eng. Abstr.) **(Pol)**

QUINIDINE

Influence of quinidine on the intestinal secretion of digoxin and digitoxin in guinea pigs. Schäfer SG, et al. **Chem Biol Interact** 1985 Oct; 55(1-2):203-13

Quinidine-induced nephrotic syndrome. Chisholm JC Jr. **J Natl Med Assoc** 1985 Nov;77(11):920-2

Effect of amiodarone on the pharmacokinetics of phenytoin, quinidine, and lidocaine in the rat. Funcillo RJ, et al. **Res Commun Chem Pathol Pharmacol** 1985 Dec;50(3):451-4

[The interaction of antiarrhythmic drugs with other drugs] Yamaguchi I. **Kokyu To Junkan** 1985 Aug;33(8):956-69 (151 ref.) **(Jpn)**

REACTION TIME

The effects of phencyclidine and ketamine on sensory thresholds and reaction times in the baboon. Lukas SE, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):743-7

RECEPTORS, ADRENERGIC

Adrenergic receptors in depression. Effects of electroconvulsive therapy. Cooper SJ, et al. **Br J Psychiatry** 1985 Jul;147:23-9

Octopamine receptors in the molluscan aortic bulb: effects of clozapine and chlordimeform. Dougan DF, et al. **Comp Biochem Physiol** [C] 1985; 82(1):193-7

Modification of behavioral response to intra-hippocampal injections of noradrenaline and adrenoceptor agonists by chronic treatment with desipramine and citalopram: functional aspects of adaptive receptor changes. Płaźnik A, et al. **Eur J Pharmacol** 1985 Nov 5; 117(2):245-52

Fat cell adrenoceptors: inter- and intraspecific differences and hormone regulation. Lafontan M, et al. **Int J Obes** 1985;9 Suppl 1:117-27 (58 ref.)

Peripheral adrenoceptors and serotonin receptors in depression. Changes associated with response to treatment with trazodone or amitriptyline. Healy D, et al. **J Affective Disord** 1985 Nov;9(3):285-96

[Concentrations of external noradrenergic axonal networks in the area of type-III neuronal aggregates and dense capillary networks of the external submucosal plexus (Schabadasch's) in the pig small intestine] Stach W, et al. **Z Mikrosk Anat Forsch** 1985;99(4):617-26 (Eng. Abstr.) **(Ger)**

[Receptors on the platelet membrane] Watanabe K, et al. **Rinsho Byori** 1985 Jul;33(7):726-33 (22 ref.) **(Jpn)**

RECEPTORS, ADRENERGIC, ALPHA

Identification of an alpha-adrenoceptor binding inhibitor: possible implications in diabetes mellitus. Wider MD, et al. **Acta Diabetol Lat** 1985 Jul-Sep;22(3):263-9

Enhancement by norepinephrine of automaticity in sheep cardiac Purkinje fibers exposed to hypoxic glucose-free Tyrode's solution: a role for alpha-adrenoceptors? Mugelli A, et al. **Circulation** 1986 Jan; 73(1):180-8

Pharmacological characterization and regional distribution of alpha-noradrenergic binding sites of rat spinal cord. Giron LT Jr, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):285-90

Alpha 2-adrenoceptor coupling to adenylate cyclase in adrenaline insensitive human platelets. Swart SS, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):113-9

Phorbol esters inhibit alpha 1-adrenergic effects and decrease the affinity of liver cell alpha 1-adrenergic receptors for (-)-epinephrine. Corvera S, et al. **J Biol Chem** 1986 Jan 15;261(2):520-6

Prejunctional alpha 2-adrenoceptors and norepinephrine release in the forearm of normal humans. Kiowski W, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 6:S144-8

Renal alpha 2-adrenoceptors, their locations and effects on sodium excretion. Pettinger WA, et al. **J Cardiovasc Pharmacol** 1985; 7 Suppl 8:S24-7

Platelet alpha 2-adrenoceptor and adenylate cyclase in patients with anorexia nervosa and bulimia. Heufelder A, et al. **J Clin Endocrinol Metab** 1985 Dec;61(6):1053-60

Studies on the role of alpha 2-adrenoceptors in the control of synaptosomal [3H]5-hydroxytryptamine release: effects of antidepressant drugs. Ellison DW, et al. **J Neurochem** 1986 Jan; 46(1):218-23

Selective alpha-2 adrenoceptor blockade by SK&F 86466: in vitro characterization of receptor selectivity. Hieble JP, et al. **J Pharmacol Exp Ther** 1986 Jan;236(1):90-6

Relationship between alpha adrenoceptor occupancy and response for the alpha-1 adrenoceptor agonist, cirazoline, and the alpha-2 adrenoceptor agonist, B-HT 933, in canine saphenous vein. Ruffolo RR Jr, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):636-43

Platelet alpha 2-adrenoceptors in major depression: relationship with urinary 4-hydroxy-3-methoxyphenylglycol and age at onset. Sacchetti E, et al. **J Psychiatr Res** 1985;19(4):579-86

Hepatic adrenoceptors involved in the glycogenolytic response to exogenous (-)-norepinephrine in the dog liver in vivo. Garceau D, et al. **Life Sci** 1985 Nov 25;37(21):1963-70

Epinephrine-stimulated maintained rubidium efflux from guinea pig hepatocytes may involve alpha 1- and alpha 2-adrenoceptors. Henley JM. **Mol Pharmacol** 1985 Nov;28(5):431-5

Prenatal exposure of rats to antidepressant drugs down-regulates beta-adrenoceptors and 5-HT2 receptors in cerebral cortex. Lack of correlation between 5-HT2 receptors and serotonin-mediated behaviour. De Ceballos ML, et al. **Neuropharmacology** 1985 Oct; 24(10):947-52

The regulation of noradrenaline synthesis in central nerve terminals by autoreceptors and heteroreceptors in rat. Birch PJ, et al. **Neurosci Lett** 1985 Aug 30;59(2):197-202

Noradrenaline mediates slow excitatory synaptic potentials in rat dorsal raphe neurons in vitro. Yoshimura M, et al. **Neurosci Lett** 1985 Nov 11;61(3):305-10

Presynaptic autoinhibition during rest and sodium-pump inhibition in isolated rat portal vein preparation. Török TL, et al. **Neuroscience** 1985 Oct;16(2):439-49

Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. Arnsten AF, et al. **Science** 1985 Dec 13;230(4731):1273-6

Studies of alpha 2-adrenergic receptors of intact and functional washed human platelets by binding of 3H-dihydroergocryptine and 3H-yohimbine--correlation of 3H-yohimbine binding with the potentiation by adrenaline of ADP-induced aggregation. Lanza F, et al. **Thromb Haemost** 1985 Aug 30;54(2):402-8

Influence of alpha- and beta-adrenoceptors on thrombin-induced serotonin release in rat platelets. Koutouzov S, et al. **Thromb Res** 1985 Oct 15;40(2):147-59

RECEPTORS, ADRENERGIC, BETA

Effects of betaxolol, propranolol, and atenolol on isoproterenol-induced beta-adrenoceptor responses. Riddell JG, et al. **Clin Pharmacol Ther** 1985 Nov;38(5):554-9

Haemodynamic effects of low and high doses of insulin during beta receptor blockade in dogs. Reikerås O, et al. **Clin Physiol** 1985 Oct; 5(5):455-67

Receptor binding of propranolol is the missing link between plasma concentration kinetics and the effect-time course in man. Wellstein A, et al. **Eur J Clin Pharmacol** 1985;29(2):131-47

Irreversible inactivation of the beta-adrenoreceptor by a partial agonist. Evidence for selective loss of the agonist high affinity binding sites. Baker SP, et al. **J Biol Chem** 1985 Dec 15;260(29):15820-8

Hepatic adrenoceptors involved in the glycogenolytic response to exogenous (-)-norepinephrine in the dog liver in vivo. Garceau D, et al. **Life Sci** 1985 Nov 25;37(21):1963-70

Effects of maternal beta sympathomimetic therapy on the neonate. Armstrong C. **Neonatal Netw** 1985 Dec;4(3):6-9

Influence of alpha- and beta-adrenoceptors on thrombin-induced serotonin release in rat platelets. Koutouzov S, et al. **Thromb Res** 1985 Oct 15;40(2):147-59

RECEPTORS, CHOLINERGIC

Antigenicity of the sequence 152-167 in alpha subunits of Torpedo acetylcholine receptor [letter] Lindstrom J, et al. **Biochem J** 1985 Oct 1;231(1):247

Antigenicity of synthetic peptides 159-169 and 151-169 of Torpedo acetylcholine receptor alpha chain [letter] McCormick DJ, et al. **Biochem J** 1985 Oct 1;231(1):245-6

Allosteric effects of diprobutine on acetylcholine receptors. Chemouilli P, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):205-14

Characterization of cholinoreceptors in the rat urinary bladder by the use of agonists and antagonists of the cholinergic system. Adami M, et al. **J Auton Pharmacol** 1985 Sep;5(3):197-205

Cholinergic receptor-mediated phosphorylation and activation of tyrosine hydroxylase in cultured bovine adrenal chromaffin cells. Pocotte SL, et al. **J Neurochem** 1986 Feb;46(2):610-22

The occurrence of long openings in the purified cholinergic receptor channel increases with acetylcholine concentration. Labarca P, et al. **J Neurosci** 1985 Dec;5(12):3409-13

The binding of 3H-acetylcholine to cholinergic receptors in bovine cerebral arteries. Shimohama S, et al. **Life Sci** 1985 Nov 18; 37(20):1887-93

The reversible cholinesterase inhibitor physostigmine has channel-blocking and agonist effects on the acetylcholine receptor-ion channel complex. Shaw KP, et al. **Mol Pharmacol** 1985 Dec; 28(6):527-38

Operantly conditioned running: effects on brain catecholamine concentrations and receptor densities in the rat. de Castro JM, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):495-500

[Molecular structures of preproenkephalins and nicotinic acetylcholine receptor] Noda M. **Seikagaku** 1985 Jun;57(6):447-71 (100 ref.) **(Jpn)**

RECEPTORS, DOPAMINE

Down-regulation of central dopamine receptors in schizophrenia. Zemlan FP, et al. **Am J Psychiatry** 1985 Nov;142(11):1334-7

Excitatory neuronal responses to dopamine in the cerebral cortex: involvement of D2 but not D1 dopamine receptors. Bradshaw CM, et al. **Br J Pharmacol** 1985 Oct;86(2):483-90

Ontogeny of dopamine, serotonin and spirodecanone receptors in rat forebrain--an autoradiographic study. Murrin LC, et al. **Brain Res** 1985 Nov;355(1):91-109

Presynaptic inhibition of dopamine synthesis in rat striatum: effects of chronic dopamine depletion and receptor blockade. Reches A, et al. **Brain Res** 1985 Nov 18;347(2):346-9

Analysis of dopamine D1 and D2 receptor involvement in d- and l-amphetamine-induced anorexia in rats. Gilbert DB, et al. **Brain Res Bull** 1985 Oct;15(4):385-9

Does endogenous dopamine modulate human sympathetic activity through DA2 receptors? Mannelli M, et al. **Eur J Clin Pharmacol** 1985; 29(2):159-64

Mechanism of action of apomorphine on rat gastric secretion. Costall B, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):279-85

Prenatal exposure of rats to antidepressants enhances agonist affinity of brain dopamine receptors and dopamine-mediated behaviour. De Ceballos ML, et al. **Eur J Pharmacol** 1985 Oct 22;116(3):257-62

SKF 38393 and apomorphine modify locomotion and exploration in rats placed on a holeboard by separate actions at dopamine D-1 and D-2 receptors. Fletcher GH, et al. **Eur J Pharmacol** 1985 Nov 19; 117(3):381-5

Prolonged inhibition of striatal dopamine receptor sites by isofloxythepin. Lau YS, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):25-31

In vivo quantitative imaging of dopamine receptors in human brain using positron emission tomography and [76Br]bromospiperone. Mazière B, et al. **Eur J Pharmacol** 1985 Aug 27;114(3):267-72

The enantiomers of SK&F 83566, a new selective D-1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D-2 agonist RU 24213. Molloy AG, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):183-6

Structural determinants of selective affinity for brain D-1 dopamine receptors within a series of 1-phenyl-1H-3-benzazepine analogues of SK&F 38393 and SCH 23390. O'Boyle KM, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):291-5

Stimulation of D-2 dopamine receptors in rat mesocortical areas inhibits the release of [3H]dopamine. Plantjé JF, et al. **Eur J Pharmacol** 1985 Aug 27;114(3):401-2

Chronic administration of D-amphetamine increases [3H]spiroperidol binding in cat brain. Trulson ME, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):267-70

Potential neuroleptic agents. 4. Chemistry, behavioral pharmacology, and inhibition of [3H]spiperone binding of 3,5-disubstituted N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxysalicylamides. de Paulis T, et al. **J Med Chem** 1986 Jan;29(1):61-9

Dopamine receptor agonist activity of some 5-(2-aminoethyl)carbostyril derivatives. Kaiser C, et al. **J Med Chem** 1985 Dec;28(12):1803-10

Neuroleptic activity of chiral trans-hexahydro-gamma-carbolines. Sarges R, et al. **J Med Chem** 1986 Jan;29(1):8-19

Specific [3H]piflutixol binding to CHAPS-solubilised rat striatal preparations involves dopamine D-2 but not D-1 binding sites. Kilpatrick GJ, et al. **J Neurochem** 1986 Feb;46(2):413-21

Presynaptic dopamine autoreceptors control tyrosine hydroxylase activation in depolarized striatal dopaminergic terminals. el Mestikawy S, et al. **J Neurochem** 1986 Jan;46(1):12-22

Regulation of anterior pituitary D2 dopamine receptors by magnesium and sodium ions. Watanabe M, et al. **J Neurochem** 1985 Dec; 45(6):1842-9

The pharmacological characterization of 3,4-dihydroxyphenylimino-2-imidazolidine (DPI) as a potent mixed alpha 1/alpha 2-adrenoceptor agonist rather than as a dopamine receptor agonist. van Oene JC, et al. **J Pharm Pharmacol** 1985 Nov; 37(11):844-7

Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. Breese GR, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):287-95

Stimulation of dopamine D-1 receptors by SKF 38393 induces EEG desynchronization and behavioral arousal. Ongini E, et al. **Life Sci** 1985 Dec 16;37(24):2327-33

Neuroendocrine aspects in monitoring of dopaminergic drugs in man. Hietala J, et al. **Methods Find Exp Clin Pharmacol** 1985 Aug; 7(8):451-4

Dopamine D2 receptor binding sites for agonists. A tetrahedral model. Seeman P, et al. **Mol Pharmacol** 1985 Nov;28(5):391-9

Consequences of perinatal drug administration on brain development: striatal opiate receptors and dopamine. Moon SL. **Natl Inst Drug Abuse Res Monogr Ser** 1985;62:129-45

Methamphetamine: toxicity to dopaminergic neurons. Seiden LS. **Natl Inst Drug Abuse Res Monogr Ser** 1985;62:100-16

Is inhibition of striatal synaptosomal tyrosine hydroxylation by dopamine agonists a measure of dopamine autoreceptor function? Fowler CJ, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):12-9

Bromocriptine potentiates the behavioural effects of directly and indirectly acting dopamine receptor agonists in mice. Jenkins OF, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):7-11

Inhibition of gonadotropin secretion induced by cholecystokinin implants in the medial preoptic area by the dopamine receptor blocker, pimozide, in the rat. Hashimoto R, et al. **Neuroendocrinology** 1986;42(1):32-7

Dopaminergic modulation of the diethylstilbestrol-induced proliferation of the anterior pituitary gland of the Fisher 344 rat. Miyazaki K, et al. **Neuroendocrinology** 1985 Nov;41(5):405-8

Amphetamine, but not reserpine, protects mice against dopaminergic neurotoxicity of MPTP. Melamed E, et al. **Neuropharmacology** 1985 Sep;24(9):923-5

D2 dopamine receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in rat striatum. Battaglia G, et al. **Neurosci Lett** 1985 Aug 30;59(2):177-82

Characteristics of D-1 dopamine receptors labelled by [3H]fluphenazine in homogenates of rat neostriatum. Cincotta M, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):85-9

Postsynaptic D1 and D2 dopamine receptors are present in rabbit renal and mesenteric arteries. Missale C, et al. **Neurosci Lett** 1985 Oct 24; 61(1-2):207-11

Dopamine uptake blockers protect against the dopamine depleting effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the mouse striatum. Ricaurte GA, et al. **Neurosci Lett** 1985 Sep 6;59(3):259-64

Inhibition of inositol phospholipid breakdown by D2 dopamine receptors in dissociated bovine anterior pituitary cells. Simmonds SH, et al. **Neurosci Lett** 1985 Oct 10;60(3):267-72

Furosemide blocks the apomorphine-elicited Cl-channel activity of rat striatal dopamine receptors functionally reconstituted into bimolecular lipid membrane. Vodyanoy V, et al. **Neurosci Lett** 1985 Nov 20; 62(1):103-6

Iron deficiency induces reversal of dopamine dependent circadian cycles: differential response to d-amphetamine and TRH. Youdim MB, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):851-5

The effect of dopamine receptor agonist treatment on haloperidol-induced supersensitivity in mice. Fayle P, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):715-20

Role of dopaminergic system(s) in mediation of the behavioural effects of bombesin. Merali Z, et al. **Pharmacol Biochem Behav** 1985 Aug; 23(2):243-8

New central dopamine agonists. Borsy J. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):227-36 (29 ref.)

Dopamine receptor binding of a novel dibenzodioxazocine derivative, EGYT-2509. Gyüre K, et al. **Pol J Pharmacol Pharm** 1985 May-Jun; 37(3):253-61

Evidence for multiple dopamine receptors involved in the modulation of acetylcholine release in the striatum. Harsing LG Jr, et al. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):383-96

Lisuride and transdihydrolisuride: differences in action on central dopaminergic functions in dependence on the location and the state of receptors. Krejči I, et al. **Pol J Pharmacol Pharm** 1985 May-Jun; 37(3):263-71

Stimulation of hippocampal dopaminergic receptors: behavioral and electrophysiological effects. Smialowski A. **Pol J Pharmacol Pharm** 1985 May-Jun;37(3):333-45

Cholecystokinin-dopamine receptor interactions as studied with cholecystokinin receptor antagonists. Murphy RB. **Prog Clin Biol Res** 1985;192:105-13

The D1 dopamine agonist SKF 38393 functions as a discriminative stimulus in rats. Kamien JB, et al. **Psychopharmacology (Berlin)** 1985; 87(3):368-70

Effects of the putative D-1 antagonist SCH 23390 on stereotyped behaviour induced by the D-2 agonist RU24213. Pugh MT, et al. **Psychopharmacology (Berlin)** 1985;87(3):308-12

Apomorphine anorexia: a behavioural and neuropharmacological analysis. Willner P, et al. **Psychopharmacology (Berlin)** 1985;87(3):351-6

Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. Farde L, et al. **Science** 1986 Jan 17;231(4735):258-61

[Changes in the sensitivity of brain dopamine and serotonin receptors during the prolonged administration of carbidine] Zharkovskii AM, et al. **Biull Eksp Biol Med** 1985 Dec;100(12):719-22 (Eng. Abstr.) **(Rus)**

RECEPTORS, ENDOGENOUS SUBSTANCES

Gonadotropin releasing hormone activation is mediated by dimerization of occupied receptors. Hazum E, et al. **Biochem Biophys Res Commun** 1985 Dec 17;133(2):449-56

Comparative characterization of thyroid hormone receptors and binding proteins in rat liver nucleus, plasma membrane, and cytosol by photoaffinity labeling with L-thyroxine. Dozin B, et al. **Biochemistry** 1985 Sep 10;24(19):5203-8

Cl-/Ca2+-dependent L-glutamate binding sites do not correspond to 2-amino-4-phosphonobutanoate-sensitive excitatory amino acid receptors. Fagg GE, et al. **Br J Pharmacol** 1985 Nov;86(3):743-51

Localization and characterization of brain somatostatin receptors as studied with somatostatin-14 and somatostatin-28 receptor radioautography. Leroux P, et al. **Brain Res** 1985 Nov 11; 347(1):74-84

Ibotenic acid decreases thyrotropin-releasing hormone receptor binding in the rat amygdala. Manaker S, et al. **Brain Res** 1985 Nov 11; 347(1):144-8

Deafferentation causes a loss of presynaptic bombesin receptors and supersensitivity of substance P receptors in the dorsal horn of the cat spinal cord. Massari VJ, et al. **Brain Res** 1985 Sep 23;343(2):268-74

Evidence that cholecystokinin interacts with specific receptors and regulates insulin release in isolated rat islets of Langerhans. Verspohl EJ, et al. **Diabetes** 1986 Jan;35(1):38-43

Regulation of pituitary gonadotropin-releasing hormone (GnRH) receptors by pulsatile GnRH in female rats: effects of estradiol and prolactin. Duncan JA, et al. **Endocrinology** 1986 Jan;118(1):320-7

Induction of growth hormone (GH) receptors in adipocytes of hypophysectomized rats by GH. Gause I, et al. **Endocrinology** 1986 Jan;118(1):119-24

Structure-activity relationship of subtypes of cholecystokinin receptors in the cat lower esophageal sphincter. Rattan S, et al. **Gastroenterology** 1986 Jan;90(1):94-102

Synthesis of Z-CCK-27-32-NH2, Z-Tyr(SO-3)-Met-Gly-Trp-Met-Asp-NH2, a cholecystokinin receptor antagonist and an inhibitor of gastrin-induced acid secretion. Briet C, et al. **Int J Pept Protein Res** 1985 Sep;26(3):294-8

Characterization of a gonadotropin-releasing hormone receptor site in term placenta and chorionic villi. Iwashita M, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):127-33

Somatostatin receptors: distribution in rat central nervous system and human frontal cortex. Uhl GR, et al. **J Comp Neurol** 1985 Oct 15;240(3):288-304

Arginine-vasopressin analogues with high antidiuretic/vasopressor selectivity. Synthesis, biological activity, and receptor binding affinity of arginine-vasopressin analogues with substitutions in positions 1, 2, 4, 7, and 8. Grzonka Z, et al. **J Med Chem** 1986 Jan;29(1):96-9

Somatostatin binding sites in human and monkey brain: localization and characterization. Beal MF, et al. **J Neurochem** 1986 Feb;46(2):359-65

[3H] Boc [Nle28, 31]CCK27-33, a new highly labelled ligand for CCK receptors: binding on brain and on pancreas. Pélaprat D, et al. **Life Sci** 1985 Dec 30;37(26):2483-90

Use of GH4C1 cell variants to demonstrate a non-spare receptor model for thyrotropin-releasing hormone action. Ramsdell JS, et al. **Mol Cell Endocrinol** 1985 Dec;43(2-3):173-80

Functional corticotropin releasing factor receptors in the primate peripheral sympathetic nervous system. Udelsman R, et al. **Nature** 1986 Jan 9-15;319(6049):147-50

Autoradiographic localization of a non-reducible somatostatin analog (125I-CGP 23996) binding sites in the rat brain: comparison with membrane binding. Epelbaum J, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):713-9

Cholecystokinin-dopamine receptor interactions as studied with cholecystokinin receptor antagonists. Murphy RB. **Prog Clin Biol Res** 1985;192:105-13

Analysis of the dual mechanism of ACTH release by arginine vasopressin and its analogs in conscious rats. Mormède P, et al. **Regul Pept** 1985 Nov 7;12(3):175-84

Vasoactive intestinal peptide effects on GH3 pituitary tumor cells: high affinity binding, affinity labeling, and adenylate cyclase stimulation. Comparison with peptide histidine isoleucine and growth hormone-releasing factor. Wood CL, et al. **Regul Pept** 1985 Nov 7;12(3):237-48

Reduction of specific arginine-vasopressin binding sites of renal medulla membranes in lithium treated rats. Mitsui T, et al. **Res Commun Chem Pathol Pharmacol** 1985 Nov;50(2):201-8

[Receptors on the platelet membrane] Watanabe K, et al. **Rinsho Byori** 1985 Jul;33(7):726-33 (22 ref.) **(Jpn)**

[Cytoreceptors in the molecular mechanisms of hormone action] Rozen VB. **Probl Endokrinol (Mosk)** 1985 Sep-Oct;31(5):21-6 (Eng. Abstr.) **(Rus)**

RECEPTORS, ENDORPHIN

Lithium and bulimia: the role of the dopaminergic and opiatergic systems [letter] Gillman MA, et al. **Am J Psychiatry** 1985 Dec;142(12):1522-3

Sex-dependent effects of neonatally administered morphiceptin and D-ala-D-leu-enkephalin on maze learning in rats. de Avila A, et al. **Behav Neural Biol** 1985 Nov;44(3):393-402

Delta and mu opiate receptor probes: fluorescent enkephalins with high receptor affinity and specificity. Mihara H, et al. **FEBS Lett** 1985 Nov 25;193(1):35-8

Studies on opioid receptor selectivity of beta-endorphin antagonists. Hammonds RG Jr, et al. **Int J Pept Protein Res** 1985 Aug;26(2):118-20

Selective cardiovascular and neuroendocrine effects of a kappa-opioid agonist in the nucleus tractus solitarii of rats. Carter DA, et al. **J Physiol (Lond)** 1985 Oct;367:363-75

Consequences of perinatal drug administration on brain development: striatal opiate receptors and dopamine. Moon SL. **Natl Inst Drug Abuse Res Monogr Ser** 1985;62:129-45

Has morphine a physiological function in the animal kingdom? [news] Kosterlitz HW. **Nature** 1985 Oct 24-30;317(6039):671-2

Opioid kappa receptors and the secretion of prolactin (PRL) and growth hormone (GH) in the rat. II. GH and PRL release-inhibiting effects of the opioid kappa receptor agonists bremazocine and U-50,488. Krulich L, et al. **Neuroendocrinology** 1986;42(1):82-7

Regional differences in mu 1-binding of [3H][D-Ala2,D-Leu5]-enkephalin: comparisons of thalamus and cortex in the rat. Goodman RR, et al. **Neurosci Lett** 1985 Aug 30;59(2):155-8

Opioid activity of pro-enkephalin-derived peptides in mouse vas deferens and guinea pig ileum. Sánchez-Blázquez P, et al. **Neurosci Lett** 1985 Nov 11;61(3):267-71

Recent developments in the bioassay of opioids. Kosterlitz HW, et al. **Regul Pept [Suppl]** 1985;4:1-7

RECEPTORS, GABA-BENZODIAZEPINE

Characterization of peripheral benzodiazepine binding sites in human term placenta. Fares F, et al. **Biochem Pharmacol** 1986 Jan 15;35(2):227-30

Convulsant and anti-convulsant gammabutyrolactones bind at the picrotoxinin/T-butylbicyclophosphorothionate (TBPS) receptor. Levine JA, et al. **Biochem Pharmacol** 1985 Dec 1;34(23):4187-90

Modulation of 5-hydroxytryptamine-induced head-twitch response by drugs acting at GABA and related receptors. Handley SL, et al. **Br J Pharmacol** 1985 Sep;86(1):297-303

The anorectic effect of FG 7142, a partial inverse agonist at benzodiazepine recognition sites, is reversed by CGS 8216 and clonazepam but not food deprivation. Cooper SJ. **Brain Res** 1985 Oct 28;346(1):190-4

Benzodiazepine receptors modulate circulating plasma vasopressin concentration. Wible JH Jr, et al. **Brain Res** 1985 Dec 16;359(1-2):368-70

Bidirectional control of palatable food consumption through a common benzodiazepine receptor: theory and evidence. Cooper SJ. **Brain Res Bull** 1985 Oct;15(4):397-410

Evidence for the pharmacological relevance of benzodiazepine receptors to anticonvulsant activity. Fisher TE, et al. **Can J Physiol Pharmacol** 1985 Nov;63(11):1477-9

Benzodiazepine binding sites in rat submaxillary gland: absence of markers of GABA system. Pérez C, et al. **Comp Biochem Physiol [C]** 1985;82(2):451-6

Regulation of [35S]t-butylbicyclophosphorothionate binding sites in rat brain by GABA, pyrethroid and barbiturate. Seifert J, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):191-8

Involvement of bicuculline-insensitive receptors in the hypothermic effect of GABA and its agonists. Serrano JS, et al. **Gen Pharmacol** 1985;16(5):505-8

Benzodiazepine receptors: multiple receptors or multiple conformations? Sieghart W. **J Neural Transm** 1985;63(3-4):191-208

Postnatal development of proteins associated with different benzodiazepine receptors. Eichinger A, et al. **J Neurochem** 1986 Jan;46(1):173-80

Solubilization of peripheral benzodiazepine-binding sites from rat kidney. Gavish M, et al. **J Neurosci** 1985 Nov;5(11):2889-93

Differential diazepam-antagonist effects of the benzodiazepine receptor ligand CGS 9895 in rodents. Katzman NJ, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):589-95

Imaging of [11C]-labelled Ro 15-1788 binding to benzodiazepine receptors in the human brain by positron emission tomography. Persson A, et al. **J Psychiatr Res** 1985;19(4):609-22

GABA, depressants and chloride ions affect the rate of dissociation of 35S-t-butylbicyclophosphorothionate binding. Maksay G, et al. **Life Sci** 1985 Dec 9;37(23):2173-80

Pharmacological profile of the imidazopyridine zolpidem at benzodiazepine receptors and electrocorticogram in rats. Arbilla S, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Sep;330(3):248-51

The regulation of noradrenaline synthesis in central nerve terminals by autoreceptors and heteroreceptors in rat. Birch PJ, et al. **Neurosci Lett** 1985 Aug 30;59(2):197-202

Differences in the properties of bovine brain benzodiazepine receptors in the cerebellum and hippocampus revealed after reduction of disulphide bonds. Korneyev AYa, et al. **Neurosci Lett** 1985 Nov 11;61(3):279-84

Studies on the depression of gamma-aminobutyric acid potentials by phloridzin in cat dorsal root ganglion cells in vitro. Stevens DR, et al. **Neurosci Lett** 1985 Sep 30;60(2):115-9

CGS 8216 and CGS 9896, novel pyrazoloquinoline benzodiazepine ligands with benzodiazepine agonist and antagonist properties. Boast CA, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):639-44

The effects of PK 11195, a ligand for benzodiazepine binding sites, in animal tests of anxiety and stress. File SE, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):737-41

Heterogeneity of benzodiazepine binding sites: a review of recent research. Hirsch JD, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):681-5 (51 ref.)

Pyrazoloquinoline benzodiazepine receptor ligands: effects on schedule-controlled behavior in dogs. Shannon HE, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):317-23

Autoradiographic demonstration of the selectivity of two 1-N-trifluoroethyl benzodiazepines for the BZD-1 receptors in the rat brain. Wamsley JK, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):973-8

On the brain endocoid for benzodiazepine recognition sites. Guidotti A, et al. **Prog Clin Biol Res** 1985;192:477-84

Endogenous inhibitors of [3H] Ro 5-4864 binding to 'peripheral-type' binding sites for benzodiazepines are present in peripheral tissues and brain. Mantione CR, et al. **Prog Clin Biol Res** 1985;192:167-73

Tribulin: an endogenous monoamine oxidase inhibitor/benzodiazepine receptor ligand. Sandler M, et al. **Prog Clin Biol Res** 1985; 192:359-62

Are 'peripheral-type' binding sites for benzodiazepines in brain related to the convulsant actions of Ro 5-4864? Weissman BA, et al. **Prog Clin Biol Res** 1985;192:197-203

Isolation and purification of an endogenous brain ligand for benzodiazepine receptor(s). Wu JY, et al. **Prog Clin Biol Res** 1985; 192:485-93

Neuropeptide modulation of GABA receptor C1- channels. Bormann J, et al. **Regul Pept [Suppl]** 1985;4:33-8

A comparison of the relative in vitro and in vivo binding affinities of various benzodiazepines and related compounds for the benzodiazepine receptor and for the peripheral benzodiazepine binding site. Groh B, et al. **Res Commun Chem Pathol Pharmacol** 1985 Sep;49(3):463-6

[Monoacylglycerol phosphatide accumulation and the alteration of the properties of benzodiazepine receptors in the brain synaptosomes] Bogdanova ED, et al. **Biull Eksp Biol Med** 1985 Dec;100(12):684-6 (Eng. Abstr.) **(Rus)**

RECEPTORS, SEROTONIN

Serotonergic regulation of prolactin and growth hormone secretion in man. Lewis DA, et al. **Acta Endocrinol (Copenh)** 1985 Oct; 110(2):152-7

The 5-HT1 receptor agonist RU-24969 decreases 5-hydroxytryptamine (5-HT) release and metabolism in the rat frontal cortex in vitro and in vivo. Brazell MP, et al. **Br J Pharmacol** 1985 Sep;86(1):209-16

Autoradiographic identification and topographical analyses of high affinity serotonin receptor subtypes as a target for the novel putative anxiolytic TVX Q 7821. Glaser T, et al. **Brain Res** 1985 Dec 9; 358(1-2):129-36

Ontogeny of dopamine, serotonin and spirodecanone receptors in rat forebrain--an autoradiographic study. Murrin LC, et al. **Brain Res** 1985 Nov;355(1):91-109

Spiperone differentiates multiple 5-hydroxytryptamine responses in rat hippocampal slices in vitro. Beck SG, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):195-7

Peripheral adrenoceptors and serotonin receptors in depression. Changes associated with response to treatment with trazodone or amitriptyline. Healy D, et al. **J Affective Disord** 1985 Nov;9(3):285-96

Differential effect of subchronic treatment with various neuroleptic agents on serotonin2 receptors in rat cerebral cortex. Andree TH, et al. **J Neurochem** 1986 Jan;46(1):191-7

Serotonin inhibits acetylcholine release from rat striatum slices: evidence for a presynaptic receptor-mediated effect. Gillet G, et al. **J Neurochem** 1985 Dec;45(6):1687-91

[3H]1-[2-(4-aminophenyl)ethyl]-4-(3-trifluoromethylphenyl)piperazin a selective radioligand for 5-HT1A receptors in rat brain. Ransom RW, et al. **J Neurochem** 1986 Jan;46(1):68-75

Effects of serotonin receptor agonists and antagonists on schedule-controlled behavior of squirrel monkeys. Brady LS, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):436-41

Up-regulation of serotonergic binding sites labeled by [3H]WB4101 following fimbrial transection and 5,7-dihydroxytryptamine-induced lesions. Morrow AL, et al. **Life Sci** 1985 Nov 18;37(20):1913-22

Prenatal exposure of rats to antidepressant drugs down-regulates beta-adrenoceptors and 5-HT2 receptors in cerebral cortex. Lack of correlation between 5-HT2 receptors and serotonin-mediated behaviour. De Ceballos ML, et al. **Neuropharmacology** 1985 Oct; 24(10):947-52

Clonazepam-induced up-regulation of serotonin1 binding sites in frontal cortex of rat. Wagner HR, et al. **Neuropharmacology** 1985 Oct; 24(10):953-6

Thyrotropin releasing hormone increases 5-hydroxytryptamine1 receptors in the limbic brain of the rat. Funatsu K, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):563-6

The anorectic action of peripherally administered 5-HT is enhanced by vagotomy. Fletcher PJ, et al. **Physiol Behav** 1985 Jun;34(6):861-6

Characterization of endogenous inhibitors of [3H]-imipramine binding and [3H]-serotonin uptake from rat serum. Angel I, et al. **Prog Clin Biol Res** 1985;192:457-64

Reactivity of the bronchial artery to 5-hydroxytryptamine. El-Fawal HA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Dec;50(3):325-36

[Changes in the sensitivity of brain dopamine and serotonin receptors during the prolonged administration of carbidine] Zharkovskii AM, et al. **Biull Eksp Biol Med** 1985 Dec;100(12):719-22 (Eng. Abstr.) **(Rus)**

REFLEX

No purging, no binge eating: a mechanism for imipramine's action in bulimia? [letter] Claman JM, et al. **Am J Psychiatry** 1985 Dec; 142(12):1515-6

Baroreflex sensitivity and pressor responses in a rat model of uraemia. Watson AJ, et al. **Clin Sci** 1985 Nov;69(5):637-40

Enalapril and autonomic reflexes and exercise performance. Reid JL, et al. **J Hypertension [Suppl]** 1983 Oct;1(1):129-34

Bilateral lesions of the striatum induced with 6-hydroxydopamine abolish apomorphine-induced yawning in rats. Dourish CT, et al. **Neuropharmacology** 1985 Nov;24(11):1051-5

Intrathecal somatostatin modulates spinal sensory and reflex mechanisms: behavioral and electrophysiological studies in the rat. Wiesenfeld-Hallin Z. **Neurosci Lett** 1985 Nov 20;62(1):69-74

[Effects of noxious and innocuous cutaneous stimulation on adrenal sympathetic efferent nerve activity in rats] Kurosawa M. **Hokkaido Igaku Zasshi** 1985 Jul;60(4):509-27 (Eng. Abstr.) **(Jpn)**

REINFORCEMENT (PSYCHOLOGY)

Measurement of reinforcement in depression: a pilot study. Hughes JR, et al. **J Behav Ther Exp Psychiatry** 1985 Sep;16(3):231-6

Reinforcement and rapid delivery systems: understanding adverse consequences of cocaine. Cohen S. **Natl Inst Drug Abuse Res Monogr Ser** 1985;61:151-7

Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. Zito KA, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):1029-36

REINFORCEMENT SCHEDULE

Individual differences in non-regulatory ingestive behavior and catecholamine systems. Mittleman G, et al. **Brain Res** 1985 Nov 25; 348(1):112-7

The effect of peripheral noradrenaline depletion on responding on a schedule of differential reinforcement of low rates of response (DRL). Salmon P, et al. **Psychopharmacology (Berlin)** 1985;87(1):77-80

RESERPINE

Tissue-specific depletion of NPY-like immunoreactivity by reserpine. Lundberg JM, et al. **Acta Physiol Scand** 1985 Mar;123(3):363-5

Effect of tranquilizers on the total acetylcholine content and acetylcholinesterase activity in the brain tissue of Arvicanthis niloticus. Fathi MM, et al. **Comp Biochem Physiol [C]** 1985;82(2):467-74

Neuropeptide Y-induced pressor responses: activation of a non-adrenergic mechanism, potentiation by reserpine and blockade by nifedipine. Mabe Y, et al. **Eur J Pharmacol** 1985 Oct 8; 116(1-2):33-9

Reserpine and phencyclidine-associated psychosis: three case reports. Berlant JL. **J Clin Psychiatry** 1985 Dec;46(12):542-4

Reserpine changes the dynamic state of enkephalin stores in rat striatum and adrenal medulla by different mechanisms. Mocchetti I, et al. **J Neurosci** 1985 Dec;5(12):3379-85

Molecular and physiological properties of tyrosine hydroxylase induced by reserpine in rat adrenal gland. Togari A, et al. **Life Sci** 1985 Oct 28;37(17):1605-11

Amphetamine, but not reserpine, protects mice against dopaminergic neurotoxicity of MPTP. Melamed E, et al. **Neuropharmacology** 1985 Sep;24(9):923-5

Reserpine-induced potentiation of the inhibitory action of neuropeptide Y on the rat vas deferens neurotransmission. Huidobro-Toro JP. **Neurosci Lett** 1985 Sep 6;59(3):247-52

Synthesis and preliminary pharmacologic assessment of the carbonates of 1-(2-thienyl)-3-dialkylamino-1-propanols. Part 4. Avramova P, et al. **Pharmazie** 1985 Aug;40(8):579

RUBIDIUM

CSF-1 stimulates Na+K+-ATPase mediated 86Rb+ uptake in mouse bone marrow-derived macrophages. Vairo G, et al. **Biochem Biophys Res Commun** 1985 Oct 15;132(1):430-7

Rubidium transport in X-irradiated human erythrocytes. Haškovec C, et al. **Int J Radiat Biol** 1985 Nov;48(5):773-83

Oxygen free-radical reduction of brain capillary rubidium uptake. Lo WD, et al. **J Neurochem** 1986 Feb;46(2):394-8

Evidence for the ordered release of rubidium ions occluded within the Na,K-ATPase of mammalian kidney. Glynn IM, et al. **J Physiol (Lond)** 1985 Nov;368:453-69

Epinephrine-stimulated maintained rubidium efflux from guinea pig hepatocytes may involve alpha 1- and alpha 2-adrenoceptors. Henley JM. **Mol Pharmacol** 1985 Nov;28(5):431-5

Subcellular flux of potassium and rubidium in amphibian oocytes. Cameron IL, et al. **Physiol Chem Phys Med NMR** 1985; 17(2):173-81

SCHIZOPHRENIA

Perphenazine decanoate in sesame oil vs. perphenazine enanthate in sesame oil: a comparative study of pharmacokinetic properties and some clinical implications. Knudsen P, et al. **Acta Psychiatr Scand [Suppl]** 1985; 322:11-4

Perphenazine decanoate vs. perphenazine enanthate: efficacy and side effects in a 6 week double-blind, comparative study of 50 drug monitored psychotic patients. Knudsen P, et al. **Acta Psychiatr Scand [Suppl]** 1985;322:15-28

Pharmacokinetic implications of different oil vehicles used in depot neuroleptic treatment. Knudsen P, et al. **Acta Psychiatr Scand [Suppl]** 1985;322:7-10

Hemodialysis in the treatment of a group of schizophrenic patients. Schulman A. **Acta Psychiatr Scand [Suppl]** 1985;321:1-127

Prodromal signs of schizophrenic relapse [letter] Herz MI, et al. **Am J Psychiatry** 1986 Jan;143(1):115-6

CSF noradrenaline and schizophrenia [letter] Kemali D, et al. **Am J Psychiatry** 1986 Jan;143(1):126-7

A high-dose, double-blind study of ceruletide in the treatment of schizophrenia. Mattes JA, et al. **Am J Psychiatry** 1985 Dec; 142(12):1482-4

Benefits of correlating neuroleptic blood level and auditory distractibility [letter] Terkelsen KG. **Am J Psychiatry** 1985 Dec;142(12):1523-4

Combination alprazolam-neuroleptic treatment of the positive and negative symptoms of schizophrenia. Wolkowitz OM, et al. **Am J Psychiatry** 1986 Jan;143(1):85-7

Down-regulation of central dopamine receptors in schizophrenia. Zemlan FP, et al. **Am J Psychiatry** 1985 Nov;142(11):1334-7

Prophylactic effects of neuroleptics in symptom-free schizophrenics: roles of dopaminergic and noradrenergic blockers. Nishikawa T, et al. **Biol Psychiatry** 1985 Nov;20(11):1161-6

High thresholds for movement perception in schizophrenia may indicate abnormal extraneous noise levels of central vestibular activity. Wertheim AH, et al. **Biol Psychiatry** 1985 Nov;20(11):1197-210

Plasma amino acids in relation to cerebrospinal fluid monoamine metabolites in schizophrenic patients and healthy controls. Bjerkenstedt L, et al. **Br J Psychiatry** 1985 Sep;147:276-82

Sulpiride and haloperidol in schizophrenia: a double-blind cross-over study of therapeutic effect, side effects and plasma concentrations. Gerlach J, et al. **Br J Psychiatry** 1985 Sep;147:283-8

Schizophrenia with good and poor outcome [letter] Quitkin F, et al. **Br J Psychiatry** 1985 Oct;147:455-6

Relapse in schizophrenia [editorial] Wing JK. **Br Med J [Clin Res]** 1985 Nov 2;291(6504):1219-20

Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. arap Mengech HN, et al. **East Afr Med J** 1984 Jun;61(6):435-8

Heatstroke in a chronic schizophrenic patient treated with high-potency neuroleptics. Lazarus A. **Gen Hosp Psychiatry** 1985 Oct;7(4):361-3

L-dopa in the treatment of negative schizophrenic symptoms: a single-subject experimental study. Kay SR, et al. **Int J Psychiatry Med** 1985-86;15(3):293-8

Can clients with schizophrenia describe feelings and beliefs about taking medication? Davidhizar RE. **J Adv Nurs** 1985 Sep;10(5):469-73

Clinical significance, evaluation, and management of secondary depression in schizophrenia. Becker RE, et al. **J Clin Psychiatry** 1985 Nov; 46(11 Pt 2):26-32

Is cholecystokinin therapeutic in chronic schizophrenia? Boza RA, et al. **J Clin Psychiatry** 1985 Nov;46(11):485-6

Maintenance therapy and the natural course of schizophrenia. Davis JM. **J Clin Psychiatry** 1985 Nov;46(11 Pt 2):18-21

Plasma levels of neuroleptic in patients receiving depot fluphenazine. Cohen BM, et al. **J Clin Psychopharmacol** 1985 Dec;5(6):328-32

Neuroleptic compliance among chronic schizophrenic outpatients: an intervention outcome report. Boczkowski JA, et al. **J Consult Clin Psychol** 1985 Oct;53(5):666-71

Computerized axial tomography scans and subtypes of schizophrenia. A review of the literature. Goetz KL, et al. **J Nerv Ment Dis** 1986 Jan; 174(1):31-41 (83 ref.)

Psychotherapy of schizophrenia. What happens to treatment dropouts. Katz HM, et al. **J Nerv Ment Dis** 1984 Jun;172(6):326-31

Prolixin group. Can nursing intervention groups lower recidivism? Selander JM, et al. **J Psychosoc Nurs Ment Health Serv** 1985 Nov; 23(11):16-20

Flupenthixol decanoate (fluanxol depot) in the treatment of chronic schizophrenic patients. Haider I. **JPMA** 1985 Sep;35(9):286-9

Membranes, methylation and lithium responsive psychoses. Hitzemann R, et al. **Nutr Health** 1984;3(3):153-62

Projection of an endocoid involved with schizophrenic reaction. Proctor CD, et al. **Prog Clin Biol Res** 1985;192:387-93

Depot fluphenazine and plasma prolactin. Gift T, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):407-12

Specificity and nonspecificity—a major problem in biologically oriented psychopathology. Heimann H. **Psychopathology** 1985;18(2-3):82-7

Early unwanted effects of fluphenazine esters related to plasma fluphenazine concentrations in schizophrenic patients. Altamura AC, et al. **Psychopharmacology (Berlin)** 1985;87(1):30-3

Plasma levels of fluphenazine during fluphenazine decanoate treatment in schizophrenia. Chang SS, et al. **Psychopharmacology (Berlin)** 1985; 87(1):55-8

Zuclopenthixol decanoate in schizophrenia: serum levels and clinical state. Jørgensen A, et al. **Psychopharmacology (Berlin)** 1985;87(3):364-7

Lithium attenuates the activation-euphoria but not the psychosis induced by d-amphetamine in schizophrenia. van Kammen DP, et al. **Psychopharmacology (Berlin)** 1985;87(1):111-5

Plasma flupentixol concentrations and clinical response in acute schizophrenia. Balant-Gorgia AE, et al. **Ther Drug Monit** 1985; 7(4):411-4

[Determination of blood haloperidol levels by radioimmunoassay—a methodological study] Zhou DF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Jun; 18(3):155-7 (Eng. Abstr.) **(Chi)**

[Course and prognosis of schizophrenia in Finland] Salokangas RK. **Duodecim** 1985;101(17):1666-75 **(Fin)**

[Prediction of therapeutic success in acute neuroleptic treatment: results of an empirical study of 243 inpatient-treated schizophrenic patients] Möller HJ, et al. **Fortschr Neurol Psychiatr** 1985 Oct;53(10):370-83 (Eng. Abstr.) **(Ger)**

[Psychopathometric study of the prognostic significance of psychopathologic findings and premorbid personality for discharge of neuroleptic treated patients with schizophrenic psychoses] Möller HJ, et al. **Nervenarzt** 1985 Sep;56(9):498-505 **(Ger)**

[Possibilities in the treatment of schizophrenia based on biochemical findings] Nagashi M. **Seishin Shinkeigaku Zasshi** 1985;87(7):435-43 **(Jpn)**

[Overcoming resistance to therapy in schizophrenia] Poliachenko AB, et al. **Vrach Delo** 1985 Aug;(8):110-1 (Eng. Abstr.) **(Rus)**

[Effect of treatment with psychotropic preparations on suppressor T-lymphocytes in juvenile continuously-progressing schizophrenia] Mikheeva TV, et al. **Zh Nevropatol Psikhiatr** 1985;85(10):1550-2 (Eng. Abstr.) **(Rus)**

[B-lymphocytes of the blood in schizophrenia: effect of psychotropic therapy] Potapova VA. **Zh Nevropatol Psikhiatr** 1985;85(9):1378-81 (Eng. Abstr.) **(Rus)**

[Clinico-catamnestic study of the development of remissions in adolescents suffering recurrent schizophrenia] Simashkova NV. **Zh Nevropatol Psikhiatr** 1985;85(10):1536-40 (Eng. Abstr.) **(Rus)**

SCHIZOPHRENIA, CHILDHOOD

[Differential diagnosis and psychopharmacotherapy of endogenous schizophrenic psychoses in childhood and adolescence] Neumärker KJ. **Z Arztl Fortbild (Jena)** 1985;79(19):831-5 **(Ger)**

SCHIZOPHRENIA, PARANOID

How effective is loxapine? [letter] Tuason VB, et al. **Am J Psychiatry** 1986 Jan;143(1):116-7

Increased CSF cortisol levels after neuroleptic treatment in schizophrenia. Gattaz WF, et al. **Psychoneuroendocrinology** 1985;10(3):351-4

[Neuromediator mechanisms of regulating immune reactions in schizophrenics] Aliev NA. **Zh Nevropatol Psikhiatr** 1985; 85(9):1382-5 (Eng. Abstr.) **(Rus)**

SELF STIMULATION

Cortical and ventral tegmental systems exert opposing influences on self-stimulation from the prefrontal cortex. Spence SJ, et al. **Behav Brain Res** 1985 Sep-Oct;17(2):117-24

Evidence for a role of the preoptic area in lateral hypothalamic self-stimulation. Muñoz C, et al. **Brain Res** 1985 Dec 9; 358(1-2):85-95

Effects of quipazine and of tryptamine on self-stimulation of median raphé nucleus and of lateral hypothalamus in rats. Broadbent J, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):943-7

Relative effectiveness of pimozide, haloperidol and trifluoperazine on self-stimulation rate-intensity functions. Lynch MR, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):777-80

A microcomputer-based method for physiologically interpretable measurement of the rewarding efficacy of brain stimulation. Campbell KA, et al. **Physiol Behav** 1985 Sep;35(3):395-403

Self-stimulation of the lateral hypothalamus and ventrolateral tegmentum: excitability characteristics of the directly stimulated substrates. Macmillan CJ, et al. **Physiol Behav** 1985 Nov;35(5):711-23

SEROTONIN

Effect of a homologous series of halogenated methanes on pulmonary uptake of 5-hydroxytryptamine in isolated perfused rat lung. Hede AR, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Oct;57(4):291-6

Species differences in the velocity and stereoselectivity of platelet 5-HT uptake in rats and humans. Smith DF. **Acta Pharmacol Toxicol (Copenh)** 1985 Oct;57(4):301-3

Effects of 5-hydroxytryptamine and related agents on endothelial cell oxidative metabolism in vitro. Kjellström BT, et al. **Acta Physiol Scand** 1985 Nov;125(3):501-4

A cholecystokinin-like peptide is present in 5-hydroxytryptamine neurons in the spinal cord of the lamprey. van Dongen PA, et al. **Acta Physiol Scand** 1985 Nov;125(3):557-60

Dietary effects on brain serotonin synthesis: relationship to appetite regulation. Fernstrom JD. **Am J Clin Nutr** 1985 Nov; 42(5 Suppl):1072-82

The effects of parasympathectomy on serotonin-induced bronchoconstriction in the cat. Bai TR, et al. **Am Rev Respir Dis** 1986 Jan;133(1):110-5

Immunohistochemical demonstration of serotonin nerve fibers in the corpus striatum of the rat, cat and monkey. Mori S, et al. **Anat Embryol (Berl)** 1985;173(1):1-5

The organization of serotonin fibers in the mammalian superior colliculus. An immunohistochemical study. Ueda S, et al. **Anat Embryol (Berl)** 1985;173(1):13-21

Gabapentin decreases monoamine release without affecting acetylcholine release in the brain. Schlicker E, et al. **Arzneimittelforschung** 1985; 35(9):1347-9

Electrolytic, but not 5,7-dihydroxytryptamine, lesions of the nucleus medianus raphe impair acquisition of a radial maze task. Asin KE, et al. **Behav Neural Biol** 1985 Nov;44(3):415-24

Obsessive-compulsive disorder and serotonin: is there a connection? Insel TR, et al. **Biol Psychiatry** 1985 Nov;20(11):1174-88

Serotonergic influences on pituitary gland and hypothalamic induction of prolactin and luteinizing hormone release in the young turkey (Meleagris gallopavo). Fehrer SC, et al. **Biol Reprod** 1985 Dec; 33(5):1064-72

Effect of angiotensin II on some behavioral and neurochemical measures of the central serotonine system. Braszko JJ, et al. **Biomed Biochim Acta** 1985;44(9):1359-68

Central effects of D-Ala2-met-enkephalinamide on the blood pressure of rats after central chemical sympathectomy or serotoninectomy. Brus R, et al. **Biomed Biochim Acta** 1985;44(5):779-83

The 5-HT1 receptor agonist RU-24969 decreases 5-hydroxytryptamine (5-HT) release and metabolism in the rat frontal cortex in vitro and in vivo. Brazell MP, et al. **Br J Pharmacol** 1985 Sep;86(1):209-16

Monoaminergic involvement in the pharmacological actions of buspirone. Skolnick P, et al. **Br J Pharmacol** 1985 Nov;86(3):637-44

Topographical dopamine and serotonin distribution and turnover in rat striatum. Beal MF, et al. **Brain Res** 1985 Dec 9;358(1-2):10-5

Presence of 5-HT-positive neurons in the medial nuclei of the solitary tract. Calzà L, et al. **Brain Res** 1985 Nov 11;347(1):135-9

Growth hormone-releasing factor modifies dopaminergic but not serotonergic activity in the arcuate nucleus of hypothalamus in the rat, as recorded in vivo by differential pulse voltammetry. Crespi F, et al. **Brain Res** 1985 Dec 2;348(2):367-70

Distribution and quantification of 5-HT nerve cell bodies in the nucleus raphe dorsalis area of C57BL and BALBc mice. Relationship between anatomy and biochemistry. Daszuta A, et al. **Brain Res** 1985 Dec 23; 360(1-2):58-64

Reduced-5-hydroxytryptamine-dependent behavior in rats following chronic corticosterone treatment. Dickinson SL, et al. **Brain Res** 1985 Oct 14;345(1):10-8

The actions of substance P and serotonin on myenteric neurons in tissue culture. Hanani M, et al. **Brain Res** 1985 Dec 9;358(1-2):276-81

Changes of the release of luteinizing hormone (LH) on the day of proestrus after lesions or stimulation of the raphe nuclei in rats. Morello H, et al. **Brain Res** 1985 Dec 23;360(1-2):311-7

Dominant social status facilitates the behavioral effects of serotonergic agonists. Raleigh MJ, et al. **Brain Res** 1985 Dec 2;348(2):274-82

Multiple high affinity binding sites for 5-hydroxytryptamine: a new class of sites distinct from 5-HT1 and S2. Robaut C, et al. **Brain Res** 1985 Nov 4;346(2):250-62

Rostral hypothalamic microinfusions of 5,7 dihydroxytryptamine produce anatomically and neurochemically selective depletions of hippocampal serotonin and increase the influence of estrogen and food deprivation on locomotor activity. Waldbillig RJ, et al. **Brain Res** 1985 Nov 11; 347(1):149-53

Kainic acid-induced release of serotonin from OFF-bipolar cells in the turtle retina. Weiler R, et al. **Brain Res** 1985 Dec 23; 360(1-2):379-83

Intraocular grafts of nucleus raphe dorsalis provide cografted spinal cord with a serotonergic innervation. Henschen A, et al. **Brain Res Bull** 1985 Sep;15(3):335-42

The involvement of brain structures in the adjuvant effect of muramyl dipeptide. Mašek K, et al. **Brain Res Bull** 1985 Nov;15(5):443-6

The role of endogenous serotonin in phasic LH release. Meyer DC, et al. **Brain Res Bull** 1985 Sep;15(3):283-6

Relationship between levels and uptake of serotonin and high affinity [3H]imipramine recognition sites in the rat brain. Hrdina PD, et al. **Can J Physiol Pharmacol** 1985 Oct;63(10):1239-44

Influence of melatonin and serotonin on the number of rat pineal 'synaptic' ribbons and spherules in vitro. Vollrath L, et al. **Cell Tissue Res** 1985; 242(3):607-11

Analytical considerations for quantitative determination of serotonin and its metabolically related products in biological matrices. Mailman RB, et al. **Clin Chem** 1985 Nov;31(11):1849-54

Studies of contents of norepinephrine and 5-hydroxytryptamine in brain--I. Normal and cold exposure. Aly MS, et al. **Comp Biochem Physiol [C]** 1985;82(1):155-8

Studies of contents of norepinephrine and 5-hydroxytryptamine in brain--II. Effect of sodium barbitone and chlorpromazine. Rahman TA, et al. **Comp Biochem Physiol [C]** 1985;82(1):159-63

Biogenic amine uptake by nerve cords from the American cockroach and the influence of amidines on amine uptake and release. Scott JA, et al. **Comp Biochem Physiol [C]** 1985;82(1):43-7

Evidence for purinergic transmission in mouse bladder and for modulation of responses to electrical stimulation by 5-hydroxytryptamine. Holt SE, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):105-11

The acute effects of methamphetamine, amphetamine and p-chloroamphetamine on the cortical serotonergic system of the rat brain: evidence for differences in the effects of methamphetamine and amphetamine. Peat MA, et al. **Eur J Pharmacol** 1985 Oct 8; 116(1-2):11-6

The biotinylation of the rabbit serotonin antibody and its application to immunohistochemical studies using the two-step ABC method. Yamada H, et al. **Histochemistry** 1985;83(4):285-9

Effects of chronically elevated intake of sweet solutions on sexual behavior of male rats. Lieblich I, et al. **Horm Behav** 1985 Sep;19(3):278-91

Oxytocic action of prostaglandin E1--role of 5-hydroxytryptamine. Acharya SB, et al. **Indian J Exp Biol** 1985 Feb;23(2):92-4

Modulation of 5-hydroxytryptamine-evoked responses of the isolated rat uterus by imidazole, a phosphodiesterase stimulator. Singh M, et al. **Indian J Physiol Pharmacol** 1985 Jan-Mar;29(1):39-42

Influence of serotonin on lymphokine secretion in vitro. Paegelow I, et al. **Int J Immunopharmacol** 1985;7(6):889-96

Calcium permeability changes and neurotransmitter release in cultured brain neurons. II. Temporal analysis of neurotransmitter release. Yarom M, et al. **J Biol Chem** 1985 Dec 25;260(30):16294-302

Effect of serotonin and its antagonist ketanserin on pial vessels. Auer LM, et al. **J Cereb Blood Flow Metab** 1985 Dec;5(4):517-22

Effect of leukotrienes, 12-HETE, histamine, bradykinin, and 5-hydroxytryptamine on in vivo rabbit cerebral arteriolar diameter. Kamitani T, et al. **J Cereb Blood Flow Metab** 1985 Dec;5(4):554-9

Immunocytochemical localization of serotonin in the rat periaqueductal gray: a quantitative light and electron microscopic study. Clements JR, et al. **J Comp Neurol** 1985 Jun 1;236(1):60-70

Segmental distribution of peptide- and 5HT-like immunoreactivity in nerve terminals and fibers of the thoracolumbar sympathetic nuclei of the cat. Krukoff TL, et al. **J Comp Neurol** 1985 Oct 1; 240(1):103-16

An immunocytochemical study of the development of central serotoninergic neurons in the chick embryo. Wallace JA. **J Comp Neurol** 1985 Jun 22;236(4):443-53

Electrical responses of cultured thyroid cells to serotonin. McGrath PA, et al. **J Endocrinol** 1985 Dec;107(3):397-401

Serotonin modulates the central pattern generator for locomotion in the isolated lamprey spinal cord. Harris-Warrick RM, et al. **J Exp Biol** 1985 May;116:27-46

3-Phenyl-1-indanamines. Potential antidepressant activity and potent inhibition of dopamine, norepinephrine, and serotonin uptake. Bøgesø KP, et al. **J Med Chem** 1985 Dec;28(12):1817-28

Central 5-HT and the respiratory response to acoustic stimulation in awake rats: effects of PCPA, 5-HTP and 8-OH-DPAT. Ahlenius S, et al. **J Neural Transm** 1985;63(3-4):285-95

Rat brain serotonin: biochemical and functional evidence for a sex difference. Carlsson M, et al. **J Neural Transm** 1985;63(3-4):297-313

The effects of manipulation of presynaptic 5-HT nerve terminals on postsynaptic 5-HT1 and 5-HT2 binding sites of the rat brain. Hall H, et al. **J Neural Transm** 1985;64(2):129-43

Studies on the role of alpha 2-adrenoceptors in the control of synaptosomal [3H]5-hydroxytryptamine release: effects of antidepressant drugs. Ellison DW, et al. **J Neurochem** 1986 Jan; 46(1):218-23

Serotonin inhibits acetylcholine release from rat striatum slices: evidence for a presynaptic receptor-mediated effect. Gillet G, et al. **J Neurochem** 1985 Dec;45(6):1687-91

Down-regulation of [3H]5-hydroxytryptamine binding sites in chick embryo brain by monoamine oxidase inhibitors or fenfluramine and potentiation by d,l-5-hydroxytryptophan. Soblosky JS, et al. **J Neurochem** 1985 Dec;45(6):1923-31

Uptake and release of tryptophan and serotonin: an HPLC method to study the flux of endogenous 5-hydroxyindoles through synaptosomes. Wolf WA, et al. **J Neurochem** 1986 Jan;46(1):61-7

Neuroimmunomodulatory interactions of norepinephrine and serotonin. Walker RF, et al. **J Neuroimmunol** 1985 Nov;10(1):41-58 (91 ref.)

Indoleacetic acid-induced hypothermia and changes in serotonin metabolism in mice. Yamada J, et al. **J Pharmacobiodyn** 1985 Jul; 8(7):564-70

Effect of an atypical barbiturate, the 2-allophanyl-2-allyl-4-valerolactone (valofan), on exploratory behaviour and brain serotonin concentrations in mice. Traversa U, et al. **J Pharmacol** 1985 Jul-Sep;16(3):279-90

[3H]5-hydroxytryptamine binding to reconstituted fraction with sulphatides, phosphatidylserine and phosphatidylinositol. Nishi A, et al. **Jpn J Pharmacol** 1985 Aug;38(4):411-7

Brain serotonin and blood pressure regulation: studies using in vivo electrochemistry and direct tissue assay. Freed CR, et al. **Life Sci** 1985 Nov 11;37(19):1783-93

Scheduled feeding versus the light-dark cycle on the rhythms of circulating tryptophan, serotonin and N-acetylserotonin in rats. Ho AK, et al. **Life Sci** 1985 Oct 28;37(17):1619-26

Up-regulation of serotonergic binding sites labeled by [3H]WB4101 following fimbrial transection and 5,7-dihydroxytryptamine-induced lesions. Morrow AL, et al. **Life Sci** 1985 Nov 18;37(20):1913-22

Age-associated alteration of serotonergic synaptic neurochemistry in rat rostral hypothalamus. Sparks DL, et al. **Neurobiol Aging** 1985 Fall; 6(3):213-7

Melatonin-induced increases in serotonin concentrations in specific regions of the chicken brain. Cassone VM, et al. **Neuroendocrinology** 1986;42(1):38-43

Serotonergic stimulation of prolactin and corticosterone secretion is mediated by different pathways from the mediobasal hypothalamus. Van de Kar LD, et al. **Neuroendocrinology** 1985 Nov;41(5):380-4

Cardio-respiratory actions of substance P, TRH and 5-HT in the nucleus tractus solitarius of rats: evidence for functional interactions of neuropeptides and amine neurotransmitters. Carter DA, et al. **Neuropeptides** 1985 Sep;6(5):425-36

(-)-Pindolol stereospecifically inhibits rat brain serotonin (5-HT) synthesis. Hjorth S, et al. **Neuropharmacology** 1985 Nov; 24(11):1143-6

Changes induced by corticosterone and adrenalectomy in synaptosomal and platelet uptake and binding of 5-HT. The relationship to [3H]imipramine binding. Lee PH, et al. **Neuropharmacology** 1985 Nov; 24(11):1043-50

Cathinone affects dopamine and 5-hydroxytryptamine neurons in vivo as measured by changes in metabolites and synthesis in four forebrain regions in the rat. Nielsen JA. **Neuropharmacology** 1985 Sep; 24(9):845-52

Serotonin modulates photoresponses in Hermissenda type-B photoreceptors. Crow T, et al. **Neurosci Lett** 1985 Sep 16;60(1):83-8

The influence of serotonergic inputs on peptide neurons in the rat suprachiasmatic nucleus: an immunocytochemical study. Kawakami F, et al. **Neurosci Lett** 1985 Nov 11;61(3):273-7

Release of endogenous 5-hydroxytryptamine from the neural and the intermediate lobe of the rat pituitary gland evoked by electrical stimulation of the pituitary stalk. Holzbauer M, et al. **Neuroscience** 1985 Jul;15(3):723-8

Immunocytochemical and electron microscopic study of serotonin neuronal organization in the dorsal raphe nucleus of the monkey. Kapadia SE, et al. **Neuroscience** 1985 Jul;15(3):729-46

Serotonin and co-localized peptides: effects on spinal motoneuron excitability. White SR. **Peptides (Fayetteville)** 1985;6 Suppl 2:123-7

The anorectic action of peripherally administered 5-HT is enhanced by vagotomy. Fletcher PJ, et al. **Physiol Behav** 1985 Jun;34(6):861-6

Histamine and serotonin independently elicit drinking in the rat. Kraly FS, et al. **Physiol Behav** 1985 Jun;34(6):963-7

Serotonin neurons on the ventral brain surface. Gorcs TJ, et al. **Proc Natl Acad Sci USA** 1985 Nov;82(21):7449-52

Formation of serotonin by rat kidneys in vivo. Stier CT Jr, et al. **Proc Soc Exp Biol Med** 1985 Dec;180(3):550-7

Involvement of peptide histidine isoleucine (PHI) in prolactin secretion induced by serotonin in rats. Tojo K, et al. **Proc Soc Exp Biol Med** 1985 Dec;180(3):558-61

Prostaglandin D2 mediated specific increase in rat brain serotonin. Bhattacharya SK, et al. **Proc West Pharmacol Soc** 1985;28:217-20

Effect of arterial endothelium on sensitivity to 5-hydroxytryptamine. Morcos NC, et al. **Proc West Pharmacol Soc** 1985;28:77-9

5-Hydroxytryptamine is an alpha agonist in rabbit blood vessels. Purdy RE, et al. **Proc West Pharmacol Soc** 1985;28:123-5

Depletion of brain serotonin by 5,7-dihydroxytryptamine alters the response to amphetamine and the habituation of locomotor activity in rats. Gately PF, et al. **Psychopharmacology (Berlin)** 1985;87(4):400-5

Reactivity of the bronchial artery to 5-hydroxytryptamine. Ei-Fawal HA, et al. **Res Commun Chem Pathol Pharmacol** 1985 Dec;50(3):325-36

Quantitative determination of serotonin released from human platelets. Marasini B, et al. **Ric Clin Lab** 1985 Jul-Sep;15(3):247-51

Influence of alpha- and beta-adrenoceptors on thrombin-induced serotonin release in rat platelets. Koutouzov S, et al. **Thromb Res** 1985 Oct 15;40(2):147-59

Studies of hepatic, brain monoamine oxidase and brain serotonin in rats. Chai KJ, et al. **Yonsei Med J** 1984;25(1):27-38

[Roles of the central serotonergic neuronal system in cardiovascular regulation] Li SJ. **Sheng Li Ko Hsueh Chin Chan** 1984 Oct; 15(4):341-3 **(Chi)**

[Effects of serotonin (5HT) and histamine on the pulmonary circulation with particular reference to arterial and venous segment resistance--comparison between an experimental study and model circuit analysis] Yamashita H, et al. **Nippon Kyobu Shikkan Gakkai Zasshi** 1985 Jul;23(7):767-75 (Eng. Abstr.) **(Jpn)**

[Effects of intracerebroventricular (I.C.V.) administration of 5-hydroxytryptamine (5-HT) on hemodynamics in conscious spontaneously hypertensive rats (SHR): relation to sympathetic nervous system] Kurumatani H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jul 20;61(7):775-83 (Eng. Abstr.) **(Jpn)**

[Distribution of thyrotropin releasing hormone in the mouse brain and effects of various amines--immunohistochemical study] Senda Y, et al. **Rinsho Shinkeigaku** 1985 Aug;25(8):973-81 (Eng. Abstr.) **(Jpn)**

[Effect of serotonin on the yield of UV-induced thymine dimers in DNA] Fraikin GIa, et al. **Biofizika** 1985 Jul-Aug;30(4):564-7 (Eng. Abstr.) **(Rus)**

[Effect of serotonin on the yield of UV- and x ray-induced DNA damage] Ivanova EV, et al. **Biokhimiia** 1985 Aug;50(8):1374-6 (Eng. Abstr.) **(Rus)**

[Changes in the level of serotonin in the brain and immunocompetent organs during the formation of the immune response] Mashek K, et al. **Fiziol Zh SSSR** 1985 Aug;71(8):992-7 (Eng. Abstr.) **(Rus)**

[Functional activity of serotonin- and histaminergic systems in humans during long-term antiorthostatic hypokinesia] Davydova NA, et al. **Kosm Biol Aviakosm Med** 1985 Sep-Oct;19(5):27-30 (Eng. Abstr.) **(Rus)**

[Role of serotonin in the development of compensatory-reparative processes after damage to the anterior areas of the cerebral cortex] Grekhova TV, et al. **Patol Fiziol Eksp Ter** 1985 Jul-Aug;(4):57-61 (Eng. Abstr.) **(Rus)**

[Mitochondrial monoamine oxidase activity and serotonin content of rat brain following gamma-irradiation] Savitskii IV, et al. **Radiobiologiia** 1985 Sep-Oct;25(5):683-5 (Eng. Abstr.) **(Rus)**

[Effect of serotonin on dental caries development in animals] Nasibullin MG. **Stomatologiia (Mosk)** 1985 Nov-Dec;64(6):13-4 (Eng. Abstr.) **(Rus)**

[Effect of irradiation on the intensity of chromatin protein synthesis in the rat liver during protection with serotonin in pulsed inhibition of translation by cycloheximide] Aslamova LI, et al. **Ukr Biokhim Zh** 1985 Nov-Dec;57(6):18-23 (Eng. Abstr.) **(Rus)**

[Effect of serotonin on the development of tissue cultures of the cerebral cortex in the rat] Chubakov AR, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):926-34 (Eng. Abstr.) **(Rus)**

[Changes in the effect of acetylcholine on septo-hippocampal reactions after serotonin administration to rabbits] Kozhedub RG. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):914-9 (Eng. Abstr.) **(Rus)**

[Effect of prolonged interaction of mice with aggressive and submissive types of behavior on the concentration of serotonin, 5-hydroxyindoleacetic acid and noradrenalin in the brain] Kudriavtseva NN, et al. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):879-83 (Eng. Abstr.) **(Rus)**

SEX BEHAVIOR, ANIMAL

Luteinizing hormone-releasing hormone facilitates the display of sexual behavior in male voles (Microtus canicaudus). Boyd SK, et al. **Horm Behav** 1985 Sep;19(3):252-64

Effects of chronically elevated intake of sweet solutions on sexual behavior of male rats. Lieblich I, et al. **Horm Behav** 1985 Sep;19(3):278-91

Serotonin type 2 antagonists inhibit lordosis behavior in the female rat: reversal with quipazine. Mendelson SD, et al. **Life Sci** 1986 Jan 6; 38(1):33-9

Luteinizing hormone releasing hormone enhances proceptivity in a primate. Kendrick KM, et al. **Neuroendocrinology** 1985 Dec; 41(6):449-53

Neuronal responsiveness to gonadotropin-releasing hormone and its correlation with sexual receptivity in the rat. Rothfeld JM, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):603-8

Conditioned suppression of sexual behavior in stallions and reversal with diazepam. McDonnell SM, et al. **Physiol Behav** 1985 Jun;34(6):951-6

Effects of estrus, estrogen-progesterone priming, and vaginal stimulation on tonic immobility, dorsal immobility, and lordosis in the female rat. Smith RL, et al. **Physiol Behav** 1985 Oct;35(4):577-81

[Genetic factors in the regulation of the hypophyseo-adrenal system in aggressive and sexual interactions of male laboratory mice] Osadchuk AV, et al. **Zh Obshch Biol** 1985 Sep-Oct;46(5):711-6 (Eng. Abstr.) **(Rus)**

SLEEP

Diurnal administration of human growth hormone-releasing factor does not modify sleep and sleep-related growth hormone secretion in normal young men. Garry P, et al. **Acta Endocrinol (Copenh)** 1985 Oct; 110(2):158-63

A third view on benzodiazepines and sleep latency [letter] Rosenbaum JF. **Am J Psychiatry** 1985 Dec;142(12):1524

Neurochemical regulation of the states of alertness. Gaillard JM. **Ann Clin Res** 1985;17(5):175-84 (59 ref.)

Tonic activity of medial preoptic norepinephrine mechanism for body temperature maintenance in sleeping and awake rats. Datta S, et al. **Brain Res Bull** 1985 Nov;15(5):447-51

Signs of synchronized sleep elicited by local application of leptazol to a circumscribed area of the ventral surface of medulla oblongata in the cat. Guertzenstein PG, et al. **Braz J Med Biol Res** 1985;

18(1):87-96

Beta-blockers and sleep: a controlled trial. Betts TA, et al. **Eur J Clin Pharmacol** 1985;28 Suppl:65-8

Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. Borbély AA, et al. **Hum Neurobiol** 1985;4(3):189-94

Sleep and electroencephalography: points of interest and points of controversy. Guilleminault C, et al. **J Clin Neurophysiol** 1984 Jul; 1(3):275-91 (115 ref.)

The prolonging effect of N,N'-diallylpentobarbital on the drug-induced sleep and motor incoordination. Yamamoto I, et al. **Res Commun Chem Pathol Pharmacol** 1985 Nov;50(2):209-19

Partial insomnia, hyperactivity and hyperdipsia induced by repeated administration of toluene in rats: their relation to brain monoamine metabolism. Arito H, et al. **Toxicology** 1985 Oct;37(1-2):99-110

[Sleep--2. Substances in the mechanism of sleep and wakefulness] Nagasaki H, et al. **Nippon Rinsho** 1985 Jul;43(7):1384-9 (19 ref.) **(Jpn)**

SLEEP STAGES

Diurnal administration of human growth hormone-releasing factor does not modify sleep and sleep-related growth hormone secretion in normal young men. Garry P, et al. **Acta Endocrinol (Copenh)** 1985 Oct; 110(2):158-63

SOCIAL ADJUSTMENT

Social effects of diazepam use: a longitudinal field study. Caplan RD, et al. **Soc Sci Med** 1985;21(8):887-98

[Psychopathometric study of the prognostic significance of psychopathologic findings and premorbid personality for discharge of neuroleptic treated patients with schizophrenic psychoses] Möller HJ, et al. **Nervenarzt** 1985 Sep;56(9):498-505 **(Ger)**

SODIUM

Sodium retention after adrenal enucleation. Perrone RD, et al. **Am J Physiol** 1986 Jan;250(1 Pt 1):E1-12 (86 ref.)

Renal sodium handling in normal humans subjected to low, normal, and extremely high sodium supplies. Roos JC, et al. **Am J Physiol** 1985 Dec;249(6 Pt 2):F941-7

Antisera to atrial natriuretic factor reduces urinary sodium excretion and increases plasma renin activity in rats. Naruse M, et al. **Biochem Biophys Res Commun** 1985 Nov 15;132(3):954-60

Early stimulation of ATP turnover by EGF + insulin. Relation to external pH and Na+/H+ exchange system. Talha S, et al. **Biochem Biophys Res Commun** 1985 Nov 27;133(1):265-73

Interhelical effects on the low-frequency modes and phase transitions of Li- and Na-DNA. Demarco C, et al. **Biopolymers** 1985 Nov; 24(11):2035-40

Evaluation of the electrophysiological consequences of GABA removal from the synaptic cleft by Na+ ion transport-coupled neuronal uptake. Cupello A, et al. **Brain Res** 1985 Dec 9;358(1-2):364-6

Further study of the correlation between Na-pump activity and membrane chemosensitivity. Ayrapetyan SN, et al. **Cell Mol Neurobiol** 1985 Sep; 5(3):231-43

Effects of an intravenous saline load on erythrocyte sodium transport in normal human subjects. Boero R, et al. **Clin Sci** 1985 Dec; 69(6):709-12

The sodium and bicarbonate dependence of bile secretion in the guinea-pig. Rutishauser SC. **Comp Biochem Physiol** [A] 1985; 82(2):317-22

Melittin-induced changes in Na and Cl movements across the skin and cornea (in vitro) of the toad Bufo marinus. McGahan MC, et al. **Comp Biochem Physiol** [C] 1985;82(2):291-6

DCCD-sensitive, Na+-dependent H+-influx process coupled to membrane potential formation in membrane vesicles of Halobacterium halobium. Murakami N, et al. **J Biochem (Tokyo)** 1985 Oct; 98(4):897-907

Effects of low extracellular sodium on cytosolic ionized calcium. Na+-Ca2+ exchange as a major calcium influx pathway in kidney cells. Snowdowne KW, et al. **J Biol Chem** 1985 Dec 5; 260(28):14998-507

Relationship of sodium sensitivity and the sympathetic nervous system. Dustan HP. **J Cardiovasc Pharmacol** 1985;7 Suppl 8:S56-63

Renal alpha 2-adrenoceptors, their locations and effects on sodium excretion. Pettinger WA, et al. **J Cardiovasc Pharmacol** 1985; 7 Suppl 8:S24-7

Determination of sodium, ephedrine and procaine in pharmaceuticals by capillary isotachophoresis. Fanali S, et al. **J Chromatogr** 1985 Aug 23; 330(2):436-8

Regulation of anterior pituitary D2 dopamine receptors by magnesium and sodium ions. Watanabe M, et al. **J Neurochem** 1985 Dec; 45(6):1842-9

Structure-activity relationship for substance P inhibition of carbamylcholine-stimulated 22Na+ flux in neuronal (PC12) and non-neuronal (BC3H1) cell lines. Simasko SM, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):601-5

Activation of acetylcholine synthesis in cat sympathetic ganglia: dependence on external choline and sodium-pump rate. Birks RI, et al. **J Physiol (Lond)** 1985 Oct;367:401-17

Serum factors affect Na+ pump activity and DNA synthesis in cultured cerebellar neural cells. Atterwill CK, et al. **Mol Cell Endocrinol** 1985 Nov;43(1):105-10

Decrease of potassium permeability by intracellular application of sodium ions in snail neurons. Walden J, et al. **Neurosci Lett** 1985 Sep 30; 60(2):139-43

Presynaptic autoinhibition during rest and sodium-pump inhibition in isolated rat portal vein preparation. Török TL, et al. **Neuroscience** 1985 Oct;16(2):439-49

[Dependence of ion transport across the plasma membrane on the density of the cell culture. I. Ion flows and the potassium and sodium content in 3 Chinese hamster cell lines (CHO)] Marakhova II, et al. **Tsitologiia** 1985 Sep;27(9):1011-20 (Eng. Abstr.) **(Rus)**

[Dependence of ion transport across the plasma membrane on cell culture density. II. Active and passive cation transport during the growth of L cell cultures] Marakhova II, et al. **Tsitologiia** 1985 Oct; 27(10):1156-63 (Eng. Abstr.) **(Rus)**

SOMATOSTATIN

Inhibitory action of somatostatin on meiotic maturation of cultured porcine follicular ova. Mori T, et al. **Acta Endocrinol (Copenh)** 1985 Nov;110(3):408-12

Rapid depletion of somatostatin in isolated mouse pancreatic islets after treatment with cysteamine. Petersson B, et al. **Acta Endocrinol (Copenh)** 1985 Oct;110(2):227-31

Capillary orientation of rat pancreatic D-cell processes: evidence for endocrine release of somatostatin. Aponte G, et al. **Am J Physiol** 1985 Nov;249(5 Pt 1):G599-606

Effect of exocrine pancreatic secretagogues on circulating somatostatin in dogs. Beglinger C, et al. **Am J Physiol** 1986 Jan; 250(1 Pt 1):G15-20

Somatostatin-like immunoreactivity in non-pyramidal neurons of the human isocortex. Braak E, et al. **Anat Embryol (Berl)** 1985; 173(2):237-46

Insulin, glucagon, pancreatic polypeptide hormone and somatostatin in the goat pancreas: demonstration by immunocytochemistry. Reddy S, et al. **Aust J Biol Sci** 1985;38(1):59-66

Octapeptide analogs of somatostatin exhibiting greatly enhanced in vivo and in vitro inhibition of growth hormone secretion in the rat. Murphy WA, et al. **Biochem Biophys Res Commun** 1985 Nov 15; 132(3):922-8

Negative inotropic effect of somatostatin in guinea-pig atrial fibres. Diez J, et al. **Br J Pharmacol** 1985 Nov;86(3):547-55

The influence of hGRF, CRF, TRH and LHRH on SRIF release from median eminence fragments. Aguila MC, et al. **Brain Res** 1985 Nov 25;348(1):180-2

The distribution of somatostatin-immunoreactive neurons in the visual cortex of adult rabbits and during postnatal development. Cajal-Agüeras SR, et al. **Brain Res** 1985 Dec 16;359(1-2):379-82

Localization and characterization of brain somatostatin receptors as studied with somatostatin-14 and somatostatin-28 receptor radioautography. Leroux P, et al. **Brain Res** 1985 Nov 11; 347(1):74-84

So-called interplexiform cells immunoreactive to tyrosine hydroxylase or somatostatin in rat retina. Negishi K, et al. **Brain Res** 1985 Oct 28; 346(1):136-40

The interaction of human pancreatic growth hormone releasing factor 1-44 with somatostatin in vivo in normal man. Davies RR, et al. **Clin Endocrinol (Oxf)** 1985 Sep;23(3):271-6

Somatostatin and water excretion in man: an intrarenal action. Walker BJ, et al. **Clin Endocrinol (Oxf)** 1985 Aug;23(2):169-74

On the mechanism of growth hormone autofeedback regulation: possible role of somatostatin and growth hormone-releasing factor. Conway S, et al. **Endocrinology** 1985 Dec;117(6):2284-92

Involvement of corticotropin-releasing factor and somatostatin in stress-induced inhibition of growth hormone secretion in the rat. Rivier C, et al. **Endocrinology** 1985 Dec;117(6):2478-82

Release of growth hormone (GH) from purified somatotrophs: interaction of GH-releasing factor and somatostatin and role of adenosine 3',5'-monophosphate. Sheppard MS, et al. **Endocrinology** 1985 Dec; 117(6):2364-70

Growth-hormone releasing factor does not antagonize somatostatin effects on pancreatic and gastric secretions. Chovet M, et al. **Experientia** 1985 Nov 15;41(11):1451-3

Isolation and characterization of proSS1-32, a peptide derived from the N-terminal region of porcine preprosomatostatin. Schmidt WE, et al. **FEBS Lett** 1985 Nov 11;192(1):141-6

An elasmobranchian somatostatin: primary structure and tissue distribution in Torpedo marmorata. Conlon JM, et al. **Gen Comp Endocrinol** 1985 Dec;60(3):406-13

Somatostatin stimulates ACTH release in brown trout (Salmo trutta L.). Langhorne P. **Gen Comp Endocrinol** 1986 Jan;61(1):71-5

Evidence for somatostatin-like immunoreactivity in discrete cells of the anterior pituitary of camel (Camelus dromedarius). Quéré M, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):187-95

Somatostatin inhibits gastric acid secretion after gastric mucosal prostaglandin synthesis inhibition by indomethacin in man. Mogard MH, et al. **Gut** 1985 Nov;26(11):1189-91

Distribution, histochemistry and ultrastructure of somatostatin-like immunoreactive cells in the gastroenteric tract of the cartilaginous fish Scyliorhinus stellaris (L.). Tagliafierro G, et al. **Histochem J** 1985 Sep;17(9):1033-41

Pertussis toxin blocks both cyclic AMP-mediated and cyclic AMP-independent actions of somatostatin. Evidence for coupling of Ni to decreases in intracellular free calcium. Koch BD, et al. **J Biol Chem** 1985 Oct 25;260(24):13138-45

Somatostatin receptors: distribution in rat central nervous system and human frontal cortex. Uhl GR, et al. **J Comp Neurol** 1985 Oct 15;240(3):288-304

Somatostatin binding sites in human and monkey brain: localization and characterization. Beal MF, et al. **J Neurochem** 1986 Feb;46(2):359-65

Purification of somatostatin from frog brain: coisolation with retinal somatostatin-like immunoreactivity. Takami M, et al. **J Neurochem** 1985 Dec;45(6):1869-74

Somatostatin, substance P and [Lys]-vasopressin interfere with the binding of [3H][D-Ala2, Met5]enkephalinamide to rat brain membranes. Maruyama M. **Jpn J Pharmacol** 1985 Aug;38(4):445-7

Somatostatin: a metabolic regulator. Dileepan KN, et al. **Life Sci** 1985 Dec 23;37(25):2335-43 (88 ref.)

Gastrointestinal somatostatin: distribution, secretion and physiological significance. McIntosh CH. **Life Sci** 1985 Dec 2;37(22):2043-58 (203 ref.)

12-O-tetradecanoyl phorbol-13-acetate (TPA) stimulates somatostatin release from isolated perfused rat stomach. Yamatani T, et al. **Life Sci** 1985 Dec 23;37(25):2415-9

Effect of somatostatin on plasma prolactin. Lugari R, et al. **Minerva Endocrinol** 1985 Apr-Jun;10(2):79-82

Involvement of hypothalamic somatostatin in the suppression of growth hormone secretion by central corticotropin-releasing factor in conscious male rats. Katakami H, et al. **Neuroendocrinology** 1985 Nov;41(5):390-3

Release of pro-opiomelanocortin-derived peptides from the pars intermedia and pars distalis of the rat pituitary: effect of corticotrophin-releasing factor and somatostatin. Kraicer J, et al. **Neuroendocrinology** 1985 Nov;41(5):363-73

Thyroidectomy abolishes pulsatile growth hormone secretion without affecting hypothalamic somatostatin. Martin D, et al. **Neuroendocrinology** 1985 Dec;41(6):476-81

Effects of hypothalamic periventricular lesions on pulsatile growth hormone secretion. Urman S, et al. **Neuroendocrinology** 1985 Nov;41(5):357-62

Independent co-release of acetylcholine and somatostatin from cardiac vagal neurones in toad. Campbell G, et al. **Neurosci Lett** 1985 Sep 16;60(1):47-50

Acetylcholinesterase and somatostatin-immunoreactivity coexist in human neocortex. Nakamura S, et al. **Neurosci Lett** 1985 Oct 24;61(1-2):183-7

Intrathecal somatostatin modulates spinal sensory and reflex mechanisms: behavioral and electrophysiological studies in the rat. Wiesenfeld-Hallin Z. **Neurosci Lett** 1985 Nov 20;62(1):69-74

Electron microscopic immunocytochemical study of somatostatin neurons in the periventricular nucleus of the rat hypothalamus with special reference to their relationships with homologous neuronal processes. Alonso G, et al. **Neuroscience** 1985 Oct;16(2):297-306

Autoradiographic localization of a non-reducible somatostatin analog (125I-CGP 23996) binding sites in the rat brain: comparison with membrane binding. Epelbaum J, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):713-9

Immunoreactive and bioactive somatostatin-like material is present in tobacco (Nicotiana tabacum). Werner H, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):797-802

CSF somatostatin in affective illness and normal volunteers. Rubinow DR, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(4):393-400

The intestinal mucosa preferentially releases somatostatin-28 in pigs. Baldissera FG, et al. **Regul Pept** 1985 Jul;11(3):251-62

Caerulein and secretin induced pancreatic growth: a possible control by endogenous pancreatic somatostatin. Sarfati PD, et al. **Regul Pept** 1985 Jul;11(3):261-73

Trophic effect of some regulatory peptides on gastric exocrine and endocrine cells of the rat. Lehy T. **Scand J Gastroenterol [Suppl]** 1984;101:27-30

[The effect of antral branch on canine antral gastrin and somatostatin concentrations in gastric vagotomy] Tsutsui M. **Nippon Geka Gakkai Zasshi** 1985 Nov;86(11):1505-16 (Eng. Abstr.) **(Jpn)**

[Natural peptides and their analogs. XXXV. Synthesis and properties of [Ala5, Orn9]somatostatin] Shvachkin IuP, et al. **Bioorg Khim** 1985 Aug;11(8):1026-36 (Eng. Abstr.) **(Rus)**

SOMATOTROPIN RELEASING HORMONE

Diurnal administration of human growth hormone-releasing factor does not modify sleep and sleep-related growth hormone secretion in normal young men. Garry P, et al. **Acta Endocrinol (Copenh)** 1985 Oct;110(2):158-63

Growth hormone-releasing factor modifies dopaminergic but not serotonergic activity in the arcuate nucleus of hypothalamus in the rat, as recorded in vivo by differential pulse voltammetry. Crespi F, et al. **Brain Res** 1985 Dec 2;348(2):367-70

Effect of hypothalamic ventromedial lesions on plasma growth hormone response to growth hormone-releasing factor in rats. Wakabayashi I, et al. **Brain Res** 1985 Oct 28;346(1):70-4

Ontogenetic appearance of immunoreactive GRF-containing neurons in the rat hypothalamus. Daikoku S, et al. **Cell Tissue Res** 1985;242(3):511-8

The interaction of human pancreatic growth hormone releasing factor 1-44 with somatostatin in vivo in normal man. Davies RR, et al. **Clin Endocrinol (Oxf)** 1985 Sep;23(3):271-6

Synthetic pancreatic growth hormone-releasing factor (GRF-40) stimulates the secretion of the endocrine pancreas. Hermansen K, et al. **Diabetes** 1986 Jan;35(1):119-23

On the mechanism of growth hormone autofeedback regulation: possible role of somatostatin and growth hormone-releasing factor. Conway S, et al. **Endocrinology** 1985 Dec;117(6):2284-92

Association of 45Ca2+ mobilization with stimulation of growth hormone (GH) release by GH-releasing factor in dispersed normal male rat pituitary cells. Login IS, et al. **Endocrinology** 1986 Jan;118(1):239-43

Release of growth hormone (GH) from purified somatotrophs: interaction of GH-releasing factor and somatostatin and role of adenosine 3',5'-monophosphate. Sheppard MS, et al. **Endocrinology** 1985 Dec;117(6):2364-70

Differential responsiveness of the somatotroph to growth hormone-releasing factor during early neonatal development in the rat. Szabo M, et al. **Endocrinology** 1986 Jan;118(1):69-73

Growth-hormone releasing factor does not antagonize somatostatin effects on pancreatic and gastric secretions. Chovet M, et al. **Experientia** 1985 Nov 15;41(11):1451-3

Synthetic human growth hormone releasing factor 1-44 (GRF) stimulates glucose transport in isolated rat adipocytes. Hauner H, et al. **Horm Metab Res** 1985 Nov;17(11):620-1

Atropine blockade of growth hormone (GH)-releasing hormone-induced GH secretion in man is not exerted at pituitary level. Casanueva FF, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):186-91

Regional distribution of human growth hormone-releasing hormone in the human hypothalamus by radioimmunoassay. Leidy JW Jr, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):372-8

Impaired growth hormone (GH) response to GH-releasing hormone in thalassemia major. Pintor C, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):263-7

Sex difference in human growth hormone (GH) response to intravenous human pancreatic GH-releasing hormone administration in young adults. Smals AE, et al. **J Clin Endocrinol Metab** 1986 Feb;62(2):336-41

Growth hormone-releasing factor analogue (hGRF1-29NH2): immunoreactive-GRF plasma levels after intravenous and subcutaneous administration. Rafferty B, et al. **J Endocrinol** 1985 Dec;107(3):R5-8

Growth hormone releasing factor (GRF) increases free arachidonate levels in the pituitary: a role for lipoxygenase products. Canonico PL, et al. **Life Sci** 1986 Jan 20;38(3):267-72

Growth hormone responses to growth hormone-releasing hormone (1-29)-NH2 and a D-Ala2 analog in normal men. Barron JL, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):575-7

Effect of hypophysectomy on immunocytochemically demonstrated growth hormone releasing factor (GHRF) in the rat brain. Merchenthaler I, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):865-7

Sensitivity of rat forebrain neurons to growth hormone-releasing hormone. Twery MJ, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):609-13

Vasoactive intestinal peptide effects on GH3 pituitary tumor cells: high affinity binding, affinity labeling, and adenylate cyclase stimulation. Comparison with peptide histidine isoleucine and growth hormone-releasing factor. Wood CL, et al. **Regul Pept** 1985 Nov 7;12(3):237-48

[Intervention of the calcium-calmodulin system in the release of growth hormone induced by somatocrinin] Mougin C, et al. **Ann Endocrinol (Paris)** 1985;46(1):61-3 (Eng. Abstr.) **(Fre)**

[Plasma assay of somatocrinin during growth hormone stimulation tests. Results in pediatrics] Evain-Brion D, et al **Arch Fr Pediatr** 1985 Aug-Sep;42 Suppl 1:575-8 (Eng. Abstr.) **(Fre)**

SPATIAL BEHAVIOR

[Delayed spatial choice in the monkey with different probabilities of signal presentation] Nikitin VS. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct; 35(5):968-70 **(Rus)**

STARTLE REACTION

Anterior cerebellar vermal stimulation: effect on behavior and basal forebrain neurochemistry in rat. Albert TJ, et al. **Biol Psychiatry** 1985 Dec;20(12):1267-76

Central 5-HT and the respiratory response to acoustic stimulation in awake rats: effects of PCPA, 5-HTP and 8-OH-DPAT. Ahlenius S, et al. **J Neural Transm** 1985;63(3-4):285-95

Fear-enhanced acoustic startle is not attenuated by acute or chronic imipramine treatment in rats. Cassella JV, et al. **Psychopharmacology (Berlin)** 1985;87(3):278-82

Cocaine: effects on acoustic startle and startle elicited electrically from the cochlear nucleus. Harty TP, et al. **Psychopharmacology (Berlin)** 1985; 87(4):396-9

STEREOTYPED BEHAVIOR

A genetic analysis of stereotypy in the mouse: dopaminergic plasticity following chronic stress. Cabib S, et al. **Behav Neural Biol** 1985 Sep; 44(2):239-48

Neurochemical aspects of the Rett syndrome. Riederer P, et al. **Brain Dev** 1985;7(3):351-60

Contralateral circling behavior induced by intranigral microinjections of taurine and GABA in rats. Kamata K, et al. **Brain Res** 1985 Sep 23; 343(2):275-82

Effect of methylphenidate pretreatment on the behavioral and biochemical responses to amphetamine. Kolta MG, et al. **Eur J Pharmacol** 1985 Nov 5;117(2):279-82

The enantiomers of SK&F 83566, a new selective D-1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D-2 agonist RU 24213. Molloy AG, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):183-6

Potential neuroleptic agents. 4. Chemistry, behavioral pharmacology, and inhibition of [3H]spiperone binding of 3,5-disubstituted N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxysalicylamides. de Paulis T, et al. **J Med Chem** 1986 Jan;29(1):61-9

Neuroleptic activity of chiral trans-hexahydro-gamma-carbolines. Sarges R, et al. **J Med Chem** 1986 Jan;29(1):8-19

Chronic clorgyline and pargyline increase apomorphine-induced stereotypy in the rat. Campbell IC, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):921-5

Effects of some antidepressant drugs on apomorphine concentration in the central nervous system of rats and apomorphine-induced stereotypy. Rurak A, et al. **Pol J Pharmacol Pharm** 1985 Jul-Aug;37(4):509-15

Behavioral evidence for cholecystokinin modulation of dopamine in the mesolimbic pathway. Crawley JH. **Prog Clin Biol Res** 1985; 192:131-8

Behavioral effects of cholecystokinin and its related peptides in rats. Itoh S, et al. **Prog Clin Biol Res** 1985;192:139-45

Effects of cholecystokinin and vasoactive intestinal peptide on locomotion and rearing in neofrontal decorticated rats. Katsuura G, et al. **Prog Clin Biol Res** 1985;192:147-50

Effects of the putative D-1 antagonist SCH 23390 on stereotyped behaviour induced by the D-2 agonist RU24213. Pugh MT, et al. **Psychopharmacology (Berlin)** 1985;87(3):308-12

[Stereotyped behavior and the nigro-strio-nigral system] Arushanian EB. **Zh Vyssh Nerv Deiat** 1985 Sep-Oct;35(5):819-32 (50 ref.) **(Rus)**

STRESS, PSYCHOLOGICAL

Psychogenic stress in women during fetal monitoring (hormonal profile). Shalev E, et al. **Acta Obstet Gynecol Scand** 1985;64(5):417-20

An approach to stress and anxiety in general practice. Manzie P. **Aust Fam Physician** 1985 Sep;14(9):894-5, 899-900

Dynamics of cholinergic synaptic mechanisms in rat hippocampus after stress. Finkelstein Y, et al. **Brain Res** 1985 Sep 23;343(2):314-9

Glucocorticoids facilitate the retention of acquired immobility during forced swimming. Veldhuis HD, et al. **Eur J Pharmacol** 1985 Sep 24; 115(2-3):211-7

Beta-blockers and psychic stress: a double-blind, placebo-controlled study of bopindolol vs lorazepam and butalbital in surgical patients. Chierichetti SM, et al. **Int J Clin Pharmacol Ther Toxicol** 1985 Sep; 23(9):510-4

A chronic technique for high frequency blood sampling/transfusion in the freely behaving rat which does not affect prolactin and corticosterone secretion. Wiersma J, et al. **J Endocrinol** 1985 Nov; 107(2):285-92

Effect of short-term swimming stress and diazepam on 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) levels in the caudate nucleus: an in vivo voltammetric study. Ikeda M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct; 331(1):23-6

Stressor invoked exacerbation of amphetamine-elicited perseveration. Anisman H, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):173-83

The effects of PK 11195, a ligand for benzodiazepine binding sites, in animal tests of anxiety and stress. File SE, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):737-41

The effects of putative anxiolytic compounds (PK 8165, PK 9084 and tracazolate) on the rat corticosterone response. File SE, et al. **Physiol Behav** 1985 Oct;35(4):583-6

Psychoneuroendocrine stress responses and mood as related to the menstrual cycle. Collins A, et al. **Psychosom Med** 1985 Nov-Dec; 47(6):512-27

[Effect of enkephalins on morphologic and hormonal manifestations of the stress reaction] Lishmanov IuB, et al. **Patol Fiziol Eksp Ter** 1985 Sep-Oct;(5):14-7 (Eng. Abstr.) **(Rus)**

[Stress-induced disorders in the antitumor immunity system and their limitation by stress-limiting factors] Meerson FZ, et al. **Vestn Akad Med Nauk SSSR** 1985;(8):23-9 (Eng. Abstr.) **(Rus)**

SUBSTANCE P

Acute continuous exposure to cigarette smoke produces discrete changes in cholecystokinin and substance P levels in the hypothalamus and preoptic area of the male rat. Fuxe K, et al. **Acta Physiol Scand** 1985 Nov;125(3):437-43

The substance P innervation of the rat hippocampal region. Davies S, et al. **Anat Embryol (Berl)** 1985;173(1):45-52

Substance P immunoreactivity in the major pelvic ganglion of the rat. Dail WG, et al. **Anat Rec** 1985 May;212(1):103-9

Immunohistochemical observation on substance P in regenerating taste buds of the rat. Nishimoto T, et al. **Anat Rec** 1985 Aug; 212(4):430-6

Amidase-like activity of calpain I and calpain II on substance P and its related peptides. Hatanaka M, et al. **Arch Biochem Biophys** 1985 Nov 1;242(2):557-62

A peptide that inhibits the mitogenic stimulation of Swiss 3T3 cells by bombesin or vasopressin. Corps AN, et al. **Biochem J** 1985 Nov 1; 231(3):781-4

Proteolytic inactivation of substance P in the epithelial layer of the intestine. Nau R, et al. **Biochem Pharmacol** 1985 Nov 15; 34(22):4019-23

Relation of substance P to catecholamine metabolism and stress. Oehme P. **Biomed Biochim Acta** 1985;44(10):1401-9 (36 ref.)

Cholecystokinin and substance P concentrations in discrete areas of the rat brain: sex differences. Frankfurt M, et al. **Brain Res** 1985 Dec 9; 358(1-2):53-8

The actions of substance P and serotonin on myenteric neurons in tissue culture. Hanani M, et al. **Brain Res** 1985 Dec 9;358(1-2):276-81

Deafferentation causes a loss of presynaptic bombesin receptors and supersensitivity of substance P receptors in the dorsal horn of the cat spinal cord. Massari VJ, et al. **Brain Res** 1985 Sep 23;343(2):268-74

Regional distribution of substance P, neurokinin alpha and neurokinin beta in rat spinal cord, nerve roots and dorsal root ganglia, and the effects of dorsal root section or spinal transection. Ogawa T, et al. **Brain Res** 1985 Dec 16;359(1-2):152-7

Comparative distribution of neuropeptide tyrosine-, vasoactive intestinal polypeptide-, substance P-immunoreactive, acetylcholinesterase-positive and noradrenergic nerves in the reproductive tract of the female rat. Papka RE, et al. **Cell Tissue Res** 1985;242(3):475-90

Calcitonin gene-related peptide is a potent inhibitor of substance P degradation. Le Greves P, et al. **Eur J Pharmacol** 1985 Sep 24; 115(2-3):309-11

Opposing hemodynamic effects of substance P on pulmonary vasculature in rabbits. Worthen GS, et al. **J Appl Physiol** 1985 Oct; 59(4):1098-103

Topographic organization of substance P and monoamine cells in the ventral medulla of the cat. Marson L, et al. **J Auton Nerv Syst** 1985 Nov;14(3):271-85

A study of the substance P innervation of the intermediate zone of the thoracolumbar spinal cord. Oldfield BJ, et al. **J Comp Neurol** 1985 Jun 1;236(1):127-40

Ontogeny of substance P-like immunoreactive fibers in the taste buds and their surrounding epithelium of the circumvallate papillae of the rat. II. Electron microscopic analysis. Yamasaki H, et al. **J Comp Neurol** 1985 Nov 22;241(4):493-502

Three-dimensional distribution of substance P-like immunoreactivity in the urinary bladder of rat. Yokokawa K, et al. **J Neural Transm** 1985; 63(3-4):209-22

Effects of substance P on carbachol-stimulated 45Ca2+ uptake into cultured adrenal chromaffin cells. Boksa P. **J Neurochem** 1985 Dec; 45(6):1895-902

Structure-activity relationship for substance P inhibition of carbamylcholine-stimulated 22Na+ flux in neuronal (PC12) and non-neuronal (BC3H1) cell lines. Simasko SM, et al. **J Pharmacol Exp Ther** 1985 Dec;235(3):601-5

Intraseptal microinjections of substance P and analogs potentiate pentobarbital-induced narcosis and depression of hippocampal cholinergic activity. Zucker JR, et al. **J Pharmacol Exp Ther** 1985 Nov; 235(2):398-401

Somatostatin, substance P and [Lys]-vasopressin interfere with the binding of [3H][D-Ala2, Met5]enkephalinamide to rat brain membranes. Maruyama M. **Jpn J Pharmacol** 1985 Aug;38(4):445-7

Modification of morphine withdrawal: effect of tuftsin, [Lys4]-tuftsinyltuftsin, tetrapeptide fragment (1-4) of substance P and its amide. Aronowski J, et al. **Life Sci** 1985 Oct 28;37(17):1649-53

Central effects of an antagonist and an antiserum to substance P on serum gonadotropin and prolactin secretion. Dees WL, et al. **Life Sci** 1985 Oct 28;37(17):1627-31

Cardiovascular effects of calcitonin gene-related peptide in the pithed rat: comparison with substance P. Haass M, et al. **Life Sci** 1985 Dec 2;37(22):2085-90

Effect of age on substance P levels in the rat mesenteric artery and vein. Duckles SP. **Neurobiol Aging** 1985 Fall,6(3):237-9

Cardio-respiratory actions of substance P, TRH and 5-HT in the nucleus tractus solitarius of rats: evidence for functional interactions of neuropeptides and amine neurotransmitters. Carter DA, et al. **Neuropeptides** 1985 Sep;6(5):425-36

Substance P-immunoreactive nerves in the rat kidney. Ferguson M, et al. **Neurosci Lett** 1985 Sep 30;60(2):183-8

Evidence that large synaptic vesicles containing substance P and small synaptic vesicles have a surface antigen in common in rat. Floor E, et al. **Neurosci Lett** 1985 Sep 30;60(2):231-7

Innervation of the feline cerebral vasculature by nerve fibers containing calcitonin gene-related peptide: trigeminal origin and co-existence with substance P. Uddman R, et al. **Neurosci Lett** 1985 Nov 20; 62(1):131-6

Co-existence of glucagon- and substance P-like immunoreactivity in the chicken retina. Katayama-Kumoi Y, et al. **Neuroscience** 1985 Oct; 16(2):417-24

Behavioral investigation of the coexistence of substance P, corticotropin releasing factor, and acetylcholinesterase in lateral dorsal tegmental neurons projecting to the medial frontal cortex of the rat. Crawley JN, et al. **Peptides (Fayetteville)** 1985 Sep-Oct;6(5):891-901

Substance K and substance P differentially modulate mesolimbic and mesocortical systems. Deutch AY, et al. **Peptides (Fayetteville)** 1985; 6 Suppl 2:113-22

Organization of LHRH cells: differential apposition of neurotensin, substance P and catecholamine axons. Hoffman GE. **Peptides (Fayetteville)** 1985 May-Jun;6(3):439-61

Spantide: failure to antagonize bombesin-induced stimulation of gastrin secretion in dogs. Pappas T, et al. **Peptides (Fayetteville)** 1985 Sep-Oct; 6(5):1001-3

Calcitonin gene-related peptide coexists with substance P in capsaicin sensitive neurons and sensory ganglia of the rat. Skofitsch G, et al. **Peptides (Fayetteville)** 1985 Jul-Aug;6(4):747-54

Neuropeptide modulation of the behavioral effects of drugs. Barrett JE, et al. **Prog Clin Biol Res** 1985;192:37-50

Substance P modulation of the mesolimbic dopamine system. Kalivas P. **Prog Clin Biol Res** 1985;192:403-8

Characterization of the metabolism of substance P and neurotensin by human angiotensin I converting enzyme and 'enkephalinase'. Skidgel RA. **Prog Clin Biol Res** 1985;192:371-8

Effect of regulatory polypeptides on the substance P stimulated lower esophageal sphincter pressure in pigs. Aggestrup S. **Regul Pept** 1985 Sep;12(1):1-7

[Peptidergic transmission and late slow EPSP in sympathetic ganglion cells] Jiang ZG. **Sheng Li Ko Hsueh Chin Chan** 1984 Oct; 15(4):301-5 **(Chi)**

[Synthesis of cyclic and non-cyclic tachykinin partial sequences. 2. Synthesis of the homocyclic substance P(6-11) hexapeptide] Neubert K, et al. **Pharmazie** 1985 Aug;40(8):532-5 (Eng. Abstr.) **(Ger)**

[Substance P. New cyclic analogs] Mutulis FK, et al. **Bioorg Khim** 1985 Sep;11(9):1276-8 (Eng. Abstr.) **(Rus)**

SUBSTANCE USE DISORDERS

Clinical management of benzodiazepine dependence [letter] Marks J. **Br Med J [Clin Res]** 1985 Oct 26;291(6503):1201-2

SYMPATHOMIMETICS

A comparison of the relative toxicities of beta-sympathomimetic tocolytic agents. Hankins GD, et al. **Am J Perinatol** 1985 Oct;2(4):338-46

cAMP- and beta-adrenergic-stimulated chloride-dependent Ca2+ secretion in frog skin. Ziyadeh FN, et al. **Am J Physiol** 1985 Nov; 249(5 Pt 2):F713-22

Spectrophotometric determination of certain sympathomimetic amines. Salem FB, et al. **Analyst** 1985 Sep;110(9):1125-9

Regulation of cerebrovascular gamma-glutamyltranspeptidase by adrenergic and cholinergic agonists. Grammas P, et al. **Biochem Pharmacol** 1985 Dec 1;34(23):4177-9

Effects of adrenergic drugs on the electrical activity of pigeon oesophagus. Mulè F, et al. **Boll Soc Ital Biol Sper** 1985 Sep 30;61(9):1365-70

Hydrostatic pressure and adrenergic drugs (agonists and antagonists): effects and interactions in fish. Sebert P, et al. **Comp Biochem Physiol** [C] 1985;82(1):207-12

Modification of behavioral response to intra-hippocampal injections of noradrenaline and adrenoceptor agonists by chronic treatment with desipramine and citalopram: functional aspects of adaptive receptor changes. Plaźnik A, et al. **Eur J Pharmacol** 1985 Nov 5; 117(2):245-52

Time change of rabbit aqueous flow under influence of adrenergic drugs. Araie M. **Exp Eye Res** 1985 Sep;41(3):391-403

Influence of adrenoreceptor agonists and antagonists on ovulation in the rabbit ovary perfused in vitro. Schmidt G, et al. **J Auton Pharmacol** 1985 Sep;5(3):241-50

Microneurography: a technique for assessing central neural effects of adrenergic drugs on sympathetic outflow in humans. Mark AL, et al. **J Cardiovasc Pharmacol** 1985;7 Suppl 8:S67-9

Effects of maternal beta sympathomimetic therapy on the neonate. Armstrong C. **Neonatal Netw** 1985 Dec;4(3):6-9

[Sydnocarb as the method of choice in persistent enuresis? Findings after 2 years of administration] Simlová M, et al. **Cesk Psychiatr** 1985 Oct; 81(5):312-3 (Eng. Abstr.) **(Cze)**

[Functional synergism of beta-adrenomimetics and seduxen during action on the uterine contractile function in an experiment] Gersamiia TV, et al. **Akush Ginekol (Mosk)** 1985 Aug;(8):65-6 **(Rus)**

[Possibilities of regulating uterine contractile function with adrenergic and cholinergic agents in an experiment] Pankratova VV, et al. **Akush Ginekol (Mosk)** 1985 Aug;(8):62-3 **(Rus)**

SYNAPTIC RECEPTORS

Is there feedback regulation of neurotransmitter release by autoreceptors? Kalsner S. **Biochem Pharmacol** 1985 Dec 1;34(23):4085-97 (86 ref.)

Cl-/Ca2+-dependent L-glutamate binding sites do not correspond to 2-amino-4-phosphonobutanoate-sensitive excitatory amino acid receptors. Fagg GE, et al. **Br J Pharmacol** 1985 Nov;86(3):743-51

Neurotensin-like immunoreactivity and neurotensin receptors in the rat hypothalamus and in the neurointermediate lobe of the pituitary gland. Goedert M, et al. **Brain Res** 1985 Dec 9;358(1-2):59-69

Deafferentation causes a loss of presynaptic bombesin receptors and supersensitivity of substance P receptors in the dorsal horn of the cat spinal cord. Massari VJ, et al. **Brain Res** 1985 Sep 23;343(2):268-74

Relationship between levels and uptake of serotonin and high affinity [3H]imipramine recognition sites in the rat brain. Hrdina PD, et al. **Can J Physiol Pharmacol** 1985 Oct;63(10):1239-44

Phencyclidine binding sites in the nucleus accumbens and phencyclidine-induced hyperactivity are decreased following lesions of the mesolimbic dopamine system. French ED, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):1-9

Tritiated imipramine binding to platelets in manic subjects. Lewis DA, et al. **J Affective Disord** 1985 Nov;9(3):207-11

Is inhibition of striatal synaptosomal tyrosine hydroxylation by dopamine agonists a measure of dopamine autoreceptor function? Fowler CJ, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):12-9

Morphine dependence and protracted abstinence: regional alterations in CNS radioligand binding. Carlson KR, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):1059-63

Characterization of endogenous inhibitors of [3H]-imipramine binding and [3H]-serotonin uptake from rat serum. Angel I, et al. **Prog Clin Biol Res** 1985;192:457-64

Characterization of the endocoid for imipramine recognition sites. Barbaccia ML, et al. **Prog Clin Biol Res** 1985;192:431-40

Evidence for an endogenous peptide ligand and antagonist for PCP receptors. Contreras PC, et al. **Prog Clin Biol Res** 1985;192:495-8

5-methoxytryptoline and close analogs as candidates for the endogenous ligand of the 3H-imipramine recognition site. Langer SZ, et al. **Prog Clin Biol Res** 1985;192:441-55

Demonstration of an imipramine endacoid in rat brain. Rehavi M, et al. **Prog Clin Biol Res** 1985;192:465-72

Cellular mechanisms for neurotensin receptor-mediated release of prolactin. Memo M, et al. **Regul Pept [Suppl]** 1985;4:200-2

[Neuroleptics in psychogeriatrics. A proposal for a more rational prescription policy] Willekens-Bogaers MA, et al. **Tijdschr Gerontol Geriatr** 1985 Oct;16(5):179-89 (Eng. Abstr.) **(Dut)**

TESTOSTERONE

Regulation of gonadotrophin secretion in male mice from birth to adulthood. Response to LRH injection, castration and testosterone replacement therapy. Jean-Faucher C, et al. **Acta Endocrinol (Copenh)** 1985 Oct;110(2):193-9

Effects of solvent exposure on testosterone levels and butyrylcholinesterase activity in mice. Kjellstrand P, et al. **Acta Pharmacol Toxicol (Copenh)** 1985 Oct;57(4):242-9

Effects of calmodulin and lipoxygenase inhibitors on LH (lutropin)- and LHRH (luliberin)-agonist-stimulated steroidogenesis in rat Leydig cells. Sullivan MH, et al. **Biochem J** 1985 Nov 15;232(1):55-9

The role of endogenous gonadotropin-releasing hormone in the control of luteinizing hormone and testosterone secretion in the juvenile male monkey, Macaca fascicularis. Cameron JL, et al. **Biol Reprod** 1985 Aug; 33(1):147-56

Effects of intermittent pulsatile infusion of luteinizing hormone-releasing hormone on dihydrotestosterone-suppressed gonadotropin secretion in castrate rams. Schanbacher BD. **Biol Reprod** 1985 Oct;33(3):603-11

Inhibition of testosterone production with ketoconazole alone and in combination with a gonadotropin releasing hormone analogue in the rat. English HF, et al. **Cancer Res** 1986 Jan;46(1):38-42

In vitro study of the direct ovarian effects of gonadotropin-releasing hormone (GnRH) in the frogs, Rana pipiens and Rana catesbeiana. Hubbard GM, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):154-61

Effect of mammalian luteinizing hormone-releasing hormone on plasma testosterone in male alligators, with observations on the nature of alligator hypothalamic gonadotropin-releasing hormone. Lance VA, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):138-43

Luteinizing hormone-releasing hormone facilitates the display of sexual behavior in male voles (Microtus canicaudus). Boyd SK, et al. **Horm Behav** 1985 Sep;19(3):252-64

Evidence that estrogen regulation of testosterone secretion in adult rams is mediated by both indirect (gonadotropin dependent) and direct (gonadotropin independent) means. Sanford LM. **J Androl** 1985 Sep-Oct;6(5):306-14

Suppression of plasma gonadotropins and testosterone in adult male monkeys (Macaca fascicularis) by a potent inhibitory analog of gonadotropin-releasing hormone. Adams LA, et al. **J Clin Endocrinol Metab** 1986 Jan;62(1):58-63

Sexual differentiation of prolactin responsiveness to thyrotropin releasing hormone (TRH) in the rat. Effects of postnatal testosterone on adenohypophyseal TRH receptor ontogenesis in male rats. Watanobe H, et al. **J Endocrinol Invest** 1985 Oct;8(5):459-64

Hormonal responses to gonadotrophin releasing hormone during testicular development in male African green monkeys. Brady AG, et al. **J Med Primatol** 1985;14(6):293-304

Stimulation of hypothalamic LHRH levels and release by gonadal steroids. Kalra PS. **J Steroid Biochem** 1985 Nov;23(5B):725-31

Hormonal effects of GnRH agonist in the human male: an approach to male contraception using combined androgen and GnRH agonist treatment. Swerdloff RS, et al. **J Steroid Biochem** 1985 Nov; 23(5B):855-61

LH-RH antagonist inhibits gonadal steroid secretion in vitro. Spona J, et al. **Peptides (Fayetteville)** 1985 May-Jun;6(3):379-82

[The effects of bromocriptine on the pulsatile pattern and the circadian profile of gonadotropins and testosterone secretion in normal adult men] Aisaka K, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Jun 20; 61(6):701-9 (Eng. Abstr.) **(Jpn)**

THERAPEUTIC EQUIVALENCY

Informed consent and generic drug substitution. DeVeaugh-Geiss J. **Clin Ther** 1985;7(5):544-8

THIORIDAZINE

Prophylactic effects of neuroleptics in symptom-free schizophrenics: roles of dopaminergic and noradrenergic blockers. Nishikawa T, et al. **Biol Psychiatry** 1985 Nov;20(11):1161-6

Physostigmine as an antidote for poisoning by combination of thioridazine and trihexyphenidyl. Beilin B, et al. **Br J Clin Pract** 1985 Oct; 39(10):400-1

Critical evaluation of thioridazine bioequivalence. Barone JA, et al. **Drug Intell Clin Pharm** 1985 Nov;19(11):847-58 (43 ref.)

Thioridazine 5-sulfoxide diastereoisomers in serum and urine from rats and man after chronic thioridazine administration. Hale PW Jr, et al. **J Anal Toxicol** 1985 Sep-Oct;9(5):197-201

High-pressure liquid chromatographic determination of thioridazine and its major metabolites in biological tissues and fluids. Allender WJ. **J Chromatogr Sci** 1985 Dec;23(12):541-5

Differential effects of thioridazine, clozapine and metoclopramide on the induction of adrenomedullary enzymes by apomorphine. Ekker M, et al. **Neuropharmacology** 1985 Nov;24(11):1063-6

THIRST

Post-training brain catecholamine levels: lack of response to water-motivated training. Gold PE, et al. **Behav Neural Biol** 1985 Nov; 44(3):425-33

THYROID HORMONES

Alterations in vitamin A and thyroid hormone status in anorexia nervosa and associated disorders. Curran-Celentano J, et al. **Am J Clin Nutr** 1985 Dec;42(6):1183-91

[Hypophyseal, thyroid and adrenal cortical hormone levels in the blood serum of newborn infants in the early neonatal period] Ametov AS, et al. **Pediatriia** 1985 Sep;(9):20-2 (Eng. Abstr.) **(Rus)**

[Cytoreceptors in the molecular mechanisms of hormone action] Rozen VB. **Probl Endokrinol (Mosk)** 1985 Sep-Oct;31(5):21-6 (Eng. Abstr.) **(Rus)**

[Effect of the intravenous administration of amiodarone on the blood concentrations of thyroid hormones and thyrotropin (letter)] Rodriguez Espinosa J, et al. **Med Clin (Barc)** 1985 Oct 12;85(11):475 **(Spa)**

THYROTROPIN

Effect of low-dose dopamine infusion on basal and stimulated TSH and prolactin concentrations in man. Connell JM, et al. **Clin Endocrinol (Oxf)** 1985 Aug;23(2):185-92

TRH analogue with C-terminal thioamide group. Synthesis, receptor binding, TSH-releasing activity and alpha-MSH-releasing activity. Kruszyński M, et al. **Experientia** 1985 Dec 15;41(12):1576-7

[Effect of the intravenous administration of amiodarone on the blood concentrations of thyroid hormones and thyrotropin (letter)] Rodriguez Espinosa J, et al. **Med Clin (Barc)** 1985 Oct 12;85(11):475 **(Spa)**

THYROXINE

Comparative characterization of thyroid hormone receptors and binding proteins in rat liver nucleus, plasma membrane, and cytosol by photoaffinity labeling with L-thyroxine. Dozin B, et al. **Biochemistry** 1985 Sep 10;24(19):5203-8

Influence of hormones and undernutrition on brain development in newborn rats. Pascual-Leone AM, et al. **Biol Neonate** 1985; 48(4):228-36

Control of plasma sex steroid-binding protein (SBP) in the little brown bat: effects of thyroidectomy and treatment with L- and D-thyroxine on the induction of SBP in adult males. Damassa DA, et al. **Biol Reprod** 1985 Dec;33(5):1138-46

Proliferative response of mouse submandibular gland to androgen but not to thyroid hormone. Okamoto S, et al. **Cell Tissue Kinet** 1985 Nov; 18(6):583-8

One-step immunoassays for free (unbound) hormones: the effect of tracer binding by serum proteins. Geiseler D, et al. **Clin Chem** 1986 Jan; 32(1 Pt 1):45-9

Free thyroxin and free triiodothyronine as measured by equilibrium dialysis and analog radioimmunoassay in serum of patients taking phenytoin and carbamazepine. Liewendahl K, et al. **Clin Chem** 1985 Dec;31(12):1993-6

Thyroid hormone induces metamorphosis of flounder larvae. Inui Y, et al. **Gen Comp Endocrinol** 1985 Dec;60(3):450-4

Effect of L-thyroxine on ovarian development and gestation in the viviparous guppy, Poecilia reticulata. Lam TJ, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):324-30

The relative potencies of L-T4 and L-T3 on the pituitary-thyroid axis in the Japanese quail. Parés-Herbuté N, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):298-305

The effect of exposure to 40 degrees on the heat production and the serum concentrations of triiodothyronine, thyroxine, and corticosterone in immature domestic fowl. Williamson RA, et al. **Gen Comp Endocrinol** 1985 Nov;60(2):178-86

Thyroxine concentrations and secretion rates in relation to pregnancy, lactation and energy balance in goats. Riis PM, et al. **J Endocrinol** 1985 Dec;107(3):421-7

Steroid and thyroid hormone profiles following a single injection of partly purified salmon gonadotropin or GnRH analogues in male and female sea lamprey. Sower SA, et al. **J Exp Zool** 1985 Sep;235(3):403-8

Re: Salivary thyroxine as an estimate of free thyroxine [letter] Al-Ansari AA, et al. **J Nucl Med** 1984 Apr;25(4):538-9

More on free thyroxine assays [letter] **Lancet** 1985 Dec 14; 2(8468):1357-8

Internal quality control of hormone determinations by RIA. Detection of clinically significant analytical errors of serum thyroxine determination. Ruokonen A, et al. **Scand J Clin Lab Invest [Suppl]** 1984; 172:93-9

[Performance of 8 methods for evaluating the free fraction of thyroxine in chronic renal insufficiency (letter)] Schlienger JL, et al. **Presse Med** 1985 Nov 2;14(37):1931 **(Fre)**

[Familial hyperthyroxinemia] Staub JJ, et al. **Dtsch Med Wochenschr** 1985 Nov 29;110(48):1870-1 **(Ger)**

TRANQUILIZING AGENTS

Flupenthixol decanoate (fluanxol depot) in the treatment of chronic schizophrenic patients. Haider I. **JPMA** 1985 Sep;35(9):286-9

TRANQUILIZING AGENTS, MAJOR

Valproate as psychotropic agent. Interactions and adverse cerebral reactions. van Sweden B, et al. **Acta Psychiatr Scand** 1985 Sep; 72(3):315-7

Psychotic patients' understanding of informed consent. Irwin M, et al. **Am J Psychiatry** 1985 Nov;142(11):1351-4

Demographic predictors of the use of injectable versus oral antipsychotic medications in outpatients. Price N, et al. **Am J Psychiatry** 1985 Dec;

142(12):1491-2

Benefits of correlating neuroleptic blood level and auditory distractibility [letter] Terkelsen KG. **Am J Psychiatry** 1985 Dec;142(12):1523-4

Behavioral, autonomic and motor effects of neuroleptic drugs in cats: motor impairment and aggression. Beleslin DB, et al. **Brain Res Bull** 1985 Sep;15(3):353-6

Prolonged inhibition of striatal dopamine receptor sites by isofloxythepin. Lau YS, et al. **Eur J Pharmacol** 1985 Oct 8;116(1-2):25-31

Structural determinants of selective affinity for brain D-1 dopamine receptors within a series of 1-phenyl-1H-3-benzazepine analogues of SK&F 38393 and SCH 23390. O'Boyle KM, et al. **Eur J Pharmacol** 1985 Sep 24;115(2-3):291-5

Heatstroke in a chronic schizophrenic patient treated with high-potency neuroleptics. Lazarus A. **Gen Hosp Psychiatry** 1985 Oct;7(4):361-3

Lithium-carbamazepine versus lithium-neuroleptic prophylaxis in bipolar illness. Shukla S, et al. **J Affective Disord** 1985 Nov;9(3):219-22

Quantification of R-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-meth benzazepine in brain and blood by use of reversed-phase high-performance liquid chromatography with electrochemical detection. Kilts CD, et al. **J Chromatogr** 1985 Aug 9;342(2):452-7

Maintenance therapy and the natural course of schizophrenia. Davis JM. **J Clin Psychiatry** 1985 Nov;46(11 Pt 2):18-21

Rapid tranquilization: the efficacy of oral concentrate. Dubin WR, et al. **J Clin Psychiatry** 1985 Nov;46(11):475-8

Neuroleptic compliance among chronic schizophrenic outpatients: an intervention outcome report. Boczkowski JA, et al. **J Consult Clin Psychol** 1985 Oct;53(5):666-71

Comparative chronic effects of buspirone or neuroleptics on rat brain dopaminergic neurotransmission. McMillen BA. **J Neural Transm** 1985; 64(1):1-12

Differential effect of subchronic treatment with various neuroleptic agents on serotonin2 receptors in rat cerebral cortex. Andree TH, et al. **J Neurochem** 1986 Jan;46(1):191-7

Flumezapine and zotepine: 5-hydroxytryptamine antagonism not involved in the lack of synergism of these antipsychotic drugs with amfonelic acid in rats. Fuller RW, et al. **J Pharm Pharmacol** 1985 Oct; 37(10):755-6

Rapid tolerance to neuroleptic-induced stimulation of dopamine release in freely moving rats. Di Chiara G, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):487-94

Effects of neuroleptics displaying antidepressant activity on behavior of rats in the forced swimming test. Górka Z, et al. **Pharmacol Biochem Behav** 1985 Aug;23(2):203-6

A clinical assessment of zuclopenthixol dihydrochloride (Clopixol tablets) in the treatment of psychotic illness. Mann BS, et al. **Pharmatherapeutica** 1985;4(6):387-92

Do neuropeptide systems mediate some of the effects of antipsychotic drugs? Bissette G, et al. **Prog Clin Biol Res** 1985;192:349-53

Increased CSF cortisol levels after neuroleptic treatment in schizophrenia. Gattaz WF, et al. **Psychoneuroendocrinology** 1985;10(3):351-4

Zuclopenthixol decanoate in schizophrenia: serum levels and clinical state. Jørgensen A, et al. **Psychopharmacology (Berlin)** 1985;87(3):364-7

Computer-assisted review of antipsychotics on acute care units. Molnar G, et al. **QRB** 1985 Sep;11(9):271-4

[Neuroleptic poisoning admitted to the Poison Treatment Center in 1980] Bjaeldager PA, et al. **Ugeskr Laeger** 1985 Sep 16;147(38):2972-5 (Eng. Abstr.) **(Dan)**

[Neuroleptics in psychogeriatrics. A proposal for a more rational prescription policy] Willekens-Bogaers MA, et al. **Tijdschr Gerontol Geriatr** 1985 Oct;16(5):179-89 (Eng. Abstr.) **(Dut)**

[Treatment of psychoses] Tirkkonen A. **Duodecim** 1985; 101(17):1686-97 **(Fin)**

[Prediction of therapeutic success in acute neuroleptic treatment: results of an empirical study of 243 inpatient-treated schizophrenic patients] Möller HJ, et al. **Fortschr Neurol Psychiatr** 1985 Oct;53(10):370-83 (Eng. Abstr.) **(Ger)**

[Psychopathometric study of the prognostic significance of psychopathologic findings and premorbid personality for discharge of neuroleptic treated patients with schizophrenic psychoses] Möller HJ, et al. **Nervenarzt** 1985 Sep;56(9):498-505 **(Ger)**

[Changes in the sensitivity of brain dopamine and serotonin receptors during the prolonged administration of carbidine] Zharkovskil AM, et al. **Biull Eksp Biol Med** 1985 Dec;100(12):719-22 (Eng. Abstr.) **(Rus)**

[B-lymphocytes of the blood in schizophrenia: effect of psychotropic therapy] Potapova VA. **Zh Nevropatol Psikhiatr** 1985;85(9):1378-81 (Eng. Abstr.) **(Rus)**

TRANQUILIZING AGENTS, MINOR

Drug therapy of anxiety disorders. Desmond P, et al. **Aust Fam Physician** 1985 Sep;14(9):876-9

Prescribing hints for the treatment of anxiety and depression. Horgan D. **Aust Fam Physician** 1985 Sep;14(9):872-5

The effects of triazolobenzodiazepines in two animal tests of anxiety and in the holeboard. File SE, et al. **Br J Pharmacol** 1985 Nov; 86(3):729-35

Autoradiographic identification and topographical analyses of high affinity serotonin receptor subtypes as a target for the novel putative anxiolytic TVX Q 7821. Glaser T, et al. **Brain Res** 1985 Dec 9; 358(1-2):129-36

Comparative chronic effects of buspirone or neuroleptics on rat brain dopaminergic neurotransmission. McMillen BA. **J Neural Transm** 1985; 64(1):1-12

Distress vocalization in rat pups. A simple screening method for anxiolytic drugs. Gardner CR. **J Pharmacol Methods** 1985 Nov;14(3):181-7

Report from the University of Chicago Drug Abuse Research Center. Johanson CE. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:76-81

Non-benzodiazepine anxiolytics: potential activity of phenylpiperazines without 3H-diazepam displacing action. Lloyd KG, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):645-52

Pharmacological and clinical effects of buspirone. Taylor DP, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):687-94 (43 ref.)

Comparison of buspirone and diazepam in generalized anxiety disorder. Jacobson AF, et al. **Pharmacotherapy** 1985 Sep-Oct;5(5):290-6

The effects of putative anxiolytic compounds (PK 8165, PK 9084 and tracazolate) on the rat corticosterone response. File SE, et al. **Physiol Behav** 1985 Oct;35(4):583-6

Disposition of the psychotropic drugs buspirone, MJ-13805 and piribedil, and of their common active metabolite 1-(2-pyrimidinyl)-piperazine in the rat. Caccia S, et al. **Xenobiotica** 1985 Oct;15(10):835-44

[Pharmaco-ethological analysis of agonistic behavior between resident and intruder mice: effects of adrenergic beta-blockers] Yoshimura H, et al. **Yakubutsu Seishin Kodo** 1985 Sep;5(3):223-9 (Eng. Abstr.) **(Jpn)**

TRANYLCYPROMINE

Hyperpyrexia following psychotropic drug overdose. Peebles-Brown AE. **Anaesthesia** 1985 Nov;40(11):1097-9

L-5HTP in depression resistant to re-uptake inhibitors An open comparative study with tranylcypromine. Nolen WA, et al. **Br J Psychiatry** 1985 Jul;147:16-22

A rapid and sensitive procedure for the simultaneous analysis of beta-phenylethylamine and tranylcypromine in rat brain using trichloroacetylation and gas chromatography. Baker GB, et al. **Res Commun Chem Pathol Pharmacol** 1985 Sep;49(3):471-4

TRIAZOLAM

Experimental assessment of the relative abuse liability of triazolam and pentobarbital. Roache JD, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1984;55:106-10

TRIFLUOPERAZINE

Effect of trifluoperazine on the action of insulin in rat adipocytes. Begum N, et al. **Endocrinology** 1986 Jan;118(1):287-92

Relative effectiveness of pimozide, haloperidol and trifluoperazine on self-stimulation rate-intensity functions. Lynch MR, et al. **Pharmacol Biochem Behav** 1985 Nov;23(5):777-80

Effects of trifluoperazine and verapamil on the hydro-osmotic response to antidiuretic hormone in the urinary bladder of the toad. Kipnowski J, et al. **Res Exp Med (Berl)** 1985;185(5):367-74

[Comparative analysis of the action of 2 calmodulin inhibitors on the contractile function of the isolated heart] Kapel'ko VI, et al. **Fiziol Zh SSSR** 1985 Sep;71(9):1095-100 (Eng. Abstr.) **(Rus)**

TRYPTAMINES

Inhibitory action of exogenous melatonin, 5-methoxytryptamine, and 6-hydroxymelatonin on sexual maturation of male rats: activity of 5-methoxytryptamine might be due to its conversion to melatonin. Lang U, et al. **Biol Reprod** 1985 Oct;33(3):618-28

5-Methyltryptamine stimulates phospholipase C-mediated breakdown of exogenous phosphoinositides by blowfly salivary gland membranes. Litosch I, et al. **J Biol Chem** 1985 Dec 25;260(30):16052-5

5-Methyltryptamine decreases net accumulation of 32P into the polyphosphoinositides from [gamma-32P]ATP in a cell-free system from blowfly salivary glands. Activation of breakdown of the newly synthesized [32P]polyphosphoinositides. Litosch I, et al. **J Biol Chem** 1986 Jan 15;261(2):638-43

Analysis of cheese for histamine, tyramine, tryptamine, histidine, tyrosine, and tryptophane. Chang SF, et al. **J Dairy Sci** 1985 Nov; 68(11):2840-6

Effects of quipazine and of tryptamine on self-stimulation of median raphé nucleus and of lateral hypothalamus in rats. Broadbent J, et al. **Pharmacol Biochem Behav** 1985 Dec;23(6):943-7

[Comparative experimental study of the effect of melatonin and 5-methoxytryptamine on the thyroid gland of rats] Rom-Bugoslavskaia ES, et al. **Farmakol Toksikol** 1985 Sep-Oct;48(5):84-9 (Eng. Abstr.) **(Rus)**

BIBLIOGRAPHY

TRYPTOPHAN

Light-induced changes in plasma tryptophan and cystine. Felten RP. **Ann NY Acad Sci** 1985;453:55-64

Cloning and expression of tryptophan genes from Brevibacterium lactofermentum in Escherichia coli. del Real G, et al. **Biochem Biophys Res Commun** 1985 Dec 31;133(3):1013-9

Stopped-flow kinetic studies of metal ion dissociation or exchange in a tryptophan-containing parvalbumin. Breen PJ, et al. **Biochemistry** 1985 Sep 10;24(19):4997-5004

Spectroscopic studies of metal ion binding to a tryptophan-containing parvalbumin. Breen PJ, et al. **Biochemistry** 1985 Sep 10; 24(19):4991-7

Photoinactivation and photoaffinity labeling of tryptophan synthase alpha 2 beta 2 complex by the product analogue 6-azido-L-tryptophan. Miles EW, et al. **Biochemistry** 1985 Aug 13;24(17):4694-703

Reactivities of tyrosine, histidine, tryptophan, and methionine in radical pair formation in flavin triplet induced protein nuclear magnetic polarization. Muszkat KA, et al. **Biochemistry** 1985 Sep 24; 24(20):5416-21

The tryptophans of gramicidin are essential for the lipid structure modulating effect of the peptide. Killian JA, et al. **Biochim Biophys Acta** 1985 Oct 24;820(1):154-6

Fluorescence quenching of the buried tryptophan residue of cod parvalbumin. Eftink MR, et al. **Biophys Chem** 1985 Aug; 22(3):173-80

The pharmacokinetics of L-tryptophan following its intravenous and oral administration. Green AR, et al. **Br J Clin Pharmacol** 1985 Oct; 20(4):317-21

Stability of tryptophan during food processing and storage. 2. A comparison of methods used for the measurement of tryptophan losses in processed foods. Nielsen HK, et al. **Br J Nutr** 1985 Mar; 53(2):293-300

Stability of tryptophan during food processing and storage. 1. Comparative losses of tryptophan, lysine and methionine in different model systems. Nielsen HK, et al. **Br J Nutr** 1985 Mar;53(2):281-92

Mutagenicity of nondialyzable melanoidins prepared from carbohydrates and L-tryptophan before and after nitrite treatment. Kinae N, et al. **Chem Pharm Bull (Tokyo)** 1985 Jun;33(6):2438-44

Studies of the fluorescence from tryptophan in melittin. Tran CD, et al. **Eur Biophys J** 1985;13(1):59-64

Protective effect of tryptophan and cysteine against carbon tetrachloride-induced liver injury. Wang D, et al. **Exp Mol Pathol** 1985 Dec;43(3):364-74

Analysis of cloned DNA from Leptospira biflexa serovar patoc which complements a deletion of the Escherichia coli trpE gene. Yelton DB, et al. **J Bacteriol** 1986 Jan;165(1):41-6

Interaction of the Escherichia coli trp aporepressor with its ligand, L-tryptophan. Arvidson DN, et al. **J Biol Chem** 1986 Jan 5; 261(1):238-43

Differential inhibition of tryptophan synthase and of tryptophanase by the two diastereoisomers of 2,3-dihydro-L-tryptophan. Implications for the stereochemistry of the reaction intermediates. Phillips RS, et al. **J Biol Chem** 1985 Nov 25;260(27):14665-70

Direct chiral resolution in an aqueous two-phase system using the counter-current distribution principle. Ekberg B, et al. **J Chromatogr** 1985 Sep 27;333(1):211-4

Chromatographic determination of N-acetyl-DL-tryptophan and octanoic acid in human albumin solutions. Nelis HJ, et al. **J Chromatogr** 1985 Oct 4;333(2):381-7

Analysis of cheese for histamine, tyramine, tryptamine, histidine, tyrosine, and tryptophane. Chang SF, et al. **J Dairy Sci** 1985 Nov; 68(11):2840-6

The anti-chlamydial and anti-proliferative activities of recombinant murine interferon-gamma are not dependent on tryptophan concentrations. de la Maza LM, et al. **J Immunol** 1985 Dec; 135(6):4198-200

Nuclear magnetic resonance study of the proton exchange rate in the operator-promoter DNA sequence of the trp operon of Escherichia coli. Lefevre JF, et al. **J Mol Biol** 1985 Oct 20;185(4):689-99

Uptake and release of tryptophan and serotonin: an HPLC method to study the flux of endogenous 5-hydroxyindoles through synaptosomes. Wolf WA, et al. **J Neurochem** 1986 Jan;46(1):61-7

Suppressive effect of dietary unsaturated fatty acids on alpha-amino-beta-carboxymuconate-epsilon-semialdehyde decarboxylase, a key enzyme of tryptophan-niacin metabolism in rat liver. Sanada H. **J Nutr Sci Vitaminol (Tokyo)** 1985 Jun; 31(3):327-37

The effect of intraluminal tryptophan and phenylalanine on small intestinal motility in the conscious dog. Bull JS, et al. **J Physiol (Lond)** 1985 Oct;367:353-62

Evidence for the role of glycosylation of proteins in the tryptophan-induced stimulation of nucleocytoplasmic translocation of mRNA in rat liver. Sidransky H, et al. **Lab Invest** 1986 Jan; 54(1):93-9

Scheduled feeding versus the light-dark cycle on the rhythms of circulating tryptophan, serotonin and N-acetylserotonin in rats. Ho AK, et al. **Life Sci** 1985 Oct 28;37(17):1619-26

Effect of indolamines on beta-endorphin release by rat anterior pituitary cells. Abou Samra AB, et al. **Neuroendocrinology** 1985 Dec; 41(6):490-3

Tyrosyl fluorescence spectra of proteins lacking tryptophan: effects of intramolecular interactions. Lux B, et al. **Photochem Photobiol** 1985 Sep; 42(3):245-51

Interaction of dietary tryptophan and social isolation on territorial aggression, motor activity, and neurochemistry in mice. Lasley SM, et al. **Psychopharmacology (Berlin)** 1985;87(3):313-21

[Tryptophan of facultative methylotrophic bacteria Pseudomonas sp. M. II. Regulation of tryptophan biosynthesis] Olekhnovich IN, et al. **Genetika** 1985 Oct;21(10):1627-33 (Eng. Abstr.) **(Rus)**

[Effect of tryptophan on gluconeogenesis in the perfused liver of irradiated rats] Borovikova GV, et al. **Radiobiologiia** 1985 Sep-Oct;25(5):636-9 (Eng. Abstr.) **(Rus)**

TRYPTOPHAN HYDROXYLASE

[Interaction of genetic and environmental components in the determination of tryptophan hydroxylase activity in the mouse brain in stress] Kulikov AV, et al. **Genetika** 1985 Oct;21(10):1680-4 (Eng. Abstr.) **(Rus)**

TYROSINE

Microbial preparation of L-[15N]tyrosine and [15N]tyramine and their gas chromatographic-mass spectrometric analyses. Kahana ZE, et al. **Anal Biochem** 1985 Sep;149(2):549-54

Reactions of nitrogen dioxide in aqueous model systems: oxidation of tyrosine units in peptides and proteins. Prütz WA, et al. **Arch Biochem Biophys** 1985 Nov 15;243(1):125-34

Evolutionary implications of features of aromatic amino acid biosynthesis in the genus Acinetobacter. Byng GS, et al. **Arch Microbiol** 1985 Nov; 143(2):122-9

Fluorescence energy transfer between Tyr 69 and Cys 374 in actin. Barden JA. **Biochem Int** 1985 Oct;11(4):583-9

Nature of sulphated macromolecules in mouse Reichert's membrane. Evidence for tyrosine O-sulphate in basement-membrane proteins. Paulsson M, et al. **Biochem J** 1985 Nov 1;231(3):571-9

Reactivities of tyrosine, histidine, tryptophan, and methionine in radical pair formation in flavin triplet induced protein nuclear magnetic polarization. Muszkat KA, et al. **Biochemistry** 1985 Sep 24; 24(20):5416-21

Rabbit antibodies with specificity for tyrosine phosphate are not reactive with tyrosine sulphate. Jones JA, et al. **Biosci Rep** 1985 Aug; 5(8):707-14

Direct identification of phosphotyrosine-containing proteins in some retrovirus-transformed cells by use of anti-phosphotyrosine antibody. Seki J, et al. **Cancer Res** 1986 Feb;46(2):907-16

Comparative distribution of neuropeptide tyrosine-, vasoactive intestinal polypeptide-, substance P-immunoreactive, acetylcholinesterase-positive and noradrenergic nerves in the reproductive tract of the female rat. Papka RE, et al. **Cell Tissue Res** 1985;242(3):475-90

Plasma tyrosine/neutral amino acid ratio correlated with clinical response to nortriptyline in endogenously depressed patients. Møller SE, et al. **J Affective Disord** 1985 Nov;9(3):223-9

Tyrosine phosphorylation of a 94-kDa protein of human fibroblasts stimulated by streptococcal lipoteichoic acid. Ganguly CL, et al. **J Biol Chem** 1985 Oct 25;260(24):13342-6

In vivo and in vitro tyrosine sulfation of a membrane glycoprotein. Liu N, et al. **J Biol Chem** 1986 Jan 15;261(2):856-61

Use of fluorinated tyrosine phosphates to probe the substrate specificity of the low molecular weight phosphatase activity of calcineurin. Martin B, et al. **J Biol Chem** 1985 Dec 5;260(28):14932-7

Analysis of cheese for histamine, tyramine, tryptamine, histidine, tyrosine, and tryptophane. Chang SF, et al. **J Dairy Sci** 1985 Nov; 68(11):2840-6

Ionic requirements and subcellular localization of tubulin tyrosinolation in human polymorphonuclear leukocytes. Nath J, et al. **J Immunol** 1986 Jan;136(2):628-35

Inhibition of monoamine oxidase selectively in brain monoamine nerves using the bioprecursor (E)-beta-fluoromethylene-m-tyrosine (MDL 72394), a substrate for aromatic L-amino acid decarboxylase. Palfreyman MG, et al. **J Neurochem** 1985 Dec;45(6):1850-60

Dietary tyrosine suppresses the rise in plasma corticosterone following acute stress in rats. Reinstein DK, et al. **Life Sci** 1985 Dec 9; 37(23):2157-63

Effects of L-dopa and L-tyrosine on release of free and conjugated dopamine, homovanillic acid and dihydroxyphenylacetic acid from slices of rat striatum. Tyce GM, et al. **Life Sci** 1985 Dec 23; 37(25):2439-48

Tyrosine availability determines stimulus-evoked dopamine release from rat striatal slices. Milner JD, et al. **Neurosci Lett** 1985 Aug 30; 59(2):215-20

Tyrosine for the treatment of depression. Gelenberg AJ, et al. **Nutr Health** 1984;3(3):163-73 (44 ref.)

Tyrosyl fluorescence spectra of proteins lacking tryptophan: effects of intramolecular interactions. Lux B, et al. **Photochem Photobiol** 1985 Sep; 42(3):245-51

Evidence for a tyrosine protonation change during the primary phototransition of bacteriorhodopsin at low temperature. Rothschild KJ, et al. **Proc Natl Acad Sci USA** 1986 Jan;83(2):347-51

Effects of L-tyrosine on brain monoamines in rats given intravenous amphetamine. Smith DG, et al. **Subst Alcohol Actions Misuse** 1984-85; 5(6):293-8

Modification of a tyrosine residue in the carboxyterminal portion of human alpha2-antiplasmin. Lijnen HR, et al. **Thromb Res** 1985 Sep 1; 39(5):625-9

TYROSINE AMINOTRANSFERASE

Effects of saikosaponins on liver tyrosine aminotransferase activity induced by cortisone in adrenalectomized rats. Hashimoto M, et al. **Planta Med** 1985 Oct;(5):401-3

TYROSINE HYDROXYLASE

Transient expression of tyrosine hydroxylase immunoreactivity in some neurons of the rat neocortex during postnatal development. Berger B, et al. **Brain Res** 1985 Nov;355(1):141-4

Differential ontogeny of three putative catecholamine cell types in the postnatal rat retina. Foster GA, et al. **Brain Res** 1985 Oct; 354(2):187-96

Stimulation of retinal dopamine biosynthesis in vivo by exogenous tetrahydrobiopterin: relationship to tyrosine hydroxylase activation. Iuvone PM, et al. **Brain Res** 1985 Dec 16;359(1-2):392-6

So-called interplexiform cells immunoreactive to tyrosine hydroxylase or somatostatin in rat retina. Negishi K, et al. **Brain Res** 1985 Oct 28; 346(1):136-40

Effect of chronic cold exposure on tyrosine hydroxylase mRNA in rat adrenal gland. Stachowiak M, et al. **Brain Res** 1985 Dec 16; 359(1-2):356-9

Laminin increases both levels and activity of tyrosine hydroxylase in calf adrenal chromaffin cells. Acheson A, et al. **J Cell Biol** 1986 Jan; 102(1):151-9

Ontogeny of phenylethanolamine N-methyltransferase- and tyrosine hydroxylase-like immunoreactivity in presumptive adrenaline neurones of the foetal rat central nervous system. Foster GA, et al. **J Comp Neurol** 1985 Jun 15;236(3):348-81

Presynaptic dopamine autoreceptors control tyrosine hydroxylase activation in depolarized striatal dopaminergic terminals. el Mestikawy S, et al. **J Neurochem** 1986 Jan;46(1):12-22

Cholinergic receptor-mediated phosphorylation and activation of tyrosine hydroxylase in cultured bovine adrenal chromaffin cells. Pocotte SL, et al. **J Neurochem** 1986 Feb;46(2):610-22

Phorbol 12,13-dibutyrate increases tyrosine hydroxylase activity in the superior cervical ganglion of the rat. Wang M, et al. **J Neurochem** 1986 Feb;46(2):388-93

Molecular and physiological properties of tyrosine hydroxylase induced by reserpine in rat adrenal gland. Togari A, et al. **Life Sci** 1985 Oct 28;37(17):1605-11

Is inhibition of striatal synaptosomal tyrosine hydroxylation by dopamine agonists a measure of dopamine autoreceptor function? Fowler CJ, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Oct;331(1):12-9

Tyrosine hydroxylase and 28K-vitamin D-dependent calcium binding protein are localized in different subpopulations of periglomerular cells of the rat olfactory bulb. Halász N, et al. **Neurosci Lett** 1985 Oct 24; 61(1-2):103-7

Low-frequency septal stimulation increases tyrosine hydroxylase activity in the hippocampus. Graham-Jones S, et al. **Pharmacol Biochem Behav** 1985 Oct;23(4):489-93

Direct activation of tyrosine hydroxylase by calmodulin. Vulliet PR. **Proc West Pharmacol Soc** 1985;28:27-30

Genes for neurotransmitter synthesis, storage and release. Joh TH. **Prog Clin Biol Res** 1985;192:423-9

VANILMANDELIC ACID

Homovanillic acid, vanillylmandelic acid and 5-hydroxyindole-3-acetic acid are undetectable in urine of the muskrat. Yoshioka M, et al. **Chem Pharm Bull (Tokyo)** 1985 May;33(5):2145-8

VASOPRESSINS

A peptide that inhibits the mitogenic stimulation of Swiss 3T3 cells by bombesin or vasopressin. Corps AN, et al. **Biochem J** 1985 Nov 1; 231(3):781-4

Opposing alpha- and beta-adrenergic mechanisms mediate dose-dependent actions of noradrenaline on supraoptic vasopressin neurones in vivo. Day TA, et al. **Brain Res** 1985 Dec 9; 358(1-2):171-9

Stimulation of 1,2-diacylglycerol accumulation in hepatocytes by vasopressin, epinephrine, and angiotensin II. Bocckino SB, et al. **J Biol Chem** 1985 Nov 15;260(26):14201-7

Vasopressin secretion as a possible target of the gamma-aminobutyric acid-mediated component of the corticosteroid feedback effect. Acs Z, et al. **J Endocrinol** 1985 Dec;107(3):303-7

DDAVP (1-desamino-8-D-arginine vasopressin): an antagonist of the pressor action of endogenous vasopressin? Derkx FH, et al. **J Hypertension [Suppl]** 1983 Dec;1(2):58-61

Functional involvement of vasopressin in the maintenance of systemic arterial blood pressures after phenoxybenzamine or phentolamine administration: studies in Long-Evans and Brattleboro rats. Winn MJ, et al. **J Pharmacol Exp Ther** 1985 Nov;235(2):500-5

The effects and interactions of angiotensin and vasopressin on the heart of unanaesthetized sheep. Caine AC, et al. **J Physiol (Lond)** 1985 Oct; 367:1-11

Effects of oxytocin and vasopressin in the central and in the autonomic nervous system. Interactions with other presumptive neurotransmitters. Dreifuss JJ, et al. **Regul Pept [Suppl]** 1985;4:165-71

Effects of trifluoperazine and verapamil on the hydro-osmotic response to antidiuretic hormone in the urinary bladder of the toad. Kipnowski J, et al. **Res Exp Med (Berl)** 1985;185(5):367-74

[Coexpression of immunoreactivity with an anti-corticoliberin immune serum and immunoreactivity with an anti-vasopressin immune serum in human hypothalamic neurons] Clavequin MC, et al. **Ann Endocrinol (Paris)** 1985;46(1):64-6 (Eng. Abstr.) **(Fre)**

[Effects of colchicine on the actions of ADH, norepinephrine and forskolin on skin permeability of the frog] Svelto M, et al. **Boll Soc Ital Biol Sper** 1985 Jul 30;61(7):989-93 (Eng. Abstr.) **(Ita)**

VASOTOCIN

Projections of luteinizing hormone-releasing hormone and vasotocin fibers to the anterior part of the preoptic nucleus in the toad, Bufo japonicus. Jokura Y, et al. **Gen Comp Endocrinol** 1985 Dec; 60(3):390-7

WAKEFULNESS

[Sleep--2. Substances in the mechanism of sleep and wakefulness] Nagasaki H, et al. **Nippon Rinsho** 1985 Jul;43(7):1384-9 (19 ref.) **(Jpn)**

ZIMELIDINE

Selective antidepressants and cerebrospinal fluid. Lack of specificity on norepinephrine and serotonin metabolites. Potter WZ, et al. **Arch Gen Psychiatry** 1985 Dec;42(12):1171-7

Obsessive-compulsive disorder and serotonin: is there a connection? Insel TR, et al. **Biol Psychiatry** 1985 Nov;20(11):1174-88

BIBLIOGRAPHY

ACETYLCHOLINE

Dissociation of the crotoxin complex promoted by acetylcholine. Canziani GA, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(2):165-80

GABA antagonists increase the release of [3H]acetylcholine from the chick retina. Agardh E. **Acta Physiol Scand** 1986 Jan;126(1):33-8

Dopamine release is enhanced while acetylcholine release is inhibited by nimodipine (Bay e 9736). Nordström O, et al. **Acta Physiol Scand** 1986 Jan;126(1):115-9

Relative activities of three calcium channel antagonists on histamine, acetylcholine and antigen-induced contractions of guinea pig ileum. Ingenito AJ. **Agents Actions** 1985 Dec;17(2):113-20

Neurotransmitters of the cochlea and cochlear nucleus: immunocytochemical evidence. Altschuler RA, et al. **Am J Otolaryngol** 1986 Mar-Apr;7(2):100-6 (59 ref.)

High-performance liquid chromatography followed by peroxyoxalate chemiluminescence detection of acetylcholine and choline utilizing immobilized enzymes. Honda K, et al. **Anal Biochem** 1986 Feb 15; 153(1):50-3

Increased agonist affinity is induced in tetranitromethane-modified muscarinic receptors. Gurwitz D, et al. **Biochemistry** 1985 Dec 31; 24(27):8086-93

The release of acetylcholine: from a cellular towards a molecular mechanism. Israël M, et al. **Biol Cell** 1985;55(1-2):1-14

The effect of cigarette smoking during pregnancy on the cholinergic system in isolated term human placental tissue. Rowell PP, et al. **Biol Reprod** 1986 Mar;34(2):344-8

The influence of enhanced K+-concentration on the uptake and acetylation of choline in hippocampus slices of rats. Rauca C, et al. **Biomed Biochim Acta** 1985;44(11-12):1621-31

Enthalpy of acetylcholine hydrolysis by acetylcholinesterase. Das YT, et al. **Biophys Chem** 1985 Nov;23(1-2):105-14

Cyclic AMP response to vasoactive intestinal peptide and beta-adrenergic or cholinergic agonists in isolated epithelial cells of rat ventral prostate. Carmena MJ, et al. **Biosci Rep** 1985 Sep;5(9):791-7

Effects of locally administered anticholinesterase agents on the secretory response of human eccrine sweat glands to acetylcholine and carbachol. Longmore J, et al. **Br J Clin Pharmacol** 1986 Feb;21(2):131-5

Frontal decortication and adaptive changes in striatal cholinergic neurons in the rat. Consolo S, et al. **Brain Res** 1986 Jan 15;363(1):128-34

Acetylcholine, aging and anatomy: differential effects in the hippocampus. Haigler HJ, et al. **Brain Res** 1986 Jan 1;362(1):157-60

The modulation of transmitter release in motor nerve endings varies with the type of muscle fiber innervated. Lev-Tov A, et al. **Brain Res** 1986 Jan 22;363(2):379-82

The effects of nerve section on the non-quantal release of ACh from the motor nerve terminal. Stanley EF, et al. **Brain Res** 1986 Feb 19; 365(2):289-92

Mechanism of the calcium-dependent stimulation of transmitter release by 4-aminopyridine in synaptosomes. Tapia R, et al. **Brain Res** 1985 Dec 30;361(1-2):373-82

Differential effects of striatal injections of dopaminergic, cholinergic and GABAergic drugs upon swimming behavior of rats. Vrijmoed-de Vries MC, et al. **Brain Res** 1986 Jan 29;364(1):77-90

Effect of acetylcholine and secretin on medullary collecting duct function in the rat. Wilson DR, et al. **Can J Physiol Pharmacol** 1986 Jan; 64(1):62-5

Effect of thiopental sodium and barbitone sodium on the total acetylcholine content and acetylcholinesterase activity in the brain tissue of Arvicanthis niloticus. Fathi MM, et al. **Comp Biochem Physiol** [C] 1986;83(1):185-90

Spontaneous release of transmitter from the growth cones of Xenopus neurons in vitro: the influence of Ca2+ and Mg2+ ions. Young SH. **Dev Biol** 1986 Feb;113(2):373-80

Generation of cortical event-related slow potentials in the rat involves nucleus basalis cholinergic innervation. Pirch JH, et al. **Electroencephalogr Clin Neurophysiol** 1986 May;63(5):464-75

Acetylcholine receptors in the gastrulating chick embryo. Laasberg T, et al. **Experientia** 1986 Apr 15;42(4):439-40

Distribution and elimination of the stereoisomers of soman and their effect on brain acetylcholine. Nordgren I, et al. **Fundam Appl Toxicol** 1985 Dec;5(6 Pt 2):S252-9

Ultraviolet spectrophotometric method for determination of cholinesterase activity with acetylcholine as a substrate. Tomita K, et al. **J Appl Biochem** 1985 Aug-Oct;7(4-5):303-10

Comparison of intraocular acetylcholine and carbachol. Yee RW, et al. **J Cataract Refract Surg** 1986 Jan;12(1):18-22

Modification of the effects of muscarinic agonists by reversible and irreversible anticholinesterase compounds in the guinea pig atrium. Freeman SE, et al. **J Mol Cell Cardiol** 1986 Mar;18(3):231-9

Stoichiometries of acetylcholine uptake, release, and drug inhibition in Torpedo synaptic vesicles: heterogeneity in acetylcholine transport and storage. Anderson DC, et al. **J Neurochem** 1986 Apr;46(4):1207-13

Acetylcholine transport and drug inhibition kinetics in Torpedo synaptic vesicles. Bahr BA, et al. **J Neurochem** 1986 Apr;46(4):1214-8

4-(1-Naphthylvinyl)pyridine decreases brain acetylcholine in vivo, but does not alter the level of acetyl-CoA. Budai D, et al. **J Neurochem** 1986 Mar;46(3):990-2

BIBLIOGRAPHY

ACETYLCHOLINE

Acetylcholine synthesis and release by a sympathetic ganglion in the presence of 2-(4-phenylpiperidino) cyclohexanol (AH5183). Collier B, et al. **J Neurochem** 1986 Mar;46(3):822-30

Effect of intrastriatal injection of diisopropylfluorophosphate on acetylcholine, dopamine, and serotonin metabolism. Robinson SE, et al. **J Neurochem** 1986 May;46(5):1632-8

Inhibition of high-affinity choline uptake and acetylcholine synthesis by quinuclidinyl and hemicholinium derivatives. Sterling GH, et al. **J Neurochem** 1986 Apr;46(4):1170-5

Serotonin enhances the excitatory acetylcholine response in the RB cell cluster of Aplysia californica. Simmons LK, et al. **J Neurosci** 1986 Mar;6(3):774-81

Acetylcholine-induced contractions in isolated rabbit pulmonary arteries: role of thromboxane A2. Altiere RJ, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):535-41

Cholinergic and GABAergic regulation of dopamine beta-hydroxylase activity in the adrenal gland of the rat. Lima L, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):265-70

Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. Parker EM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):179-92

Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. II. Release in the presence of vesicular transmitter stores. Parker EM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):193-203

Parasympathetic stimulation as a mechanism for platelet-activating factor-induced contractile responses in the lung. Stimler-Gerard NP. **J Pharmacol Exp Ther** 1986 Apr;237(1):209-13

Fast events in single-channel currents activated by acetylcholine and its analogues at the frog muscle end-plate. Colquhoun D, et al. **J Physiol (Lond)** 1985 Dec;369:501-57

Excitatory and differential disinhibitory actions of acetylcholine in the lateral geniculate nucleus of the cat. Eysel UT, et al. **J Physiol (Lond)** 1986 Jan;370:233-54

Effects of electrical stimulation and choline availability on the release and contents of acetylcholine and choline in superfused slices from rat striatum. Maire JC, et al. **J Physiol (Paris)** 1985;80(3):189-95

Changes of total acetylcholine content and the activity of related enzymes in SART (repeated cold)-stressed rat brain and duodenum. Kita T, et al. **Jpn J Pharmacol** 1986 Jan;40(1):174-7

Effects of bifemelane hydrochloride (MCI-2016) on acetylcholine release from cortical and hippocampal slices of rats. Saito K, et al. **Jpn J Pharmacol** 1985 Nov;39(3):410-4

Effects of bifemelane hydrochloride (MCI-2016) on acetylcholine and norepinephrine release from cortical slices of bilaterally carotid-artery-ligated Mongolian gerbils. Saito K, et al. **Jpn J Pharmacol** 1985 Nov;39(3):406-9

Elevation of acetylcholine levels in striatum of rat brain by LY163502, trans-(-)-5,5a,6,7,8,9a,10-octahydro-6-propylpyrimido less than 4,5-g greater than quinolin-2-amine dihydrochloride, a potent and stereospecific dopamine (D2) agonist. Bymaster FP, et al. **Life Sci** 1986 Jan 27;38(4):317-22

ACTH-(1-24) and alpha-MSH antagonize dopamine receptor-mediated inhibition of striatal dopamine and acetylcholine release. Versteeg DH, et al. **Life Sci** 1986 Mar 3;38(9):835-40

Quinacrine and 2-(4-phenylpiperidino)cyclohexanol (AH5183) inhibit acetylcholine release and synthesis in rat brain slices. Jope RS, et al. **Mol Pharmacol** 1986 Jan;29(1):45-51

Modulation of visual cortical plasticity by acetylcholine and noradrenaline. Bear MF, et al. **Nature** 1986 Mar 13-19;320(6058):172-6

Neuropharmacology. Acetylcholine and brain cells [news] Brown D. **Nature** 1986 Jan 30-Feb 5;319(6052):358-9

Acetylcholine induces burst firing in thalamic reticular neurones by activating a potassium conductance. McCormick DA, et al. **Nature** 1986 Jan 30-Feb 5;319(6052):402-5

Phosphatidylserine increases acetylcholine release from cortical slices in aged rats. Pedata F, et al. **Neurobiol Aging** 1985 Winter;6(4):337-9

Cerebral neocortical neurons in the aged rat: spontaneous activity, properties of pyramidal tract neurons and effect of acetylcholine and cholinergic drugs. Lamour Y, et al. **Neuroscience** 1985 Dec;16(4):835-44

Intracellular injection of acetylcholine blocks various potassium conductances in vagal motoneurons. Yarom Y, et al. **Neuroscience** 1985 Dec;16(4):739-52

Alteration of fetal heart rate caused by extrauterine environmental changes. Masuyama I, et al. **Nippon Juigaku Zasshi** 1986 Feb;48(1):61-8

Demonstration of a receptor in Torpedo synaptic vesicles for the acetylcholine storage blocker L-trans-2-(4-phenyl[3,4-3H]-piperidino) cyclohexanol. Bahr BA, et al. **Proc Natl Acad Sci USA** 1986 Apr;83(7):2267-70

On the mechanism of acetylcholine release. Dunant Y. **Prog Neurobiol** 1986;26(1):55-92 (231 ref.)

Presynaptic modulation by noradrenaline and an opioid of the substance P-induced release of [3H]acetylcholine from the myenteric plexus. Vizi ES, et al. **Regul Pept** 1985 Nov 28;12(4):317-25

The role of vagus nerve on histamine- and acetylcholine-induced bronchoconstriction (experiments on cats). Zimmermann I, et al. **Res Exp Med (Berl)** 1986;186(1):29-34

Cholinergic system of brain tissue in rats poisoned with the organophosphate, 0,0-dimethyl 0-(2,2-dichlorovinyl) phosphate. Kobayashi H, et al. **Toxicol Appl Pharmacol** 1986 Jan;82(1):32-9

Effects of insecticidal carbamates on brain acetylcholine content, acetylcholinesterase activity and behavior in mice. Kobayashi H, et al. **Toxicol Lett** 1985 Dec;29(2-3):153-9

Effects of beta-bungarotoxin and Naja naja atra snake venom phospholipase A2 on acetylcholine release and choline uptake in synaptosomes. Fletcher JE, et al. **Toxicon** 1986;24(1):91-9

Excitatory amino acid analogs evoke release of endogenous amino acids and acetyl choline from chick retina in vitro. Campochiaro P, et al. **Vision Res** 1985;25(10):1375-86

[Regulation of the synthesis of acetylcholine] Zhang X. **Sheng Li Ko Hsueh Chin Chan** 1985 Jul;16(3):244-7 (40 ref.) **(Chi)**

[Cholinergic hypothesis of depression] Leboyer M, et al. **Encephale** 1985 Nov-Dec;11(6):229-34 (53 ref.) (Eng. Abstr.) **(Fre)**

[Analysis of the reactivity of the sensorimotor neurons of the rat cerebral cortex to acetylcholine] Kotliar BI, et al. **Biol Nauki** 1985;(11):56-61 (Eng. Abstr.) **(Rus)**

[Reactivity of the cholinoceptive cortical neurons to the repeated action of acetylcholine] Kotliar BI, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):259-60 (Eng. Abstr.) **(Rus)**

ACHIEVEMENT

Assessing drug effects on academic performance. Gadow KD, et al. **Psychopharmacol Bull** 1985;21(4):877-86

AFFECT

Acute effects of physostigmine and neostigmine in man. Janowsky DS, et al. **Milit Med** 1986 Jan;151(1):48-51

Hormonal and behavioral effects associated with intravenous L-tryptophan administration. Winokur A, et al. **Psychopharmacology (Berlin)** 1986;88(2):213-9

AFFECTIVE DISORDERS

Neuroendocrine effects of carbamazepine in patients with affective illness. Joffe RT, et al. **Epilepsia** 1986 Mar-Apr;27(2):156-60

Chocolate, eating disorders, and affective syndromes [letter] Zimmer B, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):56-7

Investigations of melatonin secretion in man. Grof E, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):609-12

Effect of carbamazepine on mean urinary free cortisol excretion in patients with major affective illness. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1986;88(1):115-8

[Course and form variations of cyclothymic phases in lithium therapy] Banzhaf M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Dec;37(12):718-21 (Eng. Abstr.) **(Ger)**

AFFECTIVE DISORDERS, PSYCHOTIC

The prophylactic lithium treatment in affective disorders and the possibilities of the outcome prediction. Hanuš H, et al. **Sb Ved Pr Lek Fak Univ Karlovy** 1984;27(1):5-75

[The circulatory system in patients with depression during treatment with antidepressive drugs. I. Analysis of ECG records during the depressive phase of affective diseases] Rajewska J, et al. **Psychiatr Pol** 1985 Jul-Aug;19(4):271-7 (Eng. Abstr.) **(Pol)**

AGGRESSION

Predatory dominance and aggressive display under imipramine treatment in cats. Zagrodzka J, et al. **Acta Neurobiol Exp (Warsz)** 1985;45(5-6):137-49

Dopaminergic facilitation of recovery from amygdaloid lesions which affect hypothalamic defensive attack in cats. Maeda H, et al. **Brain Res** 1986 Jan 15;363(1):135-40

A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrenic patients. Tuason VB. **J Clin Psychiatry** 1986 Mar;47(3):126-9

The effects of marijuana on human physical aggression. Myerscough R, et al. **J Pers Soc Psychol** 1985 Dec;49(6):1541-6

Antagonism of picrotoxin against the taming effect of carbamazepine on footshock induced fighting behavior in mice. Nakao K, et al. **Jpn J Pharmacol** 1985 Oct;39(2):281-3

Therapeutic experience with lithium in childhood aggressivity. Vetró A, et al. **Neuropsychobiology** 1985;14(3):121-7

Must antidepressants be anticholinergic to inhibit muricide? Strickland JA, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):135-7

The effects of apomorphine, d-amphetamine and chlorpromazine on the aggressiveness of isolated Aequidens pulcher (Teleostei, Cichlidae).

Munro AD. **Psychopharmacology (Berlin)** 1986;88(1):124-8

Maternal aggression in rats: lack of interaction between chlordiazepoxide and fluprazine. Olivier B, et al. **Psychopharmacology (Berlin)** 1986; 88(1):40-3

AMINO ACIDS

Tryptophan to competing amino acids ratio in depressive disorder: relation to efficacy of antidepressive treatments. Møller SE. **Acta Psychiatr Scand [Suppl]** 1985;325:3-31 (146 ref.)

Inhibitory neuromodulation of release of amino acid neurotransmitters. Peris J, et al. **Alcohol Drug Res** 1985-86;6(4):253-64 (61 ref.)

Effect of intragastric amino acids on lower esophageal sphincter pressure and serum gastrin in man. McCallum RW, et al. **Am J Gastroenterol** 1986 Mar;81(3):168-71

Role of CCK in pancreatic exocrine response to amino acids and fats [letter] Singer MV. **Am J Physiol** 1986 Apr;250(4 Pt 1):G558-9

Plasma neutral amino acids and food preferences: possible implications in normals and depressives. Møller SE. **Bibl Nutr Dieta** 1986; (38):149-53

Transport of the aromatic amino acids into isolated rat liver cells. Properties of uptake by two distinct systems. Salter M, et al. **Biochem J** 1986 Jan 15;233(2):499-506

Action of excitatory amino acids and their antagonists on hippocampal neurons. Hablitz JJ. **Cell Mol Neurobiol** 1985 Dec;5(4):389-405

Modulatory effect of glucose, amino acids, and secretin on CCK-8-induced somatostatin and pancreatic polypeptide release in dogs. Schusdziarra V, et al. **Diabetes** 1986 May;35(5):523-9

Changes in gamma-aminobutyrate, glutamate, aspartate, glycine, and taurine contents in the striatum after unilateral nigrostriatal lesions in rats. Tanaka Y, et al. **Exp Neurol** 1986 Feb;91(2):259-68

Influence of medium amino acids on the ouabain sensitive and insensitive 86Rb+-fluxes in HeLa cells. Schaefer A, et al. **Experientia** 1986 Apr 15;42(4):436-7

Amino acid neurotransmitters in the CNS. Characteristics of the acidic amino acid exchange. Erecińska M, et al. **FEBS Lett** 1986 Apr 7; 199(1):95-9

Evidence for an excitatory amino acid as the transmitter of the auditory nerve in the in vitro mouse cochlear nucleus. Martin MR. **Hear Res** 1985;20(3):215-20

Rat brain concentration of administered amino acids: dependence on time of day for administration. Eriksson T, et al. **J Neural Transm** 1986; 65(1):83-91

Amino acid analysis demonstrates that increased plasma free tryptophan causes the increase of brain tryptophan during exercise in the rat. Chaouloff F, et al. **J Neurochem** 1986 May;46(5):1647-50

Effect of some centrally administered putative amino acid neurotransmitters on carrageenan-induced paw oedema in rats. Bhattacharya SK, et al. **J Pharm Pharmacol** 1986 Feb;38(2):144-6

Effect of 450191-S, a 1H-1,2,4-triazolyl benzophenone derivative, on cerebral content of neuroactive amino acids. Tomono S, et al. **Jpn J Pharmacol** 1985 Dec;39(4):558-61

Ouabain-induced changes in extracellular aspartate, glutamate and GABA levels in the rabbit olfactory bulb in vivo. Jacobson I, et al. **Neurosci Lett** 1986 Feb 28;64(2):211-5

Effects of amino acid neurotransmitter candidates on an identified insect motoneurone. Wafford KA, et al. **Neurosci Lett** 1986 Jan 16; 63(2):135-40

Plasma tryptophan and tyrosine ratios to competing amino acids in relation to antidepressant response to citalopram and maprotiline. A preliminary study. Møller SE, et al. **Psychopharmacology (Berlin)** 1986; 88(1):96-100

Excitatory amino acid analogs evoke release of endogenous amino acids and acetyl choline from chick retina in vitro. Campochiaro P, et al. **Vision Res** 1985;25(10):1375-86

[Interaction between chlorpromazine, hepatic protective agents and enzymes at the level of the liver cytoplasm and mitochondria and of the cerebral cortex in rats] Serban F, et al. **Rev Med Chir Soc Med Nat Iasi** 1985 Apr-Jun;89(2):273-7 (Eng. Abstr.) **(Rum)**

AMITRIPTYLINE

Overdose of cyclobenzaprine, the tricyclic muscle relaxant. O'Riordan W, et al. **Ann Emerg Med** 1986 May;15(5):592-3

Anorexia nervosa. Treatment efficacy of cyproheptadine and amitriptyline. Halmi KA, et al. **Arch Gen Psychiatry** 1986 Feb; 43(2):177-81

Imipramine and amitriptyline plasma concentrations and clinical response in major depression. Kocsis JH, et al. **Br J Psychiatry** 1986 Jan; 148:52-7

Bifunctional variations of the antidepressant amitriptyline theme. Asscher Y, et al. **Chem Pharm Bull (Tokyo)** 1985 Nov;33(11):4847-55

Changes of transition temperatures of phosphatidylcholine and phosphatidylglycerol in presence of amphiphilic drugs. Harder A, et al. **Chem Phys Lipids** 1986 Jan;39(1-2):65-71

Amitriptyline metabolism: association with debrisoquin hydroxylation in nonsmokers. Mellström B, et al. **Clin Pharmacol Ther** 1986 Apr; 39(4):369-71

Cimetidine interaction with amitriptyline. Curry SH, et al. **Eur J Clin Pharmacol** 1985;29(4):429-33

Moclobemide, a new reversible MAO inhibitor—interaction with tyramine and tricyclic antidepressants in healthy volunteers and depressive patients. Korn A, et al. **Psychopharmacology (Berlin)** 1986; 88(2):153-7

Inhibition of head twitch response to quipazine in rats by chronic amitriptyline but not fluvoxamine or citalopram. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1986;88(3):279-84

AMPHETAMINE

Effect of amphetamine on brain catecholamines, brain beta-endorphin, serum prolactin, catechol-O-methyltransferase and monoamine oxidase of various organs in the rat. Agarwal DP, et al. **Arzneimittelforschung** 1985;35(11):1639-42

Drug effects on memory: assessment of a combined active and passive avoidance task. Sahgal A, et al. **Behav Brain Res** 1985 Oct; 17(3):251-5

Pharmaco-ontogeny of reward: enhancement of self-stimulation by D-amphetamine and cocaine in 3- and 10-day-old rats. Barr GA, et al. **Brain Res** 1986 Jan;389(1-2):193-202

Multiple amphetamine injections reduce the release of ascorbic acid in the neostriatum of the rat. Kamata K, et al. **Brain Res** 1986 Jan 8; 362(2):331-8

Locus coeruleus norepinephrine-containing neurons: effects produced by acute and subchronic treatment with antipsychotic drugs and amphetamine. Ramirez OA, et al. **Brain Res** 1986 Jan 1; 362(1):165-70

Differences in amphetamine and morphine sensitivity in lateralized and non-lateralized rats: locomotor activity and drug self-administration. Glick SD, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):239-44

Study on the mechanism of the long-lasting antagonistic effect of caerulein on amphetamine-induced hyperactivity in rats. Matsubara K, et al. **Gen Pharmacol** 1986;17(1):13-7

Synthesis, identification, and acute toxicity of alpha-benzylphenethylamine and alpha-benzyl-N-methylphenethylamine. Contaminants in clandestine preparation of amphetamine and methamphetamine. Noggle FT Jr, et al. **J Assoc Off Anal Chem** 1985 Nov-Dec;68(6):1213-22

Dose response for amphetamine-induced changes in dopamine levels in push-pull perfusates of rat striatum. Kuczenski R. **J Neurochem** 1986 May;46(5):1605-11

Amphetamine-induced circling behaviour in MPTP-lesioned mice. Fung YK, et al. **J Pharm Pharmacol** 1985 Dec;37(12):922-3

Possible involvement of the central nervous system in long-term effect of caerulein on amphetamine-induced hyperactivity in rats. Matsubara K, et al. **Jpn J Pharmacol** 1985 Nov;39(3):317-21

Neuropathology and amphetamine-induced turning resulting from AF64A injections into the striatum of the rat. Stwertka SA, et al. **Life Sci** 1986 Mar 24;38(12):1105-10

Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. Young R, et al. **Med Res Rev** 1986 Jan-Mar; 6(1):99-130 (74 ref.)

Amphetamine potentiation of anti-conflict action of chlordiazepoxide. Lerner T, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):241-6

Comparison of the effects of amphetamine and a fluorinated analogue on locomotion and exploratory activity in the mouse. Dubin RE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):681-5

Brain adenylate cyclase activity in the amphetamine sensitized rat. Mamelak M, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):721-4

Effects of amphetamine and apomorphine on locomotor activity after kainic acid lesion of the nucleus accumbens septi in the rat. Kafetzopoulos E. **Psychopharmacology (Berlin)** 1986;88(3):271-4

Amphetamine, apomorphine and investigatory behavior in the rat: analysis of the structure and pattern of responses. Kelley AE, et al. **Psychopharmacology (Berlin)** 1986;88(1):66-74

Amphetamine does not affect the partial punishment effect (PPE). Weiner I, et al. **Psychopharmacology (Berlin)** 1986;88(1):119-23

AMPHETAMINES

Serotonin receptor involvement in the avoidance learning deficit caused by p-chloroamphetamine-induced serotonin release. Ogren SO. **Acta Physiol Scand** 1986 Mar;126(3):449-62

Elimination of labetalol-induced false positives in drug analyses [letter] Wu A, et al. **Clin Chem** 1986 Feb;32(2):407

Evidence for specific methylenedioxymethamphetamine (ecstasy) binding sites in the rat brain. Gehlert DR, et al. **Eur J Pharmacol** 1985 Dec 10;119(1-2):135-6

[3H]DOB: a specific agonist radioligand for 5-HT2 serotonin receptors. Titeler M, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):145-6

Fluoxetine enantiomers as antagonists of p-chloroamphetamine effects in rats. Fuller RW, et al. **Pharmacol Biochem Behav** 1986 Feb;

24(2):281–4

Comparison of the effects of amphetamine and a fluorinated analogue on locomotion and exploratory activity in the mouse. Dubin RE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):681–5

[Rapid and simple determination of methamphetamine and amphetamine in urine and serum by gas chromatography using the flame-thermionic detector] Kotoku S, et al. **Nippon Hoigaku Zasshi** 1985 Apr; 39(2):143–8 (Eng. Abstr.) **(Jpn)**

ANOREXIA NERVOSA

The treatment of anorexia nervosa. Hsu LK. **Am J Psychiatry** 1986 May; 143(5):573–81 (97 ref.)

Anorexia nervosa. Treatment efficacy of cyproheptadine and amitriptyline. Halmi KA, et al. **Arch Gen Psychiatry** 1986 Feb; 43(2):177–81

High affinity [3H]imipramine binding and serotonin uptake to platelets of adolescent females suffering from anorexia nervosa. Weizman R, et al. **Life Sci** 1986 Mar 31;38(13):1235–42

ANTIDEPRESSIVE AGENTS

Cortical beta- and alpha 2- adrenoceptor binding, hypothalamic noradrenaline and pineal melatonin concentrations measured at different times of the day after repeated treatment of rats with imipramine, zimeldine, alaproclate and amiflamine. Ask AL, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Jan;58(1):16–24

A Belgian multicentre study of fluvoxamine in depressive outpatients. Brasseur R, et al. **Acta Psychiatr Belg** 1985 Sep–Oct;85(5):636–43

Sleep, depression and the effects of antidepressant drugs. Gaillard JM, et al. **Acta Psychiatr Belg** 1985 Sep–Oct;85(5):561–7

Tryptophan to competing amino acids ratio in depressive disorder: relation to efficacy of antidepressive treatments. Møller SE. **Acta Psychiatr Scand [Suppl]** 1985;325:3–31 (146 ref.)

Drugs and depression. Harris B. **Am J Nurs** 1986 Mar;86(3):292–3

A possible synergistic effect of alprazolam and lithium carbonate [letter] Cerra D, et al. **Am J Psychiatry** 1986 Apr;143(4):552

Patient with chronic and apparently treatment-resistant dysthymia [letter] Harris SJ, et al. **Am J Psychiatry** 1986 Feb;143(2):260–1

Lithium-antidepressant combinations in the treatment of depressed, physically ill geriatric patients. Kushnir SL. **Am J Psychiatry** 1986 Mar; 143(3):378–9

Combined psychotherapy and pharmacotherapy for depression. A systematic analysis of the evidence. Conte HR, et al. **Arch Gen Psychiatry** 1986 May;43(5):471–9

Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Keller MB, et al. **Arch Gen Psychiatry** 1986 May;43(5):458–66

Effect of the antidepressant minaprine on both forms of monoamine oxidase in the rat. Kan JP, et al. **Biochem Pharmacol** 1986 Mar 15; 35(6):973–8

Plasma concentrations, information and therapy adherence during long-term treatment with antidepressants. Altamura AC, et al. **Br J Clin Pharmacol** 1985 Dec;20(6):714–6

Adverse drug reactions to first- and second-generation antidepressants: a critical evaluation of drug surveillance data. Schmidt LG, et al. **Br J Psychiatry** 1986 Jan;148:38–43

A comparison of the safety and efficacy of alprazolam and desipramine in moderately severe depression. Remick RA, et al. **Can J Psychiatry** 1985 Dec;30(8):597–601

Bifunctional variations of the antidepressant amitriptyline theme. Asscher Y, et al. **Chem Pharm Bull (Tokyo)** 1985 Nov;33(11):4847–55

Syntheses of (+/-)-2-[(inden-7-yloxy)methyl]morpholine hydrochloride (YM-08054, indeloxazine hydrochloride) and its derivatives with potential cerebral-activating and antidepressive properties. Kojima T, et al. **Chem Pharm Bull (Tokyo)** 1985 Sep;33(9):3766–74

The psychopharmacological effects of repeated doses of fluvoxamine, mianserin and placebo in healthy human subjects. Curran HV, et al. **Eur J Clin Pharmacol** 1986;29(5):601–7

Metabolism of the anti-depressant lortalamine. Elsom LF, et al. **Eur J Drug Metab Pharmacokinet** 1985 Jul–Sep;10(3):209–15

Effects of antidepressant drug combinations on cortical 5-HT2 receptors and wet-dog shakes in rats. Koshikawa F, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):273–81

Antidepressant drugs given repeatedly increase binding to alpha 1-adrenoceptors in the rat cortex. Maj J, et al. **Eur J Pharmacol** 1985 Dec 10;119(1–2):113–6

Antidepressants and protein kinases: desipramine treatment affects pineal gland cAMP-dependent protein kinase activity. Moyer JA, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):57–64

Typical and atypical antidepressant drug effects on locomotor activity after intra-accumbens injections in the rat. Oosterloo SK, et al. **Eur J Pharmacol** 1985 Nov 26;118(1–2):45–51

Antidepressive drugs can change the affinity of [3H]imipramine and [3H]paroxetine binding to platelet and neuronal membranes. Plenge P, et al. **Eur J Pharmacol** 1985 Dec 10;119(1–2):1–8

Antidepressants and protein kinases: inhibition of Ca2+-regulated myosin phosphorylation by fluoxetine and iprindole. Silver PJ, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):65–71

Circadian rhythm stability in the depressive syndrome in patients treated with antidepressant drugs. Madjirova N. **Folia Med (Plovdiv)** 1985; 27(1):5–10

Present status of drug therapy of depression in late life. Gerner RH. **J Affective Disord** 1985;Suppl 1:S23–31 (67 ref.)

Determination of fezolamine and its desmethyl metabolite in human plasma and urine by high-performance liquid chromatography. Intravenous pharmacokinetics in the beagle hound. McCoy L, et al. **J Chromatogr** 1985 Nov 8;344:211–20

Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. Feighner J, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):27–32

Alprazolam treatment of postcoronary bypass anxiety and depression. Freeman AM 3d, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):39–41

Down-regulation of dopamine D-2, 5-HT2 receptors and beta-adrenoceptors in rat brain after prolonged treatment with a new potential antidepressant, Lu 19-005. Nowak G, et al. **J Neural Transm** 1985;64(3–4):227–38

Chronic treatment with the potential antidepressant drug rolipram: the effect on the behavioural responses to adrenergic and dopaminergic receptor agonists with some biochemical correlates. Przegaliński E, et al. **J Neural Transm** 1985;64(3–4):211–26

Interaction between antidepressants and alpha 1-adrenergic receptor antagonists on the binding to alpha 1-acid glycoprotein. Ferry DG, et al. **J Pharm Sci** 1986 Feb;75(2):146–9

13C NMR studies of the molecular flexibility of antidepressants. Munro SL, et al. **J Pharm Sci** 1986 Feb;75(2):133–41

Effects of bifemelane hydrochloride (MCI-2016) on acetylcholine and norepinephrine release from cortical slices of bilaterally carotid-artery-ligated Mongolian gerbils. Saito K, et al. **Jpn J Pharmacol** 1985 Nov;39(3):406–9

Effects of bifemelane hydrochloride (MCI-2016) on acetylcholine release from cortical and hippocampal slices of rats. Saito K, et al. **Jpn J Pharmacol** 1985 Nov;39(3):410–4

Effects of bifemelane hydrochloride (MCI-2016) on experimental amnesia (passive avoidance failure) in rodents. Tobe A, et al. **Jpn J Pharmacol** 1985 Oct;39(2):153–61

Biochemical profile of midalcipran (F 2207), 1-phenyl-1-diethyl-aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug. Moret C, et al. **Neuropharmacology** 1985 Dec;24(12):1211–9

Must antidepressants be anticholinergic to inhibit muricide? Strickland JA, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):135–7

Action of antidepressant neuroleptics, chlorprothixene and levomepromazine, on the central noradrenergic system: comparison with other antidepressants. Antkiewicz-Michaluk L. **Pol J Pharmacol Pharm** 1985 Sep–Oct;37(5):673–83

Possible relationship of the locus coeruleus--hippocampal noradrenergic neurons to depression and mode of action of antidepressant drugs. Kostowski W. **Pol J Pharmacol Pharm** 1985 Nov–Dec;37(6):727–43 (57 ref.)

Effects of antidepressants on uptake and receptor systems in the brain. Fuller RW, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5–6):485–90 (22 ref.)

Platelet 3H imipramine binding: a possible predictor of response to antidepressant treatment. Hrdina PD, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):619–23

Course of clinical response to antidepressants. Lapierre YD. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):503–7

Variability of chronic antidepressant treatments on beta-adrenergic receptor sites. Suranyi-Cadotte BE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):765–8

Effects of subchronic administration of psychoactive substances on the circadian rhythm of urinary corticosterone excretion in rats. Häusler A, et al. **Psychoneuroendocrinology** 1985;10(4):421–9

Colour associations as predictors of the effectiveness of anti-depressant pharmacotherapy in endogenous depressive patients. Demeter E, et al. **Psychopathology** 1985;18(5–6):305–9

Scales of potential use in the psychopharmacologic treatment of depressed children and adolescents. Petti TA. **Psychopharmacol Bull** 1985; 21(4):951–77

The effects of some putative antidepressant agents on the schedule-controlled behavior of the pigeon. Lamb RJ, et al. **Psychopharmacology (Berlin)** 1986;88(3):368–73

Plasma tryptophan and tyrosine ratios to competing amino acids in relation to antidepressant response to citalopram and maprotiline. A preliminary study. Møller SE, et al. **Psychopharmacology (Berlin)** 1986; 88(1):96–100

Effects of antidepressant drugs, selective noradrenaline-or 5-hydroxytryptamine uptake inhibitors, on apomorphine-induced hypothermia in mice. Pawłowski L, et al. **Psychopharmacology (Berlin)** 1986;88(2):240–6

[Novel comparative profile of the clinical activity of antidepressive agents] Ansseau M, et al. **Acta Psychiatr Belg** 1985 Sep–Oct;85(5):644–61 (Eng.

Abstr.) **(Fre)**

[Resistant depressions in chronicity phase. Clinical and pharmacological aspects. Apropos of 25 cases] Houillon P, et al. **Ann Med Psychol (Paris)** 1985 Jul;143(7):628–33 **(Fre)**

[A serotoninergic antidepressive, indalpine] Rigal J. **Ann Med Psychol (Paris)** 1985 Jul;143(7):664–76 **(Fre)**

[The effects of new (dialkoxy–2,3–phenyl) methylhydrazides and their N–benzyl derivatives on rats and mice subjected to a variety of tests in relation to antidepressive effect] Papadaki–Valiraki A, et al. **Ann Pharm Fr** 1985;43(2):155–60 (Eng. Abstr.) **(Fre)**

[Hematologic effects associated with taking indalpine. Cooperative study by French drug surveillance centers] Castot A, et al. **Therapie** 1985 Sep–Oct;40(5):337–41 (Eng. Abstr.) **(Fre)**

[Possibilities and limitations of treating depressive disorders in practice] Gastpar M. **Ther Umsch** 1986 Jan;43(1):50–5 (Eng. Abstr.) **(Ger)**

[Antidepressant drugs and central monoaminergic receptors] Asakura M, et al. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):303–19 (143 ref.) (Eng. Abstr.) **(Jpn)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. II. Comparison of the effects of various thymoleptics on the psychopathological symptoms of endogenous depressive syndromes] Strzyżewski W, et al. **Psychiatr Pol** 1985 Sep–Oct;19(5):363–9 (Eng. Abstr.) **(Pol)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. III. Analysis of the factors affecting the effectiveness of treatment with thymoleptics] Twarowska–Hauser J, et al. **Psychiatr Pol** 1985 Sep–Oct;19(5):370–5 (Eng. Abstr.) **(Pol)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. I. Analysis of the clinical effect of antidepressive drugs with various pharmacological profiles] Twarowska–Hauser J, et al. **Psychiatr Pol** 1985 Sep–Oct; 19(5):357–62 (Eng. Abstr.) **(Pol)**

[Stages in the development of neuroses in the dog and effects of preparations with antidepressive and tranquilizing properties] Mekhedova AIa, et al. **Zh Vyssh Nerv Deiat** 1985 Nov–Dec; 35(6):1147–55 (Eng. Abstr.) **(Rus)**

ANXIETY

The neuropsychology of anxiety. Gray JA. **Issues Ment Health Nurs** 1985; 7(1–4):201–28

The universal enervating triad: psychopharmaceutical considerations of anxiety, schizophrenia, and depression. Miller TW, et al. **Issues Ment Health Nurs** 1984;6(3–4):275–91

Reversibility of serotonin irritation syndrome with atmospheric anions. Giannini AJ, et al. **J Clin Psychiatry** 1986 Mar;47(3):141–3

Alprazolam treatment of postcoronary bypass anxiety and depression. Freeman AM 3d, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):39–41

An open clinical trial of clonazepam in the treatment of patients with recurrent panic attacks. Beaudry P, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):589–92

Buspirone: anxiolytic? Pecknold JC, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):639–42

Relaxation–induced anxiety: additional findings. McKeachie WJ. **Psychol Rep** 1985 Dec;57(3 Pt 2):1277–8

The effects of compounds related to gamma–aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: extinction and successive discrimination. Buckland C, et al. **Psychopharmacology (Berlin)** 1986;88(3):285–95

Differential effect of benzodiazepine sedation in high and low anxious patients in a 'real life' stress setting. O'Boyte CA, et al. **Psychopharmacology (Berlin)** 1986;88(2):226–9

Plasma catecholamines at rest and exercise in subjects with high– and low–trait anxiety. Péronnet F, et al. **Psychosom Med** 1986 Jan–Feb; 48(1–2):52–8

ANXIETY DISORDERS

Double–blind comparison of buspirone and clorazepate in anxious outpatients. Cohn JB, et al. **Am J Med** 1986 Mar 31;80(3B):10–6

Neuroendocrine effects of buspirone in patients with generalized anxiety disorder. Cohn JB, et al. **Am J Med** 1986 Mar 31;80(3B):36–40

Clonazepam in the treatment of patients with recurrent panic attacks. Beaudry P, et al. **J Clin Psychiatry** 1986 Feb;47(2):83–5

Effective short–term treatment of generalized anxiety disorder with trifluoperazine. Mendels J, et al. **J Clin Psychiatry** 1986 Apr; 47(4):170–4

One–year follow–up of anxious patients treated with diazepam. Rickels K, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):32–6

The epidemiology of anxiety. Reich J. **J Nerv Ment Dis** 1986 Mar; 174(3):129–36 (85 ref.)

Forms of atypical depression and their response to antidepressant drugs. Davidson J, et al. **Psychiatry Res** 1986 Feb;17(2):87–95

What do the neurosciences tell us about anxiety disorders? A comment. Marks I, et al. **Psychol Med** 1986 Feb;16(1):9–12

[Psychiatric indications for beta–adrenergic inhibitors] Féline A, et al. **Therapie** 1985 Nov–Dec;40(6):413–6 (Eng. Abstr.) **(Fre)**

[Indicative patterns of the use of anxiolytic agents in pharmacies and the severity of symptoms] de Matos EG, et al. **AMB** 1985 Jul–Aug; 31(7–8):116–20 (Eng. Abstr.) **(Por)**

APOMORPHINE

Dopamine agonist treatment of schizophrenia with N–propylnorapomorphine. Tamminga CA, et al. **Arch Gen Psychiatry** 1986 Apr;43(4):398–402

Effect of forebrain commissurotomy on recovery from unilateral 6–OHDA lesions of the substantia nigra and circling induced by apomorphine. Steiner H, et al. **Behav Brain Res** 1985 Oct; 17(3):245–9

Mouse strain differences in apomorphine–induced behavior: an empirical and methodological study. Randall PK, et al. **Behav Neurosci** 1986 Feb; 100(1):85–92

Oscillations in apomorphine–induced stereotypies during 1 year of apomorphine administration. Csernansky JG, et al. **Biol Psychiatry** 1986 Apr;21(4):402–5

Behavior performed at onset of drug action and apomorphine stereotypy. Szechtman H. **Eur J Pharmacol** 1986 Feb 11;121(1):49–56

CCK–8 antagonizes apomorphine–induced growth hormone secretion in normal subjects. Nair NP, et al. **Horm Metab Res** 1986 Jan; 18(1):53–5

Concentration–response relations for apomorphine effects on heart rate in conscious rats. Paalzow LK, et al. **J Pharm Pharmacol** 1986 Jan; 38(1):28–34

Effect of subchronic treatment with methamphetamine on apomorphine–induced changes in locomotor activity in mice. Watanabe H, et al. **Jpn J Pharmacol** 1986 Jan;40(1):185–7

A comparative study of the locomotor activity effects of apomorphine and the 'atypical dopamine agonists' (piribedil and S3608). Offermeier J, et al. **Life Sci** 1986 Mar 10;38(10):895–903

Lateralized and compulsive exteroceptive orientation in rats treated with apomorphine. Pisa M, et al. **Neurosci Lett** 1986 Feb 14;64(1):41–6

Modulation of apomorphine–induced climbing behavior by estradiol. Fung YK, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):139–41

Different behavioural patterns induced by the dopamine agonist apomorphine analysed by multivariate statistics. Ståhle L, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):291–8

Lateralizing effects of apomorphine on taxis, postural support and rotation in rats. Pisa M, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5–6):525–31

Effects of amphetamine and apomorphine on locomotor activity after kainic acid lesion of the nucleus accumbens septi in the rat. Kafetzopoulos E. **Psychopharmacology (Berlin)** 1986;88(3):271–4

Amphetamine, apomorphine and investigatory behavior in the rat: analysis of the structure and pattern of responses. Kelley AE, et al. **Psychopharmacology (Berlin)** 1986;88(1):66–74

The effects of apomorphine, d–amphetamine and chlorpromazine on the aggressiveness of isolated Aequidens pulcher (Teleostei, Cichlidae). Munro AD. **Psychopharmacology (Berlin)** 1986;88(1):124–8

Effects of antidepressant drugs, selective noradrenaline–or 5–hydroxytryptamine uptake inhibitors, on apomorphine–induced hypothermia in mice. Pawłowski L, et al. **Psychopharmacology (Berlin)** 1986;88(2):240–6

Effects of central dopamine depletion on the d–amphetamine discriminative stimulus in rats. Woolverton WL, et al. **Psychopharmacology (Berlin)** 1986;88(2):196–200

[The effect of various new GABAergics on motor and oral stereotypes with apomorphine in the rat] Vamvakidès A, et al. **J Pharmacol** 1985 Oct–Dec;16(4):403–11 (Eng. Abstr.) **(Fre)**

APPETITE

Interference with central actions of angiotensin II suppresses sodium appetite. Weiss ML, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 2):R250–9

Running to the taste of salt in mineralocorticoid–treated rats. Schulkin J, et al. **Horm Behav** 1985 Dec;19(4):413–25

AROMATIC AMINO ACID DECARBOXYLASES

A diphenol oxidase gene is part of a cluster of genes involved in catecholamine metabolism and sclerotization in Drosophila. II. Molecular localization of the Dox–A2 coding region. Pentz ES, et al. **Genetics** 1986 Apr;112(4):843–59

AROUSAL

The effect of phobic anxiety on plasma beta–endorphin: a single–subject experiment. Thyer BA, et al. **Behav Res Ther** 1986;24(2):237–41

Acute effects of physostigmine and neostigmine in man. Janowsky DS, et al. **Milit Med** 1986 Jan;151(1):48–51

Effect of hypoxia on ventilatory and arousal responses to CO2 during NREM sleep with and without flurazepam in young adults. Gothe B, et al. **Sleep** 1986;9(1):24-37

[Mechanisms of action of noise] Ising H. **Schriftenr Ver Wasser Boden Lufthyg** 1985;65:413-24 **(Ger)**

ASSOCIATION

Colour associations as predictors of the effectiveness of anti-depressant pharmacotherapy in endogenous depressive patients. Demeter E, et al. **Psychopathology** 1985;18(5-6):305-9

ATTENTION

6-Hydroxydopamine treatment does not affect the young rat's ability to modify its response when changing from food to water deprivation. Brenner E, et al. **Behav Brain Res** 1986 Jan;19(1):89-92

Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. Sebrechts MM, et al. **Pediatrics** 1986 Feb;77(2):222-8

ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY

Methylphenidate treatment of cocaine abusers without attention deficit disorder: a negative report. Gawin F, et al. **Am J Drug Alcohol Abuse** 1985;11(3-4):193-7

Prediction of methylphenidate (Ritalin) responsiveness through sensory integrative testing. Kimball JG. **Am J Occup Ther** 1986 Apr; 40(4):241-8

Pemoline and urinary excretion of catecholamines and indoleamines in children with attention deficit disorder. Zametkin AJ, et al. **Am J Psychiatry** 1986 Mar;143(3):359-62

Behavioral effects of low-dose methylphenidate in childhood attention deficit disorder: implications for a mechanism of stimulant drug action. Solanto MV. **J Am Acad Child Psychiatry** 1986 Jan;25(1):96-101

Short term effects of methylphenidate on the cognitive, learning and academic performance of children with attention deficit disorder in the laboratory and the classroom. Douglas VI, et al. **J Child Psychol Psychiatry** 1986 Mar;27(2):191-211

Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. Sebrechts MM, et al. **Pediatrics** 1986 Feb;77(2):222-8

Clinical management of children with hyperactivity. A shift in diagnostic and therapeutic emphasis. Hesterly SO. **Postgrad Med** 1986 Apr; 79(5):299-305

AUDITORY PERCEPTION

Simulation of mechanical to neural transduction in the auditory receptor. Meddis R. **J Acoust Soc Am** 1986 Mar;79(3):702-11

AUTISM, INFANTILE

Dopamine-beta-hydroxylase (DBH) and homovanillic acid (HVA) in autistic children. Garnier C, et al. **J Autism Dev Disord** 1986 Mar; 16(1):23-9

Further speculations on possible dopamine-opioid link in autism [letter] Sandyk R. **J Autism Dev Disord** 1986 Mar;16(1):89-90

Fenfluramine and autism: careful reappraisal is in order [editorial] Gualtieri CT. **J Pediatr** 1986 Mar;108(3):417-9

Behavioral and cognitive measures used in psychopharmacological studies of infantile autism. Campbell M, et al. **Psychopharmacol Bull** 1985; 21(4):1047-53

AVOIDANCE LEARNING

Serotonin receptor involvement in the avoidance learning deficit caused by p-chloroamphetamine-induced serotonin release. Ogren SO. **Acta Physiol Scand** 1986 Mar;126(3):449-62

Evidence for a role of brain serotonergic neurotransmission in avoidance learning. Ogren SO. **Acta Physiol Scand [Suppl]** 1985;544:1-71

Place-aversion conditioned by phencyclidine in rats: development of tolerance and pharmacologic antagonism. Iwamoto ET. **Alcohol Drug Res** 1985-86;6(4):265-76

Interaction between nootropic drugs and methamphetamine on avoidance acquisition but not on locomotor activity in mice. Sansone M, et al. **Arch Int Pharmacodyn Ther** 1985 Dec;278(2):229-35

Drug effects on memory: assessment of a combined active and passive avoidance task. Sahgal A, et al. **Behav Brain Res** 1985 Oct; 17(3):251-5

Deficits in inhibitory avoidance after neurotoxic lesions of the ventral striatum are neurochemically and behaviorally selective. Schwarting R, et al. **Behav Brain Res** 1985 Dec;18(3):279-83

Disruption of neophobia, conditioned odor aversion, and conditioned taste aversion in rats with hippocampal lesions. Miller JS, et al. **Behav Neural Biol** 1986 Mar;45(2):240-53

Brief exposure to contingent reinforcement produces a sustained increment in the strength of an elicited response. Hutchinson RR, et al. **J Exp Anal Behav** 1986 Mar;45(2):189-94

Effects of bifemelane hydrochloride (MCI-2016) on experimental amnesia (passive avoidance failure) in rodents. Tobe A, et al. **Jpn J Pharmacol** 1985 Oct;39(2):153-61

Discriminative and aversive properties of beta-carboline-3-carboxylic acid ethyl ester, a benzodiazepine receptor inverse agonist, in rhesus monkeys. Takada K, et al. **Life Sci** 1986 Mar 17;38(11):1049-56

Conditioned taste aversions and changes in motor activity in lithium-treated rats. Mediating role of the area postrema. Ladowsky RL, et al. **Neuropharmacology** 1986 Jan;25(1):71-7

Shuttle-box deficits induced by inescapable shocks in rats: reversal by the beta-adrenoreceptor stimulants clenbuterol and salbutamol. Martin P, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):177-81

Effect of angiotensin II on passive avoidance performance after bilateral lesion of the nucleus accumbens septi. Winnicka MM, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):897-901

Conditioned taste aversions induced by 1-5-hydroxytryptophan are mediated by the area postrema. Ossenkopp KP, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):745-8

Serotonin, septal lesions, and shock-escape learning in rats. Mattingly BA, et al. **Psychol Rep** 1986 Feb;58(1):3-9

Effects of lithium and rubidium on shock-induced changes in open-field activity. Hines G. **Psychopharmacology (Berlin)** 1986;88(2):209-12

Effects of propranolol on conditioned suppression, discriminated punishment and discriminated non-reward in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1986;88(2):252-7

Effects of diazepam and pentobarbital on discrete lever-press avoidance response in mice: baseline-dependent changes. Kuribara H, et al. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):343-8

AZEPINES

The effects of dilazep on reperfusion arrhythmias. Sugiyama S, et al. **Arzneimittelforschung** 1985;35(12):1802-4

Reversibility of granulocyte adhesion using polyamine-grafted nylon-6 as a new column substrate for granulocyte separation. Yui N, et al. **Biomaterials** 1985 Nov;6(6):409-15

B-HT 958 lowers blood pressure and heart rate in the rat through stimulation of dopamine receptors. Brown MJ, et al. **Br J Pharmacol** 1986 Feb;87(2):361-70

A single-dose pharmacokinetic study of the antisickling agent cetiedil. Orringer EP, et al. **Clin Pharmacol Ther** 1986 Mar;39(3):276-81

Brotizolam radioimmunoassay: development, evaluation, and application to human plasma samples. Bechtel WD, et al. **J Pharm Sci** 1985 Dec; 74(12):1265-9

Enhancing effect of absorption promoters on percutaneous absorption of a model dye (6-carboxyfluorescein) as poorly absorbable drugs. II. Study on the absorption promoting effect of azone. Ohshima T, et al. **J Pharmacobiodyn** 1985 Nov;8(11):900-5

Effects of the antiplatelet agents, dipyridamole and dilazep dihydrochloride, on in vivo platelet function and proteinuria. Inage H, et al. **Nippon Jinzo Gakkai Shi** 1985 Sep;27(9):1261-70

Effects of dilazep dihydrochloride (Dilazep) and its dose-dependent influence on rabbit acute serum sickness nephritis. Inage H, et al. **Nippon Jinzo Gakkai Shi** 1985 Sep;27(9):1253-60

BEHAVIOR

The neurochemistry of behavior. Panksepp J. **Annu Rev Psychol** 1986; 37:77-107

Behavioral changes caused by nutrients. Lieberman HR. **Bibl Nutr Dieta** 1986;(38):219-24

Perspectives in Canadian neuro-psychopharmacology. Proceedings of the eighth annual meeting of the Canadian College of Neuropsychopharmacology. May 5-8, 1985, London, Ontario. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):463-768

Behavioral, biochemical, and blood pressure responses to alprazolam in healthy subjects: interactions with yohimbine. Charney DS, et al. **Psychopharmacology (Berlin)** 1986;88(2):133-40

The behavioral actions of diazepam and oxazepam are similar. Mewaldt SP, et al. **Psychopharmacology (Berlin)** 1986;88(2):165-71

[Phencyclidine: behavioral effects and molecular targets] Vignon J. **Biochimie** 1985 Sep;67(9):XI-XVI **(Fre)**

[Integrative relations in the structure of human behavior] Scripcaru G, et al. **Rev Med Chir Soc Med Nat Iasi** 1985 Apr-Jun;89(2):207-12 (25 ref.) (Eng. Abstr.) **(Rum)**

BEHAVIOR, ANIMAL

Evidence for a modulatory influence of centrally administered substance P on a 5-hydroxytryptamine-mediated behavioural response in the male rat. Ogren SO, et al. **Acta Physiol Scand** 1985 Dec;125(4):743-5

GABA-specificity of behaviour responses to picrotoxin injected into the colliculus superior of cats. Jaspers R, et al. **Behav Brain Res** 1985 Oct-Nov;18(1):63-9

Dopamine depletion, stimulation or blockade in the rat disrupts spatial navigation and locomotion dependent upon beacon or distal cues. Whishaw IQ, et al. **Behav Brain Res** 1985 Oct-Nov;18(1):11-29

The behavioral effects of depletions of brain serotonin induced by 5,7-dihydroxytryptamine vary with time after administration. Gately PF, et al. **Behav Neural Biol** 1986 Jan;45(1):31–42

Mouse strain differences in apomorphine-induced behavior: an empirical and methodological study. Randall PK, et al. **Behav Neurosci** 1986 Feb; 100(1):85–92

Clonidine modulates locus coeruleus metabolic hyperactivity induced by stress in behaving rats. Quintin L, et al. **Brain Res** 1986 Jan 8; 362(2):366–9

Central serotonergic responses and behavioural adaptation to repeated immobilisation: the effect of the corticosterone synthesis inhibitor metyrapone. Kennett GA, et al. **Eur J Pharmacol** 1985 Dec 17; 119(3):143–52

Subtypes of the 5-HT receptor mediating the behavioural responses to 5-methoxy-N,N-dimethyltryptamine in the rat. Tricklebank MD, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):15–24

Behavioral effects of substance P in rats. Barbeau A, et al. **Int J Neurol** 1980;14(2–4):239–52

Antagonists of central and peripheral behavioral actions of cholecystokinin octapeptide. Crawley JN, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):320–30

Behavioral and receptor binding studies of phencyclidine (PCP) and lithium interaction in the rat. Mattia A, et al. **Life Sci** 1986 Mar 17; 38(11):975–84

A parametric study of the behavioral effects of phencyclidine in adult cats. Levine MS, et al. **Neuropharmacology** 1985 Dec;24(12):1181–5

Interaction of the cholinergic and catecholaminergic systems of the brain during a change in the motivational behavior of animals. Sadykhova EF, et al. **Neurosci Behav Physiol** 1985 Nov–Dec;15(6):471–6

Behavioral and neurochemical changes after intracisternal capsaicin treatment of the guinea pig. Gamse R, et al. **Neurosci Lett** 1986 Mar 14;64(3):287–92

Behavioral effects of a dimethylsulfonium analog of dopamine after injection into the nucleus accumbens and the striatum. Boldry R, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):223–8

Modulation of apomorphine-induced climbing behavior by estradiol. Fung YK, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):139–41

Interstrain correlation between behavioural effects of lithium and effects on cortical cyclic AMP. Hamburger-Bar R, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):9–13

The effects of fluoxetine and zimeldine on the behavior of olfactory bulbectomized rats. Joly D, et al. **Pharmacol Biochem Behav** 1986 Feb; 24(2):199–204

Different behavioural patterns induced by the dopamine agonist apomorphine analysed by multivariate statistics. Ståhle L, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):291–8

Dissociations between the effects of hallucinogens on behavior and raphe unit activity in behaving cats. Trulson ME. **Pharmacol Biochem Behav** 1986 Feb;24(2):351–7

The influence of chronic treatment with psychotropic drugs on behavioral changes by social isolation. Oehler J, et al. **Pol J Pharmacol Pharm** 1985 Nov–Dec;37(6):841–9

Perspectives in Canadian neuro-psychopharmacology. Proceedings of the eighth annual meeting of the Canadian College of Neuropsychopharmacology. May 5–8, 1985, London, Ontario. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):463–768

Behavioral and neurochemical effects of (–)- and (+/–)-cathinone: dose-response and time-course. Nielsen JA, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):739–43

Developmental, behavioral, and opiate receptor changes after prenatal or postnatal beta-endorphin, CRF, or Tyr-MIF-1. Zadina JE, et al. **Psychoneuroendocrinology** 1985;10(4):367–83

Behavioural responses to diazepam of drug-naive and experienced monkeys (Macaca mulatta). Bradley CM, et al. **Psychopharmacology (Berlin)** 1986;88(1):112–4

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: extinction and successive discrimination. Buckland C, et al. **Psychopharmacology (Berlin)** 1986;88(3):285–95

Imidazole has similar behavioural effects to yohimbine. Ferrari F, et al. **Psychopharmacology (Berlin)** 1986;88(1):58–62

[Behavioral changes in rhesus monkeys induced by repeated administration of ephedrine] Kato S. **Seishin Shinkeigaku Zasshi** 1985; 87(8):583–94 (Eng. Abstr.) **(Jpn)**

[Behavioral effects of thyroliberin on animals of various species] Krylov SS, et al. **Farmakol Toksikol** 1986 Jan–Feb;49(1):30–3 (Eng. Abstr.) **(Rus)**

[Effect of acute and chronic deprivation of catecholaminergic system activity induced by 6-hydroxydopamine on the behavior of the rat] Gromova EA, et al. **Zh Vyssh Nerv Deiat** 1985 Nov–Dec; 35(6):1133–41 (Eng. Abstr.) **(Rus)**

[Concentration of monoamines in the brain of minks differing in their reaction to man] Nikulina EM, et al. **Zh Vyssh Nerv Deiat** 1985 Nov–Dec;35(6):1142–6 (Eng. Abstr.) **(Rus)**

BENACTYZINE

[Participation of the cholinergic system in central mechanisms of the cortico-limbic regulation of visceral functions] Beller NN, et al. **Fiziol Zh SSSR** 1986 Jan;72(1):61–8 **(Rus)**

BENZAZEPINES

Effects of verapamil and diltiazem on human platelet function. Addonizio VP Jr, et al. **Am J Physiol** 1986 Mar;250(3 Pt 2):H366–71

Role of the renal kinin-prostaglandin system in diltiazem-induced natriuresis. Seino M, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 2):F197–202

Effect of diltiazem on hemodynamics and regional blood flows in the newborn piglet. Clozel M, et al. **Dev Pharmacol Ther** 1986; 9(1):32–43

Some atypical neuroleptics inhibit [3H]SCH 23390 binding in vivo. Andersen PH, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):143–4

Dopamine D1 receptor mediation of the discriminative stimulus properties of SKF 38393. Cunningham KA, et al. **Eur J Pharmacol** 1985 Dec 10; 119(1–2):121–5

Guanine nucleotide regulation of agonist interactions at [3H]SCH23390-labeled D1 dopamine receptors in rat striatum. Hess EJ, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):31–8

[3H]SCH 23390 binding sites increase after chronic blockade of D-1 dopamine receptors. Porceddu ML, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):367–70

Selective antagonism of the hypotensive effects of dopamine agonists in spontaneously hypertensive rats. McCoy CE, et al. **Hypertension** 1986 Apr;8(4):298–302

Ganglionic dopamine receptors as mediators of the inhibition of neurogenic vasoconstriction produced by fenoldopam. Lokhandwala MF, et al. **J Auton Pharmacol** 1985 Dec;5(4):301–5

The renal response to diltiazem and nifedipine: comparison with nitroprusside. Blackshear JL, et al. **J Cardiovasc Pharmacol** 1986 Jan–Feb;8(1):37–43

High-performance liquid chromatographic determination of diltiazem and four of its metabolites in plasma. Application to pharmacokinetics. Goebel KJ, et al. **J Chromatogr** 1985 Dec 13;345(2):355–63

Centrally-induced vasodepressor responses to diltiazem, a calcium channel blocker, in rats. Iyoda I, et al. **J Hypertens** 1985 Dec; 3(6):639–44

Different effects of calcium-antagonists on automaticity in single pacemaker cells and in synchronized networks of cultured embryonic heart muscle cells. Koidl B, et al. **J Mol Cell Card**iol 1986 Feb; 18(2):207–17

Effects of bepridil and diltiazem on [3H]nitrendipine binding to canine cardiac sarcolemma. Potentiation of pharmacological effects of nitrendipine by bepridil. Balwierczak JL, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):40–8

The benzazepine SCH 23390 increases plasma levels of cortisol in the conscious dog. Goiny M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):111–2

Evidence for the site of action of glycerol trinitrate and diltiazem in inhibiting vasoconstrictor responses to norepinephrine in isolated renal arteries. Gross GJ, et al. **Pharmacology** 1986;32(1):1–10

Control of the light-regulated current in rod photoreceptors by cyclic GMP, calcium, and l-cis-diltiazem. Stern JH, et al. **Proc Natl Acad Sci USA** 1986 Feb;83(4):1163–7

Effect of DA1 receptor blockade with SCH 23390 on the renal response to electrical stimulation of the renal nerves. Bradley T, et al. **Proc Soc Exp Biol Med** 1986 Apr;181(4):492–7

[Diltiazem: a new calcium antagonist in the Netherlands] Robbens EJ, et al. **Ned Tijdschr Geneeskd** 1986 Mar 22;130(12):535–7 **(Dut)**

[New psychotropic agents. 2. Synthesis and pharmacologic activity of derivatives of 5H-pyrrolo[1,2-b][1,2,5]benzotriazepines] Stefancich G, et al. **Farmaco [Sci]** 1985 Dec;40(12):930–41 (Eng. Abstr.) **(Ita)**

[Evaluation of the effectiveness and safety in the use of cold-diltiazem-potassium cardioplegia in coronary artery bypass surgery: a first clinical trial] Kitamura S, et al. **Nippon Geka Gakkai Zasshi** 1985 Sep;86(9):1199–202 (Eng. Abstr.) **(Jpn)**

BENZODIAZEPINE TRANQUILIZERS

A comparison of the soft gelatin capsule and the tablet form of temazepam. Salonen M, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Jan; 58(1):49–54

Benzodiazepines, but not antidepressants or neuroleptics, induce dose-dependent development of tolerance to lorazepam in psychiatric patients. Aranko K, et al. **Acta Psychiatr Scand** 1985 Nov; 72(5):436–46

Double-blind comparison of buspirone and clorazepate in anxious outpatients. Cohn JB, et al. **Am J Med** 1986 Mar 31;80(3B):10–6

Preliminary evidence for the utility of carbamazepine in alprazolam withdrawal. Klein E, et al. **Am J Psychiatry** 1986 Feb;143(2):235–6

Relative bioavailability in humans for oral tablets and solutions of lormetazepam. Zecca L, et al. **Arzneimittelforschung** 1985; 35(12):1870-2

Comparative pharmacokinetics of midazolam and loprazolam in healthy subjects after oral administration. Jochemsen R, et al. **Biopharm Drug Dispos** 1986 Jan-Feb;7(1):53-61

Electron-capture gas chromatographic determination of loprazolam in plasma and a pharmacokinetic application. Levasseur FA, et al. **Biopharm Drug Dispos** 1985 Oct-Dec;6(4):381-7

Sedation in outpatient oral surgery. Comparison of temazepam by mouth and diazepam i.v. O'Boyle CA, et al. **Br J Anaesth** 1986 Apr; 58(4):378-84

Comment: Addiction liability of benzodiazepines and buspirone [letter] Nelson RC. **Drug Intell Clin Pharm** 1986 Mar;20(3):233-4

The clinical pharmacology and dental uses of benzodiazepines in the elderly. Culbertson VL. **Gerodontics** 1985 Dec;1(6):252-9

Alprazolam treatment of postcoronary bypass anxiety and depression. Freeman AM 3d, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):39-41

Indirect dopaminergic effects of tofisopam, a 2,3-benzodiazepine, and their inhibition by lithium. Chopin P, et al. **J Pharm Pharmacol** 1985 Dec;37(12):917-9

Relation between time courses of pharmacological effects and of plasma levels of camazepam and its active metabolites in rats. Morino A, et al. **J Pharmacobiodyn** 1985 Aug;8(8):597-606

Prescribing and dispensing of benzodiazepines by pharmacists. Newgreen DB, et al. **Med J Aust** 1986 Mar 31;144(7):370-1

Resistance to the anti-anxiety effect of buspirone in patients with a history of benzodiazepine use [letter] Schweizer E, et al. **N Engl J Med** 1986 Mar 13;314(11):719-20

Effects of clorazepate dipotassium and placebo on psychomotor skills. Moodley P, et al. **Percept Mot Skills** 1985 Dec;61(3 Pt 2):1121-2

Benzodiazepine suppression of cortisol secretion: a measure of anxiolytic activity? Gram LF, et al. **Pharmacopsychiatry** 1986 Jan;19(1):19-22

Prescription and misuse of benzodiazepines in the Federal Republic of Germany. Müller-Oerlinghausen B. **Pharmacopsychiatry** 1986 Jan; 19(1):8-13

Opioid benzodiazepine tifluadom and drug-induced hyperactivity in mice: lack of benzodiazepine-like effects. Sansone M, et al. **Pol J Pharmacol Pharm** 1985 Sep-Oct;37(5):585-90

Differential effect of benzodiazepine sedation in high and low anxious patients in a 'real life' stress setting. O'Boyte CA, et al. **Psychopharmacology (Berlin)** 1986;88(2):226-9

Disruption of schedule-controlled behavior by Ro 15-1788 one day after acute treatment with benzodiazepines. Spealman RD. **Psychopharmacology (Berlin)** 1986;88(3):398-400

Species differences in the disposition and metabolism of camazepam. Morino A, et al. **Xenobiotica** 1985 Dec;15(12):1033-43

[Determination of diazepam and medazepam by precipitation with tetraphenylboron sodium] Garcia Madrid H, et al. **J Pharm Belg** 1985 Nov-Dec;40(6):435-8 (Eng. Abstr.) **(Fre)**

[The biological basis of drug dependence. II. The benzodiazepines] Bobon D. **Rev Med Liege** 1986 Mar 1;41(5):165-73 **(Fre)**

[The control of drug release of heavy-soluble, weak basic drugs in matrix tablets using the example of medazepam] Zessin G, et al. **Pharmazie** 1986 Jan;41(1):39-42 (Eng. Abstr.) **(Ger)**

[Indicative patterns of the use of anxiolytic agents in pharmacies and the severity of symptoms] de Matos EG, et al. **AMB** 1985 Jul-Aug; 31(7-8):116-20 (Eng. Abstr.) **(Por)**

[Correlation of the clinical pharmacological action of a single dose of fenazepam with the EEG dynamics and pharmacokinetics] Uvarova LG, et al. **Farmakol Toksikol** 1986 Jan-Feb;49(1):66-9 (Eng. Abstr.) **(Rus)**

[Correlation between the pharmacokinetic indices and the pharmacological effects of fenazepam in an experiment] Zherdev VP, et al. **Farmakol Toksikol** 1985 Nov-Dec;48(6):67-70 (Eng. Abstr.) **(Rus)**

BENZODIAZEPINONES

Clonazepam-induced up-regulation of serotonin1 and serotonin2 binding sites in rat frontal cortex. Wagner HR, et al. **Adv Neurol** 1986; 43:645-51

Structure of the anthramycin-d(ATGCAT)2 adduct from one- and two-dimensional proton NMR experiments in solution. Graves DE, et al. **Biochemistry** 1985 Dec 17;24(26):7573-81

Comparative pharmacokinetics of midazolam and loprazolam in healthy subjects after oral administration. Jochemsen R, et al. **Biopharm Drug Dispos** 1986 Jan-Feb;7(1):53-61

Electron-capture gas chromatographic determination of loprazolam in plasma and a pharmacokinetic application. Levasseur FA, et al. **Biopharm Drug Dispos** 1985 Oct-Dec;6(4):381-7

Oral pirenzepine does not affect esophageal pressures in man. Blackwell JN, et al. **Dig Dis Sci** 1986 Mar;31(3):230-5

The Ro 15-1788 cue: evidence for benzodiazepine agonist and inverse agonist properties. De Vry J, et al. **Eur J Pharmacol** 1985 Dec 17; 119(3):193-7

Long-term exposure of cortical cell cultures to clonazepam reduces benzodiazepine receptor binding. Sher PK. **Exp Neurol** 1986 May; 92(2):360-8

Muscarinic acetylcholine receptors in rat gastric mucosa. A radioautographic study using a potent muscarinic antagonist, 3H-pirenzepine. Nakamura M, et al. **Histochemistry** 1985; 83(6):479-87

Computer-controlled large scale production of high specific activity [11C]RO 15-1788 for PET studies of benzodiazepine receptors. Suzuki K, et al. **Int J Appl Radiat Isot** 1985 Dec;36(12):971-6

Clonazepam: a novel therapeutic adjunct. Freinhar JP, et al. **Int J Psychiatry Med** 1985-86;15(4):321-8

Clonazepam in the treatment of patients with recurrent panic attacks. Beaudry P, et al. **J Clin Psychiatry** 1986 Feb;47(2):83-5

Behavioral studies with anxiolytic drugs. II. Interactions of zopiclone with ethyl-beta-carboline-3-carboxylate and Ro 15-1788 in squirrel monkeys. Barrett JE, et al. **J Pharmacol Exp Ther** 1986 Feb; 236(2):313-9

Interactions of Ro 15-1788, CGS 8216 and diazepam on head-turning in rats. Goldstein JM, et al. **Life Sci** 1986 Feb 3;38(5):459-63

Antagonism of the effects of the atypical benzodiazepine, Ro 5-4864 on intracranial self-stimulation in the rat. Pellow S, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):193-7

Effects of the benzodiazepine receptor ligands midazolam, Ro 15-1788, and Ro 5-4864, alone and in combinations, on platelet serotonin uptake. Lingjaerde O. **Pharmacopsychiatry** 1986 Jan;19(1):15-8

An open clinical trial of clonazepam in the treatment of patients with recurrent panic attacks. Beaudry P, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):589-92

Effects of chlordiazepoxide training dose on the mixed agonist-antagonist properties of benzodiazepine receptor antagonist Ro 15-1788, in a drug discrimination procedure. De Vry J, et al. **Psychopharmacology (Berlin)** 1986;88(2):177-83

Effects of clonazepam and ethosuximide on the responding of pigeons under a fixed-consecutive-number schedule with and without an external discriminative stimulus. Picker M, et al. **Psychopharmacology (Berlin)** 1986;88(3):325-30

Disruption of schedule-controlled behavior by Ro 15-1788 one day after acute treatment with benzodiazepines. Spealman RD. **Psychopharmacology (Berlin)** 1986;88(3):398-400

Antimanic effects of clonazepam. Chouinard G. **Psychosomatics** 1985 Dec; 26(12 Suppl):7-12

Clonazepam for panic disorders and agitation. Fontaine R. **Psychosomatics** 1985 Dec;26(12 Suppl):13-8

Effect of selective and non-selective antimuscarinics on rectosigmoid motility and gastrointestinal transit. Jaup BH, et al. **Scand J Gastroenterol** 1985 Nov;20(9):1101-9

[Effects of blocking muscarinic receptors with pirenzepine on the functional plasma flow of the liver in man and in the rat] Avagnina P, et al. **Recenti Prog Med** 1985 Nov;76(11):553-7 (Eng. Abstr.)**(Ita)**

[Inhibitory effects of pirenzepine on cholinergic stimulation of exocrine rat pancreas in vitro] Otsuki M, et al. **Nippon Shokakibyo Gakkai Zasshi** 1985 Dec;82(12):2959-63 (Eng. Abstr.) **(Jpn)**

[Reduction of clonazepam with enteric bacteria] Kuroiwa M, et al. **Yakugaku Zasshi** 1985 Oct;105(10):960-5 (Eng. Abstr.) **(Jpn)**

[Correlation of the clinical pharmacological action of a single dose of fenazepam with the EEG dynamics and pharmacokinetics] Uvarova LG, et al. **Farmakol Toksikol** 1986 Jan-Feb;49(1):66-9 (Eng. Abstr.) **(Rus)**

[Correlation between the pharmacokinetic indices and the pharmacological effects of fenazepam in an experiment] Zherdev VP, et al. **Farmakol Toksikol** 1985 Nov-Dec;48(6):67-70 (Eng. Abstr.) **(Rus)**

BIOGENIC AMINES

Effects of meclofenoxate on the level and turnover of biogenic monoamines in the rat brain. Petkov VV, et al. **Arzneimittelforschung** 1985;35(12):1778-81

Effects of dietary vanadium exposure on levels of regional brain neurotransmitters and their metabolites. Sharma RP, et al. **Biochem Pharmacol** 1986 Feb 1;35(3):461-5

Examination of spinal monoamine receptors through which brainstem opiate-sensitive systems act in the rat. Jensen TS, et al. **Brain Res** 1986 Jan 15;363(1):114-27

Effect of hypoxia on brainstem concentration of biogenic amines in postnatal rabbits. McNamara MC, et al. **Brain Res** 1986 Mar; 390(2):253-8

Interaction of neuropeptides and biogenic amines on cyclic adenosine monophosphate accumulation in hypothalamic nuclei. Redgate ES, et al. **Brain Res** 1986 Feb 12;365(1):61-9

Stress by forced swimming in the rat: effects of mianserin and moclobemide on GABAergic-monoaminergic systems in the brain. Cicardo VH, et al. **Comp Biochem Physiol [C]** 1986;83(1):133-5

The reliability of monoamine levels in the kindled brain. Nishimura S, et al. **Folia Psychiatr Neurol Jpn** 1985;39(3):321-2

Rat brain monoamine metabolism and hypobaric hypoxia: a new approach. Trouvin JH, et al. **Gen Pharmacol** 1986;17(1):69-73

Effect of 24-hour sleep deprivation on biogenic amine turnover. Bol'shakova TD, et al. **Hum Physiol** 1985 Jul-Aug;11(4):291-5

Simultaneous analysis of twelve biogenic amine metabolites in plasma, cerebrospinal fluid and urine by capillary column gas chromatography-high-resolution mass spectrometry with selected-ion monitoring. Davis BA, et al. **J Chromatogr** 1986 Jan 24; 374(2):227-38

Determination of the biogenic amines and their major metabolites in single human brain tissue samples using a combined extraction procedure and high-performance liquid chromatography with electrochemical detection. Herregodts P, et al. **J Chromatogr** 1985 Nov 29; 345(1):33-42

Effects of chronic lithium treatment on brain monoamine metabolism and amphetamine-induced locomotor stimulation in rats. Berggren U. **J Neural Transm** 1985;64(3-4):239-50

Interhemispheric fusion. Mandell AJ. **J Psychoactive Drugs** 1985 Oct-Dec; 17(4):257-66

Studies on qingyangshen (root of cynanchum otophyllum). II. Effect of qingyangshen on metabolism of central monoamines. Kuang PG, et al. **J Tradit Chin Med** 1985 Sep;5(3):191-4

Simultaneous determination of dopamine serotonin, 3,4-dihydroxyphenyl-acetic acid, homovanillic acid, 3-methoxytyramine and 5-hydroxyindole-3-acetic acid by high performance liquid chromatography with electrochemical detection. Yokoo H, et al. **Kurume Med J** 1985;32(1):75-80

Local release of monoamines in the gastrointestinal tract: an in vivo study in rabbits. Meirieu O, et al. **Life Sci** 1986 Mar 3;38(9):827-34

Age-related alterations in monoamine release from rat striatum: an in vivo electrochemical study. Rose GM, et al. **Neurobiol Aging** 1986 Mar-Apr;7(2):77-82

Amine-mediated toxicity. The effects of dopamine, norepinephrine, 5-hydroxytryptamine, 6-hydroxydopamine, ascorbate, glutathione and peroxide on the in vitro activities of creatine and adenylate kinases in the brain of the rat. Maker HS, et al. **Neuropharmacology** 1986 Jan; 25(1):25-32

Influence of monoamines on content of luteinizing hormone-releasing hormone in different regions of the hypothalamus of male rats. Markaryan RL, et al. **Neurosci Behav Physiol** 1985 Sep-Oct; 15(5):407-10

Role of neurotransmitter in forensic medicine (Report I). A simple and sensitive analysis of biogenic amines and metabolites in tissues by high performance liquid chromatography with electrochemical detection. Endo T, et al. **Nippon Hoigaku Zasshi** 1985 Aug;39(4):260-7

Selection for growth alters the feeding response to injections of biogenic amines. Denbow DM, et al. **Pharmacol Biochem Behav** 1986 Jan; 24(1):39-42

Inhibition of rat kidney histamine-N-methyltransferase by biogenic amines. Fuhr N, et al. **Pharmacology** 1986;32(2):114-20

Effects of ECT on sleep and CSF biogenic amines in affective illness. Hoffmann G, et al. **Psychiatry Res** 1985 Nov;16(3):199-206

Developing rat brain monoamine levels following in utero exposure to a mixture of 2,4-dichlorophenoxyacetic and 2,4,5-trichlorophenoxyacetic acids. Mohammad FK, et al. **Toxicol Lett** 1985 Dec;29(2-3):215-23

[Comparison of effects of electroacupuncture stimulations of two different intensities and frequencies on monoamine neurotransmitters in rat brain regions] Wang YJ, et al. **Chen Tzu Yen Chiu** 1985;10(1):24-9 (Eng. Abstr.) **(Chi)**

[Effect of some isoquinoline alkaloids on monoamines in the rat brain] Liu GQ, et al. **Yao Hsueh Hsueh Pao** 1985 Aug;20(8):566-70 (Eng. Abstr.) **(Chi)**

[Ergot alkaloids and central monoaminergic receptors] Goldstein M. **J Pharmacol** 1985;16 Suppl 3:21-7 (Eng. Abstr.) **(Fre)**

[Organ distribution of ruthenocenyl biogenic amine derivatives--radiodiagnostic agents for the adrenals and ovaries?] Wenzel M, et al. **Strahlenther Onkol** 1986 Jan;162(1):51-6 (Eng. Abstr.) **(Ger)**

[Effect of chronic exposure to nitrogen dioxide on biogenic amine levels in the brain of guinea pigs] Felińska W, et al. **Med Pr** 1985; 36(4):236-43 (Eng. Abstr.) **(Pol)**

[Hypothalamic monoamines and nonapeptides in the regulation of thyroid function in the early ontogeny of birds] Karpezo NA, et al. **Ontogenez** 1985 Nov-Dec;16(6):589-96 (Eng. Abstr.) **(Rus)**

[Concentration of monoamines in the brain of minks differing in their reaction to man] Nikulina EM, et al. **Zh Vyssh Nerv Deiat** 1985 Nov-Dec;35(6):1142-6 (Eng. Abstr.) **(Rus)**

BIOLOGICAL PSYCHIATRY

[The new biological revolution in psychiatry: a Latin American point of view (1st part)] Alarcón R. **Acta Psiquiatr Psicol Am Lat** 1985 Jun; 31(2):131-42 (Eng. Abstr.) **(Spa)**

BIOTRANSFORMATION

Increased response of cytochrome P-450 dependent biotransformation reactions in rat liver to repeated administration of inducers. Kleeberg U, et al. **Arch Toxicol [Suppl]** 1985;8:361-5

BIPOLAR DISORDER

Drugs and depression. Harris B. **Am J Nurs** 1986 Mar;86(3):292-3

Depression. What does it mean? Minot SR. **Am J Nurs** 1986 Mar; 86(3):284-8

A possible synergistic effect of alprazolam and lithium carbonate [letter] Cerra D, et al. **Am J Psychiatry** 1986 Apr;143(4):552

Lithium ion transport by erythrocytes of randomly selected blood donors and manic-depressive patients: lack of association with affective illness. Richelson E, et al. **Am J Psychiatry** 1986 Apr;143(4):457-62

Danazol and the rapid-cycling patient [letter] Goldstein JA. **J Clin Psychiatry** 1986 Mar;47(3):153-4

Prediction of lithium dose: a mathematical alternative to the test-dose method. Zetin M, et al. **J Clin Psychiatry** 1986 Apr;47(4):175-8

Lorazepam in resistant mania [letter] Jobling M, et al. **Lancet** 1986 Mar 1;1(8479):510

Relationship between cerebrospinal fluid somatostatin and peripheral thyroid hormones with carbamazepine treatment. Joffe RT, et al. **Neuropsychobiology** 1985;14(3):115-7

Carbamazepine in treatment and prophylaxis of manic-depressive disorder. Strömgren LS, et al. **Psychiatr Dev** 1985 Winter; 3(4):349-67 (41 ref.)

Pro-opiomelanocortin-related peptides in cerebrospinal fluid: a study of manic-depressive disorder. Berrettini WH, et al. **Psychiatry Res** 1985 Dec;16(4):287-302

Effects of ECT on sleep and CSF biogenic amines in affective illness. Hoffmann G, et al. **Psychiatry Res** 1985 Nov;16(3):199-206

Colour associations as predictors of the effectiveness of anti-depressant pharmacotherapy in endogenous depressive patients. Demeter E, et al. **Psychopathology** 1985;18(5-6):305-9

Decrease in plasma levels of 3,4-dihydroxyphenylethyleneglycol in major depression. Scatton B, et al. **Psychopharmacology (Berlin)** 1986; 88(2):220-5

[Lithium and other preventive agents in affective disorders in 1984] Souček K. **Cesk Psychiatr** 1985 Dec;81(6):363-6 **(Cze)**

[GABA receptor function and manic depressive disease] Hetmar O, et al. **Nord Med** 1986;101(2):62-5 (Eng. Abstr.) **(Dan)**

[Course and form variations of cyclothymic phases in lithium therapy] Banzhaf M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Dec; 37(12):718-21 (Eng. Abstr.) **(Ger)**

[Amineptine: clinical considerations on a new antidepressive] Carreca A, et al. **Clin Ter** 1985 Dec 31;115(6):449-52 (Eng. Abstr.) **(Ita)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. II. Comparison of the effects of various thymoleptics on the psychopathological symptoms of endogenous depressive syndromes] Strzyżewski W, et al. **Psychiatr Pol** 1985 Sep-Oct;19(5):363-9 (Eng. Abstr.) **(Pol)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. III. Analysis of the factors affecting the effectiveness of treatment with thymoleptics] Twarowska-Hauser J, et al. **Psychiatr Pol** 1985 Sep-Oct;19(5):370-5 (Eng. Abstr.) **(Pol)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. I. Analysis of the clinical effect of antidepressive drugs with various pharmacological profiles] Twarowska-Hauser J, et al. **Psychiatr Pol** 1985 Sep-Oct; 19(5):357-62 (Eng. Abstr.) **(Pol)**

BLOOD-BRAIN BARRIER

Influence of long-term immobilization stress on regional blood-brain barrier permeability, cerebral blood flow and 5-HT level in conscious normotensive young rats. Sharma HS, et al. **J Neurol Sci** 1986 Jan; 72(1):61-76

Permeability of the blood-brain barrier to neuropeptides: the case for penetration. Banks WA, et al. **Psychoneuroendocrinology** 1985; 10(4):385-99

BOMBESIN

Effects of intrahypothalamically administered norepinephrine, serotonin and bombesin on thermoregulation in the deermouse (Peromyscus maniculatus). Lin LH, et al. **Brain Res** 1986 Feb 5;364(2):212-9

Interactions of bombesin and substance P at the feline lower esophageal sphincter. Reynolds JC, et al. **J Clin Invest** 1986 Feb;77(2):436-40

Water intake modifications induced by tachykinins, bombesins and opioid peptides. de Caro G, et al. **Peptides** 1985;6 Suppl 3:181-5

Trophic effect of bombesin on the rat pancreas: is it mediated by the release of gastrin or cholecystokinin? Lhoste E, et al. **Peptides** 1985; 6 Suppl 3:89-97

Combined effect of chronic bombesin and secretin or cholecystokinin on the rat pancreas. Lhoste E, et al. **Peptides** 1985;6 Suppl 3:83-7

BRADYKININ

Substance P, 5-hydroxytryptamine, and bradykinin stimulate abdominal visceral afferents. Lew WY, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 2):R465-73

[In vivo and in vitro effects of bradykinin on the release of beta-endorphin-like immunoreactivity] Shimizu I, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Dec 20;61(12):1330-40 (Eng. Abstr.) **(Jpn)**

BUTYLAMINES

Metabolic fate of N-nitrodibutylamine in the rat. Suzuki E, et al. **Jpn J Cancer Res** 1986 Jan;77(1):39-44

[Aminooxypropylamine--an effective inhibitor of ornithine decarboxylase in vitro and in vivo] Khomutov RM, et al. **Bioorg Khim** 1985 Nov; 11(11):1574-6 (Eng. Abstr.) **(Rus)**

[Hygienic standard for tert-butylamine in water] Rudelko VA, et al. **Gig Sanit** 1985 Dec;(12):70-1 **(Rus)**

BUTYROPHENONE TRANQUILIZERS

Determination of lenperone in dog plasma by high-performance liquid chromatography. Osman MA, et al. **J Chromatogr** 1985 Dec 13; 345(2):430-5

Effect of timiperone, a new antipsychotic drug, on the sleep-wakefulness cycle in cats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Nov; 39(3):391-4

BUTYROPHENONES

Pharmacokinetic and metabolic study of itanoxone in the crab Pachygrapsus marmoratus (Decapoda, Brachyura): comparative study with clofibric acid. Lautier J, et al. **Comp Biochem Physiol [C]** 1986; 83(1):143-7

Chronic proglumide increases [3H]spiperone binding in the rat brain. Bean AJ, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):97-101

D-2 dopamine receptor-mediated inhibition of pro-opiomelanocortin synthesis in rat intermediate lobe. Abolition by pertussis toxin or activators of adenylate cyclase. Cote TE, et al. **J Biol Chem** 1986 Apr 5;261(10):4555-61

Determination of lenperone in dog plasma by high-performance liquid chromatography. Osman MA, et al. **J Chromatogr** 1985 Dec 13; 345(2):430-5

Effect of timiperone, a new antipsychotic drug, on the sleep-wakefulness cycle in cats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Nov; 39(3):391-4

Do antipsychotic drugs and serotonin down regulate [3H]-spiroperidol binding sites in human cortex? Andorn AC. **Life Sci** 1986 Apr 7; 38(14):1251-60

Analysis of [3H]spiperone binding sites in the rat striatum and frontoparietal cortex by means of quantitative receptor autoradiography after inactivation of dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vivo: selective protection by sulpiride in the striatum. Fuxe K, et al. **Neurosci Lett** 1986 Feb 28;64(2):163-8

Synthesis of N-methyl and N-11C-methyl spiperone by phase transfer catalysis in anhydrous solvent. Omokawa H, et al. **Radioisotopes** 1985 Sep;34(9):480-5

CARBAMAZEPINE

Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? Arana GW, et al. **Am J Psychiatry** 1986 May;143(5):650-1

Positive effects of carbamazepine on behavioral dyscontrol in borderline personality disorder. Gardner DL, et al. **Am J Psychiatry** 1986 Apr; 143(4):519-22

Preliminary evidence for the utility of carbamazepine in alprazolam withdrawal. Klein E, et al. **Am J Psychiatry** 1986 Feb;143(2):235-6

Dopaminergic effects of carbamazepine. Relationship to clinical response in affective illness. Post RM, et al. **Arch Gen Psychiatry** 1986 Apr; 43(4):392-6

The influence of carbamazepine on the heme biosynthetic pathway. Schoenfeld N, et al. **Biochem Med** 1985 Dec;34(3):280-6

Carbamazepine and dopaminergic supersensitivity [letter] Csernansky JG, et al. **Biol Psychiatry** 1986 Feb;21(2):238-9

Antipyrine metabolite kinetics in healthy human volunteers during multiple dosing of phenytoin and carbamazepine. Shaw PN, et al. **Br J Clin Pharmacol** 1985 Dec;20(6):611-8

Improved gas-chromatographic determination of carbamazepine. Bhatia HM. **Clin Chem** 1986 Mar;32(3):563-4

The effect of storage conditions on the stability of carbamazepine and carbamazepine-10,11-epoxide in plasma. Mendez-Alvarez E, et al. **Clin Chim Acta** 1986 Feb 15;154(3):243-6

Ranitidine does not alter single-dose carbamazepine pharmacokinetics in healthy adults. Dalton MJ, et al. **Drug Intell Clin Pharm** 1985 Dec; 19(12):941-4

Neuroendocrine effects of carbamazepine in patients with affective illness. Joffe RT, et al. **Epilepsia** 1986 Mar-Apr;27(2):156-60

Gas chromatographic assay for oxcarbazepine and its main metabolites in plasma. von Unruh GE, et al. **J Chromatogr** 1985 Nov 29; 345(1):67-76

Efficacy of carbamazepine as an antidepressant in chronic resistant depressives. Prasad AJ. **J Indian Med Assoc** 1985 Jul;83(7):235-7

Carbamazepine-erythromycin interaction. Case studies and clinical significance. Wroblewski BA, et al. **JAMA** 1986 Mar 7; 255(9):1165-7

Antagonism of picrotoxin against the taming effect of carbamazepine on footshock induced fighting behavior in mice. Nakao K, et al. **Jpn J Pharmacol** 1985 Oct;39(2):281-3

Relationship between cerebrospinal fluid somatostatin and peripheral thyroid hormones with carbamazepine treatment. Joffe RT, et al. **Neuropsychobiology** 1985;14(3):115-7

Carbamazepine in treatment and prophylaxis of manic-depressive disorder. Strömgren LS, et al. **Psychiatr Dev** 1985 Winter; 3(4):349-67 (41 ref.)

Effect of carbamazepine on mean urinary free cortisol excretion in patients with major affective illness. Rubinow DR, et al. **Psychopharmacology (Berlin)** 1986;88(1):115-8

Cross-reactivity assessment of oxcarbazepine and its metabolites in the EMIT assay of carbamazepine plasma levels. Kumps A, et al. **Ther Drug Monit** 1986;8(1):95-7

[Crystallographic behavior of carbamazepine preparations under compression pressure] Kala H, et al. **Pharmazie** 1986 Jan;41(1):61-2 **(Ger)**

CARBIDOPA

Liquid chromatographic determination of levodopa, levodopa-carbidopa, and related impurities in solid dosage forms. Ting S. **J Assoc Off Anal Chem** 1986 Jan-Feb;69(1):169-73

Differential effect of carbidopa on the concentration of rat pineal and hypothalamic indoleamines. Oxenkrug GF, et al. **J Pineal Res** 1984; 1(4):349-53

[Effect of Nakom on the activity of the hypothalamo-hypophyseo-adrenal system] Slavnov VN, et al. **Farmakol Toksikol** 1986 Jan-Feb; 49(1):26-9 (Eng. Abstr.) **(Rus)**

CATECHOL ESTROGENS

A rapid, sensitive and quantitative high-performance liquid chromatographic determination of catecholestrogens in human serum. Sagara Y, et al. **Asia Oceania J Obstet Gynaecol** 1985 Dec; 11(4):597-604

Semiquinone anion radicals of catechol(amine)s, catechol estrogens, and their metal ion complexes. Kalyanaraman B, et al. **Environ Health Perspect** 1985 Dec;64:185-98

Evidence that 6-hydroxydopamine is an inhibitor of catechol-O-methyltransferase in intact tissue. Reid JJ, et al. **J Pharm Pharmacol** 1986 Jan;38(1):46-50

Effect of continuous intraventricular estrogen or catechol estrogen treatment on catecholamine turnover in various brain regions. Panek DU, et al. **J Pharmacol Exp Ther** 1986 Mar;236(3):646-52

Studies of catecholestrogen metabolism during normal pregnancy: changes of plasma catecholestrogen levels after DHA-S or E1-S injection. Sagara Y, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 Jan; 38(1):89-94

Estrogens with reduced catechol-forming capacity fail to induce implantation in the rat. Dey SK, et al. **Proc Soc Exp Biol Med** 1986 Feb;181(2):215-8

CATECHOLAMINES

Co-release of neuropeptide Y (NPY)-like immunoreactivity and catecholamines in newborn infants. Lundberg JM, et al. **Acta Physiol Scand** 1986 Mar;126(3):471-3

Plasma catecholamine responses to physiologic stimuli in normal human pregnancy. Barron WM, et al. **Am J Obstet Gynecol** 1986 Jan; 154(1):80-4

Refined carbohydrate increases blood pressure and catecholamine excretion in SHR and WKY. Fournier RD, et al. **Am J Physiol** 1986 Apr;250(4 Pt 1):E381-5

Explanted and implanted notochord of amphibian anuran embryos. Histofluorescence study on the ability to synthesize catecholamines. Godin I. **Anat Embryol (Berl)** 1986;173(3):393-9

Differential effects of ketamine isomers on neuronal and extraneuronal catecholamine uptake mechanisms. Lundy PM, et al. **Anesthesiology** 1986 Mar;64(3):359-63

Coupling of H+ gradients to catecholamine transport in chromaffin granules. Johnson RG, et al. **Ann NY Acad Sci** 1985;456:254-67 (32 ref.)

Effect on human platelets of catecholamines at levels achieved in the circulation. Ardlie NG, et al. **Atherosclerosis** 1985 Dec;

58(1-3):251-9

Effect of denervation and/or reserpine-induced changes on adrenomedullary catecholamines in pigeon: a fluorescence histochemical study. Mahata SK, et al. **Basic Appl Histochem** 1985;29(4):331-6

Studies on the uptake and release of propranolol and the effects of propranolol on catecholamines in cultures of bovine adrenal chromaffin cells. Boksa P. **Biochem Pharmacol** 1986 Mar 1;35(5):805-15

Acidic catecholamine metabolites: substrates for human phenolsulphotransferase M. Carter SB, et al. **Biochem Pharmacol** 1986 Apr 1;35(7):1205-6

Catecholamine synthesis: physiological coupling to precursor supply. Milner JD, et al. **Biochem Pharmacol** 1986 Mar 15;35(6):875-81

Evidence for a catecholamine-mediated slow hyperpolarizing synaptic response in parasympathetic ganglia. Akasu T, et al. **Brain Res** 1986 Feb 19;365(2):365-8

Neurotransmitter synthesis, storage, and turnover in neonatally deafferented sympathetic neurons. Smolen AJ, et al. **Brain Res** 1985 Dec;355(2):211-8

Central vasopressin in the modulation of catecholamine release in conscious rats. King KA, et al. **Can J Physiol Pharmacol** 1985 Dec; 63(12):1501-5

Cardiovascular responses and plasma catecholamines in old age. Sachs C, et al. **Clin Physiol** 1985 Dec;5(6):553-65

Influence of thyroidectomy on brain catecholamines during the postnatal period. Leret ML, et al. **Comp Biochem Physiol [C]** 1986; 83(1):117-21

Coexpression of somatostatin-like immunoreactivity and catecholaminergic properties in neural crest derivatives: comodulation of peptidergic and adrenergic differentiation in cultured neural crest. García-Arrarás JE, et al. **Dev Biol** 1986 Mar;114(1):247-57

Stress-induced elevation of testosterone concentration in high ranking baboons: role of catecholamines. Sapolsky RM. **Endocrinology** 1986 Apr; 118(4):1630-5

Semiquinone anion radicals of catechol(amine)s, catechol estrogens, and their metal ion complexes. Kalyanaraman B, et al. **Environ Health Perspect** 1985 Dec;64:185-98

Plasma renin activity, aldosterone and catecholamine levels when swimming and running. Guezennec CY, et al. **Eur J Appl Physiol** 1986; 54(6):632-7

Capillary-venous differences of free plasma catecholamines at rest and during graded exercise. Lehmann M, et al. **Eur J Appl Physiol** 1985; 54(5):502-5

Chronic clonidine treatment and its withdrawal: effects on blood pressure and catecholamine synthesizing enzymes in brain-stem nuclei. Atkinson J, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):97-106

d- and l-isomers of fenfluramine differ markedly in their interaction with brain serotonin and catecholamines in the rat. Invernizzi R, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):9-15

Genotypic variation in age-related changes in peripheral catecholamines. Brennan MJ, et al. **Exp Gerontol** 1985;20(5):285-90

Brain catecholamine content and turnover in aging rats. Carfagna N, et al. **Exp Gerontol** 1985;20(5):265-9

Inactivation of potassium-evoked adrenomedullary catecholamine release in the presence of calcium, strontium or BAY-K-8644. Sala F, et al. **FEBS Lett** 1986 Feb 3;196(1):34-8

A diphenol oxidase gene is part of a cluster of genes involved in catecholamine metabolism and sclerotization in Drosophila. II. Molecular localization of the Dox-A2 coding region. Pentz ES, et al. **Genetics** 1986 Apr;112(4):843-59

A diphenol oxidase gene is part of a cluster of genes involved in catecholamine metabolism and sclerotization in drosophila. I. Identification of the biochemical defect in Dox-A2 [l(2)37Bf] mutants. Pentz ES, et al. **Genetics** 1986 Apr;112(4):823-41

Differences in catecholamine excretion rates, blood pressure and lifestyle among young Western Samoan men. James GD, et al. **Hum Biol** 1985 Dec;57(4):635-47

Plasma catecholamines in chronic renal disease. Elias AN, et al. **Int J Artif Organs** 1985 Sep;8(5):243-4

Changes of sympathetic activity during tooth extraction. Papadimitriou P, et al. **Int J Oral Maxillofac Surg** 1986 Apr;15(2):148-51

Fluorescent histochemical demonstration of catecholamines in brown adipose tissue from obese (ob/ob) and lean mice acclimated at different temperatures. Ashwell M, et al. **J Auton Nerv Syst** 1985 Dec; 14(4):377-86

Uterine contractility and actions of catecholamines in longitudinal and circular uterine layers from ovariectomised guinea-pigs: the effects of ovarian steroids. Adam SP, et al. **J Auton Pharmacol** 1985 Dec; 5(4):317-24

Selectivities of some agonists acting at alpha 1- and alpha 2-adrenoreceptors in the rat vas deferens. Leedham JA, et al. **J Auton Pharmacol** 1986 Mar;6(1):39-46

Catecholamine-stimulated GTPase cycle. Multiple sites of regulation by beta-adrenergic receptor and Mg2+ studied in reconstituted receptor-Gs vesicles. Brandt DR, et al. **J Biol Chem** 1986 Feb 5; 261(4):1656-64

Catecholamine modulation of embryonic palate mesenchymal cell DNA synthesis. Pisano MM, et al. **J Cell Physiol** 1986 Jan;126(1):84-92

Simplified determination of the brain catecholamines norepinephrine, 5-hydroxyindoleacetic acid, dopamine and 5-hydroxytryptamine by high-performance liquid chromatography using electrochemical detection. Gregory VM, et al. **J Chromatogr** 1985 Nov 29; 345(1):140-4

Measurement of urinary catecholamines and their catechol metabolites and precursor by liquid chromatography with column-switching and on-line fluorimetric and electrochemical detection. Julien C, et al. **J Chromatogr** 1985 Nov 8;344:51-60

High-performance liquid chromatography of plasma catecholamines using 1,2-diphenylethylenediamine as precolumn fluorescence derivatization reagent. Mitsui A, et al. **J Chromatogr** 1985 Nov 8;344:61-70

Distribution of catecholamines between fetal and maternal compartments during human pregnancy with emphasis on L-dopa and dopamine. Peleg D, et al. **J Clin Endocrinol Metab** 1986 May;62(5):911-4

Catecholamine innervation of the caudal spinal cord in the rat. Schrøder HD, et al. **J Comp Neurol** 1985 Dec 15;242(3):358-68

Regional specialization of the rat retina: catecholamine-containing amacrine cell characterization and distribution. Versaux-Botteri C, et al. **J Comp Neurol** 1986 Jan 15;243(3):422-33

Acute effects of oral or parenteral aspartame on catecholamine metabolism in various regions of rat brain. Yokogoshi H, et al. **J Nutr** 1986 Mar; 116(3):356-64

A potentiometric study of lithium complexation with catecholamines. Sandmann BJ, et al. **J Pharm Sci** 1986 Jan;75(1):73-7

Effect of continuous intraventricular estrogen or catechol estrogen treatment on catecholamine turnover in various brain regions. Panek DU, et al. **J Pharmacol Exp Ther** 1986 Mar;236(3):646-52

Quantitative analysis of the contribution of pulmonary and hind limb circulation to the clearance of exogenous catecholamines. Sumikawa K, et al. **J Pharmacol Exp Ther** 1986 Mar;236(3):759-63

Hamster and rat pineal gland beta-adrenoceptor characterization with iodocyanopindolol and the effect of decreased catecholamine synthesis on the receptor. Craft CM, et al. **J Pineal Res** 1985;2(1):51-66

Alternating lateralization of plasma catecholamines and nasal patency in humans. Kennedy B, et al. **Life Sci** 1985 Mar 31;38(13):1203-14

Potassium ion is indispensable to the catecholamine releasing response of dog adrenals to gamma-aminobutyric acid. Kitayama S, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):66-9

Does the carrier of chromaffin granules transport the protonated or the uncharged species of catecholamines? Kobold G, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):209-19

Effects of combined administration of L-tryptophan and tricyclic antidepressants on alpha 2- and beta-adrenoceptors and monoamine levels in rat brain. Russell VA, et al. **Neurochem Res** 1985 Dec; 10(12):1661-71

Postmortem central catecholamines and antemortem cognitive impairment in elderly schizophrenics and controls. Bridge TP, et al. **Neuropsychobiology** 1985;14(2):57-61

24-hour plasma levels of prolactin, cortisol, growth hormone and catecholamines in schizophrenic patients. Kemali D, et al. **Neuropsychobiology** 1985;14(3):109-14

Interaction of the cholinergic and catecholaminergic systems of the brain during a change in the motivational behavior of animals. Sadykhova EF, et al. **Neurosci Behav Physiol** 1985 Nov-Dec;15(6):471-6

Conjugated catecholamines in rats transfused with perfluorocarbon blood substitute. Wilson JX, et al. **Neurosci Lett** 1985 Dec 18;62(3):329-33

Supersensitivity of the renal tubule to catecholamines in the chronically denervated canine kidney. Szénási G, et al. **Pflugers Arch** 1986 Jan; 406(1):57-9

Catecholamine excretion and beta-adrenergic responsiveness in estrogen-treated rats. Carlberg KA, et al. **Pharmacology** 1986; 32(3):147-56

Changes in brain catecholamine levels following DL-dopa are not potentiated by deuterium substitution. Dewar KM, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):675-80

Cerebrospinal fluid studies of monoamine metabolism in schizophrenia. van Kammen DP, et al. **Psychiatr Clin North Am** 1986 Mar; 9(1):81-97 (94 ref.)

A comparison between chlordiazepoxide and CL 218,872, a synthetic non-benzodiazepine ligand for benzodiazepine receptors, on serotonin and catecholamine turnover in brain. McElroy JF, et al. **Psychopharmacology (Berlin)** 1986;88(1):105-8

Plasma catecholamine concentrations in lambs and calves during the perinatal period. Richet E, et al. **Reprod Nutr Dev** 1985; 25(6):1007-16

Maternal plasma concentrations of catecholamines and cyclic nucleotides during labor and following delivery. Ohno H, et al. **Res Commun Chem Pathol Pharmacol** 1986 Feb;51(2):183-94

Effect of different denervation procedures on catecholamines in the gut. Graffner H, et al. **Scand J Gastroenterol** 1985 Dec;20(10):1276-80

Role of protein kinase C in the synthesis of catecholamine by isolated bovine adrenal medullary cells. Houchi H. **Tokushima J Exp Med** 1985 Jun;32(1-2):17-22

Ontogeny of catecholamine and GABA levels in rat brain: lack of effect

of perinatal lead exposure. Bailey CC, et al. **Toxicol Lett** 1986 Jan; 30(1):97–102

[Catecholamines and mental stress] Christensen NJ. **Ugeskr Laeger** 1986 Jan 27;148(5):233–7 (Eng. Abstr.) **(Dan)**

[Catecholaminergic nuclei of sheep encephalon. Immunocytochemical study. I. Myelencephalon and metencephalon] Tillet Y, et al. **C R Acad Sci [III]** 1986;302(4):125–30 (Eng. Abstr.) **(Fre)**

[Dopamine-stimulated glycosylation of rat hippocampal proteins in vitro: structure-response relationship] Pchalek V, et al. **Biomed Biochim Acta** 1985;44(11–12):1651–8 (Eng. Abstr.) **(Ger)**

[The responses of autonomic nervous system during bicycle ergometer exercise in healthy young men--special reference to parasympathetic nervous system activity] Suematsu M, et al. **Kokyu To Junkan** 1985 Nov;33(11):1317–21 **(Jpn)**

[Effects of catecholamines on the neuromuscular blocking action of a non-depolarizing muscle relaxant--Part II. Experimental studies on the anti-neuromuscular blocking actions of catecholamines and the mechanisms of these actions in the dog] Omote T, et al. **Masui** 1985 Nov;34(11):1487–98 (Eng. Abstr.) **(Jpn)**

[Effects of different salt intakes on urinary output of catecholamines and renal sympathetic nerve activity] Yamazaki H, et al. **Nippon Jinzo Gakkai Shi** 1985 Nov;27(11):1565–70 (Eng. Abstr.) **(Jpn)**

[Excretion of catecholamines and their various metabolites in children aged 10–12 years in relation to their mental development] Orgacka H, et al. **Endokrynol Pol** 1985;36(5):285–92 (Eng. Abstr.) **(Pol)**

[The role of catecholamines in vasomotor rhinitis] Blinowski JT. **Pneumonol Pol** 1985 Oct;53(10):487–91 (Eng. Abstr.) **(Pol)**

[Catecholamine and serotonin content in the lymph nodes following deafferentation] Izranov VA. **Biull Eksp Biol Med** 1986 Mar; 101(3):276–7 (Eng. Abstr.) **(Rus)**

[Characteristics of the neuromodulating effect of peripherally administered thyroliberin on the rat brain] Misin'sh IP, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):50–2 (Eng. Abstr.) **(Rus)**

[Effect of changes in the catecholamine content in the brain on the chemoreactive properties of the sensorimotor cortex neurons of rats] Kruglikov RI, et al. **Izv Akad Nauk SSSR [Biol]** 1985 Nov–Dec; (6):832–40 (Eng. Abstr.) **(Rus)**

[Effect of acute and chronic deprivation of catecholaminergic system activity induced by 6-hydroxydopamine on the behavior of the rat] Gromova EA, et al. **Zh Vyssh Nerv Deiat** 1985 Nov–Dec; 35(6):1133–41 (Eng. Abstr.) **(Rus)**

CENTRAL NERVOUS SYSTEM AGENTS

A common structural model for central nervous system drugs and their receptors. Lloyd EJ, et al. **J Med Chem** 1986 Apr;29(4):453–62

Effect of various centrally acting drugs on the efflux of dopamine metabolites from the rat brain. Westerink BH, et al. **J Neurochem** 1986 Apr;46(4):1145–52

CHILD BEHAVIOR DISORDERS

Therapeutic experience with lithium in childhood aggressivity. Vetró A, et al. **Neuropsychobiology** 1985;14(3):121–7

CHILD DEVELOPMENT DISORDERS, PERVASIVE

Use of lithium and flupenthixol in a patient with pervasive developmental disorder [letter] Shafey H. **Am J Psychiatry** 1986 May;143(5):681

Use of lithium and flupenthixol in a patient with pervasive developmental disorder [letter] Shafey H. **J Am Acad Child Psychiatry** 1986 Jan; 25(1):137–8

CHILD PSYCHOLOGY

Depression in children. Epstein MH, et al. **J Sch Health** 1986 Jan; 56(1):10–2

CHLORAMINES

Inactivation of Campylobacter jejuni by chlorine and monochloramine. Blaser MJ, et al. **Appl Environ Microbiol** 1986 Feb;51(2):307–11

[Additional comments on the possibilities of using Chloramine B and Dikonit in a mixture with detergents] Kneiflová J. **Cesk Epidemiol Mikrobiol Imunol** 1986 Feb;35(1):44–9 (Eng. Abstr.) **(Cze)**

CHLORDIAZEPOXIDE

The occurrence of chlordiazepoxide degradation products in sudden deaths associated with chlordiazepoxide overdosage. Entwistle N, et al. **J Forensic Sci Soc** 1986 Jan–Feb;26(1):45–54

Tranylcypromine and chlordiazepoxide intoxication [letter] Young S, et al. **Med J Aust** 1986 Feb 3;144(3):166–7

Chlordiazepoxide directly enhances positive ingestive reactions in rats. Berridge KC, et al. **Pharmacol Biochem Behav** 1986 Feb; 24(2):217–21

Amphetamine potentiation of anti-conflict action of chlordiazepoxide. Lerner T, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):241–6

Dose-dependent impairment in the performance of a go–no go successive discrimination by chlordiazepoxide. Cole SO, et al. **Psychopharmacology (Berlin)** 1986;88(2):184–6

Effects of chlordiazepoxide training dose on the mixed agonist-antagonist properties of benzodiazepine receptor antagonist Ro 15–1788, in a drug discrimination procedure. De Vry J, et al. **Psychopharmacology (Berlin)** 1986;88(2):177–83

A comparison between chlordiazepoxide and CL 218,872, a synthetic non-benzodiazepine ligand for benzodiazepine receptors, on serotonin and catecholamine turnover in brain. McElroy JF, et al. **Psychopharmacology (Berlin)** 1986;88(1):105–8

Maternal aggression in rats: lack of interaction between chlordiazepoxide and fluprazine. Olivier B, et al. **Psychopharmacology (Berlin)** 1986; 88(1):40–3

P-CHLOROPHENYLALANINE

Altered responsiveness to substance P and 5-hydroxytryptamine in cat dorsal horn neurons after 5-HT depletion with p-chlorophenylalanine. Jeftinija S, et al. **Brain Res** 1986 Mar 12;368(1):107–15

CHLORPROMAZINE

Inhibition of fibroblast proliferation by myelotoxic drugs. Pisciotta AV, et al. **Ann NY Acad Sci** 1985;459:198–210

Functional properties of covalent beta-endorphin peptide/calmodulin complexes. Chlorpromazine binding and phosphodiesterase activation. Giedroc DP, et al. **Biochemistry** 1985 Feb 26;24(5):1203–11

Mechanism of cationic amphiphilic drug inhibition of purified lysosomal phospholipase A1. Kubo M, et al. **Biochemistry** 1985 Nov 5; 24(23):6515–20

Effects of chlorpromazine and other calmodulin antagonists on phosphatidylcholine-induced vesiculation of platelet plasma membranes. Kobayashi T, et al. **Biochim Biophys Acta** 1986 Feb 13;855(1):58–62

Partition of chlorpromazine into lipid bilayer membranes: the effect of membrane structure and composition. Luxnat M, et al. **Biochim Biophys Acta** 1986 Apr 14;856(2):274–82

Lateral diffusion of small solutes and partition of amphipaths in defect structures of lipid bilayers. Müller HJ, et al. **Biochim Biophys Acta** 1986 Apr 14;856(2):283–9

Determination of chlorpromazine and its major metabolites by gas chromatography/mass spectrometry: application to biological fluids. Gruenke LD, et al. **Biomed Mass Spectrom** 1985 Dec;12(12):707–13

Irreversible binding with biological macromolecules and effects in bacterial mutagenicity tests of the radical cation of promethazine and photoactivated promethazine. Comparison with chlorpromazine. De Mol NJ, et al. **Chem Biol Interact** 1986 Jan;57(1):73–83

Changes of transition temperatures of phosphatidylcholine and phosphatidylglycerol in presence of amphiphilic drugs. Harder A, et al. **Chem Phys Lipids** 1986 Jan;39(1–2):65–71

Chlorpromazine dissociates effects of colchicine on metabolism of triglycerides and alkaline phosphatase activity in rat liver. Selvakumar D, et al. **Indian J Biochem Biophys** 1984 Dec;21(6):400–1

Chlorpromazine inhibition of muscarinic-cholinergic responses in the rat parotid gland. Van der Ven PF, et al. **J Dent Res** 1986 Mar; 65(3):382–6

Brief exposure to contingent reinforcement produces a sustained increment in the strength of an elicited response. Hutchinson RR, et al. **J Exp Anal Behav** 1986 Mar;45(2):189–94

Effects of chlorpromazine on fixed-ratio responding: modification by fixed-interval discriminative stimuli. Witkin JM. **J Exp Anal Behav** 1986 Mar;45(2):195–205

Influence of chlorpromazine on the accumulation of 5-hydroxytryptamine by interaction with ATP. Gasco MR, et al. **J Pharm Sci** 1985 Nov; 74(11):1188–91

Influence of dietary lipids on the effect of chlorpromazine on membrane properties of rabbit red cells. Housley G, et al. **Proc R Soc Lond [Biol]** 1986 Feb 22;227(1246):43–51

Chlorpromazine and pimozide alter reinforcement efficacy and motor performance. Heyman GM, et al. **Psychopharmacology (Berlin)** 1986; 88(3):346–53

The effects of apomorphine, d-amphetamine and chlorpromazine on the aggressiveness of isolated Aequidens pulcher (Teleostei, Cichlidae). Munro AD. **Psychopharmacology (Berlin)** 1986;88(1):124–8

Therapeutic monitoring of chlorpromazine. III: Minimal interconversion between chlorpromazine and metabolites in human blood. Hawes EM, et al. **Ther Drug Monit** 1986;8(1):37–41

Plasma nor1-chlorpromazine concentrations: effects of age, race, and sex. Young RC. **Ther Drug Monit** 1986;8(1):23–6

Diazepam and chlorpromazine stimulate feeding in dwarf goats. Anika SM. **Vet Res Commun** 1985 Sep;9(4):309–12

[Interaction between chlorpromazine, hepatic protective agents and enzymes at the level of the liver cytoplasm and 'mitochondria and of the cerebral cortex in rats] Serban F, et al.

Rev Med Chir Soc Med Nat Iasi 1985 Apr-Jun;89(2):273-7 (Eng. Abstr.) **(Rum)**

[Effect of chlorpromazine on the graft versus host reaction] Grin J, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(3):337-47 (Eng. Abstr.) **(Spa)**

CHLORPROTHIXENE

Action of antidepressant neuroleptics, chlorprothixene and levomepromazine, on the central noradrenergic system: comparison with other antidepressants. Antkiewicz-Michaluk L. **Pol J Pharmacol Pharm** 1985 Sep-Oct;37(5):673-83

[Comparison of the effects of chlorprothixene and haloperidol on hypothalamic function in patients with paranoid schizophrenia] Horodnicki JM, et al. **Psychiatr Pol** 1985 May-Jun;19(3):181-7 (Eng. Abstr.) **(Pol)**

COCAINE

Medical and psychiatric complications of cocaine abuse with possible points of pharmacological treatment. Estroff TW, et al. **Adv Alcohol Subst Abuse** 1985 Fall-1986 Winter;5(1-2):61-76

Methylphenidate treatment of cocaine abusers without attention deficit disorder: a negative report. Gawin F, et al. **Am J Drug Alcohol Abuse** 1985;11(3-4):193-7

Interpersonal psychotherapy adapted for ambulatory cocaine abusers. Rounsaville BJ, et al. **Am J Drug Alcohol Abuse** 1985; 11(3-4):171-91

Comparison of 4% lidocaine/0.5% phenylephrine with 5% cocaine: which dilates the nasal passage better? Sessler CN, et al. **Anesthesiology** 1986 Feb;64(2):274-7

Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. Gawin FH, et al. **Arch Gen Psychiatry** 1986 Feb; 43(2):107-13

Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Reith ME, et al. **Biochem Pharmacol** 1986 Apr 1; 35(7):1123-9

Pharmaco-ontogeny of reward: enhancement of self-stimulation by D-amphetamine and cocaine in 3- and 10-day-old rats. Barr GA, et al. **Brain Res** 1986 Jan;389(1-2):193-202

More treatment centres responding to growing cocaine use. Korcok M. **Can Med Assoc J** 1986 Feb 15;134(4):415-8

Cocaine infants: a new arrival at hospitals' step? Newald J. **Hospitals** 1986 Apr 5;60(7):96

Cocaine increases natural killer cell activity. Van Dyke C, et al. **J Clin Invest** 1986 Apr;77(4):1387-90

Treatment of depression in chronic cocaine and phencyclidine abuse with desipramine. Giannini AJ, et al. **J Clin Pharmacol** 1986 Mar; 26(3):211-4

Intranasal topical cocaine: Moffett's method or topical cocaine paste? Quiney RE. **J Laryngol Otol** 1986 Mar;100(3):279-83

Characteristics of tolerance, recovery from tolerance and cross-tolerance for cocaine used as a discriminative stimulus. Wood DM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):120-5

Pharmacological approaches to cocaine addiction. Dackis CA, et al. **J Subst Abuse Treat** 1985;2(3):139-45 (46 ref.)

Cocaine abuse and eating disorders [letter] Jonas JM, et al. **Lancet** 1986 Feb 15;1(8477):390-1

Pimozide blocks establishment but not expression of cocaine-produced environment-specific conditioning. Beninger RJ, et al. **Life Sci** 1986 Apr 14;38(15):1425-31

Effects of cocaine on the electrical activity of single noradrenergic neurons from locus coeruleus. Pitts DK, et al. **Life Sci** 1986 Mar 31; 38(13):1229-34

Pneumomediastinum and cervical emphysema from the inhalation of 'free based' cocaine: report of three cases. Aroesty DJ, et al. **Otolaryngol Head Neck Surg** 1986 Mar;94(3):372-4

Maternal cocaine abuse and effect on the newborn. Madden JD, et al. **Pediatrics** 1986 Feb;77(2):209-11

Comparative discriminative stimulus properties of dl-cathinone, d-amphetamine, and cocaine in rats. Huang D, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):205-10

Locomotor depression in mice by norcocaine does not involve central alpha 2-adrenergic or presynaptic dopamine receptors. Reith ME, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):305-7

6-Hydroxydopamine lesions of the medial prefrontal cortex fail to influence intravenous self-administration of cocaine. Martin-Iverson MT, et al. **Psychopharmacology (Berlin)** 1986;88(3):310-4

Effects of central dopamine depletion on the d-amphetamine discriminative stimulus in rats. Woolverton WL, et al. **Psychopharmacology (Berlin)** 1986;88(2):196-200

Cocaine: it costs too much [editorial] Macdonald DI. **Public Health Rep** 1986 Mar-Apr;101(2):121-2

[Repair of cocaine-induced perforations of the nasal septum (or the glider-wing mucosal flap)] Chalaye JC, et al. **Ann Chir Plast Esthet** 1985;30(3):229-35 (Eng. Abstr.) **(Fre)**

[Modifications of the hepatotoxicity of cocaine on Swiss mice by various inhibitors] Cornette C, et al. **C R Soc Biol (Paris)** 1985;179(3):320-6 (Eng. Abstr.) **(Fre)**

COGNITION

Effortful and automatic cognitive processes in depression. Roy-Byrne PP, et al. **Arch Gen Psychiatry** 1986 Mar;43(3):265-7

Short term effects of methylphenidate on the cognitive, learning and academic performance of children with attention deficit disorder in the laboratory and the classroom. Douglas VI, et al. **J Child Psychol Psychiatry** 1986 Mar;27(2):191-211

Cognitive-behavioural treatment for benzodiazepine dependence [letter] Sanchez-Craig M, et al. **Lancet** 1986 Feb 15;1(8477):388

Measures of cognitive functioning appropriate for use in pediatric psychopharmacological research studies. Swanson JM. **Psychopharmacol Bull** 1985;21(4):887-90

COGNITION DISORDERS

Cognitive symptoms in late-life depression and their treatment. Siegfried K. **J Affective Disord** 1985;Suppl 1:S33-40

COLOR PERCEPTION

[Drug-induced functional disorders of cone function and cone interaction] Zrenner E, et al. **Fortschr Ophthalmol** 1985;82(6):589-94 (Eng. Abstr.) **(Ger)**

COMPULSIVE BEHAVIOR

The Leyton Obsessional Inventory-Child Version. Berg CJ, et al. **J Am Acad Child Psychiatry** 1986 Jan;25(1):84-91

CONDITIONING (PSYCHOLOGY)

Pimozide blocks establishment but not expression of cocaine-produced environment-specific conditioning. Beninger RJ, et al. **Life Sci** 1986 Apr 14;38(15):1425-31

CONDITIONING, CLASSICAL

Conditioned rotational behavior in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra. Carey RJ. **Brain Res** 1986 Feb 19;365(2):379-82

Destruction of intrinsic neurons in the lateral hypothalamus disrupts the classical conditioning of autonomic but not behavioral emotional responses in the rat. Iwata J, et al. **Brain Res** 1986 Mar 12; 368(1):161-6

CONDITIONING, OPERANT

Conditionability of caudate dopamine activity in the caudate nucleus of cats demonstrated by in vivo electrochemistry. Brozoski TJ, et al. **Brain Res** 1986 Feb 5;364(2):275-83

Comparison of drug effects on fixed-ratio performance and chain performance maintained under a second-order fixed-ratio schedule. Winsauer PJ, et al. **J Exp Anal Behav** 1985 Nov;44(3):367-76

Effects of chlorpromazine on fixed-ratio responding: modification by fixed-interval discriminative stimuli. Witkin JM. **J Exp Anal Behav** 1986 Mar;45(2):195-205

Effects of cholinergic drugs on aversive operant behavior induced by dorsal central gray stimulation in rats. Moriyama M, et al. **Jpn J Pharmacol** 1985 Nov;39(3):339-47

Discriminative properties of the psychostimulant dl-cathinone in a two lever operant task. Lack of evidence for dopaminergic mediation. Goudie AJ, et al. **Neuropharmacology** 1986 Jan;25(1):85-94

Effects of MK-212 (6-chloro-2[1-piperazinyl]pyrazine) on schedule-controlled behavior and their reversal by 5-HT antagonists in the pigeon. Mansbach RS, et al. **Neuropharmacology** 1986 Jan; 25(1):13-9

Visceral cortex lesions block conditioned taste aversions induced by morphine. Mackey WB, et al. **Pharmacol Biochem Behav** 1986 Jan; 24(1):71-8

Chronic haloperidol treatment: effects on operant responding and inter-response time. Heath GF, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):697-701

Conditioned taste aversions induced by 1-5-hydroxytryptophan are mediated by the area postrema. Ossenkopp KP, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):745-8

Chlorpromazine and pimozide alter reinforcement efficacy and motor performance. Heyman GM, et al. **Psychopharmacology (Berlin)** 1986; 88(3):346-53

The effects of some putative antidepressant agents on the schedule-controlled behavior of the pigeon. Lamb RJ, et al. **Psychopharmacology (Berlin)** 1986;88(3):368-73

Different effects of haloperidol and extinction on instrumental behaviours. Salamone JD. **Psychopharmacology (Berlin)** 1986;88(1):18-23

Effects of propranolol on conditioned suppression, discriminated punishment and discriminated non-reward in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1986;88(2):252-7

Disruption of schedule-controlled behavior by Ro 15-1788 one day after acute treatment with benzodiazepines. Spealman RD. **Psychopharmacology (Berlin)** 1986;88(3):398-400

Amphetamine does not affect the partial punishment effect (PPE). Weiner I, et al. **Psychopharmacology (Berlin)** 1986;88(1):119-23

Effects of diazepam and pentobarbital on discrete lever-press avoidance response in mice: baseline-dependent changes. Kuribara H, et al. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):343-8

CONFLICT (PSYCHOLOGY)

Amphetamine potentiation of anti-conflict action of chlordiazepoxide. Lerner T, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):241-6

CONVULSIVE THERAPY

[Catamnestic evaluation of the treatment of schizophrenia using insulin coma] Pavlovský P, et al. **Cesk Psychiatr** 1985 Dec;81(6):391-6 (Eng. Abstr.) **(Cze)**

CORTICOSTERONE

Inhibition of corticosteroidogenesis by etomidate. Goverde HJ, et al. **Acta Anaesthesiol Belg** 1985 Dec;36(4):375-80

The role of thyroid and adrenal cortical hormones in the modulation of the gonadal function in birds. Péczely P. **Acta Biol Hung** 1985; 36(1):45-70

Effects of prolactin administration on the zona glomerulosa of the rat adrenal cortex: stereology and plasma hormone concentrations. Mazzocchi G, et al. **Acta Endocrinol (Copenh)** 1986 Jan;111(1):101-5

LPS-caused secretion of corticosterone is mediated by histamine through histidine decarboxylase. Suzuki S, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):E243-7

Pituitary-dependent and -independent secretion of CS caused by bacterial endotoxin in rats. Suzuki S, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):E470-4

Replacement therapy against increased hydroxyurea toxicity in pituitary or adrenal ablated rats. Vacca M, et al. **Arch Toxicol [Suppl]** 1985; 8:385-9

Effect of stress-related hormones on short term memory. Gibbs ME, et al. **Behav Brain Res** 1986 Jan;19(1):1-6

In vitro interactions between Sertoli cells and steroidogenic cells. Perrard-Sapori MH, et al. **Biochem Biophys Res Commun** 1986 Jan 29; 134(2):957-62

Glucocorticoid regulation of hepatic cytosolic glucocorticoid receptors in vivo and its relationship to induction of tyrosine aminotransferase. Shirwany TA, et al. **Biochim Biophys Acta** 1986 Apr 8;886(1):162-8

Short- and long-term effects of ACTH on the adrenal zona glomerulosa of the rat. A coupled stereological and enzymological study. Mazzocchi G, et al. **Cell Tissue Res** 1986;243(2):303-10

Are endogenous glucocorticoids involved in short-term regulation of hepatic glycogen metabolism? Viskupič E, et al. **Endocrinol Exp (Bratisl)** 1985 Dec;19(4):283-9

Endogenous corticoids and lung development in the fetal rabbit. Hümmelink R, et al. **Endocrinology** 1986 Apr;118(4):1622-9

Effects of extrahypothalamic structures on the hypothalamic cell nuclear binding of corticosterone. Weidenfeld J, et al. **Exp Brain Res** 1985; 61(1):91-3

Basal plasma corticosterone level after bilateral selective lesions of the olfactory pathways in the rat. Cattarelli M, et al. **Experientia** 1986 Feb 15;42(2):169-71

Flight stimulates adrenocortical activity in pigeons (Columba livia). Haase E, et al. **Gen Comp Endocrinol** 1986 Mar;61(3):424-7

Serum inflammatory responses of transcortin binding activities and of total and free corticosterone and progesterone levels in developing rats: a kinetic approach. Savu L, et al. **Int J Tissue React** 1985;7(6):443-8

Effects of pinealectomy and aging on the serum corticosterone circadian rhythm in rats. Oxenkrug GF, et al. **J Pineal Res** 1984;1(2):181-5

Diurnal rhythm of alpha 2-noradrenergic receptors in the paraventricular nucleus and other brain areas: relation to circulating corticosterone and feeding behavior. Jhanwar-Uniyal M, et al. **Life Sci** 1986 Feb 3; 38(5):473-82

Plasma corticosterone responses to electrical stimulation of the amygdaloid complex: cytoarchitectural specificity. Dunn JD, et al. **Neuroendocrinology** 1986;42(3):211-7

Interaction between corticosterone and alpha-2-noradrenergic system of the paraventricular nucleus in relation to feeding behavior. Roland CR, et al. **Neuroendocrinology** 1986;42(4):296-305

Effects of stimulation of the preoptic area on hypothalamic paraventricular nucleus unit activity and corticosterone secretion in freely moving rats. Saphier D, et al. **Neuroendocrinology** 1986;42(2):167-73

Norepinephrine depletion in the paraventricular nucleus inhibits the adrenocortical responses to neural stimuli. Feldman S, et al. **Neurosci Lett** 1986 Feb 28;64(2):191-5

Effects of polyunsaturated fatty acids and hormones on synaptogenesis in serum-free medium cultures of mouse fetal hypothalamic cells. Tixier-Vidal A, et al. **Neuroscience** 1986;17(1):115-32

Endocrine response to acute cold exposure by lactating and non-lactating Norway rats. Adels LE, et al. **Physiol Behav** 1986 Jan;36(1):179-81

Selective breeding of chickens for corticosterone response to social stress. Gross WB, et al. **Poult Sci** 1985 Dec;64(12):2230-3

Corticosterone sampling of laying hens in different management systems. Koelkebeck KW, et al. **Poult Sci** 1986 Jan;65(1):183-5

Daily variation of corticosterone and thyroid hormones in broiler cockerels. Smoak KD, et al. **Poult Sci** 1986 Jan;65(1):197-8

In vivo responsiveness of the broilers' adrenocortical system. Smoak KD, et al. **Poult Sci** 1986 Jan;65(1):194-6

The mechanism of the effect of K+ on the steroidogenesis of rat zona glomerulosa cells of the adrenal cortex: role of cyclic AMP. Hyatt PJ, et al. **Proc R Soc Lond [Biol]** 1986 Feb 22;227(1246):21-42

Lithium and twenty-four hour rhythms of serum corticosterone, prolactin and growth hormone in pigmented eye rats. Seggie J, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):755-8

Role of prostacyclin on steroidogenesis by frog interrenal gland in vitro. Delarue C, et al. **Prostaglandins** 1986 Jan;31(1):5-17

Effects of subchronic administration of psychoactive substances on the circadian rhythm of urinary corticosterone excretion in rats. Häusler A, et al. **Psychoneuroendocrinology** 1985;10(4):421-9

Enhanced elevation of corticosterone following arecoline administration to rats selectively bred for increased cholinergic function. Overstreet DH, et al. **Psychopharmacology (Berlin)** 1986;88(1):129-30

Identification of 19-nor-corticosterone in rat urine. Dale SL, et al. **Steroids** 1985 Jan;45(1):91-8

[Evaluation of the inhibitory effect of circulating corticosteroids on circadian stimulated and stress induced secretion of ACTH in rats] Ixart G, et al. **C R Soc Biol (Paris)** 1985;179(3):346-51 (Eng. Abstr.) **(Fre)**

[Effect of muscimol (GABA-agonist) on thalamo-hypothalamic regulation by corticotropic efferents (thalamic model)] Ramade F, et al. **C R Soc Biol (Paris)** 1985;179(3):383-8 (Eng. Abstr.) **(Fre)**

[Studies on preferential binding to glucocorticoid of rat liver anionic glutathione S-transferase] Maruyama H, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Sep 20;61(9):893-911 (Eng. Abstr.) **(Jpn)**

[Effect of RL-175 on testosterone and corticosterone levels in the plasma of male albino rats] Lokhov RE, et al. **Vopr Med Khim** 1985 Nov-Dec; 31(6):86-8 (Eng. Abstr.) **(Rus)**

[The effect of sex factors on the interaction of progesterone and glucocorticoids during increased tyrosine aminotransferase and tryptophane pyrrolase activity in the liver in rats] Németh S. **Bratisl Lek Listy** 1986 Jan;85(1):19-23 (Eng. Abstr.) **(Slo)**

[Effect of clorgyline and of alpha-methyl-p-tyrosine on the plasma levels of corticosterone in the rat] Pinilla J, et al. **Rev Esp Fisiol** 1985 Dec; 41(4):411-6 (Eng. Abstr.) **(Spa)**

CORTICOTROPIN

Plasma adrenocorticotrophin, cortisol and aldosterone responses to ovine corticotrophin-releasing factor and vasopressin in sheep. Pradier P, et al. **Acta Endocrinol (Copenh)** 1986 Jan;111(1):93-100

ACTH and prolactin deficiency. Puig ML, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):296-9

Antler cycle and thermolabile and thermostable alkaline phosphatase in white-tailed deer; circannual and circadian rhythms and variation after thyroxine, dexamethasone and ACTH administration. Sempéré AJ, et al. **Acta Endocrinol (Copenh)** 1986 Jan;111(1):133-9

By 95 days of gestation CRF increases plasma ACTH and cortisol in ovine fetuses. Hargrave BY, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):E422-7

Interaction between CRF and angiotensin II in control of ACTH and adrenal steroids. Keller-Wood M, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 2):R396-402

Long-term effects of hypothalamic paraventricular lesion on CRF content and stimulated ACTH secretion. Makara GB, et al. **Am J Physiol** 1986 Mar;250(3 Pt 1):E319-24

Renin, ACTH, and adrenocortical function during hypoxia and hemorrhage in conscious rats. Raff H, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 2):R240-4

The relationship of beta-endorphin and ACTH in the cerebrospinal fluid and plasma of adult surgical patients. Scheller MS, et al. **Ann Clin Res** 1985;17(6):323-6

Dual activation of the inositol-triphosphate-calcium and cyclic nucleotide intracellular signaling systems by adrenocorticotropin in rat adrenal cells. Farese RV, et al. **Biochem Biophys Res Commun** 1986 Mar 28; 135(3):742-8

Discordant changes between immunoreactive ACTH and beta-endorphin in rat brain and pituitary during early development. Kapcala LP. **Brain Res** 1986 Feb 5;364(2):350-9

Short- and long-term effects of ACTH on the adrenal zona glomerulosa of the rat. A coupled stereological and enzymological study. Mazzocchi G, et al. **Cell Tissue Res** 1986;243(2):303-10

The regulation of the corticomelanotropic cell activity in Aves--II. Effect of various peptides on the release of ACTH from dispersed, perfused duck pituitary cells. Castro MG, et al. **Comp Biochem Physiol [A]** 1986; 83(1):71-5

Are endogenous glucocorticoids involved in short-term regulation of hepatic glycogen metabolism? Viskupič E, et al. **Endocrinol Exp (Bratisl)** 1985 Dec;19(4):283-9

Responses of plasma adrenocorticotropin and cortisol to intravenous injection of synthetic ovine corticotropin releasing factor in the morning and early evening in normal human subjects. Watabe T, et al. **Endocrinol Jpn** 1985 Oct;32(5):771-9

Stimulation of adenosine 3',5'-monophosphate production in rat Sertoli cells by alpha-melanotropin-stimulating hormone (alpha MSH) and des-acetyl alpha MSH. Boitani C, et al. **Endocrinology** 1986 Apr; 118(4):1513-8

In vitro stimulation and inhibition of adrenocorticotropin release by pituitary cells from ovine fetuses and lambs. Durand P, et al. **Endocrinology** 1986 Apr;118(4):1387-94

Long term culture of primary rat pituitary adrenocorticotropin/endorphin-producing cells in serum-free medium. May V, et al. **Endocrinology** 1986 Apr;118(4):1284-95

Spontaneous and stimulated adrenocorticotropin and vasopressin pulsatile secretion in the pituitary venous effluent of the horse. Redekopp C, et al. **Endocrinology** 1986 Apr;118(4):1410-6

Dopaminergic modulation of ACTH-induced grooming. Spruijt BM, et al. **Eur J Pharmacol** 1986 Jan 29;120(3):249-56

The possible potassium involvement in the modulation of the long-term trophic action of ACTH on the rat adrenal zona fasciculata. Robba C, et al. **Exp Clin Endocrinol** 1985 Dec;86(3):371-4

Lack of glycosilation of pro-opiomelanocortin might account for the periodic acid-Schiff-negative reaction in ACTH cells of teleost fishes. Iturriza FC, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):229-36

In vitro study of frog (Rana ridibunda Pallas) interrenal function by use of a simplified perifusion system. VIII. Structure-activity relationship of synthetic ACTH fragments and gamma-MSH. Leboulenger F, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):187-96

Comparative effects of corticotropin-releasing factor, arginine vasopressin, and related neuropeptides on the secretion of ACTH and alpha-MSH by frog anterior pituitary cells and neurointermediate lobes in vitro. Tonon MC, et al. **Gen Comp Endocrinol** 1986 Mar; 61(3):438-45

Rise in plasma beta-endorphin and ACTH in response to hyperthermia in sauna. Ježová D, et al. **Horm Metab Res** 1985 Dec;17(12):693-4

Inhibition of spontaneous ACTH release and improved response to CRF in sheep premedicated with the enkephalin analogue DAMME. Redekopp CA, et al. **Horm Metab Res** 1985 Dec;17(12):646-9

Beta-endorphin attenuates the serum cortisol response to exogenous adrenocorticotropin. Beyer HS, et al. **J Clin Endocrinol Metab** 1986 May;62(5):808-11

Effect of ketoconazole on adrenocorticotrophic hormone secretion in vitro and in vivo. Burrin JM, et al. **J Endocrinol** 1986 Jan; 108(1):37-41

Cholecystokinin-8 stimulates adrenocorticotropin release from anterior pituitary cells. Reisine T, et al. **J Pharmacol Exp Ther** 1986 Mar; 236(3):621-6

Effect of etomidate on hypercortisolism due to ectopic ACTH production [letter] Gärtner R, et al. **Lancet** 1986 Feb 1;1(8475):275

ACTH increases adrenal medullary PNMT activity in neonatal rats. Banerji TK, et al. **Life Sci** 1986 Jan 27;38(4):343-9

Intra-cerebroventricular captopril reduces plasma ACTH and vasopressin responses to hemorrhagic stress. Cameron VA, et al. **Life Sci** 1986 Feb 10;38(6):553-9

ACTH-(1-24) and alpha-MSH antagonize dopamine receptor-mediated inhibition of striatal dopamine and acetylcholine release. Versteeg DH, et al. **Life Sci** 1986 Mar 3;38(9):835-40

Vanadium inhibits ACTH-mediated but not cyclic AMP-dependent adrenal steroidogenesis. Hayashi Y, et al. **Mol Cell Endocrinol** 1986 Jan; 44(1):17-24

Atrial natriuretic factor does not affect basal, forskolin- and CRF-stimulated adenylate cyclase activity, cAMP formation or ACTH secretion, but does stimulate cGMP synthesis in anterior pituitary. Heisler S, et al. **Mol Cell Endocrinol** 1986 Feb;44(2):125-31

Centrally administered inhibitors of the generation and action of angiotensin II do not attenuate the increase in ACTH secretion produced by ether stress in rats. Buckner FS, et al. **Neuroendocrinology** 1986;42(2):97-101

Glutamate decarboxylase activity in the pituitary in the presence of a change in the corticotropin level in the rat organism. Mishunina TM, et al. **Neurosci Behav Physiol** 1985 Sep-Oct;15(5):439-42

Atrial natriuretic peptide inhibits the stimulation of aldosterone secretion by ACTH in vitro and in vivo. Chartier L, et al. **Proc Soc Exp Biol Med** 1986 May;182(1):132-6

Implication of the serotoninergic system in the decreased ACTH response to stress after lesion of the amygdaloid central nucleus. Beaulieu S, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):665-9

[Passive immunization with an anti-oCRF41 immune serum inhibits the circadian increase of plasma ACTH in rats] Ixart G, et al. **C R Acad Sci [III]** 1985;301(14):659-64 (Eng. Abstr.) **(Fre)**

[Evaluation of the inhibitory effect of circulating corticosteroids on circadian stimulated and stress induced secretion of ACTH in rats] Ixart G, et al. **C R Soc Biol (Paris)** 1985;179(3):346-51 (Eng. Abstr.) **(Fre)**

[Responses of plasma cortisol and ACTH to stimulation by the synthetic ovine ACTH-releasing factor in normal man (letter)] Dewailly D, et al. **Presse Med** 1985 Dec 7;14(42):2148 (Fre)

CORTICOTROPIN RELEASING HORMONE

Plasma adrenocorticotrophin, cortisol and aldosterone responses to ovine corticotrophin-releasing factor and vasopressin in sheep. Pradier P, et al. **Acta Endocrinol (Copenh)** 1986 Jan;111(1):93-100

Application of avidin-biotinized peroxidase (ABC) method for immunocytochemical localization of corticotropin-releasing factor (CRF) in rat hypothalamus. Miśkowiak B, et al. **Acta Histochem (Jena)** 1985;77(2):127-31

Effects of morphine on hypothalamic corticotropin-releasing factor (CRF), norepinephrine and dopamine in non-stressed and stressed rats. Suemaru S, et al. **Acta Med Okayama** 1985 Dec;39(6):463-70

Corticotropin-releasing factor can stimulate gonadotropin secretion by human fetal pituitaries in superfusion. Blumenfeld Z, et al. **Am J Obstet Gynecol** 1986 Mar;154(3):606-12

By 95 days of gestation CRF increases plasma ACTH and cortisol in ovine fetuses. Hargrave BY, et al. **Am** J **Physiol** 1986 Apr; 250(4 Pt 1):E422-7

Interaction between CRF and angiotensin II in control of ACTH and adrenal steroids. Keller-Wood M, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 2):R396-402

Long-term effects of hypothalamic paraventricular lesion on CRF content and stimulated ACTH secretion. Makara GB, et al. **Am J Physiol** 1986 Mar;250(3 Pt 1):E319-24

Demonstration that corticotropin-releasing factor binding to rat peripheral tissues is modulated by glucocorticoid treatment in vivo and in vitro. Dave JR, et al. **Biochem Biophys Res Commun** 1986 Jan 14; 134(1):255-60

Corticotropin-releasing factor and intraocular pressure. Liu JH. **Curr Eye Res** 1985 Dec;4(12):1247-52

Brain corticotropin-releasing factor (CRF) and catecholamine responses in acutely stressed rats. Suemaru S, et al. **Endocrinol Jpn** 1985 Oct; 32(5):709-18

Responses of plasma adrenocorticotropin and cortisol to intravenous injection of synthetic ovine corticotropin releasing factor in the morning and early evening in normal human subjects. Watabe T, et al. **Endocrinol Jpn** 1985 Oct;32(5):771-9

hpGRF-44-NH2, lot no. 92-81-5G-41-47, is (human) growth hormone-releasing factor containing no trace of (ovine) corticotropin-releasing factor. Ling N, et al. **Endocrinology** 1986 Mar; 118(3):1249-51

Corticotropin-releasing factor binding to the anterior pituitary receptor is modulated by divalent cations and guanyl nucleotides. Perrin MH, et al. **Endocrinology** 1986 Mar;118(3):1171-9

Identification of a putative GH-releasing factor (GRF) batch as predominantly ovine CRF with a small quantity of human GRF. Tannenbaum GS, et al. **Endocrinology** 1986 Mar;118(3):1246-8

Immunoreactivity of hypothalamo-neurohypophysial neurons which secrete corticotropin-releasing hormone (CRH) and vasopressin (Vp): immunocytochemical evidence for a correlation with their functional state in colchicine-treated rats. Alonso G, et al. **Exp Brain Res** 1986; 61(3):497-505

Inhibition of spontaneous ACTH release and improved response to CRF in sheep premedicated with the enkephalin analogue DAMME. Redekopp CA, et al. **Horm Metab Res** 1985 Dec;17(12):646-9

Corticotrophin-releasing factor-like immunoreactivity and bioactivity of human fetal and adult hypothalami. Ackland JF, et al. **J Endocrinol** 1986 Feb;108(2):171-80

The physiological significance of arginine vasopressin in potentiating the response to corticotrophin-releasing factor in sheep. Redekopp C, et al. **J Endocrinol** 1986 Feb;108(2):309-12

Stimulation and inhibition of food intake in sheep by centrally-administered hypothalamic releasing factors. Ruckebusch Y, et al. **Life Sci** 1986 Mar 10;38(10):929-34

Atrial natriuretic factor does not affect basal, forskolin- and CRF-stimulated adenylate cyclase activity, cAMP formation or ACTH secretion, but does stimulate cGMP synthesis in anterior pituitary. Heisler S, et al. **Mol Cell Endocrinol** 1986 Feb;44(2):125-31

Corticotropin-releasing factor and forskolin increase proopiomelanocortin messenger RNA levels in rat anterior and intermediate cells in vitro. Loeffler JP, et al. **Neurosci Lett** 1985 Dec 18;62(3):383-7

The coexistence of oxytocin and corticotropin-releasing factor in the hypothalamus: an immunocytochemical study in the rat, sheep and hedgehog. Papadopoulos GC, et al. **Neurosci Lett** 1985 Dec 4; 62(2):213-8

Effects of sauvagine, urotensin I and CRF on food intake in rats. Negri L, et al. **Peptides** 1985;6 Suppl 3:53-7

Developmental, behavioral, and opiate receptor changes after prenatal or postnatal beta-endorphin, CRF, or Tyr-MIF-1. Zadina JE, et al.

Psychoneuroendocrinology 1985;10(4):367-83

Stress-induced inhibition of reproductive functions: role of endogenous corticotropin-releasing factor. Rivier C, et al. **Science** 1986 Feb 7; 231(4738):607-9

[Passive immunization with an anti-oCRF41 immune serum inhibits the circadian increase of plasma ACTH in rats] Ixart G, et al. **C R Acad Sci [III]** 1985;301(14):659-64 (Eng. Abstr.) **(Fre)**

[Responses of plasma cortisol and ACTH to stimulation by the synthetic ovine ACTH-releasing factor in normal man (letter)] Dewailly D, et al. **Presse Med** 1985 Dec 7;14(42):2148 **(Fre)**

[Hypothalamic factors: current findings] Sizonenko PC. **Schweiz Med Wochenschr** 1986 Mar 1;116(9):271-4 (Eng. Abstr.) **(Fre)**

CROSS-CULTURAL COMPARISON

Pharmacotherapy of chronic hospitalized schizophrenics: prescription practices. Wilson WH, et al. **Neuropsychobiology** 1985;14(2):75-82

DELUSIONS

Two cases of 'pure' or 'primary' erotomania successfully treated with pimozide. Munro A, et al. **Can J Psychiatry** 1985 Dec;30(8):619-22

Monosymptomatic hypochondriacal psychosis manifesting as delusions of infestation: case studies of treatment with haloperidol. Andrews E, et al. **J Clin Psychiatry** 1986 Apr;47(4):188-90

DEMENTIA

The concept of subcortical and cortical dementia: another look. Whitehouse PJ. **Ann Neurol** 1986 Jan;19(1):1-6 (84 ref.)

Postmortem central catecholamines and antemortem cognitive impairment in elderly schizophrenics and controls. Bridge TP, et al. **Neuropsychobiology** 1985;14(2):57-61

DEPRESSION

Plasma neutral amino acids and food preferences: possible implications in normals and depressives. Møller SE. **Bibl Nutr Dieta** 1986;(38):149-53

Circadian rhythm stability in the depressive syndrome in patients treated with antidepressant drugs. Madjirova N. **Folia Med (Plovdiv)** 1985; 27(1):5-10

Present status of drug therapy of depression in late life. Gerner RH. **J Affective Disord** 1985;Suppl 1:S23-31 (67 ref.)

General management of depression in late life. Murphy E. **J Affective Disord** 1985;Suppl 1:S7-10

Antidepressant-resistant depression in the elderly [editorial] Borson S, et al. **J Am Geriatr Soc** 1986 Mar;34(3):245-7

Treatment of depression in chronic cocaine and phencyclidine abuse with desipramine. Giannini AJ, et al. **J Clin Pharmacol** 1986 Mar; 26(3):211-4

Alprazolam treatment of postcoronary bypass anxiety and depression. Freeman AM 3d, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):39-41

Depression in children. Epstein MH, et al. **J Sch Health** 1986 Jan; 56(1):10-2

A double-blind comparison of once-daily flupenthixol and mianserin in depressed hospital out-patients. Majid I. **Pharmatherapeutica** 1986; 4(7):405-10

Evidence for the locus coeruleus involvement in desipramine action in animal models of depression. Danysz W, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):855-64

[Value of amineptin in the treatment of different depressive states. Apropos of 112 cases treated as part of a national multi-centric study] Marie-Cardine M, et al. **Encephale** 1985 Jul-Aug;11(4):175-7 (Eng. Abstr.) **(Fre)**

[The circulatory system in patients with depression during treatment with antidepressive drugs. I. Analysis of ECG records during the depressive phase of affective diseases] Rajewska J, et al. **Psychiatr Pol** 1985 Jul-Aug;19(4):271-7 (Eng. Abstr.) **(Pol)**

DEPRESSION, INVOLUTIONAL

[Vital disorders of the mouth (glossodynia) in depressive involutional psychoses] Maier C. **Nervenarzt** 1986 Feb;57(2):113-5 (Eng. Abstr.) **(Ger)**

DEPRESSIVE DISORDER

A Belgian multicentre study of fluvoxamine in depressive outpatients. Brasseur R, et al. **Acta Psychiatr Belg** 1985 Sep-Oct;85(5):636-43

Tryptophan to competing amino acids ratio in depressive disorder: relation to efficacy of antidepressive treatments. Møller SE. **Acta Psychiatr Scand [Suppl]** 1985;325:3-31 (146 ref.)

Depression. Acute care in the hospital. Campbell L. **Am J Nurs** 1986 Mar;86(3):288-91

Drugs and depression. Harris B. **Am J Nurs** 1986 Mar;86(3):292-3

Depression. What does it mean? Minot SR. **Am J Nurs** 1986 Mar; 86(3):284-8

An association between norepinephrine-to-epinephrine ratio and suicidal ideation in depression [letter] **Am J Psychiatry** 1986 May; 143(5):683-4

Change in serum antidepressant level at a constant dose of medication [letter] Chisholm DD. **Am J Psychiatry** 1986 Mar;143(3):388

Antidepressant effect of a tryptophan hydroxylase activation inhibitor, AGN 2979 [letter] Clerc G, et al. **Am J Psychiatry** 1986 Feb; 143(2):264-5

Patient with chronic and apparently treatment-resistant dysthymia [letter] Harris SJ, et al. **Am J Psychiatry** 1986 Feb;143(2):260-1

Lithium-antidepressant combinations in the treatment of depressed, physically ill geriatric patients. Kushnir SL. **Am J Psychiatry** 1986 Mar; 143(3):378-9

Lithium augmentation in psychotic depression refractory to combined drug treatment. Nelson JC, et al. **Am J Psychiatry** 1986 Mar; 143(3):363-6

Tricyclic nonresponders: phenomenology and treatment. Roose SP, et al. **Am J Psychiatry** 1986 Mar;143(3):345-8

Combined psychotherapy and pharmacotherapy for depression. A systematic analysis of the evidence. Conte HR, et al. **Arch Gen Psychiatry** 1986 May;43(5):471-9

Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Keller MB, et al. **Arch Gen Psychiatry** 1986 May;43(5):458-66

Treatment for depression. 'Standard' clinical practice as an unexamined topic. Kupfer DJ, et al. **Arch Gen Psychiatry** 1986 May; 43(5):509-11

Dopaminergic effects of carbamazepine. Relationship to clinical response in affective illness. Post RM, et al. **Arch Gen Psychiatry** 1986 Apr; 43(4):392-6

Effortful and automatic cognitive processes in depression. Roy-Byrne PP, et al. **Arch Gen Psychiatry** 1986 Mar;43(3):265-7

Social skills training: an effective treatment for unipolar non-psychotic depression? Jackson HJ, et al. **Aust NZ J Psychiatry** 1985 Dec; 19(4):342-53 (52 ref.)

Seasonal variation of platelet serotonin uptake and 3H-imipramine binding in normal and depressed subjects. Egrise D, et al. **Biol Psychiatry** 1986 Mar;21(3):283-92

Urinary excretion of free tyramine and of norepinephrine and its metabolites in unipolar depressed patients. Roy A, et al. **Biol Psychiatry** 1986 Feb;21(2):221-4

Desmethylimipramine treatment increases melatonin production in humans. Sack RL, et al. **Biol Psychiatry** 1986 Apr;21(4):406-10

Plasma concentrations, information and therapy adherence during long-term treatment with antidepressants. Altamura AC, et al. **Br J Clin Pharmacol** 1985 Dec;20(6):714-6

Should plasma or urinary MHPG be measured in psychiatric research? A critical comment. Filser JG, et al. **Br J Psychiatry** 1986 Jan; 148:95-7

Cerebrospinal fluid vasopressin--changes in depression. Gjerris A, et al. **Br J Psychiatry** 1985 Dec;147:696-701

Imipramine and amitriptyline plasma concentrations and clinical response in major depression. Kocsis JH, et al. **Br J Psychiatry** 1986 Jan; 148:52-7

Management of depression in general practice [editorial] Brandon S. **Br Med J [Clin Res]** 1986 Feb 1;292(6516):287-9

A comparison of the safety and efficacy of alprazolam and desipramine in moderately severe depression. Remick RA, et al. **Can J Psychiatry** 1985 Dec;30(8):597-601

Abstinence from night sleep as a treatment for endogenous depressions. The earliest observations in a Danish mental hospital (1954) and an analysis of the causal mechanism. Ostenfeld I. **Dan Med Bull** 1986 Feb; 33(1):45-9

Growth hormone release after desipramine in depressive illness. Meesters P, et al. **Eur Arch Psychiatry Neurol Sci** 1985;235(3):140-2

Hypothalamic releasing factor in primary and situational depression. Dekeyser YF. **Int J Neurol** 1980;14(2-4):269-72

The universal enervating triad: psychopharmaceutical considerations of anxiety, schizophrenia, and depression. Miller TW, et al. **Issues Ment Health Nurs** 1984;6(3-4):275-91

Cognitive symptoms in late-life depression and their treatment. Siegfried K. **J Affective Disord** 1985;Suppl 1:S33-40

Therapeutic effects of serotonin uptake inhibitors in depression. Asberg M, et al. **J Clin Psychiatry** 1986 Apr;47 Suppl:23-35 (199 ref.)

Atypical depression and seasonal energy syndrome [letter] Pies R. **J Clin Psychiatry** 1986 Feb;47(2):98

Clinical studies on the phenylethylamine hypothesis of affective disorder: urine and blood phenylacetic acid and phenylalanine dietary supplements. Sabelli HC, et al. **J Clin Psychiatry** 1986 Feb; 47(2):66-70

Stability of the postpsychotic depression syndrome. Siris SG, et al. **J Clin Psychiatry** 1986 Feb;47(2):86-8

Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. Feighner J, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):27-32

Efficacy of carbamazepine as an antidepressant in chronic resistant depressives. Prasad AJ. **J Indian Med Assoc** 1985 Jul;83(7):235-7

Biological markers in depression. Monoamine metabolites in urine of depressed patients and normal subjects. Vandel S, et al. **Pharmacopsychiatry** 1985 Nov;18(6):347-50

Neurotransmitter metabolites and endocrine responses in depression. Hasey GM, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):613-7

Platelet 3H imipramine binding: a possible predictor of response to antidepressant treatment. Hrdina PD, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):619-23

Course of clinical response to antidepressants. Lapierre YD. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):503-7

Forms of atypical depression and their response to antidepressant drugs. Davidson J, et al. **Psychiatry Res** 1986 Feb;17(2):87-95

Effects of ECT on sleep and CSF biogenic amines in affective illness. Hoffmann G, et al. **Psychiatry Res** 1985 Nov;16(3):199-206

Human plasma melatonin is elevated during treatment with the monoamine oxidase inhibitors clorgyline and tranylcypromine but not deprenyl. Murphy DL, et al. **Psychiatry Res** 1986 Feb;17(2):119-27

Visual flicker in depression: response criteria, confidence ratings and response times. Herskovic JE, et al. **Psychol Med** 1986 Feb; 16(1):187-97

Colour associations as predictors of the effectiveness of anti-depressant pharmacotherapy in endogenous depressive patients. Demeter E, et al. **Psychopathology** 1985;18(5-6):305-9

Scales of potential use in the psychopharmacologic treatment of depressed children and adolescents. Petti TA. **Psychopharmacol Bull** 1985; 21(4):951-77

Moclobemide, a new reversible MAO inhibitor--interaction with tyramine and tricyclic antidepressants in healthy volunteers and depressive patients. Korn A, et al. **Psychopharmacology (Berlin)** 1986; 88(2):153-7

Plasma tryptophan and tyrosine ratios to competing amino acids in relation to antidepressant response to citalopram and maprotiline. A preliminary study. Møller SE, et al. **Psychopharmacology (Berlin)** 1986; 88(1):96-100

Decrease in plasma levels of 3,4-dihydroxyphenylethyleneglycol in major depression. Scatton B, et al. **Psychopharmacology (Berlin)** 1986; 88(2):220-5

Depression in primary care: evolving concepts and approach to therapy. Rucker L, et al. **South Med J** 1986 Feb;79(2):215-22 (94 ref.)

[Novel comparative profile of the clinical activity of antidepressive agents] Ansseau M, et al. **Acta Psychiatr Belg** 1985 Sep-Oct;85(5):644-61 (Eng. Abstr.) **(Fre)**

[Resistant depressions in chronicity phase. Clinical and pharmacological aspects. Apropos of 25 cases] Houillon P, et al. **Ann Med Psychol (Paris)** 1985 Jul;143(7):628-33 **(Fre)**

[Cholinergic hypothesis of depression] Leboyer M, et al. **Encephale** 1985 Nov-Dec;11(6):229-34 (53 ref.) (Eng. Abstr.) **(Fre)**

[Value of amineptin in the treatment of different depressive states. Apropos of 112 cases treated as part of a national multi-centric study] Marie-Cardine M, et al. **Encephale** 1985 Jul-Aug;11(4):175-7 (Eng. Abstr.) **(Fre)**

[Circadian rhythms of the central temperature and blood cortisol in endogenous depression] Souetre E, et al. **Encephale** 1985 Sep-Oct; 11(5):185-98 (Eng. Abstr.) **(Fre)**

[Possibilities and limitations of treating depressive disorders in practice] Gastpar M. **Ther Umsch** 1986 Jan;43(1):50-5 (Eng. Abstr.) **(Ger)**

[Amineptine: clinical considerations on a new antidepressive] Carreca A, et al. **Clin Ter** 1985 Dec 31;115(6):449-52 (Eng. Abstr.) **(Ita)**

[The circulatory system in patients with depression during treatment with antidepressive drugs. II. Effect of therapeutic doses of thymoleptics on ECG records in patients with endogenous depression] Rajewska J. **Psychiatr Pol** 1985 Jul-Aug;19(4):278-84 (Eng. Abstr.) **(Pol)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. II. Comparison of the effects of various thymoleptics on the psychopathological symptoms of endogenous depressive syndromes] Strzyżewski W, et al. **Psychiatr Pol** 1985 Sep-Oct;19(5):363-9 (Eng. Abstr.) **(Pol)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. I. Analysis of the clinical effect of antidepressive drugs with various pharmacological profiles] Twarowska-Hauser J, et al. **Psychiatr Pol** 1985 Sep-Oct; 19(5):357-62 (Eng. Abstr.) **(Pol)**

[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. III. Analysis of the factors affecting the effectiveness of treatment with thymoleptics] Twarowska-Hauser J, et al. **Psychiatr Pol** 1985 Sep-Oct;19(5):370-5 (Eng. Abstr.) **(Pol)**

DESIPRAMINE

Sleep, depression and the effects of antidepressant drugs. Gaillard JM, et al. **Acta Psychiatr Belg** 1985 Sep-Oct;85(5):561-7

Treating bulimia with desipramine. A double-blind, placebo-controlled study. Hughes PL, et al. **Arch Gen Psychiatry** 1986 Feb;43(2):182-6

Desmethylimipramine treatment increases melatonin production in humans. Sack RL, et al. **Biol Psychiatry** 1986 Apr;21(4):406-10

A comparison of the safety and efficacy of alprazolam and desipramine in moderately severe depression. Remick RA, et al. **Can J Psychiatry** 1985 Dec;30(8):597-601

Treatment of childhood hyperactivity with desipramine: plasma drug concentration, cardiovascular effects, plasma and urinary catecholamine levels, and clinical response. Donnelly M, et al. **Clin Pharmacol Ther** 1986 Jan;39(1):72-81

Growth hormone release after desipramine in depressive illness. Meesters P, et al. **Eur Arch Psychiatry Neurol Sci** 1985;235(3):140-2

Antidepressants and protein kinases: desipramine treatment affects pineal gland cAMP-dependent protein kinase activity. Moyer JA, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):57-64

Liquid chromatographic determination of identity, content, and content uniformity of desipramine, fluphenazine, and promazine. Beaulieu N, et al. **J Assoc Off Anal Chem** 1986 Jan-Feb;69(1):178-9

A sensitive colorimetric method for the determination of imipramine hydrochloride and desipramine hydrochloride. el-Yazbi FA, et al. **J Clin Hosp Pharm** 1985 Dec;10(4):373-7

Treatment of depression in chronic cocaine and phencyclidine abuse with desipramine. Giannini AJ, et al. **J Clin Pharmacol** 1986 Mar; 26(3):211-4

Tricyclic antidepressants in vivo methylation: response to Lydiard and co-workers [letter] Narasimhachari N. **J Clin Psychopharmacol** 1986 Feb;6(1):61-2

Agonist interactions with beta-adrenergic receptors following chronic administration of desipramine or the atypical antidepressants, iprindole and mianserin. Hancock AA, et al. **J Recept Res** 1985;5(5-6):311-34

Antagonism by dopamine, but not noradrenaline receptor blockers of the anti-immobility activity of desipramine after different treatment schedules in the rat. Pulvirenti L, et al. **Pharmacol Res Commun** 1986 Jan;18(1):73-80

Evidence for the locus coeruleus involvement in desipramine action in animal models of depression. Danysz W, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):855-64

DESOXYCORTICOSTERONE

Body sodium in rats: response to DOCA, adrenalectomy, changes in salt intake, and a salt load. Simpson FO, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 2):F551-8

Deoxycorticosterone biosynthesis in kidney tissue of experimental animals. Characterization of steroid 21-hydroxylase activity in guinea pig kidney. Casey ML, et al. **Ann NY Acad Sci** 1985;458:232-7

Replacement therapy against increased hydroxyurea toxicity in pituitary or adrenal ablated rats. Vacca M, et al. **Arch Toxicol [Suppl]** 1985; 8:385-9

Mineralocorticoid escape during kallikrein inhibition. Overlack A, et al. **Clin Sci** 1986 Jan;70(1):13-7

Running to the taste of salt in mineralocorticoid-treated rats. Schulkin J, et al. **Horm Behav** 1985 Dec;19(4):413-25

Sodium transport by rat cortical collecting tubule. Effects of vasopressin and desoxycorticosterone. Reif MC, et al. **J Clin Invest** 1986 Apr; 77(4):1291-8

Mineralocorticoid effect on K+ permeability of the rabbit cortical collecting tubule. Stokes JB. **Kidney Int** 1985 Oct;28(4):640-5

DEXTROAMPHETAMINE

Relationship of limbic dopamine levels to amphetamine- and anticholinergic-induced hyperactivity in the rat. Carey RJ. **Biol Psychiatry** 1986 Mar;21(3):317-21

Comparison of drug effects on fixed-ratio performance and chain performance maintained under a second-order fixed-ratio schedule. Winsauer PJ, et al. **J Exp Anal Behav** 1985 Nov;44(3):367-76

Effects of chronic lithium treatment on brain monoamine metabolism and amphetamine-induced locomotor stimulation in rats. Berggren U. **J Neural Transm** 1985;64(3-4):239-50

Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. Parker EM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):179-92

Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. II. Release in the presence of vesicular transmitter stores. Parker EM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):193-203

Central noradrenaline depletion attenuates amphetamine-induced locomotor behavior. Mohammed AK, et al. **Neurosci Lett** 1986 Feb 28;64(2):139-44

Unilateral dopamine depletions attenuate the response of striatal neurons to systemic amphetamine in both hemispheres. Basse-Tomusk AE, et al. **Neuroscience** 1985 Dec;16(4):845-50

Comparative discriminative stimulus properties of dl-cathinone, d-amphetamine, and cocaine in rats. Huang D, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):205-10

Central noradrenaline depletion antagonizes aspects of d-amphetamine-induced hyperactivity in the rat. Archer T, et al. **Psychopharmacology (Berlin)** 1986;88(2):141-6

The effects of apomorphine, d-amphetamine and chlorpromazine on the aggressiveness of isolated Aequidens pulcher (Teleostei, Cichlidae). Munro AD. **Psychopharmacology (Berlin)** 1986;88(1):124-8

Effects of central dopamine depletion on the d-amphetamine discriminative stimulus in rats. Woolverton WL, et al. **Psychopharmacology (Berlin)** 1986;88(2):196-200

DIAZEPAM

Cardiovascular changes in dogs given diazepam and diazepam-ketamine. Haskins SC, et al. **Am J Vet Res** 1986 Apr;47(4):795-8

Diazepam and free plasma bupivacaine concentration [letter] Burke D. **Anesth Analg** 1986 Mar;65(3):314

Variability of the respiratory response to diazepam. Bailey PL, et al. **Anesthesiology** 1986 Apr;64(4):460-5

Preliminary study of the pharmacokinetics of desmethyldiazepam administered as drops or tablets. Yeates RA, et al. **Arzneimittelforschung** 1986;36(1):138-40

Diazepam inhibits potassium-induced aldosterone secretion in adrenal glomerulosa cell. Shibata H, et al. **Biochem Biophys Res Commun** 1986 Mar 28;135(3):994-9

Influence of benzodiazepine (diazepam) by single and repeated treatment on the growth of Tetrahymena. Darvas Z, et al. **Biomed Biochim Acta** 1985;44(11-12):1725-8

Diazepam and midazolam for sedation during bronchoscopy [letter] Dundee JW, et al. **Br J Anaesth** 1986 Apr;58(4):466-7

Sedation in outpatient oral surgery. Comparison of temazepam by mouth and diazepam i.v. O'Boyle CA, et al. **Br J Anaesth** 1986 Apr; 58(4):378-84

Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. Cohen AF, et al. **Br J Clin Pharmacol** 1985 Dec;20(6):619-29

One-year follow-up of anxious patients treated with diazepam. Rickels K, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):32-6

Diazepam in blood of Danish drivers: occurrence as shown by gas-liquid chromatographic assay following radioreceptor screening. Worm K, et al. **J Forensic Sci Soc** 1985 Nov-Dec;25(6):407-12

Estimation of the blood-plasma concentration ratio of diazepam in the rat. Klotz U. **J Pharmacokinet Biopharm** 1985 Jun;13(3):347-8

Plasma concentrations of diazepam and N-desmethyldiazepam in Asian children after an intravenous or rectal dose of diazepam. Quak SH, et al. **J Singapore Paediatr Soc** 1985;27(3-4):200-3

Developmental alterations in maturing rats caused by chronic prenatal and postnatal diazepam treatments. Shibuya T, et al. **Jpn J Pharmacol** 1986 Jan;40(1):21-9

Cognitive-behavioural treatment for benzodiazepine dependence [letter] Sanchez-Craig M, et al. **Lancet** 1986 Feb 15;1(8477):388

Interactions of Ro 15-1788, CGS 8216 and diazepam on head-turning in rats. Goldstein JM, et al. **Life Sci** 1986 Feb 3;38(5):459-63

Supraspinal depressant action of diazepam on the crossed extensor reflex. Kawasaki K, et al. **Neurosci Lett** 1986 Jan 16;63(2):175-9

Stressor-provoked response patterns in a swim task: modification by diazepam. Prince CR, et al. **Pharmacol Biochem Behav** 1986 Feb; 24(2):323-8

Behavioural responses to diazepam of drug-naive and experienced monkeys (Macaca mulatta). Bradley CM, et al. **Psychopharmacology (Berlin)** 1986;88(1):112-4

The pharmacokinetics of diazepam and desmethyldiazepam in rat brain and plasma. Friedman H, et al. **Psychopharmacology (Berlin)** 1986; 88(3):267-70

The behavioral actions of diazepam and oxazepam are similar. Mewaldt SP, et al. **Psychopharmacology (Berlin)** 1986;88(2):165-71

Differential effect of benzodiazepine sedation in high and low anxious patients in a 'real life' stress setting. O'Boyte CA, et al. **Psychopharmacology (Berlin)** 1986;88(2):226-9

Diazepam and chlorpromazine stimulate feeding in dwarf goats. Anika SM. **Vet Res Commun** 1985 Sep;9(4):309-12

Effects of diazepam and pentobarbital on discrete lever-press avoidance response in mice: baseline-dependent changes. Kuribara H, et al. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):343-8

[Determination of diazepam and medazepam by precipitation with tetraphenylboron sodium] Garcia Madrid H, et al. **J Pharm Belg** 1985 Nov-Dec;40(6):435-8 (Eng. Abstr.) **(Fre)**

[The effect of diazepam on neonatal neurobehavioral response] Kojima S, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Dec; 37(12):2784-90 (Eng. Abstr.) **(Jpn)**

[Effect of anticonvulsants on serum protein binding of 14C-diazepam] Mimaki T, et al. **No To Hattatsu** 1985 Nov;17(6):485-90 (Eng. Abstr.) **(Jpn)**

[Stages in the development of neuroses in the dog and effects of preparations with antidepressive and tranquilizing properties] Mekhedova AIa, et al. **Zh Vyssh Nerv Deiat** 1985 Nov-Dec; 35(6):1147-55 (Eng. Abstr.) **(Rus)**

[The effect of premedication with diazepam on patient cooperation during dental treatment] Jakšić M. **Vojnosanit Pregl** 1985 Sep-Oct; 42(5):357-9 (Eng. Abstr.) **(Ser)**

[Simple-blind clinical study with sublingual lorazepam vs. injectable diazepam as premedication in colonoscopies] Costas CD, et al. **Acta Gastroenterol Latinoam** 1985;15(1):43-8 (Eng. Abstr.) **(Spa)**

DIBENZAZEPINES

Inhibition of fibroblast proliferation by myelotoxic drugs. Pisciotta AV, et al. **Ann NY Acad Sci** 1985;459:198-210

Locus coeruleus norepinephrine-containing neurons: effects produced by acute and subchronic treatment with antipsychotic drugs and amphetamine. Ramirez OA, et al. **Brain Res** 1986 Jan 1; 362(1):165-70

Stress by forced swimming in the rat: effects of mianserin and moclobemide on GABAergic-monoaminergic systems in the brain. Cicardo VH, et al. **Comp Biochem Physiol** [C] 1986;83(1):133-5

The psychopharmacological effects of repeated doses of fluvoxamine, mianserin and placebo in healthy human subjects. Curran HV, et al. **Eur J Clin Pharmacol** 1986;29(5):601-7

Absolute bioavailability of mianserin tablets and solution in healthy humans. Timmer CJ, et al. **Eur J Drug Metab Pharmacokinet** 1985 Oct-Dec;10(4):315-23

Synchronizing EEG effect of mianserin. Bo P, et al. **Farmaco [Sci]** 1985 Dec;40(12):909-20

Simultaneous determination of metapramine and its demethylated metabolites in plasma by gas chromatography-mass spectrometry. Bougerolle AM, et al. **J Chromatogr** 1985 Nov 29;345(1):59-66

Alpha-adrenolytic properties of apogalanthamine and azapetine analogs. Ishida Y, et al. **J Pharmacobiodyn** 1985 Nov;8(11):917-23

Agonist interactions with beta-adrenergic receptors following chronic administration of desipramine or the atypical antidepressants, iprindole and mianserin. Hancock AA, et al. **J Recept Res** 1985;5(5-6):311-34

Mianserin and agranulocytosis [letter] Morgan CA, et al. **Med J Aust** 1986 Feb 3;144(3):165

Classification of sulpiride, clozapine and haloperidol by toposelective recording from different brain structures in the immobilized rat (stereo-EEG). Dimpfel W, et al. **Neuropsychobiology** 1985; 14(3):157-64

A double-blind comparison of once-daily flupenthixol and mianserin in depressed hospital out-patients. Majid I. **Pharmatherapeutica** 1986; 4(7):405-10

Electrophysiological effects of a new antiarrhythmic substance Bonnecor (AWD 19-166, GS 015) on mammalian myocardium. Nilius B, et al. **Pharmazie** 1985 Dec;40(12):847-51

Electrical effects of the new antiarrhythmic compound Bonnecor (AWD 19-166, GS 015) under arrhythmogenic conditions. Nilius B. **Pharmazie** 1985 Dec;40(12):855-6

Inotropic effects of the antiarrhythmic compound Bonnecor (AWD 19-166, GS 015). Nilius B, et al. **Pharmazie** 1985 Dec;40(12):854

[Pharmacokinetics and pharmacodynamics of 3-carbethoxyamino-5-dimethylamino-acetyl-iminodibenzyl hydrochloride (Bonnecor, AWD 19-166, GS 015) in the cat] Kaverina NV, et al. **Pharmazie** 1985 Dec;40(12):868-9 (Eng. Abstr.) **(Ger)**

[Characteristics of the anti-arrhythmic action of 3-carbethoxyamino-5-dimethylaminoacetyl-imino-dibenzyl hydrochloride (Bonnecor, AWD 19-166, GS 015)] Kaverina NV, et al. **Pharmazie** 1985 Dec;40(12):840-4 (Eng. Abstr.) **(Ger)**

[Antiarrhythmic effectiveness of 3-carbalkoxyamino-5-(omega-aminoacyl)-10,11-dihydro-5H-dibenz-[azepines] Kaverina NV, et al. **Pharmazie** 1985 Dec;40(12):830-2 (Eng. Abstr.) **(Ger)**

[Pharmacokinetics and metabolism of 3-carbethoxyamino-5-dimethylamino-acetyl-iminodibenzyl hydrochloride (Bonnecor, AWD 19-166, GS 015) in the rat] Klemm W, et al. **Pharmazie** 1985 Dec;40(12):864-7 (Eng. Abstr.) **(Ger)**

[Pharmaceutical characterization and spectroscopy of Bonnecor (AWD 19-166, GS 015)] Mayer W, et al. **Pharmazie** 1985 Dec;40(12):832-5 (Eng. Abstr.) **(Ger)**

[Summarized presentation of studies on the toxicology of 3-carbethoxyamino-5-dimethylamino-acetyl-10,11-dihydrobenz[b,f]azepine hydrochloride (Bonnecor, GS 015, AWD 19-166)] Nürnberger H, et al. **Pharmazie** 1985 Dec;40(12):871-3 (Eng. Abstr.) **(Ger)**

[New derivatives of 10,11-dihydro-5H-dibenz[b,f]azepine with antiarrhythmic action] Wunderlich H, et al. **Pharmazie** 1985 Dec; 40(12):827-30 (Eng. Abstr.) **(Ger)**

[Synthesis of 3-carbethoxyamino-5-dimethylamino-[1-14C]-acetyl-10,11-dihydro-5h-dibenz[b,f]azepine hydrochloride (Bonnecor, AWD 19-166, GS 015)] Zerjatke W. **Pharmazie** 1985 Dec;40(12):874 (Eng. Abstr.) **(Ger)**

[EEG changes with leponex medication] Kursawe HK, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Dec;37(12):705-12 (Eng. Abstr.) **(Ger)**

[Detection of Leponex (clozapine) in biological material] Kozlova IS, et al. **Sud Med Ekspert** 1986 Jan-Mar;29(1):43-4 (Eng. Abstr.) **(Rus)**

DIBENZOTHIEPINS

Prolongation of cardiac allograft survival with the PAF antagonist BN-52021 and the thromboxane receptor antagonists L640035 and L636499. Foegh ML, et al. **Adv Prostaglandin Thromboxane Leukotriene Res** 1985;15:381-4

In vivo voltammetry in the suprachiasmatic nucleus of the rat: effects of RU24969, methiothepin and ketanserin. Martin KF, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):135-9

Stereoselective blockade at the 5-HT autoreceptor and inhibition of radioligand binding to central 5-HT recognition sites by the optical isomers of methiothepin. Hibert M, et al. **Neuropharmacology** 1986 Jan; 25(1):1-4

DIBENZOXAZEPINES

Amoxapine-associated agranulocytosis with thrombocytosis occurring early during recovery. Sedlacek SM, et al. **Am J Med** 1986 Mar; 80(3):533-6

Side effects of the new antidepressants [letter] Mattes JA. **Am J Psychiatry** 1986 Feb;143(2):261

A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrenic patients. Tuason VB. **J Clin Psychiatry** 1986 Mar;47(3):126-9

Determination of amoxapine and its metabolites in human serum by high-performance liquid chromatography. Kobayashi A, et al. **Neuropharmacology** 1985 Dec;24(12):1253-6

DIBENZOXEPINS

Increase in the cardiotonic action and in the therapeutic margin of digoxin by the adrenergic beta-stimulant doxaminol in cats. Sponer G, et al. **Arzneimittelforschung** 1985;35(11):1663-7

Inhibition of prostaglandin generation in the rabbit brain in-vivo by AD-1590, a non-steroidal anti-inflammatory agent with potent antipyretic activity. Nakamura H, et al. **J Pharm Pharmacol** 1985 Dec; 37(12):894-8

DIETHYLAMINES

A solid sorbent air sampling and analytical procedure for methyl-, dimethyl-, ethyl-, and diethylamine. Elskamp CJ, et al. **Am Ind Hyg Assoc J** 1986 Jan;47(1):41-9

DIIODOTYROSINE

Ultrastructural changes elicited in the Tetrahymena by primary exposure (imprinting) and reexposure to hormone. Csaba G, et al. **Z Mikrosk Anat Forsch** 1985;99(6):884-90

DISCRIMINATION (PSYCHOLOGY)

Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. Young R, et al. **Med Res Rev** 1986 Jan-Mar; 6(1):99-130 (74 ref.)

A comparison of the discriminative stimulus properties of phencyclidine, given intraperitoneally or intraventricularly in rats. Slifer BL, et al. **Neuropharmacology** 1985 Dec;24(12):1175-9

Comparative discriminative stimulus properties of dl-cathinone, d-amphetamine, and cocaine in rats. Huang D, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):205-10

Dose-dependent impairment in the performance of a go-no go successive discrimination by chlordiazepoxide. Cole SO, et al. **Psychopharmacology (Berlin)** 1986;88(2):184-6

Effects of clonazepam and ethosuximide on the responding of pigeons under a fixed-consecutive-number schedule with and without an external discriminative stimulus. Picker M, et al. **Psychopharmacology (Berlin)** 1986;88(3):325-30

Effects of central dopamine depletion on the d-amphetamine discriminative stimulus in rats. Woolverton WL, et al. **Psychopharmacology (Berlin)** 1986;88(2):196-200

DISCRIMINATION LEARNING

Dopamine D1 receptor mediation of the discriminative stimulus properties of SKF 38393. Cunningham KA, et al. **Eur J Pharmacol** 1985 Dec 10; 119(1-2):121-5

Visual discrimination learning and interhemispheric transfer in the cat, as affected by 6-hydroxydopamine. Sprague JM, et al. **Exp Brain Res** 1985;61(1):43-53

Brief exposure to contingent reinforcement produces a sustained increment in the strength of an elicited response. Hutchinson RR, et al. **J Exp Anal Behav** 1986 Mar;45(2):189-94

Effects of chlorpromazine on fixed-ratio responding: modification by fixed-interval discriminative stimuli. Witkin JM. **J Exp Anal Behav** 1986 Mar;45(2):195-205

Discriminative and aversive properties of beta-carboline-3-carboxylic acid ethyl ester, a benzodiazepine receptor inverse agonist, in rhesus monkeys. Takada K, et al. **Life Sci** 1986 Mar 17;38(11):1049-56

Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. Young R, et al. **Med Res Rev** 1986 Jan-Mar; 6(1):99-130 (74 ref.)

Discriminative properties of the psychostimulant dl-cathinone in a two lever operant task. Lack of evidence for dopaminergic mediation. Goudie AJ, et al. **Neuropharmacology** 1986 Jan;25(1):85-94

Effects of chlordiazepoxide training dose on the mixed agonist-antagonist properties of benzodiazepine receptor antagonist Ro 15-1788, in a drug discrimination procedure. De Vry J, et al. **Psychopharmacology (Berlin)** 1986;88(2):177-83

[Drug discrimination: methodology and current problems] Watanabe S. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):289-302 (68 ref.) (Eng. Abstr.) **(Jpn)**

DOPA

Interaction of several mono- and dihydroxybenzene derivatives of various depigmenting potencies with L-3,4-dihydroxyphenylalanine-melanin. Menter JM, et al. **Arch Biochem Biophys** 1986 Feb 1;244(2):846-56

Sub-chronic administration of (-)-3-PPP and central dopamine receptor sensitivity changes. Hjorth S, et al. **J Neural Transm** 1985; 64(3-4):187-98

Changes in brain catecholamine levels following DL-dopa are not potentiated by deuterium substitution. Dewar KM, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):675-80

DOPAMINE

Effects of morphine on hypothalamic corticotropin-releasing factor (CRF), norepinephrine and dopamine in non-stressed and stressed rats. Suemaru S, et al. **Acta Med Okayama** 1985 Dec;39(6):463-70

Modification of reserpine induced rigidity by dopaminergic and alpha-adrenergic drugs. Anderson RJ. **Acta Neurol Scand** 1985 Dec; 72(6):584-9

Evidence against a functional role for dopamine-4-sulphate in the kidney. Bradley T, et al. **Acta Physiol Scand** 1985 Dec;125(4):739-41

Dopamine release is enhanced while acetylcholine release is inhibited by nimodipine (Bay e 9736). Nordström O, et al. **Acta Physiol Scand** 1986 Jan;126(1):115-9

Dissociation between renal prostaglandin E2 and renin release. Effects of glucagon, dopamine and cyclic AMP in dogs. Vikse A, et al. **Acta Physiol Scand** 1985 Dec;125(4):619-26

Effect of long-term application of Oxyphenon on biogenic amine levels in female rat brain. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:295-301

Effect of Oxyphenon on norepinephrine and dopamine levels in male rat brain. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985; 112:303-8

Comparison of the effect of single and repeated administration of Oxyphenon on norepinephrine and dopamine levels in female rat brains. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:309-12

Effect of intravenous infusion of low-dose dopamine on renal function in normal individuals and in patients with renal disease. ter Wee PM, et al. **Am J Nephrol** 1986;6(1):42-6

Modulation of luteinizing hormone immunoreactivity and bioactivity by dopamine but not norepinephrine in women. Barnes RB, et al. **Am J Obstet Gynecol** 1986 Feb;154(2):445-50

Variability and selectivity of anterior pituitary response to dopamine agonists throughout the normal menstrual cycle. Kletzky OA, et al. **Am J Obstet Gynecol** 1986 Feb;154(2):362-7

Neurotransmitters of the cochlea and cochlear nucleus: immunocytochemical evidence. Altschuler RA, et al. **Am J Otolaryngol** 1986 Mar-Apr;7(2):100-6 (59 ref.)

Neural not tubular dopamine increases glomerular filtration rate in perfused rat kidneys. Baines AD, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 2):F674-9

Pulmonary inactivation of vasopressors following cardiac operations. Hochberg MS, et al. **Ann Thorac Surg** 1986 Feb;41(2):200-3

Dopaminergic effects of carbamazepine. Relationship to clinical response in affective illness. Post RM, et al. **Arch Gen Psychiatry** 1986 Apr; 43(4):392-6

3H-dopamine uptake and 3H-haloperidol binding in striatum after administration of methyl mercury to rats. Komulainen H, et al. **Arch Toxicol** 1985 Sep;57(4):268-71

Catecholaminergic and serotoninergic brain structures in European green frogs: an autoradiographical study. Diederen JH, et al. **Basic Appl Histochem** 1985;29(4):297-308

The influence of estrogen on nigrostriatal dopamine activity: behavioral and neurochemical evidence for both pre- and postsynaptic components. Becker JB, et al. **Behav Brain Res** 1986 Jan;19(1):27-33

Lateralized decrease in self-stimulation induced by haloperidol in rats with unilateral 6-hydroxydopamine lesions. Carey RJ. **Behav Brain Res** 1985 Dec;18(3):215-22

Deficits in spatial-memory tasks following lesions of septal dopaminergic terminals in the rat. Simon H, et al. **Behav Brain Res** 1986 Jan; 19(1):7-16

BIBLIOGRAPHY

Dopamine depletion, stimulation or blockade in the rat disrupts spatial navigation and locomotion dependent upon beacon or distal cues. Whishaw IQ, et al. **Behav Brain Res** 1985 Oct–Nov;18(1):11–29

Disturbances in exploratory behavior and functional recovery in the Y and radial mazes following dopamine depletion of the lateral septum. Taghzouti K, et al. **Behav Neural Biol** 1986 Jan;45(1):48–56

Influences of amino acids on the circadian rhythms of brain neurotransmitters. Angelova C, et al. **Bibl Nutr Dieta** 1986;(38):72–81

Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Reith ME, et al. **Biochem Pharmacol** 1986 Apr 1;35(7):1123–9

Relationship of limbic dopamine levels to amphetamine- and anticholinergic–induced hyperactivity in the rat. Carey RJ. **Biol Psychiatry** 1986 Mar;21(3):317–21

The use of capillary gas chromatography/mass spectrometry for the determination of acidic dopamine metabolites in human brain. Michotte Y, et al. **Biomed Mass Spectrom** 1985 Dec;12(12):704–6

Conditionability of caudate dopamine activity in the caudate nucleus of cats demonstrated by in vivo electrochemistry. Brozoski TJ, et al. **Brain Res** 1986 Feb 5;364(2):275–83

Intrastriatal grafting of dopamine–containing neuronal cell suspensions: effects of mixing with target or non–target cells. Brundin P, et al. **Brain Res** 1986 Jan;389(1–2):77–84

The mechanism of action of MPTP and MPP+ on endogenous dopamine release from the rat corpus striatum superfused in vitro. Chang GD, et al. **Brain Res** 1986 Mar 12;368(1):134–40

Selective activation of mesolimbic and mesocortical dopamine metabolism in rat brain by infusion of a stable substance P analogue into the ventral tegmental area. Elliott PJ, et al. **Brain Res** 1986 Jan 15;363(1):145–7

Synaptic connections between serotoninergic axon terminals and tyrosine hydroxylase–immunoreactive neurons in the arcuate nucleus of the rat hypothalamus. A combination of electron microscopic autoradiography and immunocytochemistry. Kiss J, et al. **Brain Res** 1986 Feb 5;364(2):284–94

Effects of ventro–medial mesencephalic tegmentum (VMT) stimulation on the spontaneous activity of nucleus accumbens neurones: influence of the dopamine system. Le Douarin C, et al. **Brain Res** 1986 Jan 22;363(2):290–8

Dopaminergic facilitation of recovery from amygdaloid lesions which affect hypothalamic defensive attack in cats. Maeda H, et al. **Brain Res** 1986 Jan 15;363(1):135–40

Two simian virus 40 (SV40)–transformed cell lines from the mouse striatum and mesencephalon presenting astrocytic characters. II. Interactions with mesencephalic neurons. Mallat M, et al. **Brain Res** 1986 Apr;391(1):23–31

KCl–induced calcium–independent release of endogenous dopamine from rat brain slices. Okuma Y, et al. **Brain Res** 1986 Jan 15;363(1):47–52

Does triiodothyronine influence the morphogenesis of fetal mouse mesencephalic dopaminergic neurons cultured in chemically defined medium? Puymirat J, et al. **Brain Res** 1985 Dec;355(2):315–7

Differential effects of striatal injections of dopaminergic, cholinergic and GABAergic drugs upon swimming behavior of rats. Vrijmoed–de Vries MC, et al. **Brain Res** 1986 Jan 29;364(1):77–90

In vivo measurement of spontaneous release and metabolism of dopamine from intrastriatal nigral grafts using intracerebral dialysis. Zetterström T, et al. **Brain Res** 1986 Jan 8;362(2):344–9

Effects of dopamine and norepinephrine on neuronal activity of the olfactory tubercle. Guevara–Aguilar R, et al. **Brain Res Bull** 1985 Dec;15(6):665–8

Activation of striatal dopaminergic grafts by haloperidol. Herman JP, et al. **Brain Res Bull** 1985 Dec;15(6):543–6

Brain dopamine activity following intranigral or intrathalamic drug injections in the rat. Kilpatrick IC, et al. **Brain Res Bull** 1985 Dec;15(6):553–61

Antidromic discharge property of meso–accumbens dopaminergic VTA neurons in rats. Shinba T, et al. **Brain Res Bull** 1985 Dec;15(6):579–86

Activation of specific central dopamine pathways: locomotion and footshock. Speciale SG, et al. **Brain Res Bull** 1986 Jan;16(1):33–8

Effects of chronic methamphetamine on the nigral–striatal dopamine system in rat brain: tyrosine hydroxylase immunochemistry and quantitative light microscopic studies. Trulson ME, et al. **Brain Res Bull** 1985 Dec;15(6):569–77

Right ventricular function and pulmonary hemodynamics during dopamine infusion in burned patients. Martyn J, et al. **Chest** 1986 Mar;89(3):357–60

Effects of dopamine on renal function in the rat isolated perfused kidney. McGrath B, et al. **Clin Exp Pharmacol Physiol** 1985 Jul–Aug;12(4):343–52

Dopamine in rat kidney slices—its production and its histofluorescent localization. Hagege J, et al. **Contrib Nephrol** 1985;49:140–4

Impaired effect of dopamine on cardiac output during octopamine infusion. Tajimi K, et al. **Crit Care Med** 1986 Mar;14(3):192–4

Dopamine–induced migrating myoelectrical complex–like activity in human duodenum. Marzio L, et al. **Dig Dis Sci** 1986 Apr;31(4):349–54

D–2 dopaminergic agonists and adenosine 3',5'–monophosphate directly regulate the synthesis of alpha–melanocyte–stimulating hormone–like peptides by cultured rat melanotrophs. Beaulieu M, et al. **Endocrinology** 1986 Mar;118(3):1032–9

Dopamine and L–dopa: inhibition of thyrotropin–stimulated thyroidal thyroxine release. Maayan ML, et al. **Endocrinology** 1986 Feb;118(2):632–6

Striatal and mesolimbic dopaminergic contribution to 3,4–dihydroxyphenylacetic acid sulfate in rat plasma. Boudet C, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):113–8

Evidence for the release of 1–methyl–4–phenylpyridinium (MPP+) from rat striatal neurons in vitro. Keller HH, et al. **Eur J Pharmacol** 1985 Dec 17;119(3):247–50

1–Methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) administration to C57–black mice leads to parallel decrements in neostriatal dopamine content and tyrosine hydroxylase activity. Mayer RA, et al. **Eur J Pharmacol** 1986 Jan 29;120(3):375–7

GM1 monosialoganglioside inner ester induces early recovery of striatal dopamine uptake in rats with unilateral nigrostriatal lesion. Raiteri M, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):347–50

Visual discrimination learning and interhemispheric transfer in the cat, as affected by 6–hydroxydopamine. Sprague JM, et al. **Exp Brain Res** 1985;61(1):43–53

Effect of thyrotropin–releasing hormone and dopamine on the in vitro secretion of prolactin by the bullfrog pituitary gland. Seki T, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):197–202

Effect of low–dose dopamine infusion on insulin and glucagon release in fasting normal man. Connell JM, et al. **Horm Metab Res** 1986 Jan;18(1):67–8

Parathyroid hormone and calcitonin secretion in man: effect of dopamine agonists and antagonists. Williams GA, et al. **Horm Metab Res** 1986 Jan;18(1):64–6

Selective antagonism of the hypotensive effects of dopamine agonists in spontaneously hypertensive rats. McCoy CE, et al. **Hypertension** 1986 Apr;8(4):298–302

Dopamine influences the light peak in the perfused mammalian eye. Dawis SM, et al. **Invest Ophthalmol Vis Sci** 1986 Mar;27(3):330–5

Influences of endogenous dopamine on carotid body discharge and ventilation. Chow CM, et al. **J Appl Physiol** 1986 Feb;60(2):370–5

Further speculations on possible dopamine–opioid link in autism [letter] Sandyk R. **J Autism Dev Disord** 1986 Mar;16(1):89–90

A study of the relationship between dopamine and noradrenaline content and transmural pressure in the mesenteric arteries of the dog. Azevedo I, et al. **J Auton Pharmacol** 1986 Mar;6(1):33–7

Angiotensin II and dopamine modulate both cAMP and inositol phosphate productions in anterior pituitary cells. Involvement in prolactin secretion. Enjalbert A, et al. **J Biol Chem** 1986 Mar 25;261(9):4071–5

Automated method to estimate catecholamine and indoleamine content and turnover rates. Freeman GB, et al. **J Chromatogr** 1986 Jan 24;374(2):239–49

Increased dopaminergic activity inhibits basal and metoclopramide–stimulated prolactin and thyrotropin secretion. Agner T, et al. **J Clin Endocrinol Metab** 1986 Apr;62(4):778–82

Endogenous dopaminergic dysfunction: a novel form of human growth hormone deficiency and short stature. Huseman CA, et al. **J Clin Endocrinol Metab** 1986 Mar;62(3):484–90

Distribution of catecholamines between fetal and maternal compartments during human pregnancy with emphasis on L–dopa and dopamine. Peleg D, et al. **J Clin Endocrinol Metab** 1986 May;62(5):911–4

Gonadotropin–releasing hormone neurosecretion in the human hypothalamus: in vitro regulation by dopamine. Rasmussen DD, et al. **J Clin Endocrinol Metab** 1986 Mar;62(3):479–83

Periventricular dopaminergic neurons terminating in the neuro–intermediate lobe of the cat hypophysis. Luppi PH, et al. **J Comp Neurol** 1986 Feb 8;244(2):204–12

Age–dependent changes in the mechanisms regulating dopamine uptake in the central nervous system. Missale C, et al. **J Gerontol** 1986 Mar;41(2):136–9

Synthesis and toxicity toward nigrostriatal dopamine neurons of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) analogues. Fries DS, et al. **J Med Chem** 1986 Mar;29(3):424–7

Evaluation of hypothalamic dopaminergic function by neuropharmacologic means in aged women. Cocchi D, et al. **J Neural Transm** 1985;64(3–4):199–210

Dopaminergic regulation of cone retinomotor movement in isolated teleost retinas: II. Modulation by gamma–aminobutyric acid and serotonin. Dearry A, et al. **J Neurochem** 1986 Apr;46(4):1022–31

Dopaminergic regulation of cone retinomotor movement in isolated teleost retinas: I. Induction of cone contraction is mediated by D2 receptors. Dearry A, et al. **J Neurochem** 1986 Apr;46(4):1006–21

Monoamine neurotransmitter metabolism and locomotor activity during chemical hypoxia. Freeman GB, et al. **J Neurochem** 1986 Mar;46(3):733–8

Characterization of sodium-dependent [3H]GBR-12935 binding in brain: a radioligand for selective labelling of the dopamine transport complex. Janowsky A, et al. **J Neurochem** 1986 Apr;46(4):1272-6

Brain dialysis: in vivo metabolism of dopamine and serotonin by monoamine oxidase A but not B in the striatum of unrestrained rats. Kato T, et al. **J Neurochem** 1986 Apr;46(4):1277-82

Dose response for amphetamine-induced changes in dopamine levels in push-pull perfusates of rat striatum. Kuczenski R. **J Neurochem** 1986 May;46(5):1605-11

Release of endogenous 3,4-dihydroxyphenylethylamine and its metabolites from the isolated neurointermediate lobe of the rat pituitary gland. Effects of electrical stimulation and of inhibition of monoamine oxidase and reuptake. Racké K, et al. **J Neurochem** 1986 Mar; 46(3):745-52

Effect of intrastriatal injection of diisopropylfluorophosphate on acetylcholine, dopamine, and serotonin metabolism. Robinson SE, et al. **J Neurochem** 1986 May;46(5):1632-8

Dopamine action in the nucleus accumbens. DeFrance JF, et al. **J Neurophysiol** 1985 Dec;54(6):1568-77

Stimulation of the lateral habenula inhibits dopamine-containing neurons in the substantia nigra and ventral tegmental area of the rat. Christoph GR, et al. **J Neurosci** 1986 Mar;6(3):613-9

Investigation of the failure of parenterally administered haloperidol to antagonize dopamine released from micropipettes in the caudate. Johnson SW, et al. **J Neurosci** 1986 Feb;6(2):572-80

Endogenous dopamine can modulate inhibition of substantia nigra pars reticulata neurons elicited by GABA iontophoresis or striatal stimulation. Waszczak BL, et al. **J Neurosci** 1986 Jan;6(1):120-6

Indirect dopaminergic effects of tofisopam, a 2,3-benzodiazepine, and their inhibition by lithium. Chopin P, et al. **J Pharm Pharmacol** 1985 Dec;37(12):917-9

Re-evaluation of the L-dopa loading effect on dopamine metabolism in rat striatum. el Gemayel G, et al. **J Pharm Pharmacol** 1986 Feb; 38(2):134-6

Evidence for dopamine release and metabolism beyond the control of nerve impulses and dopamine receptors in rat substantia nigra. Nissbrandt H, et al. **J Pharm Pharmacol** 1985 Dec;37(12):884-9

Effect of nialamide on the metabolism of dopamine injected into the nucleus accumbens of old rats. Cousin KM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):25-30

Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: studies in vivo. Galloway MP, et al. **J Pharmacol Exp Ther** 1986 Mar;236(3):689-98

Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. II. Release in the presence of vesicular transmitter stores. Parker EM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):193-203

Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. Parker EM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):179-92

Cholecystokinin octapeptides alter the release of endogenous dopamine from the rat nucleus accumbens in vitro. Voigt M, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):147-53

Regulation of dopamine synthesis in the medial prefrontal cortex: studies in brain slices. Wolf ME, et al. **J Pharmacol Exp Ther** 1986 Mar; 236(3):699-707

The hypothalamo-hypophyseal rat explant in vitro: endocrinological studies of the pars intermedia dopaminergic neural input. Davis MD. **J Physiol (Lond)** 1986 Jan;370:381-93

Effects of neurotransmitters or drugs on the in vivo release of dopamine and its metabolites. Kito S, et al. **Jpn J Pharmacol** 1986 Jan; 40(1):57-67

Effects of neuroleptics on dopamine release from striatal slices. Yamada S, et al. **Kurume Med J** 1985;32(2):127-30

ACTH-(1-24) and alpha-MSH antagonize dopamine receptor-mediated inhibition of striatal dopamine and acetylcholine release. Versteeg DH, et al. **Life Sci** 1986 Mar 3;38(9):835-40

Inhibition of prolactin release and blockade of adenohypophyseal cell cyclic AMP accumulation are two dissociable effects of dopaminergic and non-dopaminergic drugs. Lafond J, et al. **Mol Cell Endocrinol** 1986 Mar;44(3):219-25

Dopamine, acting through D-2 receptors, inhibits rat striatal adenylate cyclase by a GTP-dependent process. Cooper DM, et al. **Mol Pharmacol** 1986 Feb;29(2):113-9

Sex differences in [3H]-estradiol binding in brain and pituitary after acute dopaminergic treatment. In vivo studies in the rat. Gietzen DW, et al. **Neuroendocrinology** 1986;42(4):334-43

Serotonin and dopamine independently regulate pituitary beta-endorphin release in vivo. Sapun-Malcolm D, et al. **Neuroendocrinology** 1986; 42(3):191-6

Biochemical correlates of motor changes caused by the manipulation of dopamine function in the substantia nigra of the mouse. Bradbury AJ, et al. **Neuropharmacology** 1985 Dec;24(12):1155-61

Laterality of dopamine function and neuroleptic action in the amygdala in the rat. Bradbury AJ, et al. **Neuropharmacology** 1985 Dec; 24(12):1163-70

Effects of avermectin B1a and picrotoxin on striatal release of dopamine with reference to replacement of extracellular chloride with nitrate. Ishiko J, et al. **Neuropharmacology** 1985 Dec;24(12):1147-54

Ascorbic acid reduces the dopamine depletion induced by MPTP. Wagner GC, et al. **Neuropharmacology** 1985 Dec;24(12):1261-2

Dopaminergic toxicity of rotenone and the 1-methyl-4-phenylpyridinium ion after their stereotaxic administration to rats: implication for the mechanism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity. Heikkila RE, et al. **Neurosci Lett** 1985 Dec 18;62(3):389-94

Novel synaptic responses mediated by dopamine and gamma-aminobutyric acid in neuroendocrine cells of the intermediate pituitary. MacVicar BA, et al. **Neurosci Lett** 1986 Feb 14; 64(1):35-40

Prolonged changes in dopaminergic terminal excitability and short changes in dopaminergic neuron discharge rate after short peripheral stimulation in monkey. Romo R, et al. **Neurosci Lett** 1985 Dec 18; 62(3):335-40

The norepinephrine and dopamine content of the cat carotid body in vivo under normoxic and hypoxic conditions. Starlinger H, et al. **Neurosci Lett** 1986 Feb 14;64(1):65-8

Different developmental schedules of dopaminergic and noradrenergic neurons in dissociation culture of fetal rat midbrain and hindbrain. Ahnert-Hilger G, et al. **Neuroscience** 1986;17(1):157-65

Unilateral dopamine depletions attenuate the response of striatal neurons to systemic amphetamine in both hemispheres. Basse-Tomusk AE, et al. **Neuroscience** 1985 Dec;16(4):845-50

Release and metabolism of [3H]dopamine in the neurointermediate lobe of the rat pituitary gland. Racké K, et al. **Neuroscience** 1985 Nov; 16(3):501-10

Treat shock with dopamine. Gever LN. **Nursing** 1986 Mar;16(3):93

Effects of dopamine and noradrenaline on Ca channels of cultured sensory and sympathetic neurons of chick. Marchetti C, et al. **Pflugers Arch** 1986 Feb;406(2):104-11

Striatally-mediated response of some structurally rigid analogues of dopamine. Antonian L, et al. **Pharmacol Biochem Behav** 1986 Feb; 24(2):253-8

Behavioral effects of a dimethylsulfonium analog of dopamine after injection into the nucleus accumbens and the striatum. Boldry R, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):223-8

Alteration of the turnover of dopamine and 5-hydroxytryptamine in rat brain associated with hypothermia. Okuda C, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):79-83

Antagonism by dopamine, but not noradrenaline receptor blockers of the anti-immobility activity of desipramine after different treatment schedules in the rat. Pulvirenti L, et al. **Pharmacol Res Commun** 1986 Jan;18(1):73-80

Submaximal plasma prolactin response to TRH and dopamine activity in man. Spoov J. **Pharmacopsychiatry** 1985 Nov;18(6):330-2

Further evidence that central neurotensin inhibits pituitary prolactin secretion by stimulating dopamine release from the hypothalamus. Tojo K, et al. **Proc Soc Exp Biol Med** 1986 Apr;181(4):517-22

Some factors affecting striatal 3-methoxytyramine concentrations in the mouse and rat. McQuade PS, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):725-9

Cholecystokinin peptides, dopamine and schizophrenia--a review. Nair NP, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):515-24 (60 ref.)

CSF dopamine turnover and positive schizophrenic symptoms after withdrawal of long-term neuroleptic treatment. Frecska E, et al. **Psychiatry Res** 1985 Nov;16(3):221-6

Effects of central dopamine depletion on the d-amphetamine discriminative stimulus in rats. Woolverton WL, et al. **Psychopharmacology (Berlin)** 1986;88(2):196-200

Formation of dopamine sulfate from L-dopa by perfusion of dog kidney. Tsunematsu T. **Tokushima J Exp Med** 1985 Jun;32(1-2):23-9

Neurobiochemical alterations induced by the artificial sweetener aspartame (NutraSweet). Coulombe RA Jr, et al. **Toxicol Appl Pharmacol** 1986 Mar 30;83(1):79-85

[Comparison of the dopaminergic activity of the new Czechoslovak ergoline derivate transdihydrolisuride (Tergurid Spofa) with lisuride] Schreiber V, et al. **Bratisl Lek Listy** 1986 Jan;85(1):14-8 (Eng. Abstr.) **(Cze)**

[Dopamine-stimulated glycosylation of rat hippocampal proteins in vitro: structure-response relationship] Pchalek V, et al. **Biomed Biochim Acta** 1985;44(11-12):1651-8 (Eng. Abstr.) **(Ger)**

[The role of dopamine in the dyspeptic symptom complex] Kurtz W. **Fortschr Med** 1986 Jan 23;104(4):93-6 (Eng. Abstr.) **(Ger)**

[Role of the pituitary in modulating the effect of the dopaminergic and serotoninergic systems on the immune response] Al'perina EL, et al. **Fiziol Zh SSSR** 1985 Nov;71(11):1428-32 (Eng. Abstr.) **(Rus)**

[The hypothalamo-hypophyseal dopaminergic system in rats] Alexandrová M. **Cesk Fysiol** 1986;35(1):17-28 (76 ref.) **(Slo)**

DOPAMINE BETA-HYDROXYLASE

Light and electron microscopic immunohistochemistry on the localization of cytochrome P-450 of the side chain cleavage system and of cytochrome P-450 of 11 beta-hydroxylase in the bovine adrenal cortical cells. Ishimura K, et al. **Arch Histol Jpn** 1985 Dec;48(5):541-6

Olefin oxygenation and N-dealkylation by dopamine beta-monooxygenase: catalysis and mechanism-based inhibition. Padgette SR, et al. **Biochemistry** 1985 Oct 8;24(21):5826-39

Postnatal development of dopamine-beta-hydroxylase-immunoreactive fibers of the spinal cord of the rat. Aramant RB, et al. **Brain Res** 1986 Mar;390(2):161-71

Dopamine-beta-hydroxylase (DBH) and homovanillic acid (HVA) in autistic children. Garnier C, et al. **J Autism Dev Disord** 1986 Mar; 16(1):23-9

The mechanism of inactivation of dopamine beta-hydroxylase by hydrazines. Fitzpatrick PF, et al. **J Biol Chem** 1986 Apr 5; 261(10):4510-8

Studies on the binding of copper to dopamine beta-monooxygenase and other proteins using the Cu2+ ion-selective electrode. Syvertsen C, et al. **J Inorg Biochem** 1986 Jan;26(1):63-76

Cholinergic and GABAergic regulation of dopamine beta-hydroxylase activity in the adrenal gland of the rat. Lima L, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):265-70

Determination of dopamine-beta-hydroxylase in cerebrospinal fluid by high-performance liquid chromatography with electrochemical detection. Dillen L, et al. **J Pharmacol Methods** 1986 Feb; 15(1):51-63

Reserpine and the monoaminergic regulation of adrenal dopamine beta-hydroxylase activity. Lima L, et al. **Neuroscience** 1986; 17(1):235-45

DOXAPRAM

Sensitive nitrogen-phosphorus capillary gas chromatographic assay for doxapram in premature infants. Torok-Both GA, et al. **J Chromatogr** 1985 Nov 8;344:372-7

DOXEPIN

Doxepin-cimetidine interaction: increased doxepin bioavailability during cimetidine treatment. Abernethy DR, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):8-12

Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. Feighner J, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):27-32

DRUG EVALUATION

Measurement of compliance. Sleator EK. **Psychopharmacol Bull** 1985; 21(4):1089-93

DRUG SCREENING

[Behavioral and pharmacological studies of methamphetamine-induced stereotypy of mice by the open field method] Nakamura K, et al. **Yakugaku Zasshi** 1985 Aug;105(8):775-83 (Eng. Abstr.) **(Jpn)**

DRUG TOLERANCE

Characteristics of tolerance, recovery from tolerance and cross-tolerance for cocaine used as a discriminative stimulus. Wood DM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):120-5

ELECTROCONVULSIVE THERAPY

Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Keller MB, et al. **Arch Gen Psychiatry** 1986 May;43(5):458-66

Effects of ECT on sleep and CSF biogenic amines in affective illness. Hoffmann G, et al. **Psychiatry Res** 1985 Nov;16(3):199-206

ELECTROENCEPHALOGRAPHY

Synchronizing EEG effect of mianserin. Bo P, et al. **Farmaco [Sci]** 1985 Dec;40(12):909-20

Classification of sulpiride, clozapine and haloperidol by toposelective recording from different brain structures in the immobilized rat (stereo-EEG). Dimpfel W, et al. **Neuropsychobiology** 1985; 14(3):157-64

The physiology and pharmacology of hippocampal formation theta rhythms. Bland BH. **Prog Neurobiol** 1986;26(1):1-54 (279 ref.)

[EEG changes with leponex medication] Kursawe HK, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Dec;37(12):705-12 (Eng. Abstr.) **(Ger)**

[Correlation of the clinical pharmacological action of a single dose of fenazepam with the EEG dynamics and pharmacokinetics] Uvarova LG, et al. **Farmakol Toksikol** 1986 Jan-Feb;49(1):66-9 (Eng. Abstr.) **(Rus)**

ELECTROLYTES

Effect of luminally administered serotonin and substance P on jejunal handling of water and electrolytes. McFadden D, et al. **Am J Surg** 1986 Jan;151(1):81-6

Water and electrolyte absorption from a human Thiry-Vella ileal loop. Responses to systemic administration of gastrin, glucagon, secretin, and cholecystokinin. Lai EC, et al. **Ann Surg** 1986 Apr;203(4):434-8

Investigations of nerve populations influencing ion transport that can be stimulated electrically, by serotonin and by a nicotinic agonist. Keast JR, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov; 331(2-3):260-6

[Changes in serum electrolytes and cardiovascular function: a possible cause of shock during nasal operation using local anesthetics] Okamoto K, et al. **Nippon Jibiinkoka Gakkai Kaiho** 1985 Sep;88(9):1146-52 (Eng. Abstr.) **(Jpn)**

ELECTROSHOCK

Brain histamine turnover enhanced by footshock. Yoshitomi I, et al. **Brain Res** 1986 Jan 1;362(1):195-8

Activation of specific central dopamine pathways: locomotion and footshock. Speciale SG, et al. **Brain Res Bull** 1986 Jan;16(1):33-8

Electroconvulsive shock: effect on pineal and hypothalamic indoles. McIntyre IM, et al. **J Pineal Res** 1984;1(3):273-9

EMOTIONS

Increase of circulating beta-endorphin-like immunoreactivity correlates with the change in feeling of pleasantness after running. Wildmann J, et al. **Life Sci** 1986 Mar 17;38(11):997-1003

[Neurochemical aspects of the emotional reactivity and motor activity of rats in new circumstances] Kulagin DA, et al. **Usp Fiziol Nauk** 1986 Jan-Mar;17(1):92-109 (99 ref.) **(Rus)**

[Disorders of positive emotions in schizophrenics: survey of research, (problems, hypotheses)] Poliakov IuF, et al. **Zh Nevropatol Psikhiatr** 1985;85(12):1857-62 (45 ref.) **(Rus)**

ENDORPHINS

Proceedings of the International Narcotics Research Conference. North Falmouth, Massachusetts, June 23-28, 1985. **Alcohol Drug Res** 1985-86; 6(2-3):63-252

Peptide biosynthesis. Cox BM. **Alcohol Drug Res** 1985-86;6(2-3):85-6

Molecular biological approaches. Schwartz J. **Alcohol Drug Res** 1985-86; 6(2-3):81-3

Evaluation on the treatment of morphine addiction by acupuncture Chinese herbs and opioid peptides. Yang MM, et al. **Am J Chin Med** 1986;14(1-2):46-50

Apgar scores and cerebrospinal fluid beta-endorphinlike immunoreactivity [letter] Todd D. **Am J Dis Child** 1986 Feb; 140(2):91-2

Plasma immunoreactive beta-endorphin in exercise-associated amenorrhea. Laatikainen T, et al. **Am J Obstet Gynecol** 1986 Jan; 154(1):94-7

The relationship of beta-endorphin and ACTH in the cerebrospinal fluid and plasma of adult surgical patients. Scheller MS, et al. **Ann Clin Res** 1985;17(6):323-6

The effect of phobic anxiety on plasma beta-endorphin: a single-subject experiment. Thyer BA, et al. **Behav Res Ther** 1986;24(2):237-41

Beta-endorphin is present in active and inactive forms in rat gastric antrum. Rosenquist GL, et al. **Biochem Biophys Res Commun** 1986 Jan 14;134(1):14-20

Breakdown of small enkephalin derivatives and adrenal peptide E by human plasma. Boarder MR, et al. **Biochem Pharmacol** 1986 Mar 15; 35(6):1043-7

Tertiary structure in deletion analogues of human beta-endorphin: resistance to leucine aminopeptidase action. Bewley TA, et al. **Biochemistry** 1985 Nov 5;24(23):6568-71

Functional properties of covalent beta-endorphin peptide/calmodulin complexes. Chlorpromazine binding and phosphodiesterase activation. Giedroc DP, et al. **Biochemistry** 1985 Feb 26;24(5):1203-11

Identification of distinct binding site subunits of mu and delta opioid receptors. Howard AD, et al. **Biochemistry** 1986 Jan 28;25(2):357-60

Discordant changes between immunoreactive ACTH and beta-endorphin in rat brain and pituitary during early development. Kapcala LP. **Brain Res** 1986 Feb 5;364(2):350-9

Hypothalamic opioids and the acute-phase glycoprotein response in guinea pigs. Ahokas RA, et al. **Brain Res Bull** 1985 Dec; 15(6):603-8

Opioid antagonists in circulatory shock [editorial] Groeger JS. **Crit Care Med** 1986 Feb;14(2):170-1

Central regulation of intestinal basal and stimulated water and ion transport by endogenous opiates in dogs. Primi MP, et al. **Dig Dis Sci** 1986 Feb;31(2):172-6

Secretion into the culture medium of a foreign gene product from Escherichia coli: use of the ompF gene for secretion of human

beta-endorphin. Nagahari K, et al. **EMBO J** 1985 Dec 16; 4(13A):3589-92
Modulation of luteinizing hormone(LH) release by clonidine and opioid peptides in castrated male rats. Koh T, et al. **Endocrinol Jpn** 1985 Oct; 32(5):653-9
Long term culture of primary rat pituitary adrenocorticotropin/endorphin-producing cells in serum-free medium. May V, et al. **Endocrinology** 1986 Apr;118(4):1284-95
A diurnal rhythm in proopiomelanocortin messenger ribonucleic acid that varies concomitantly with the content and secretion of beta-endorphin in the intermediate lobe of the rat pituitary. Millington WR, et al. **Endocrinology** 1986 Feb;118(2):829-34
The effect of training on responses of beta-endorphin and other pituitary hormones to insulin-induced hypoglycemia. Mikines KJ, et al. **Eur J Appl Physiol** 1985;54(5):476-9
Opioid peptides. Conformational studies of dermorphin and its constitutive fragments by circular dichroism. IX. Scatturin A, et al. **Farmaco [Sci]** 1985 Oct;40(10):709-16
Chemical characterization and opioid activity of an exorphin isolated from in vivo digests of casein. Meisel H. **FEBS Lett** 1986 Feb 17; 196(2):223-7
Immunoreactive beta-endorphin in human ovaries. Aleem FA, et al. **Fertil Steril** 1986 Apr;45(4):507-11
Plasma beta-endorphin levels in anovulatory states: changes after treatments for the induction of ovulation. Petraglia F, et al. **Fertil Steril** 1986 Feb;45(2):185-90
Rise in plasma beta-endorphin and ACTH in response to hyperthermia in sauna. Ježová D, et al. **Horm Metab Res** 1985 Dec;17(12):693-4
Effect of third ventricular injection of beta-endorphin on the electrophysiological responses of some regions of endocrine hypothalamus. Tandon OP, et al. **Indian J Physiol Pharmacol** 1985 Apr-Jun;29(2):75-82
Further speculations on possible dopamine-opioid link in autism [letter] Sandyk R. **J Autism Dev Disord** 1986 Mar;16(1):89-90
The size of enzymes acetylating alpha-melanocyte-stimulating hormone and beta-endorphin. Chappell MC, et al. **J Biol Chem** 1986 Jan 25; 261(3):1088-91
Competitive binding of dynorphin-(1-13) and beta-endorphin to cerebroside sulfate in solution. Wu CS, et al. **J Biol Chem** 1986 Mar 15;261(8):3687-91
Separation and detection of closely related endorphins by liquid chromatography-electrochemistry. Fleming LH, et al. **J Chromatogr** 1986 Feb 14;375(1):65-73
Beta-endorphin attenuates the serum cortisol response to exogenous adrenocorticotropin. Beyer HS, et al. **J Clin Endocrinol Metab** 1986 May;62(5):808-11
No evidence for the presence of beta-casomorphins in human plasma after ingestion of cows' milk or milk products. Teschemacher H, et al. **J Dairy Res** 1986 Feb;53(1):135-8
Immunoreactive dynorphin B in sacral primary afferent fibers of the cat. Basbaum AI, et al. **J Neurosci** 1986 Jan;6(1):127-33
Spinal release of immunoreactive Met-enkephalin by intraventricular beta-endorphin and its analogs in anesthetized rats. Tseng LF, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):65-74
Effect of short photoperiod on hypothalamic methionine-enkephalin and LHRH content and serum beta-endorphin-like immunoreactivity (beta-end LI) levels in golden hamsters. Kumar MS, et al. **J Pineal Res** 1984;1(2):197-205
Food deprivation-induced changes in the level of opioid peptides in the pituitary and brain of rat. Vaswani KK, et al. **Life Sci** 1986 Jan 13; 38(2):197-201
Increase of circulating beta-endorphin-like immunoreactivity correlates with the change in feeling of pleasantness after running. Wildmann J, et al. **Life Sci** 1986 Mar 17;38(11):997-1003
Pharmacology of opioids. Part 1. Basic aspects. Mather LE. **Med J Aust** 1986 Apr 14;144(8):424-7
Opioid peptides decrease noradrenaline release and blood pressure in the rabbit at peripheral receptors. Szabo B, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):50-6
Serotonin and dopamine independently regulate pituitary beta-endorphin release in vivo. Sapun-Malcolm D, et al. **Neuroendocrinology** 1986; 42(3):191-6
Modulation by Leu-enkephalin of peptide release from perifused neurointermediate pituitary. II. Inhibition of calcium-mediated secretion of alpha-MSH and beta-endorphin. Al Zein M, et al. **Neuroendocrinology** 1986;42(3):248-54
Distribution of immunoreactive alpha-neo-endorphin in the rat brain. Smiałowska M, et al. **Neurosci Lett** 1985 Dec 18;62(3):359-64
Water intake modifications induced by tachykinins, bombesins and opioid peptides. de Caro G, et al. **Peptides** 1985;6 Suppl 3:181-5
Native opioid-like peptides in Squilla mantis ganglia. Marino G, et al. **Peptides** 1985;6 Suppl 3:403-6
Changes in the activity of rat cortical and hippocampal neurones after the iontophoretic administration of beta-endorphin, glutamate and GABA. Strejčková A, et al. **Physiol Bohemoslov** 1985;34(6):567-73
Serotonergic regulation of the brain and gut beta-endorphin and dynorphin content in the rat. Majeed NH, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):909-18
Isolation and structure of a C-terminally amidated nonopioid peptide, amidorphin-(8-26), from bovine striatum: a major product of proenkephalin in brain but not in adrenal medulla. Liebisch DC, et al. **Proc Natl Acad Sci USA** 1986 Mar;83(6):1936-40
Gamma-type endorphins: neurolepticum-like and antipsychotic action. Van Ree JM, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):561-7
Plasma immunoreactive beta-endorphin in bulimics. Fullerton DT, et al. **Psychol Med** 1986 Feb;16(1):59-63
Developmental, behavioral, and opiate receptor changes after prenatal or postnatal beta-endorphin, CRF, or Tyr-MIF-1. Zadina JE, et al. **Psychoneuroendocrinology** 1985;10(4):367-83
Circadian rhythms of beta-endorphin in the aged. Casale G, et al. **Z Gerontol** 1985 Nov-Dec;18(6):340-2
[Neurochemical characteristics of opioid peptides] Vion-Dury J, et al. **Presse Med** 1986 Mar 8;15(10):475-9 (21 ref.) (Eng. Abstr.) **(Fre)**
[Kinetics of the increase in serum levels of beta-endorphin after ingestion of dihydroergotamine methanesulfonate. Influence of the dosage form] Kerdelhue B. **Therapie** 1985 Nov-Dec;40(6):465-8 (Eng. Abstr.) **(Fre)**
[Endogenous opiates and the gastrointestinal tract. Physioanatomic notes (review)] De Simone M, et al. **Minerva Dietol Gastroenterol** 1985 Oct-Dec;31(4):613-7 (Eng. Abstr.) **(Ita)**
[Plasma beta endorphin in man during partial immersion in water using the therapeutic method] Digiesi V, et al. **Minerva Med** 1986 Feb 28; 77(7-8):209-13 (Eng. Abstr.) **(Ita)**
[In vivo and in vitro effects of bradykinin on the release of beta-endorphin-like immunoreactivity] Shimizu I, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Dec 20;61(12):1330-40 (Eng. Abstr.) **(Jpn)**
[The role of mu- and delta-opiate receptors in the realization of the autonomic effects of opioid peptides] Martynova ER, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):60-3 (Eng. Abstr.) **(Rus)**
[Mechanisms of action of beta-endorphin on the secretion of hypophyseal hormones] Slavnov VN, et al. **Probl Endokrinol (Mosk)** 1986 Jan-Feb; 32(1):49-52 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, LEUCINE

Leu-enkephalin impairs memory of an appetitive maze response in mice. Linden D, et al. **Behav Neurosci** 1986 Feb;100(1):33-8
Structure-activity relationships of enkephalins containing serially replaced thiomethylene amide bond surrogates. Spatola AF, et al. **Life Sci** 1986 Apr 7;38(14):1243-9
Proposals for the mu-active conformation of the enkephalin analog Tyr-cyclol(-N gamma-D-A2-bu-Gly-Phe-Leu-). Maigret B, et al. **Mol Pharmacol** 1986 Mar;29(3):314-20
Modulation by Leu-enkephalin of peptide release from perifused neurointermediate pituitary. II. Inhibition of calcium-mediated secretion of alpha-MSH and beta-endorphin. Al Zein M, et al. **Neuroendocrinology** 1986;42(3):248-54
[Conformation of the enkephalin cycloanalog Lys-Tyr-Gly-Gly-Phe-Leu-] Balodis IuIu, et al. **Bioorg Khim** 1985 Nov;11(11):1468-75 (Eng. Abstr.) **(Rus)**
[Changes in the met- and leu-enkephalin levels in the rat brain during burn shock] Zaets TL, et al. **Biull Eksp Biol Med** 1986 Jan; 101(1):10-1 (Eng. Abstr.) **(Rus)**
[Effect of enkephalins on the function of the calcium-regulating endocrine glands in shock] Zoloev GK, et al. **Biull Eksp Biol Med** 1986 Mar; 101(3):284-7 (Eng. Abstr.) **(Rus)**
[Effect of enkephalins on metabolic indices in acute experimental blood loss in rats] Zoloev GK. **Patol Fiziol Eksp Ter** 1985 Nov-Dec; (6):25-8 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, METHIONINE

Enkephalin analogue in schizophrenia. Double blind cross-over trial. Joergensen A, et al. **Acta Psychiatr Scand** 1986 Jan;73(1):45-8
Crystal structure of methionine-enkephalin. Mastropaolo D, et al. **Biochem Biophys Res Commun** 1986 Jan 29;134(2):698-703
Chronic treatment with five different neuroleptics elicits behavioral supersensitivity to opiate infusion into the nucleus accumbens. Stinus L, et al. **Biol Psychiatry** 1986 Jan;21(1):34-48
Local and remote effects of intra-caudate administration of GABA-related drugs on Met-enkephalin release in the basal ganglia. Bourgoin S, et al. **Brain Res** 1985 Dec 30;361(1-2):361-72
Ultrastructural localization of enkephalin immunoreactivity in the substantia nigra of the monkey. Inagaki S, et al. **Brain Res** 1986 Jan 1;362(1):171-4
Distribution of immunoreactive metorphamide (adrenorphin) in discrete regions of the rat brain: comparison with Met-enkephalin-Arg6-Gly7-Leu8. Zamir N, et al. **Brain Res** 1985 Dec 30;361(1-2):193-9
Central regulation of intestinal basal and stimulated water and ion transport by endogenous opiates in dogs. Primi MP, et al. **Dig Dis Sci** 1986 Feb;31(2):172-6

Modulation of luteinizing hormone(LH) release by clonidine and opioid peptides in castrated male rats. Koh T, et al. **Endocrinol Jpn** 1985 Oct; 32(5):653-9

Metorphamide levels in chromaffin cells increase after treatment with reserpine. Eiden LE, et al. **J Neurochem** 1986 May;46(5):1651-4

Spinal release of immunoreactive Met-enkephalin by intraventricular beta-endorphin and its analogs in anesthetized rats. Tseng LF, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):65-74

Effect of short photoperiod on hypothalamic methionine-enkephalin and LHRH content and serum beta-endorphin-like immunoreactivity (beta-end LI) levels in golden hamsters. Kumar MS, et al. **J Pineal Res** 1984;1(2):197-205

Characterization of aminopeptidases responsible for inactivating endogenous (Met5)enkephalin in brain slices using peptidase inhibitors and anti-aminopeptidase M antibodies. Giros B, et al. **Mol Pharmacol** 1986 Mar;29(3):281-7

Presynaptic modulation by noradrenaline and an opioid of the substance P-induced release of [3H]acetylcholine from the myenteric plexus. Vizi ES, et al. **Regul Pept** 1985 Nov 28;12(4):317-25

Methionine-enkephalin does not alter human platelet aggregatory response. Given MB, et al. **Thromb Res** 1985 Dec 1;40(5):711-4

[Changes in the met- and leu-enkephalin levels in the rat brain during burn shock] Zaets TL, et al. **Biull Eksp Biol Med** 1986 Jan; 101(1):10-1 (Eng. Abstr.) **(Rus)**

ENKEPHALINS

Neurotransmitters of the cochlea and cochlear nucleus: immunocytochemical evidence. Altschuler RA, et al. **Am J Otolaryngol** 1986 Mar-Apr;7(2):100-6 (59 ref.)

Reptilian enkephalins: implications for the evolution of proenkephalin. Lindberg I, et al. **Arch Biochem Biophys** 1986 Feb 15;245(1):1-7

Localization of substance P- and enkephalin-like immunoreactivity in the human paravertebral sympathetic ganglia. Del Fiacco M, et al. **Basic Appl Histochem** 1985;29(4):309-20

Breakdown of small enkephalin derivatives and adrenal peptide E by human plasma. Boarder MR, et al. **Biochem Pharmacol** 1986 Mar 15; 35(6):1043-7

Glutamic acid decarboxylase and enkephalin immunoreactive axon terminals in the rat neostriatum synapse with striatonigral neurons. Aronin N, et al. **Brain Res** 1986 Feb 12;365(1):151-8

Distribution of enkephalin-immunoreactive cell bodies in relation to serotonin-containing neurons in the raphe nuclei of the cat: immunohistochemical evidence for the coexistence of enkephalins and serotonin in certain cells. Léger L, et al. **Brain Res** 1986 Jan 1; 362(1):63-73

Properties of antidromically identified neurons in the enkephalinergic magnocellular dorsal nucleus of the guinea pig hypothalamus. Poulain P. **Brain Res** 1986 Jan 1;362(1):74-82

Addiction, nutrition and health. Russell CA. **Dent Health (London)** 1985 Nov-Dec;24(5):7, 9-11

Identification of a 27-kDa enkephalin-containing protein associated with bovine adrenal medullary chromaffin granule membranes by immunoblotting. Birch NP, et al. **FEBS Lett** 1986 Mar 3; 197(1-2):173-8

NOE data at 500 MHz reveal the proximity of phenyl and tyrosine rings in enkephalin. Gupta G, et al. **FEBS Lett** 1986 Mar 31; 198(2):245-50

The prohormone processing activity is enriched in a low-density subpopulation of chromaffin granules. Maret GE, et al. **FEBS Lett** 1986 Jan 20;195(1-2):258-60

Cloning and expression in Escherichia coli of the synthetic proenkephalin analogue gene. Hostomský Z, et al. **Gene** 1985;39(2-3):269-74

'Enkephalinase', a newly characterised dipeptidyl carboxypeptidase: properties and possible role in enkephalinergic transmission. Schwartz JC, et al. **Int J Neurol** 1980;14(2-4):195-204 (45 ref.)

The ultrastructure of enkephalin-immunoreactive neurons in the interpeduncular nucleus of the rat. Mahalik TJ, et al. **J Comp Neurol** 1986 Feb 15;244(3):360-8

Geometrical correspondence between phenazocine and the enkephalins. Froimowitz M, et al. **J Med Chem** 1986 Apr;29(4):573-8

Dynorphin- and enkephalin-like immunoreactivity is altered in limbic-basal ganglia regions of rat brain after repeated electroconvulsive shock. Kanamatsu T, et al. **J Neurosci** 1986 Mar;6(3):644-9

GABAergic regulation of enkephalin in rat striatum: alterations in Met5-enkephalin level, precursor content and preproenkephalin messenger RNA abundance. Sivam SP, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):326-31

The stimulation of food intake by selective agonists of mu, kappa and delta opioid receptors. Gosnell BA, et al. **Life Sci** 1986 Mar 24; 38(12):1081-8

Nomenclature for enkephalin degrading peptidases. Hersh LB. **Life Sci** 1986 Mar 31;38(13):1151-3 (17 ref.)

Effect of various enkephalin analogs and dipeptides on the enzymatic activity of enkephalinase B isolated from calf-brain striatum. van Amsterdam JG, et al. **Life Sci** 1986 Mar 24;38(12):1111-8

Detection of the mRNA coding for enkephalin precursor in the rat brain and adrenal by using an 'in situ' hybridization procedure. Bloch B, et al. **Neurosci Lett** 1986 Feb 14;64(1):29-34

Inputs to motoneurones in the hypoglossal nucleus of the rat: light and electron microscopic immunocytochemistry for choline acetyltransferase, substance P and enkephalins using monoclonal antibodies. Connaughton M, et al. **Neuroscience** 1986;17(1):205-24

Isolation and structure of a C-terminally amidated nonopioid peptide, amidorphin-(8-26), from bovine striatum: a major product of proenkephalin in brain but not in adrenal medulla. Liebisch DC, et al. **Proc Natl Acad Sci USA** 1986 Mar;83(6):1936-40

Permissive effect of dexamethasone on the increase of proenkephalin mRNA induced by depolarization of chromaffin cells. Naranjo JR, et al. **Proc Natl Acad Sci USA** 1986 Mar;83(5):1513-7

Activation of mouse T-helper cells induces abundant preproenkephalin mRNA synthesis. Zurawski G, et al. **Science** 1986 May 9; 232(4751):772-5

[Enkephalins] Grzeszczak W, et al. **Przegl Lek** 1985;42(10):714-8 **(Pol)**

[Effect of vasopressin and enkephalin analogs on the chemoreactive properties of the sensorimotor cortex neurons in rats] Kruglikov RI, et al. **Biol Nauki** 1985;(11):61-6 (Eng. Abstr.) **(Rus)**

ENURESIS

Childhood enuresis: prevalence, perceived impact, and prescribed treatments. Foxman B, et al. **Pediatrics** 1986 Apr;77(4):482-7

EPHEDRINE

Use of orthogonal polynomials for unequal intervals to eliminate interference in spectrophotometric analysis. Simultaneous determination of ephedrine hydrochloride and diphenhydramine hydrochloride in two-component mixtures. Korany MA, et al. **Analyst** 1986 Jan; 111(1):41-4

Possible involvement of beta 2-adrenoceptors in hyperthermic effect of l-ephedrine in rats. Yamahara J, et al. **J Pharmacobiodyn** 1985 Aug; 8(8):591-6

The effect of chronic ephedrine treatment on substrate utilization, the sympathoadrenal activity, and energy expenditure during glucose-induced thermogenesis in man. Astrup A, et al. **Metabolism** 1986 Mar;35(3):260-5

No promethazine in Nyquil [letter] Lewis ET. **N Engl J Med** 1986 Apr 3;314(14):927

[Gas chromatographic analysis of ephedrine] Pham C, et al. **Acta Pharm Hung** 1986 Jan;56(1):16-25 (Eng. Abstr.) **(Hun)**

[Behavioral changes in rhesus monkeys induced by repeated administration of ephedrine] Kato S. **Seishin Shinkeigaku Zasshi** 1985; 87(8):583-94 (Eng. Abstr.) **(Jpn)**

EPINEPHRINE

Comparative study of mechanical responses of hepatic arteries strips to adrenalin in presence of pyridoxine and pyridoxal-5'-phosphate. Bettini V, et al. **Acta Vitaminol Enzymol** 1985;7(3-4):155-66

Glucoregulatory role of cortisol and epinephrine interactions studied in adrenalectomized dogs. Gauthier C, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):E393-401

Ontogeny of epinephrine-induced anorexia in rats. Rodriguez-Zendejas AM, et al. **Am J Physiol** 1986 Feb;250(2 Pt 2):R313-7

An association between norepinephrine-to-epinephrine ratio and suicidal ideation in depression [letter] **Am J Psychiatry** 1986 May; 143(5):683-4

The metabolic and ventilatory response to the infusion of stress hormones. Weissman C, et al. **Ann Surg** 1986 Apr;203(4):408-12

Epinephrine. Use, adverse effects, and dosage calculation. Kochansky SW. **AORN J** 1986 Apr;43(4):852-5

Responses of adrenal catecholamine secretion to lateral hypothalamic stimulation and lesion in rats. Katafuchi T, et al. **Brain Res** 1986 Jan 15;363(1):141-4

Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. Liang KC, et al. **Brain Res** 1986 Mar 12;368(1):125-33

Paradoxical effects of epinephrine on cAMP synthesis and degradation in rat adipocytes. Fatemi SH. **Cell Mol Biol** 1985;31(5):349-56

Parenteral adrenergic bronchodilators and potassium. Küng M. **Chest** 1986 Mar;89(3):322-3

Adrenergic coronary tone during submaximal exercise in the dog is produced by circulating catecholamines. Evidence for adrenergic denervation supersensitivity in the myocardium but not in coronary vessels. Chilian WM, et al. **Circ Res** 1986 Jan;58(1):68-82

Effect of epinephrine on cerebral and myocardial perfusion in an infant animal preparation of cardiopulmonary resuscitation. Schleien CL, et al. **Circulation** 1986 Apr;73(4):809-17

Selective alpha 2 receptor blockade facilitates the insulin response to adrenaline but not to glucose in man. Struthers AD, et al. **Clin Endocrinol (Oxf)** 1985 Nov;23(5):539-46

Cardiovascular and metabolic responses to low dose adrenaline infusion: an invasive study in humans. Freyschuss U, et al. **Clin Sci** 1986 Feb;

70(2):199-206

Plasma adrenaline measurements [letter] McCulloch R, et al. **Clin Sci** 1986 Feb;70(2):211-2

Catecholamine-mediated injury to endothelium in rabbit perfused aorta: a quantitative analysis by scanning electron microscopy. Makhmudov RM, et al. **Cor Vasa** 1985;27(6):456-63

Human aqueous humor catecholamines. Autzen T, et al. **Curr Eye Res** 1985 Dec;4(12):1269-71

Further studies on the effect of retrobulbar epinephrine injection on ocular and optic nerve blood flow. Jay WM, et al. **Curr Eye Res** 1986 Jan; 5(1):63-7

Acute influence of cigarette smoke in platelets, catecholamines and neurophysins in the normal conditions of daily life. de Lorgeril M, et al. **Eur Heart J** 1985 Dec;6(12):1063-8

Reproducibility of plasma catecholamine concentrations at rest and during exercise in man. Péronnet F, et al. **Eur J Appl Physiol** 1986; 54(6):555-8

Evidence that epinephrine acts preferentially as an antilipolytic agent in abdominal human subcutaneous fat cells: assessment by analysis of beta and alpha 2 adrenoceptor properties. Berlan M, et al. **Eur J Clin Invest** 1985 Dec;15(6):341-8

Plasma catecholamines and glucose during moderate exercise in the trout: comparison with bursts of violent activity. Ristori MT, et al. **Exp Biol** 1985;44(4):247-53

Cardiac function and plasma catecholamines during upright exercise in healthy young subjects. Kelbaek H, et al. **Int J Cardiol** 1986 Mar; 10(3):223-35

Free plasma catecholamines, heart rates, lactate levels, and oxygen uptake in competition weight lifters, cyclists, and untrained control subjects. Lehmann M, et al. **Int J Sports Med** 1986 Feb;7(1):18-21

Plasma norepinephrine concentration reflects pharmacological alteration of sympathetic activity in the conscious cat. Hubbard JW, et al. **J Auton Nerv Syst** 1986 Jan;15(1):93-100

Insulin antagonizes epinephrine activation of the membrane transport of fatty acids. Potential site for hormonal suppression of lipid mobilization. Abumrad NA, et al. **J Biol Chem** 1986 Mar 5;261(7):2999-3001

Hormone-stimulated polyphosphoinositide breakdown in rat liver plasma membranes. Roles of guanine nucleotides and calcium. Uhing RJ, et al. **J Biol Chem** 1986 Feb 15;261(5):2140-6

Epinephrine infusion decreases magnesium plasma concentration in humans [letter] Belz GG, et al. **J Cardiovasc Pharmacol** 1985 Nov-Dec; 7(6):1205-6

Pharmacologic support of the myocardium following aortocoronary bypass surgery: a comparative study. Balderman SC, et al. **J Clin Pharmacol** 1986 Mar;26(3):175-83

Unusual responses of cultured Fundulus heteroclitus melanophores to epinephrine and ions, paradox of K+ versus Na+. Clark CR, et al. **J Exp Zool** 1985 Dec;236(3):361-4

In vivo hyperglycemic effect of (-)- and (+)-epinephrine in dogs. Kowarski CR, et al. **J Pharm Sci** 1986 Jan;75(1):78-9

Microvascular reactivity of in vitro blood perfused juxtameduliary nephrons from rats. Casellas D, et al. **Kidney Int** 1985 Nov; 28(5):752-9

Infiltration of adrenaline before thyroidectomy [letter] Mair IM. **Lancet** 1971 Dec 11;2(7737):1324

Epinephrine and norepinephrine stimulation of adenylate cyclase in bovine retina homogenate: evidence for interaction with the dopamine D1 receptor. Vanderheyden P, et al. **Life Sci** 1986 Mar 31; 38(13):1221-7

In vitro effects of betamethasone, adrenaline and noradrenaline on normal human T-lymphocyte rosettes. Kumar R, et al. **Mater Med Pol** 1985 Jul-Sep;17(3):170-1

Desensitization of epinephrine-initiated platelet aggregation does not alter binding to the alpha 2-adrenergic receptor or receptor coupling to adenylate cyclase. Motulsky HJ, et al. **Mol Pharmacol** 1986 Jan; 29(1):1-6

Regulation of thyrotropin secretion by the central epinephrine system. Studies in the chronically cannulated rat. Terry LC. **Neuroendocrinology** 1986;42(2):102-8

Action of isoproterenol and epinephrine on the guinea pig taenia coli studied by intracellular microelectrodes. Tomita T, et al. **Nippon Heikatsukin Gakkai Zasshi** 1985 Jul;21 Suppl:55-9

Plasma catecholamines at rest and exercise in subjects with high- and low-trait anxiety. Péronnet F, et al. **Psychosom Med** 1986 Jan-Feb; 48(1-2):52-8

Potentiation of adrenaline-induced platelet aggregation by angiotensin II. Ding YA, et al. **Thromb Haemost** 1985 Oct 30;54(3):717-20

Synergism between thrombin and epinephrine in human platelets: different dose-response relationships for aggregation and dense granule secretion. Steen VM, et al. **Thromb Haemost** 1985 Oct 30;54(3):680-3

Leukotrienes potentiate the effects of epinephrine and thrombin on human platelet aggregation. Mehta P, et al. **Thromb Res** 1986 Mar 1; 41(5):731-8

[The effect of adrenaline, pilocarpine and timolol on axoplasmic transport in the optic nerve. I. Findings in normotensive eyes] Brožek B, et al. **Cesk Oftalmol** 1985 Feb;41(1):13-6 (Eng. Abstr.) **(Cze)**

[Synergism between adrenaline and PAF-acether on human platelets: interference by Hydergine] Fouque F, et al. **J Pharmacol** 1985; 16 Suppl 3:145-51 (Eng. Abstr.) **(Fre)**

[The photo- and thermostability of adrenaline solutions. 1. The stability of adrenaline solutions] Thoma K, et al. **Pharm Acta Helv** 1986; 61(1):2-9 (Eng. Abstr.) **(Ger)**

[Stabilization of adrenaline solutions. 2. The stability of adrenaline solutions] Thoma K, et al. **Pharm Acta Helv** 1986;61(2):34-41 (Eng. Abstr.) **(Ger)**

[Changes in serum electrolytes and cardiovascular function: a possible cause of shock during nasal operation using local anesthetics] Okamoto K, et al. **Nippon Jibiinkoka Gakkai Kaiho** 1985 Sep;88(9):1146-52 (Eng. Abstr.) **(Jpn)**

[Epinephrine uptake and release and presynaptic alpha 2-adrenoceptic regulation in the guinea pig hypothalamus] Fujii Y, et al. **Nippon Yakurigaku Zasshi** 1986 Jan;87(1):11-7 (Eng. Abstr.) **(Jpn)**

[Selected elements of the physiology of physical exertion as the introduction to physiopathology in obstetrics and perinatology. II. Factors of physiological regulation of energy metabolism during physical exertion. Neurohormonal regulation: the adrenergic system] Brodziński W. **Ginekol Pol** 1985 Oct;56(10):585-91 (Eng. Abstr.) **(Pol)**

[Effect of adrenaline and noradrenaline on the vascular antiaggregation activity in cats] Gabrielian ES, et al. **Farmakol Toksikol** 1986 Jan-Feb; 49(1):56-8 (Eng. Abstr.) **(Rus)**

[Changes in adrenergic inhibition of the secretion of parietal cells of gastric glands after resection and section of the proximal portion of the small intestine] Trefilov AB. **Fiziol Zh SSSR** 1985 Dec;71(12):1597-601 (Eng. Abstr.) **(Rus)**

[Adrenergic reactivity of the heart and coronary vessels in hemotransfusion shock] Khomaziuk AI, et al. **Vestn Akad Med Nauk SSSR** 1985;(12):74-80 (Eng. Abstr.) **(Rus)**

[The effect of catecholamines and histamine on liver circulation] Antal J, et al. **Bratisl Lek Listy** 1986 Mar;85(3):249-57 (Eng. Abstr.) **(Slo)**

ESTRADIOL

Short-term effects of oestradiol and 4-hydroxyoestradiol on gonadotrophin-releasing hormone induced luteinizing hormone secretion by rat pituitary cells in culture. Emons G, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):312-20

The effect of oestrogen and relaxin on uterine and cervical enzymes: collagenase, proteoglycanase and beta-glycuronidase. Too CK, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):394-403

Effects of oestradiol-17 beta and LRH upon the two fractions of pituitary follicle-stimulating hormone separated by concanavalin-A chromatography. Ulloa-Aguirre A, et al. **Acta Endocrinol (Copenh)** 1985 Dec;110(4):475-82

Effects of estradiol and some antiestrogens (clomiphene, tamoxifen, and hydroxytamoxifen) on luteinizing hormone secretion by rat pituitary cells in culture. Emons G, et al. **Arch Gynecol** 1986;237(4):199-211

Effect of single or repeated estrogen administration on tuberoinfundibular GABA neurons and anterior pituitary GABA receptors: biochemical and functional studies. Apud JA, et al. **Brain Res** 1985 Dec 30; 361(1-2):146-53

The sialagogue response of striatal dopamine receptors to L-dopa is not influenced by castration or chronic estrogen treatment. Pazo JH, et al. **Brain Res Bull** 1986 Jan;16(1):1-4

Plasma noradrenaline and its relationship to plasma oestradiol in normal women during the menstrual cycle. Davidson L, et al. **Clin Exp Pharmacol Physiol** 1985 Sep-Oct;12(5):489-93

Biphasic stimulatory effects of estrogen on gonadotropin surges induced by continuous administration of gonadotropin-releasing hormone in women. Araki S, et al. **Endocrinol Jpn** 1985 Oct;32(5):595-605

Effect of ovariectomy and estrogen on [3H]imipramine binding to different regions of rat brain. Stockert M, et al. **Eur J Pharmacol** 1985 Dec 17; 119(3):255-7

Bromocriptine and sulpiride competitively inhibit estrogen binding to its receptor in the adrenal gland. Lüthy IA, et al. **Experientia** 1986 Feb 15;42(2):136-8

Inhibition of estradiol-induced gonadotropin release in ovariectomized rhesus macaques by a gonadotropin-releasing hormone antagonist. Norman RL, et al. **Fertil Steril** 1986 Feb;45(2):288-91

Sex differences in [3H]-estradiol binding in brain and pituitary after acute dopaminergic treatment. In vivo studies in the rat. Gietzen DW, et al. **Neuroendocrinology** 1986;42(4):334-43

Effect of ovarian steroids to stimulate region-specific hypothalamic 5-hydroxytryptamine synthesis in ovariectomized rats. King TS, et al. **Neuroendocrinology** 1986;42(4):344-50

Androgenic and estrogenic control of the self-priming effect of LHRH in the castrated male rat. Nazian SJ. **Neuroendocrinology** 1986; 42(2):112-9

Influence of neonatal injection of estradiol and testosterone on hypothalamo-hypophyseal-gonadal interrelationships and fertility in male rats. Baranov VG, et al. **Neurosci Behav Physiol** 1985 Sep-Oct; 15(5):404-7

Modulation of apomorphine-induced climbing behavior by estradiol.

Fung YK, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):139-41

Increased clearance rate of plasma thyroxine accompanies estradiol-induced vitellogenesis in male Japanese quail. Robinson GA, et al. **Poult Sci** 1985 Dec;64(12):2397-9

[Study on the central action of catecholestrogen: effect of 2-hydroxyestrogens on the preovulatory LH surge] Okatani Y. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 Feb;38(2):151-60 (Eng. Abstr.) **(Jpn)**

EXPLORATORY BEHAVIOR

Disturbances in exploratory behavior and functional recovery in the Y and radial mazes following dopamine depletion of the lateral septum. Taghzouti K, et al. **Behav Neural Biol** 1986 Jan;45(1):48-56

The effects of yohimbine on exploratory and locomotor behaviour are attributable to its effects at noradrenaline and not at benzodiazepine receptors. Chopin P, et al. **Neuropharmacology** 1986 Jan;25(1):53-7

Comparison of the effects of amphetamine and a fluorinated analogue on locomotion and exploratory activity in the mouse. Dubin RE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):681-5

Amphetamine, apomorphine and investigatory behavior in the rat: analysis of the structure and pattern of responses. Kelley AE, et al. **Psychopharmacology (Berlin)** 1986;88(1):66-74

EXTINCTION (PSYCHOLOGY)

Different effects of haloperidol and extinction on instrumental behaviours. Salamone JD. **Psychopharmacology (Berlin)** 1986;88(1):18-23

FEAR

Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks. A double-blind comparison of zimeldine, imipramine and placebo. Evans L, et al. **Acta Psychiatr Scand** 1986 Jan;73(1):49-53

CO2 inhalation in the treatment of panic attacks. Griez E, et al. **Behav Res Ther** 1986;24(2):145-50

Destruction of intrinsic neurons in the lateral hypothalamus disrupts the classical conditioning of autonomic but not behavioral emotional responses in the rat. Iwata J, et al. **Brain Res** 1986 Mar 12; 368(1):161-6

Clonazepam in the treatment of patients with recurrent panic attacks. Beaudry P, et al. **J Clin Psychiatry** 1986 Feb;47(2):83-5

Urinary norepinephrine excretion in panic and phobic disorders. Dajas F, et al. **J Neural Transm** 1986;65(1):75-81

An open clinical trial of clonazepam in the treatment of patients with recurrent panic attacks. Beaudry P, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):589-92

Clonazepam for panic disorders and agitation. Fontaine R. **Psychosomatics** 1985 Dec;26(12 Suppl):13-8

FENFLURAMINE

Food deprivation fails to potentiate intravenous self-administration of fenfluramine in naive rats. Papasava M, et al. **Appetite** 1986 Mar; 7(1):55-61

d- and l-isomers of fenfluramine differ markedly in their interaction with brain serotonin and catecholamines in the rat. Invernizzi R, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):9-15

Fenfluramine and autism: careful reappraisal is in order [editorial] Gualtieri CT. **J Pediatr** 1986 Mar;108(3):417-9

Effects of serotonin antagonists on the performance of a simple food acquisition task in rats treated with fenfluramine isomers. Thurlby PL, et al. **Pharmacol Res Commun** 1985 Dec;17(12):1129-39

FK 33-824

Inhibition of spontaneous ACTH release and improved response to CRF in sheep premedicated with the enkephalin analogue DAMME. Redekopp CA, et al. **Horm Metab Res** 1985 Dec;17(12):646-9

Effect of adrenergic antagonism on the growth hormone, prolactin and cortisol response to a synthetic opioid agonist in man. Bouloux PM, et al. **Horm Res** 1986;23(2):83-90

FLICKER FUSION

Visual flicker in depression: response criteria, confidence ratings and response times. Herskovic JE, et al. **Psychol Med** 1986 Feb; 16(1):187-97

FLUPHENAZINE

Effect of prolonged dopamine receptor blockade on lactotroph activity in the rat pituitary gland. Prysor-Jones RA, et al. **Acta Endocrinol (Copenh)** 1985 Dec;110(4):469-74

Liquid chromatographic determination of identity, content, and content uniformity of desipramine, fluphenazine, and promazine. Beaulieu N, et al. **J Assoc Off Anal Chem** 1986 Jan-Feb;69(1):178-9

[3H]Fluphenazine binding to brain membranes: simultaneous measurement of D-1 and D-2 receptor sites. Morgan DG, et al. **J Neurochem** 1986 May;46(5):1623-31

FLURAZEPAM

Simple thin-layer chromatographic method for the investigation of six related compounds in flurazepam hydrochloride and its capsules. Klein CM, et al. **J Chromatogr** 1985 Dec 20;350(1):273-8

Effect of CGS-8216 on high-dose flurazepam convulsive threshold. Bourn WM, et al. **Pharmacology** 1986;32(3):131-3

Effect of hypoxia on ventilatory and arousal responses to CO2 during NREM sleep with and without flurazepam in young adults. Gothe B, et al. **Sleep** 1986;9(1):24-37

FOOD DEPRIVATION

Food deprivation fails to potentiate intravenous self-administration of fenfluramine in naive rats. Papasava M, et al. **Appetite** 1986 Mar; 7(1):55-61

Food deprivation-induced changes in the level of opioid peptides in the pituitary and brain of rat. Vaswani KK, et al. **Life Sci** 1986 Jan 13; 38(2):197-201

FSH

Acute effects of GnRF-induced gonadotrophin secretion upon ovarian steroid secretion in the ferret. Matson C, et al **Acta Endocrinol (Copenh)** 1986 Mar;111(3):373-7

Effects of oestradiol-17 beta and LRH upon the two fractions of pituitary follicle-stimulating hormone separated by concanavalin-A chromatography. Ulloa-Aguirre A, et al. **Acta Endocrinol (Copenh)** 1985 Dec;110(4):475-82

Estrogen inhibition of LH and FSH secretion: effects of a GnRH antagonist. Charlesworth MC, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):E341-5

Androgen and progesterone effects on follicle-stimulating hormone and luteinizing hormone secretion in anestrous mares. Thompson DL Jr, et al. **Biol Reprod** 1986 Feb;34(1):51-7

Induction of ovulation in primate models. Kenigsberg D, et al. **Endocr Rev** 1986 Feb;7(1):34-43 (45 ref.)

Biphasic stimulatory effects of estrogen on gonadotropin surges induced by continuous administration of gonadotropin-releasing hormone in women. Araki S, et al. **Endocrinol Jpn** 1985 Oct;32(5):595-605

Evidence that pulsatile follicle-stimulating hormone secretion is independent of endogenous luteinizing hormone-releasing hormone. Culler MD, et al. **Endocrinology** 1986 Feb;118(2):609-12

Prolactin (PRL), follicle-stimulating hormone, and luteinizing hormone are regulators of testicular PRL receptors in golden hamsters. Klemcke HG, et al. **Endocrinology** 1986 Feb;118(2):773-82

Increased frequency of pulsatile luteinizing hormone-releasing hormone administration selectively decreases follicle-stimulating hormone levels in men with idiopathic azoospermia. Gross KM, et al. **Fertil Steril** 1986 Mar;45(3):392-6

Temporal relationship between the onset of daily gonadotrophin surges and of puberty in female golden hamsters. Donham RS, et al. **J Endocrinol** 1986 Feb;108(2):219-24

Testosterone maintains pituitary and serum FSH and spermatogenesis in gonadotrophin-releasing hormone antagonist-suppressed rats. Rea MA, et al. **J Endocrinol** 1986 Jan;108(1):101-7

Stimulation of gonadotropin release by a non-GnRH peptide sequence of the GnRH precursor. Millar RP, et al. **Science** 1986 Apr 4; 232(4746):68-70

GABA

Comparative studies of fresh and postmortem isolated rat cortical synaptosomes: uptake and potassium-evoked release of gamma-aminobutyric acid. Kálmán M, et al. **Acta Biol Hung** 1985; 36(1):87-91

GABA antagonists increase the release of [3H]acetylcholine from the chick retina. Agardh E. **Acta Physiol Scand** 1986 Jan;126(1):33-8

Neurotransmitters of the cochlea and cochlear nucleus: immunocytochemical evidence. Altschuler RA, et al. **Am J Otolaryngol** 1986 Mar-Apr;7(2):100-6 (59 ref.)

Ion-coupled neurotransmitter transport across the synaptic plasma membrane. Kanner BI, et al. **Ann NY Acad Sci** 1985;456:153-61 (40 ref.)

Cardiovascular effects of L-glutamate and gamma-aminobutyric acid injected into the rostral ventrolateral medulla in normotensive and spontaneously hypertensive rats. Kubo T, et al. **Arch Int Pharmacodyn Ther** 1986 Jan;279(1):150-61

GABA-specificity of behaviour responses to picrotoxin injected into the colliculus superior of cats. Jaspers R, et al. **Behav Brain Res** 1985 Oct-Nov;18(1):63-9

Distribution of GABA binding site subtypes in rat pituitary gland. Anderson RA, et al. **Brain Res** 1986 Feb 12;365(1):78-84

Effect of single or repeated estrogen administration on tuberoinfundibular

GABA neurons and anterior pituitary GABA receptors: biochemical and functional studies. Apud JA, et al. **Brain Res** 1985 Dec 30; 361(1-2):146-53

Local and remote effects of intra-caudate administration of GABA-related drugs on Met-enkephalin release in the basal ganglia. Bourgoin S, et al. **Brain Res** 1985 Dec 30;361(1-2):361-72

The action of oxygen and oxygen at high pressure on inhibitory transmission. Colton CA, et al. **Brain Res** 1986 Jan 29;364(1):151-8

Gamma-aminobutyric acid-immunoreactivity in the rat hippocampus. A light and electron microscopic study with anti-GABA antibodies. Gamrani H, et al. **Brain Res** 1986 Jan 29;364(1):30-8

Release of gamma-aminobutyric acid from the visual cortex of young kittens. Hicks TP, et al. **Brain Res** 1986 Jan;389(1-2):299-304

GABAergic neurons in rat hippocampal culture. Hoch DB, et al. **Brain Res** 1986 Feb;390(1):53-64

Subpopulations of rat cerebellar astrocytes in primary culture: morphology, cell surface antigens and [3H]GABA transport. Johnstone SR, et al. **Brain Res** 1986 Jan;389(1-2):63-75

Ontogeny of GABAergic neurons in chick brain: studies in vivo and in vitro. Jong YJ, et al. **Brain Res** 1986 Feb;390(1):83-90

Further behavioral analysis of GABA-mediated inhibition in the early chick embryo. Maderdrut JL, et al. **Brain Res** 1986 Feb; 390(1):157-60

Cogeneration of retrogradely labeled corticocortical projection and GABA-immunoreactive local circuit neurons in cerebral cortex. Miller MW. **Brain Res** 1985 Dec;355(2):187-92

Influence of a benzodiazepine, midazolam, and gamma-aminobutyric acid (GABA) on basal somatostatin secretion from cerebral and diencephalic neurons in dispersed cell culture. Stryker TD, et al. **Brain Res** 1986 Jan 8;362(2):339-43

Effect of clonidine and gamma-aminobutyric acid on the discharges of medullo-spinal sympathoexcitatory neurons in the rat. Sun MK, et al. **Brain Res** 1986 Mar 12;368(1):1-17

Mechanism of the calcium-dependent stimulation of transmitter release by 4-aminopyridine in synaptosomes. Tapia R, et al. **Brain Res** 1985 Dec 30;361(1-2):373-82

Differential effects of striatal injections of dopaminergic, cholinergic and GABAergic drugs upon swimming behavior of rats. Vrijmoed-de Vries MC, et al. **Brain Res** 1986 Jan 29;364(1):77-90

Effects of gamma-aminobutyric acid on cones and bipolar cells of the tiger salamander retina. Wu SM. **Brain Res** 1986 Feb 12;365(1):70-7

Studies of angiotensin I converting enzyme: effects of kinins, bacitracin, gamma-aminobutyric and epsilon-aminocaproic acids, and related compounds on substrate binding and catalysis in vitro. Odya CE, et al. **Can J Physiol Pharmacol** 1986 Jan;64(1):50-4

Role of uptake in gamma-aminobutyric acid (GABA)-mediated responses in guinea pig hippocampal neurons. Hablitz JJ, et al. **Cell Mol Neurobiol** 1985 Dec;5(4):353-71

GABA neurones in retinas of different species and their postnatal development in situ and in culture in the rabbit retina. Osborne NN, et al. **Cell Tissue Res** 1986;243(1):117-23

Stress by forced swimming in the rat: effects of mianserin and moclobemide on GABAergic-monoaminergic systems in the brain. Cicardo VH, et al. **Comp Biochem Physiol** [C] 1986;83(1):133-5

On GABAergic mechanisms in the optokinetic nystagmus of the frog: effects of bicuculline, allylglycine and SR 95103, a new GABA antagonist. Bonaventure N, et al. **Eur J Pharmacol** 1985 Nov 26; 118(1-2):61-8

Enhancement of GABA binding by the benzodiazepine partial agonist CGS9896. Meiners BA, et al. **Eur J Pharmacol** 1985 Dec 10; 119(1-2):61-5

Autoradiographic localization of GABA-regulated chloride ionophore binding sites using [3H]t-butylbicycloorthobenzoate. O'Connor LH, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):141-2

GABAB receptors in the rabbit uterus may mediate contractile responses. Riesz M, et al. **Eur J Pharmacol** 1985 Dec 17;119(3):199-204

Quantitative distribution of GABA-immunoreactive neurons in the visual cortex (area 17) of the cat. Gabbott PL, et al. **Exp Brain Res** 1986; 61(2):323-31

GABA-immunoreactive neurons in the dorsal lateral geniculate nucleus of the rat: characterisation by combined Golgi-impregnation and immunocytochemistry. Gabbott PL, et al. **Exp Brain Res** 1986; 61(2):311-22

The relationship between GABA immunoreactivity and labelling by local uptake of [3H]GABA in the striate cortex of monkey. Kisvárday ZF, et al. **Exp Brain Res** 1986;62(1):89-98

The proportion and size of GABA-immunoreactive neurons in the magnocellular and parvocellular layers of the lateral geniculate nucleus of the rhesus monkey. Montero VM, et al. **Exp Brain Res** 1986; 62(1):215-23

Binocular interactions in the lateral geniculate nucleus of the cat: GABAergic inhibition reduced by dominant afferent activity. Pape HC, et al. **Exp Brain Res** 1986;61(2):265-71

Afferent fibers from the septum terminate on gamma-aminobutyric acid (GABA-) interneurons and granule cells in the area dentata of the rat. Schwerdtfeger WK. **Experientia** 1986 Apr 15;42(4):392-4

Effect of amygdala kindling on GABA neurons: histochemical and biochemical detection of GABA-T activity. Itagaki S, et al. **Folia Psychiatr Neurol Jpn** 1985;39(3):297-300

Changes in GABAergic system parameters after chronic administration of bicuculline. Pérez C, et al. **Gen Pharmacol** 1985;16(6):629-32

Presence of gamma-aminobutyric acid and its specific receptor binding sites in the human term placenta. Erdö SL, et al. **Gynecol Obstet Invest** 1985;20(4):199-203

The postganglionic excitatory innervation of the mouse urinary bladder and its modulation by prejunctional GABAB receptors. Santicioli P, et al. **J Auton Pharmacol** 1986 Mar;6(1):53-66

Determination of progabide and its acid metabolite in biological fluids by high-performance liquid chromatography on silica column with ultraviolet detection. Ascalone V, et al. **J Chromatogr** 1985 Nov 8; 344:231-9

Postnatal development of 3H-GABA-accumulating cells in rabbit retina. Redburn DA, et al. **J Comp Neurol** 1986 Jan 1;243(1):41-57

Comparative distribution of 3H-GABA uptake and GAD immunoreactivity in goldfish retinal amacrine cells: a double-label analysis. Yazulla S, et al. **J Comp Neurol** 1986 Feb 8;244(2):149-62

GABA-noradrenergic interaction: evidence for differential sites of action for GABA-A and GABA-B receptors. Suzdak PD, et al. **J Neural Transm** 1985;64(3-4):163-72

Dopaminergic regulation of cone retinomotor movement in isolated teleost retinas: II. Modulation by gamma-aminobutyric acid and serotonin. Dearry A, et al. **J Neurochem** 1986 Apr;46(4):1022-31

A search for receptors modulating the release of gamma-[3H]aminobutyric acid in rabbit caudate nucleus slices. Limberger N, et al. **J Neurochem** 1986 Apr;46(4):1109-17

Release of previously incorporated gamma-[3H]aminobutyric acid in rabbit caudate nucleus slices. Limberger N, et al. **J Neurochem** 1986 Apr;46(4):1102-8

Gamma-aminobutyric acid affects the developmental expression of neuron-associated proteins in cerebellar granule cell cultures. Meier E, et al. **J Neurochem** 1986 Apr;46(4):1256-62

Is GABA-stimulated [3H]flunitrazepam binding modulated by benzodiazepine receptor ligands? [letter] Mennini T. **J Neurochem** 1986 Apr;46(4):1326-7

Maitotoxin-induced release of gamma-[3H]aminobutyric acid from cultures of striatal neurons. Shalaby IA, et al. **J Neurochem** 1986 Apr; 46(4):1161-5

Interaction of t-butylbicyclophosphorothionate with gamma-aminobutyric acid-gated chloride channels in cultured cerebral neurons. Tehrani MH, et al. **J Neurochem** 1986 May;46(5):1542-8

Uptake of gamma-aminobutyric acid by brain tissue preparations: a reevaluation. Wood JD, et al. **J Neurochem** 1986 Mar;46(3):739-44

Endogenous dopamine can modulate inhibition of substantia nigra pars reticulata neurons elicited by GABA iontophoresis or striatal stimulation. Waszczak BL, et al. **J Neurosci** 1986 Jan;6(1):120-6

Cholinergic and GABAergic regulation of dopamine beta-hydroxylase activity in the adrenal gland of the rat. Lima L, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):265-70

GABAergic regulation of enkephalin in rat striatum: alterations in Met5-enkephalin level, precursor content and preproenkephalin messenger RNA abundance. Sivam SP, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):326-31

Ranitidine potentiates ileum contractions caused by GABA and electrical stimulation. Trzeciakowski JP, et al. **Life Sci** 1986 Jan 13; 38(2):173-82

Further evidence for, and nature of, the facilitatory GABAergic influence on central noradrenergic transmission. Dennis T, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):225-34

Potassium ion is indispensable to the catecholamine releasing response of dog adrenals to gamma-aminobutyric acid. Kitayama S, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):66-9

A comparison of methods for removal of endogenous GABA from brain membranes prepared for binding assays. Fisher TE, et al. **Neurochem Res** 1986 Jan;11(1):1-8

GABA uptake in embryonic palate mesenchymal cells of two mouse strains. Wee EL, et al. **Neurochem Res** 1985 Dec;10(12):1673-88

Uptake and autoreceptor-controlled release of [3H]-GABA by the hypothalamic median eminence and pituitary neurointermediate lobe. Anderson R, et al. **Neuroendocrinology** 1986;42(4):277-84

Prolongation of gamma-aminobutyric acid-mediated inhibitory postsynaptic potentials by 4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-ol (THPO). Korn SJ, et al. **Neurosci Lett** 1986 Feb 14;64(1):47-52

Neurogenesis of GABAergic neurons in the rat dentate gyrus: a combined autoradiographic and immunocytochemical study. Lübbers K, et al. **Neurosci Lett** 1985 Dec 18;62(3):317-22

Novel synaptic responses mediated by dopamine and gamma-aminobutyric acid in neuroendocrine cells of the intermediate pituitary. MacVicar BA, et al. **Neurosci Lett** 1986 Feb 14; 64(1):35-40

Ultrastructural immunocytochemistry of gamma-aminobutyrate in the cerebral and cerebellar cortex of the rat. Seguela P, et al.

Neuroscience 1985 Dec;16(4):865-74

The role of GABAergic inhibition in the response properties of neurones in cat visual area 18. Vidyasagar TR, et al. **Neuroscience** 1986; 17(1):49-55

Benzodiazepine binding sites in mice forebrain and kidneys: evidence for similar regulation by GABA agonists. Rägo LK, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):1-3

Effect of bicuculline on sexual activity in castrated male rats. Fernandez-Guasti A, et al. **Physiol Behav** 1986;36(2):235-7

Changes in the activity of rat cortical and hippocampal neurones after the iontophoretic administration of beta-endorphin, glutamate and GABA. Strejčková A, et al. **Physiol Bohemoslov** 1985;34(6):567-73

Involvement of noradrenaline in potentiation of the head-twitch response by GABA-related drugs. Singh L, et al. **Psychopharmacology (Berlin)** 1986;88(3):315-9

Parvalbumin in most gamma-aminobutyric acid-containing neurons of the rat cerebral cortex. Celio MR. **Science** 1986 Feb 28; 231(4741):995-7

The action of inhibitory neurotransmitters, gamma-aminobutyric acid and glycine may distinguish between the area centralis and the peripheral retina in cats. Priest TD, et al. **Vision Res** 1985;25(12):1761-70

[The effect of various new GABAergics on motor and oral stereotypes with apomorphine in the rat] Vamvakidès A, et al. **J Pharmacol** 1985 Oct-Dec;16(4):403-11 (Eng. Abstr.) **(Fre)**

[Effect of thyrotropin releasing hormone (TRH) on GABA (gamma aminobutyric acid) metabolism in mouse and rat brains: as to the activities of GAD (glutamic acid decarboxylase), GABA-T (GABA-transaminase) and GABA re-uptake] Kurahashi K, et al. **No To Shinkei** 1985 Dec;37(12):1211-6 (Eng. Abstr.) **(Jpn)**

[Gamma-aminobutyric acid (GABA) activates three types of receptor-ionophore complex] Akaike N. **Yakugaku Zasshi** 1985 Oct; 105(10):926-36 (Eng. Abstr.) **(Jpn)**

[Gamma-aminobutyric acid and bulbar mechanisms of regulating hemodynamics] Gurevich MI, et al. **Fiziol Zh** 1986 Jan-Feb; 32(1):107-14 (73 ref.) **(Rus)**

[Effect of gamma-aminobutyric acid on neurons of the spinal lymphatic center] Serbeniuk TsV, et al. **Fiziol Zh SSSR** 1985 Nov; 71(11):1386-92 (Eng. Abstr.) **(Rus)**

[Sensitivity to GABA of the soma and dendrites of pyramidal cells in isolated sections of hippocampus in the rat] Artemenko DP, et al. **Neirofiziologiia** 1985;17(6):737-47 (Eng. Abstr.) **(Rus)**

[Comparative sensitivity of the somas and dendrites of pyramidal neurons of the hippocampus to glutamate, aspartate and GABA in isolated sections of rat brain] Artemenko DP, et al. **Neirofiziologiia** 1985; 17(6):837-40 (Eng. Abstr.) **(Rus)**

GALVANIC SKIN RESPONSE

The pharmacodynamic response of the basal skin potential to quinidine gluconate. Ando HY, et al. **Life Sci** 1986 Feb 3;38(5):417-24

GENERALIZATION, STIMULUS

TFMPP may produce its stimulus effects via a 5-HT1B mechanism. McKenney JD, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):43-7

GENETICS, BEHAVIORAL

[Genetical aspects of hormonal modification of the stress reactivity. II. Modification in early ontogenesis of the stress reactivity of adult gray rats selected for behavior toward man] Dygalo NN, et al. **Genetika** 1986 Mar;22(3):500-6 (Eng. Abstr.) **(Rus)**

GLUCURONIDASE

The effect of oestrogen and relaxin on uterine and cervical enzymes: collagenase, proteoglycanase and beta-glycuronidase. Too CK, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):394-403

Intrauterine position affects sex-accessory biochemistry in adult female mice. Wechman R Jr, et al. **Biol Reprod** 1985 Nov;33(4):803-7

Furosemide 1-O-acyl glucuronide. In vitro biosynthesis and pH-dependent isomerization to beta-glucuronidase-resistant forms. Rachmel A, et al. **Drug Metab Dispos** 1985 Nov-Dec;13(6):705-10

Beta-glucuronidase mutants of the nematode Caenorhabditis elegans. Sebastiano M, et al. **Genetics** 1986 Mar;112(3):459-68

Effect of sodium thiomalate on immune complex-induced release of lysosomal enzymes from human polymorphonuclear leucocytes. Carević O. **Immunopharmacology** 1986 Feb;11(1):7-11

The distribution of N-acetyl-beta-glucosaminidase, beta-glucuronidase, acid alpha-naphthyl acetate esterase and alpha-naphthyl acetate esterase in subpopulations of thymocytes, bone marrow cells and other lymphoid organs in mice. Rodriguez-Segade S, et al. **Int J Biochem** 1986; 18(2):149-53

The influence of the host on expression of intestinal microbial enzyme activities involved in metabolism of foreign compounds. Cole CB, et al. **J Appl Bacteriol** 1985 Dec;59(6):549-53

beta-Glucuronidase and hyperbilirubinaemia in breast-fed and formula-fed babies. Gourley GR, et al. **Lancet** 1986 Mar 22; 1(8482):644-6

Two roles for guanine nucleotides in the stimulus-secretion sequence of neutrophils. Barrowman MM, et al. **Nature** 1986 Feb 6-12; 319(6053):504-7

GONADOTROPINS, PITUITARY

Inhibition of estradiol-induced gonadotropin release in ovariectomized rhesus macaques by a gonadotropin-releasing hormone antagonist. Norman RL, et al. **Fertil Steril** 1986 Feb;45(2):288-91

Relationship between pituitary GnRH-binding sites and pituitary release of gonadotrophins in post-partum beef cows. Leung K, et al. **J Reprod Fertil** 1986 Jan;76(1):53-63

The antiprogesterone steroid RU-486 does not impair gonadotropin-stimulated luteal adenylyl cyclase activity or gonadotropin release by pituitary cells. Rojas FJ, et al. **J Steroid Biochem** 1985 Dec;23(6A):1053-8

Pre-menstrual syndrome--are gonadotropins the cause of the condition? Coulson CJ. **Med Hypotheses** 1986 Mar;19(3):243-55 (83 ref.)

HABITUATION (PSYCHOPHYSIOLOGY)

Synaptic plasticity in vitro: cell culture of identified Aplysia neurons mediating short-term habituation and sensitization. Rayport SG, et al. **J Neurosci** 1986 Mar;6(3):759-63

HALOPERIDOL

Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? Arana GW, et al. **Am J Psychiatry** 1986 May;143(5):650-1

3H-dopamine uptake and 3H-haloperidol binding in striatum after administration of methyl mercury to rats. Komulainen H, et al. **Arch Toxicol** 1985 Sep;57(4):268-71

Effect of dithiocarbamate fungicides and thiurams on 3H-haloperidol binding in rat brain. Komulainen H, et al. **Arch Toxicol [Suppl]** 1985; 8:77-9

Lateralized decrease in self-stimulation induced by haloperidol in rats with unilateral 6-hydroxydopamine lesions. Carey RJ. **Behav Brain Res** 1985 Dec;18(3):215-22

Prefrontal cortex: possible site of antipsychotic action of haloperidol. Chang WH, et al. **Biol Psychiatry** 1986 Apr;21(4):422-4

Acute and chronic effects of haloperidol on plasma and brain homovanillic acid in the rat. Chang WH, et al. **Biol Psychiatry** 1986 Apr; 21(4):374-81

Locus coeruleus norepinephrine-containing neurons: effects produced by acute and subchronic treatment with antipsychotic drugs and amphetamine. Ramirez OA, et al. **Brain Res** 1986 Jan 1; 362(1):165-70

Activation of striatal dopaminergic grafts by haloperidol. Herman JP, et al. **Brain Res Bull** 1985 Dec;15(6):543-6

Simultaneous microdetermination of biperiden, haloperidol, and trihexyphenidyl in plasma and its application to pharmacokinetic analysis after concomitant intravenous administration of the drugs to rabbits. Yokogawa K, et al. **Chem Pharm Bull (Tokyo)** 1985 Oct; 33(10):4581-6

The effect of antimuscarinic agents on haloperidol induced behavioral hypersensitivity. Carvey PM, et al. **Eur J Pharmacol** 1986 Jan 21; 120(2):193-9

A novel long-lasting dopamine receptor blocker: haloperidol-bovine serum albumin conjugate. Garrigues AM, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):313-9

Norepinephrine with its precursors and their antagonists haloperidol and phentolamine interact with dye free radicals in opposite ways. Marinov BS. **FEBS Lett** 1986 Mar 17;198(1):130-4

Measurement of haloperidol and reduced haloperidol in human plasma using reversed-phase high-performance liquid chromatography. Miller RL, et al. **J Chromatogr** 1986 Jan 24;374(2):405-8

Monosymptomatic hypochondriacal psychosis manifesting as delusions of infestation: case studies of treatment with haloperidol. Andrews E, et al. **J Clin Psychiatry** 1986 Apr;47(4):188-90

A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrenic patients. Tuason VB. **J Clin Psychiatry** 1986 Mar;47(3):126-9

Dosage strategies with long-acting injectable neuroleptics, including haloperidol decanoate. Kane JM. **J Clin Psychopharmacol** 1986 Feb; 6(1 Suppl):20S-23S

Variable dose studies provide misleading therapeutic windows [letter] Van Putten T, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):55-6

A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety, and dosage equivalence. Vasavan Nair NP, et al. **J Clin Psychopharmacol** 1986 Feb;6(1 Suppl):30S-37S

In vivo displacement by 3-PPP enantiomers of N,N-dipropyl-5,6-ADTN from dopamine receptor-binding sites in rat striatum. Carlsson A, et al. **J Neural Transm** 1985;64(3-4):173-85

Investigation of the failure of parenterally administered haloperidol to antagonize dopamine released from micropipettes in the caudate. Johnson SW, et al. **J Neurosci** 1986 Feb;6(2):572-80

Ultrasonic vocalization in rat pups: effects of early postnatal exposure to haloperidol. Cagiano R, et al. **Life Sci** 1986 Apr 14; 38(15):1417-23

Classification of sulpiride, clozapine and haloperidol by toposelective recording from different brain structures in the immobilized rat (stereo-EEG). Dimpfel W, et al. **Neuropsychobiology** 1985; 14(3):157-64

Submaximal plasma prolactin response to TRH and dopamine activity in man. Spoov J. **Pharmacopsychiatry** 1985 Nov;18(6):330-2

Chronic haloperidol treatment: effects on operant responding and inter-response time. Heath GF, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):697-701

Effects of haloperidol on somatostatin-like immunoreactivity in the CSF of Schizophrenic patients. Gattaz WF, et al. **Psychiatry Res** 1986 Jan; 17(1):1-6

Different effects of haloperidol and extinction on instrumental behaviours. Salamone JD. **Psychopharmacology (Berlin)** 1986;88(1):18-23

Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. Salzman C, et al. **Psychosomatics** 1986 Jan; 27(1 Suppl):17-22

[Plasma assay of haloperidol by high performance liquid chromatography] Hequet D, et al. **Ann Biol Clin (Paris)** 1985;43(5):739-42 (Eng. Abstr.) **(Fre)**

[Comparison of the effects of chlorprothixene and haloperidol on hypothalamic function in patients with paranoid schizophrenia] Horodnicki JM, et al. **Psychiatr Pol** 1985 May-Jun;19(3):181-7 (Eng. Abstr.) **(Pol)**

[Chronic treatment of schizophrenia with injectable bromperidol decanoate] Suárez Richards M. **Acta Psiquiatr Psicol Am Lat** 1985 Sep; 31(3).222-8 (Eng. Abstr.) **(Spa)**

HEXOBARBITAL

Prostaglandin D2-induced potentiation of hexobarbitone hypnosis in rats: role of 5-hydroxytryptamine. Bhattacharya SK, et al. **J Pharm Pharmacol** 1985 Dec;37(12):915-6

[Effect of noise on xenobiotic detoxication in the liver] Nikiforov B, et al. **Gig Sanit** 1985 Nov;(11):58-9 **(Rus)**

HISTAMINE

Histamine receptor activation by unsaturated (allyl and propargyl) homologs of histamine. Banning JW, et al. **Agents Actions** 1985 Dec; 17(2):138-44

Relative activities of three calcium channel antagonists on histamine, acetylcholine and antigen-induced contractions of guinea pig ileum. Ingenito AJ. **Agents Actions** 1985 Dec;17(2):113-20

LPS-caused secretion of corticosterone is mediated by histamine through histidine decarboxylase. Suzuki S, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):E243-7

Simultaneous determination of histamine and N tau-methylhistamine with high-performance liquid chromatography using electrochemical detection. Mine K, et al. **Anal Biochem** 1986 Jan;152(1):127-35

The effect of short-term immunotherapy with Pollinex on anti-IgE and antigen-induced histamine release from sensitive human basophils. Chyrek-Borowska S, et al. **Arch Immunol Ther Exp (Warsz)** 1985; 33(6):777-82

A study of the H2-receptor for histamine stimulating adenylate cyclase in homogenates of guinea-pig lung parenchyma. Foreman JC, et al. **Br J Pharmacol** 1986 Jan;87(1):37-44

Brain histamine turnover enhanced by footshock. Yoshitomi I, et al. **Brain Res** 1986 Jan 1;362(1):195-8

Effects of histamine and related compounds on thyrotropin secretion in rats. Mitsuma T, et al. **Horm Res** 1986;23(2):99-105

Biochemical and morphological correlates of transmitter type in C2, an identified histaminergic neuron in Aplysia. Schwartz JH, et al. **J Comp Neurol** 1986 Mar 15;245(3):401-21

Presynaptic inhibition produced by an identified presynaptic inhibitory neuron. II. Presynaptic conductance changes caused by histamine. Kretz R, et al. **J Neurophysiol** 1986 Jan;55(1):131-46

Lack of direct splanchnic nerve inhibitory effects on histamine-induced gastric acid secretion in rats. Yokotani K, et al. **J Pharmacol Exp Ther** 1986 Mar;236(3):770-5

Histaminergic mechanisms in the vertebrate visual system. Nowak JZ. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):783-819 (138 ref.)

The role of vagus nerve on histamine- and acetylcholine-induced bronchoconstriction (experiments on cats). Zimmermann I, et al. **Res Exp Med (Berl)** 1986;186(1):29-34

[The effect of catecholamines and histamine on liver circulation] Antal J, et al. **Bratisl Lek Listy** 1986 Mar;85(3):249-57 (Eng. Abstr.) **(Slo)**

HOMOVANILLIC ACID

Dopaminergic effects of carbamazepine. Relationship to clinical response in affective illness. Post RM, et al. **Arch Gen Psychiatry** 1986 Apr; 43(4):392-6

Prefrontal cortex: possible site of antipsychotic action of haloperidol. Chang WH, et al. **Biol Psychiatry** 1986 Apr;21(4):422-4

Acute and chronic effects of haloperidol on plasma and brain homovanillic acid in the rat. Chang WH, et al. **Biol Psychiatry** 1986 Apr; 21(4):374-81

Homovanillic acid (HVA) urinary excretion and day/night rhythm of chronic schizophrenic patients. Preliminary observations. Mathieu P, et al. **Encephale** 1985 Sep-Oct;11(5):199-202

Dopamine-beta-hydroxylase (DBH) and homovanillic acid (HVA) in autistic children. Garnier C, et al. **J Autism Dev Disord** 1986 Mar; 16(1):23-9

Sensitive determination of tyrosine metabolites, p-hydroxyphenylacetic acid, 4-hydroxy-3-methoxyphenyl-acetic acid and 4-hydroxy-3-methoxymandelic acid, by gas chromatography-negative-ion chemical-ionization mass spectrometry. Application to a stable isotope-labelled tracer experiment to investigate their metabolism in man. Shimamura M, et al. **J Chromatogr** 1986 Jan 10;374(1):17-26

Motor activity increases tryptophan, 5-hydroxyindoleacetic acid, and homovanillic acid in ventricular cerebrospinal fluid of the conscious rat. Chaouloff F, et al. **J Neurochem** 1986 Apr;46(4):1313-6

Effect of various centrally acting drugs on the efflux of dopamine metabolites from the rat brain. Westerink BH, et al. **J Neurochem** 1986 Apr;46(4):1145-52

Relationship between dominance hierarchy, cerebrospinal fluid levels of amine transmitter metabolites (5-hydroxyindole acetic acid and homovanillic acid) and plasma cortisol in monkeys. Yodyingyuad U, et al. **Neuroscience** 1985 Dec;16(4):851-8

Biological markers in depression. Monoamine metabolites in urine of depressed patients and normal subjects. Vandel S, et al. **Pharmacopsychiatry** 1985 Nov;18(6):347-50

Menstrual cycle affects plasma HVA [letter] Petty F, et al. **Psychiatry Res** 1986 Feb;17(2):169-71

Homovanillic acid in caudate and pre-frontal cortex following acute and chronic neuroleptic administration. Bowers MB Jr, et al. **Psychopharmacology (Berlin)** 1986;88(1):63-5

[Monoamine metabolite levels in cerebrospinal fluid of schizophrenic patients] Imazu Y, et al. **Seishin Shinkeigaku Zasshi** 1985; 87(9):634-42 **(Jpn)**

HOSTILITY

A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrenic patients. Tuason VB **J Clin Psychiatry** 1986 Mar;47(3):126-9

HYDANTOINS

A modified system for thiazolinone conversion to thiohydantoin derivatives and their separation by high-pressure liquid chromatography. Bhown AS, et al. **Anal Biochem** 1985 Nov 1; 150(2):457-62

Assay of mephenytoin metabolism in human liver microsomes by high-performance liquid chromatography. Meier UT, et al. **Anal Biochem** 1985 Dec;151(2):286-91

Mephenytoin hydroxylase activity in human liver: inhibition by steroids. Jurima M, et al. **Drug Metab Dispos** 1985 Nov-Dec;13(6):746-9

Effect of prostacyclin (PGI2) and a prostaglandin analogue BW 245C on galactosamine-induced hepatic necrosis. Noda Y, et al. **J Hepatol** 1986;2(1):53-64

HYDRAZINES

Fluorescent hydrazides for the high-performance liquid chromatographic determination of biological carbonyls. Anderson JM. **Anal Biochem** 1986 Jan;152(1):146-53

Structure-activity relationship studies of antiviral N-quinolin-4-yl-N'-benzylidenehydrazine derivatives by discriminant analysis. Gombar VK. **Arzneimittelforschung** 1985;35(11):1633-6

Inactivation of myoglobin by ortho-substituted arylhydrazines. Formation of prosthetic heme aryl-iron but not N-aryl adducts. Ortiz de Montellano PR, et al. **Biochemistry** 1985 Feb 26;24(5):1147-52

The role of formaldehyde in hydrazine-induced methylation of liver DNA guanine. Bosan WS, et al. **Carcinogenesis** 1986 Mar;7(3):413-8

Tetraformyltrisazine and hydrazine-induced methylation of liver DNA guanine. Lambert CE, et al. **Carcinogenesis** 1986 Mar;7(3):419-22

Effect of benserazid and 6-hydroxydopamine on the development of the last larval instar of the house cricket, Acheta domestica L. Rózsa KS, et al. **Comp Biochem Physiol** [C] 1986;83(1):83-8

Free radical-mediated activation of hydrazine derivatives. Kalyanaraman B, et al. **Environ Health Perspect** 1985 Dec;64:179-84

The mechanism of inactivation of dopamine beta-hydroxylase by hydrazines. Fitzpatrick PF, et al. **J Biol Chem** 1986 Apr 5; 261(10):4510-8

Determination of the activity of 16 hydrazine derivatives in the

BIBLIOGRAPHY

bioluminescence test for genotoxic agents. Levi BZ, et al. **Mutat Res** 1986 Apr;173(4):233-7

Generation of anaphylatoxin activity related to C3a, by treatment of human serum with the nitrogen nucleophile N2H4 or the chaotrope KSCN. von Zabern I, et al. **Scand J Immunol** 1985 Dec; 22(6):639-51

Antiaggregatory effects of thromboxane receptor antagonists in vivo. Darius H, et al. **Thromb Res** 1985 Dec 1;40(5):663-75

[The effects of new (dialkoxy-2,3-phenyl) methylhydrazides and their N-benzyl derivatives on rats and mice subjected to a variety of tests in relation to antidepressive effect] Papadaki-Valiraki A, et al. **Ann Pharm Fr** 1985;43(2):155-60 (Eng. Abstr.) **(Fre)**

[DMNH—a new competent indicator for measuring the chemiluminescence of neutrophilic granulocytes and monocytes] Eschenbach C, et al. **Klin Wochenschr** 1985 Dec 2;63(23):1218-25 (Eng. Abstr.) **(Ger)**

HYDRAZONES

Effects of derivatives of hydroxypyruvaldehyde phenylosazone on the Ca2+-adenosine triphosphatase activity of porcine erythrocyte membrane. Nakabayashi T, et al. **Chem Pharm Bull (Tokyo)** 1985 Aug; 33(8):3510-3

Properties of S-adenosylmethionine decarboxylase from rabbit liver: effects of some hydrazone compounds on its activity. Balaña-Fouce R, et al. **Comp Biochem Physiol [B]** 1986;83(1):221-5

HYDROXYBUTYRATES

Pulmonary surfactant lipid synthesis from ketone bodies, lactate and glucose in newborn rats. Sheehan PM, et al. **Lipids** 1985 Dec; 20(12):835-41

[Effect of lithium oxybutyrate on the serotonin and 5-hydroxyindoleacetic acid content in the brain of rabbits] Saratikov AS, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):312-5 (Eng. Abstr.) **(Rus)**

[Toxicity and narcotic effect of sodium oxybutyrate and ketalar at different periods of combined radiation lesion, burn injury and irradiation exposure] Il'iuchenok TIu, et al. **Farmakol Toksikol** 1985 Nov-Dec; 48(6):87-9 (Eng. Abstr.) **(Rus)**

HYDROXYDOPAMINES

The effect of 6-hydroxydopamine infused into the third cerebral ventricle on the plasma cortisol concentration in sheep subjected to repeated and prolonged stress stimuli. Domański E, et al. **Acta Endocrinol (Copenh)** 1985 Dec;110(4):546-52

Studies of neurotensin-dopamine receptor interactions in striatal membranes of the male rat. The influence of 6-hydroxydopamine-induced dopamine receptor supersensitivity. Fuxe K, et al. **Acta Physiol Scand** 1986 Jan;126(1):147-9

6-Hydroxydopamine treatment does not affect the young rat's ability to modify its response when changing from food to water deprivation. Brenner E, et al. **Behav Brain Res** 1986 Jan;19(1):89-92

Lateralized decrease in self-stimulation induced by haloperidol in rats with unilateral 6-hydroxydopamine lesions. Carey RJ. **Behav Brain Res** 1985 Dec;18(3):215-22

Effect of forebrain commissurotomy on recovery from unilateral 6-OHDA lesions of the substantia nigra and circling induced by apomorphine. Steiner H, et al. **Behav Brain Res** 1985 Oct; 17(3):245-9

Conditioned rotational behavior in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra. Carey RJ. **Brain Res** 1986 Feb 19;365(2):379-82

Disruption of corticospinal plasticity by 6-hydroxydopamine as measured by intracortical microstimulation in rats. Castro AJ, et al. **Brain Res** 1986 Jan;389(1-2):295-8

Visual behavior of monocularly deprived kittens treated with 6-hydroxydopamine. Gordon B, et al. **Brain Res** 1986 Jan; 389(1-2):21-9

Comparative effects of the neurotoxins N-chloroethyl-N-ethyl-2-bromobenzylamine hydrochloride (DSP4) and 6-hydroxydopamine on hypothalamic noradrenergic, dopaminergic and 5-hydroxytryptaminergic neurons in the male rat. Lookingland KJ, et al. **Brain Res** 1986 Feb 19;365(2):228-34

Effect of benserazid and 6-hydroxydopamine on the development of the last larval instar of the house cricket, Acheta domestica L. Rózsa KS, et al. **Comp Biochem Physiol [C]** 1986;83(1):83-8

Visual discrimination learning and interhemispheric transfer in the cat, as affected by 6-hydroxydopamine. Sprague JM, et al. **Exp Brain Res** 1985;61(1):43-53

Neuroimmunomodulation: impairment of humoral immune responsiveness by 6-hydroxydopamine treatment. Cross RJ, et al. **Immunology** 1986 Jan;57(1):145-52

Doses of 6-hydroxydopamine sufficient to deplete norepinephrine are not sufficient to decrease plasticity in the visual cortex. Trombley P, et al. **J Neurosci** 1986 Jan;6(1):266-73

Evidence that 6-hydroxydopamine is an inhibitor of catechol-O-methyltransferase in intact tissue. Reid JJ, et al. **J Pharm Pharmacol** 1986 Jan;38(1):46-50

6-Hydroxydopamine lesions of the medial prefrontal cortex fail to influence intravenous self-administration of cocaine. Martin-Iverson MT, et al. **Psychopharmacology (Berlin)** 1986;88(3):310-4

[Fluorohistochemical changes of serotonin in the APUD cells after injection of 6-hydroxydopamine intraperitoneally] Peng JY, et al. **Chen Tzu Yen Chiu** 1985;10(4):298-303 (Eng. Abstr.) **(Chi)**

[Effect of 6-hydroxydopamine on the ultrastructure of non-catecholaminergic elements of the dorsal hippocampus] Semenov SP. **Arkh Anat Gistol Embriol** 1986 Jan;90(1):23-7 (Eng. Abstr.) **(Rus)**

[Effect of acute and chronic deprivation of catecholaminergic system activity induced by 6-hydroxydopamine on the behavior of the rat] Gromova EA, et al. **Zh Vyssh Nerv Deiat** 1985 Nov-Dec; 35(6):1133-41 (Eng. Abstr.) **(Rus)**

HYDROXYINDOLEACETIC ACID

Pemoline and urinary excretion of catecholamines and indoleamines in children with attention deficit disorder. Zametkin AJ, et al. **Am J Psychiatry** 1986 Mar;143(3):359-62

Recent advances in high-performance liquid chromatographic analysis of small molecules. Application of high-performance liquid chromatography with electrochemical detection to the study of neurotransmitters in vivo. Routledge C, et al. **Biochem Soc Trans** 1985 Dec;13(6):1058-61

Effects of prenatal exposure to lithium on indoleamines in maturing mouse brain. Hoff KM, et al. **Gen Pharmacol** 1986;17(1):101-3

Motor activity increases tryptophan, 5-hydroxyindoleacetic acid, and homovanillic acid in ventricular cerebrospinal fluid of the conscious rat. Chaouloff F, et al. **J Neurochem** 1986 Apr;46(4):1313-6

An investigation of demethylation in the metabolism of methoxytryptamine and methoxytryptophol. Leone RM, et al. **J Pineal Res** 1985;2(1):87-94

Differential effect of carbidopa on the concentration of rat pineal and hypothalamic indoleamines. Oxenkrug GF, et al. **J Pineal Res** 1984; 1(4):349-53

Relationship between dominance hierarchy, cerebrospinal fluid levels of amine transmitter metabolites (5-hydroxyindole acetic acid and homovanillic acid) and plasma cortisol in monkeys. Yodyingyuad U, et al. **Neuroscience** 1985 Dec;16(4):851-8

Biological markers in depression. Monoamine metabolites in urine of depressed patients and normal subjects. Vandel S, et al. **Pharmacopsychiatry** 1985 Nov;18(6):347-50

[Monoamine metabolite levels in cerebrospinal fluid of schizophrenic patients] Imazu Y, et al. **Seishin Shinkeigaku Zasshi** 1985; 87(9):634-42 **(Jpn)**

[Effect of lithium oxybutyrate on the serotonin and 5-hydroxyindoleacetic acid content in the brain of rabbits] Saratikov AS, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):312-5 (Eng. Abstr.) **(Rus)**

HYDROXYTRYPTOPHAN

Influence of sequential doses of 5-hydroxytryptophan on prolactin release. Sueldo CE, et al. **Am J Obstet Gynecol** 1986 Feb;154(2):424-7

Prolactin release after 5-hydroxytryptophan treatment requires an intact neurointermediate pituitary lobe. Johnston CA, et al. **Endocrinology** 1986 Feb;118(2):805-10

Therapeutic effects of serotonin uptake inhibitors in depression. Asberg M, et al. **J Clin Psychiatry** 1986 Apr;47 Suppl:23-35 (199 ref.)

Stimulation of the serotonin autoreceptor prevents the calcium-calmodulin-dependent increase of serotonin biosynthesis in rat raphe slices. Sawada M, et al. **J Neurochem** 1986 Mar;46(3):963-7

Differential effect of carbidopa on the concentration of rat pineal and hypothalamic indoleamines. Oxenkrug GF, et al. **J Pineal Res** 1984; 1(4):349-53

Conditioned taste aversions induced by 1-5-hydroxytryptophan are mediated by the area postrema. Ossenkopp KP, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):745-8

HYDROXYZINE

Comparison of the suppressive effect of astemizole, terfenadine, and hydroxyzine on histamine-induced wheals and flares in humans. Gendreau-Reid L, et al. **J Allergy Clin Immunol** 1986 Feb; 77(2):335-40

HYPERKINESIS

Treatment of childhood hyperactivity with desipramine: plasma drug concentration, cardiovascular effects, plasma and urinary catecholamine levels, and clinical response. Donnelly M, et al. **Clin Pharmacol Ther** 1986 Jan;39(1):72-81

HYPOCHONDRIASIS

Monosymptomatic hypochondriacal psychosis manifesting as delusions of infestation: case studies of treatment with haloperidol. Andrews E, et al. **J Clin Psychiatry** 1986 Apr;47(4):188-90

IMIPRAMINE

Predatory dominance and aggressive display under imipramine treatment in cats. Zagrodzka J, et al. **Acta Neurobiol Exp (Warsz)** 1985; 45(5-6):137-49

High-affinity imipramine binding and serotonin uptake in platelets of eight adolescent and ten adult obsessive-compulsive patients. Weizman A, et al. **Am J Psychiatry** 1986 Mar;143(3):335-9

Seasonal variation of platelet serotonin uptake and 3H-imipramine binding in normal and depressed subjects. Egrise D, et al. **Biol Psychiatry** 1986 Mar;21(3):283-92

Imipramine and amitriptyline plasma concentrations and clinical response in major depression. Kocsis JH, et al. **Br J Psychiatry** 1986 Jan; 148:52-7

Changes of transition temperatures of phosphatidylcholine and phosphatidylglycerol in presence of amphiphilic drugs. Harder A, et al. **Chem Phys Lipids** 1986 Jan;39(1-2):65-71

Veratrine- and glutamate-stimulated cGMP production in cultured rat neurons is differentially inhibited by imipramine. Novelli A, et al. **Eur J Pharmacol** 1985 Nov 26;118(1-2):189-90

Antidepressive drugs can change the affinity of [3H]imipramine and [3H]paroxetine binding to platelet and neuronal membranes. Plenge P, et al. **Eur J Pharmacol** 1985 Dec 10;119(1-2):1-8

Effect of ovariectomy and estrogen on [3H]imipramine binding to different regions of rat brain. Stockert M, et al. **Eur J Pharmacol** 1985 Dec 17; 119(3):255-7

Extractional-spectrophotometric determination of microquantities of the antidepressant imipramine with picric acid. Baltova E, et al. **Folia Med (Plovdiv)** 1984;26(2):53-8

A sensitive colorimetric method for the determination of imipramine hydrochloride and desipramine hydrochloride. el-Yazbi FA, et al. **J Clin Hosp Pharm** 1985 Dec;10(4):373-7

Agoraphobia: relative and combined effectiveness of therapist-assisted in vivo exposure and imipramine. Mavissakalian M, et al. **J Clin Psychiatry** 1986 Mar;47(3):117-22

Binding of [3H]imipramine to mouse cerebrocortical membranes and to glass fiber filters. Reith ME. **J Neurochem** 1986 Mar;46(3):760-6

Subcellular site of action of imipramine in rodent brain. Wood MD, et al. **J Neurochem** 1986 Apr;46(4):999-1005

Modulation of peripheral beta-1 and alpha-2 receptor sensitivities by the administration of the tricyclic antidepressant, imipramine, alone and in combination with alpha-2 antagonists to rats. Keith RA, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):356-63

High affinity [3H]imipramine binding and serotonin uptake to platelets of adolescent females suffering from anorexia nervosa. Weizman R, et al. **Life Sci** 1986 Mar 31;38(13):1235-42

Pharmacokinetics of imipramine are affected by age and sex in rats. Wilson MA, et al. **Life Sci** 1986 Feb 24;38(8):711-8

Platelet 3H imipramine binding: a possible predictor of response to antidepressant treatment. Hrdina PD, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):619-23

Platelet 3H-imipramine binding and steroid hormones serum concentrations during the menstrual cycle. Poirier MF, et al. **Psychopharmacology (Berlin)** 1986;88(1):86-9

Disabling fear of AIDS responsive to imipramine. Jenike MA, et al. **Psychosomatics** 1986 Feb;27(2):143-4

[The circulatory system in patients with depression during treatment with antidepressive drugs. II. Effect of therapeutic doses of thymoleptics on ECG records in patients with endogenous depression] Rajewska J. **Psychiatr Pol** 1985 Jul-Aug;19(4):278-84 (Eng. Abstr.) **(Pol)**

[Interaction of piracetam with 3H-imipramine binding sites and the GAMA-benzodiazepine receptor complex of brain membranes] Rozhanets VV, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):40-2 (Eng. Abstr.) **(Rus)**

[Problems of drug recognition. Imipramine receptors] Shimanovskii NL, et al. **Farmakol Toksikol** 1986 Jan-Feb;49(1):103-7 (36 ref.) **(Rus)**

IMPRINTING (PSYCHOLOGY)

Androgens and imprinting: differential effects of testosterone on filial preference in the domestic chick. Bolhuis JJ, et al. **Behav Neurosci** 1986 Feb;100(1):51-6

Ultrastructural changes elicited in the Tetrahymena by primary exposure (imprinting) and reexposure to hormone. Csaba G, et al. **Z Mikrosk Anat Forsch** 1985;99(6):884-90

ISOCARBOXAZID

Case report of successful treatment of bulimia with isocarboxazid [letter] Kronig MH. **Am J Psychiatry** 1986 Apr;143(4):551-2

LACTATES

Free plasma catecholamines, heart rates, lactate levels, and oxygen uptake in competition weight lifters, cyclists, and untrained control subjects. Lehmann M, et al. **Int J Sports Med** 1986 Feb;7(1):18-21

Determination of alpha-naphthoxylactic acid, a major metabolite of propranolol, in plasma by high-performance liquid chromatography [letter] Harrison PM, et al. **J Chromatogr** 1986 Jan 10;374(1):223-5

Pulmonary surfactant lipid synthesis from ketone bodies, lactate and glucose in newborn rats. Sheehan PM, et al. **Lipids** 1985 Dec; 20(12):835-41

LEARNING

Effortful and automatic cognitive processes in depression. Roy-Byrne PP, et al. **Arch Gen Psychiatry** 1986 Mar;43(3):265-7

Pesticide-drug interaction in rats. Fenyvesi G, et al. **Arch Toxicol [Suppl]** 1985;8:269-71

Short term effects of methylphenidate on the cognitive, learning and academic performance of children with attention deficit disorder in the laboratory and the classroom. Douglas VI, et al. **J Child Psychol Psychiatry** 1986 Mar;27(2):191-211

Difference in learning and retention by Albino-Swiss mice. Part 2. Effect of some anxiolytic drugs. Valzelli L, et al. **Methods Find Exp Clin Pharmacol** 1985 Nov;7(11):569-72

Assessing drug effects on academic performance. Gadow KD, et al. **Psychopharmacol Bull** 1985;21(4):877-86

Lessons from snails and other models [news] Barnes DM. **Science** 1986 Mar 14;231(4743):1246-9

LEVODOPA

The sialagogue response of striatal dopamine receptors to L-dopa is not influenced by castration or chronic estrogen treatment. Pazo JH, et al. **Brain Res Bull** 1986 Jan;16(1):1-4

Dopamine and L-dopa: inhibition of thyrotropin-stimulated thyroidal thyroxine release. Maayan ML, et al. **Endocrinology** 1986 Feb; 118(2):632-6

The time-dependent inactivation of human brain dihydropteridine reductase by the oxidation products of L-dopa. Waring P. **Eur J Biochem** 1986 Mar 3;155(2):305-10

Liquid chromatographic determination of levodopa, levodopa-carbidopa, and related impurities in solid dosage forms. Ting S. **J Assoc Off Anal Chem** 1986 Jan-Feb;69(1):169-73

Distribution of catecholamines between fetal and maternal compartments during human pregnancy with emphasis on L-dopa and dopamine. Peleg D, et al. **J Clin Endocrinol Metab** 1986 May;62(5):911-4

Re-evaluation of the L-dopa loading effect on dopamine metabolism in rat striatum. el Gemayel G, et al. **J Pharm Pharmacol** 1986 Feb; 38(2):134-6

L-dopa reverses the effects of MPP+ toxicity. Wagner GC, et al. **Psychopharmacology (Berlin)** 1986;88(3):401-2

Formation of dopamine sulfate from L-dopa by perfusion of dog kidney. Tsunematsu T. **Tokushima J Exp Med** 1985 Jun;32(1-2):23-9

[Activation of glomerular guanylate cyclase by L-dopa and expansion of the extracellular volume] Sraer JD. **Nephrologie** 1985;6(5):248-9 **(Fre)**

[Effect of Nakom on the activity of the hypothalamo-hypophyseo-adrenal system] Slavnov VN, et al. **Farmakol Toksikol** 1986 Jan-Feb; 49(1):26-9 (Eng. Abstr.) **(Rus)**

[Use of L-DOPA and a traveling pulse magnetic field to treat patients with neurocirculatory dystonia] Chogovadze VA. **Klin Med (Mosk)** 1986 Jan;64(1):63-6 **(Rus)**

LH

Short-term effects of oestradiol and 4-hydroxyoestradiol on gonadotrophin-releasing hormone induced luteinizing hormone secretion by rat pituitary cells in culture. Emons G, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):312-20

Acute effects of GnRF-induced gonadotrophin secretion upon ovarian steroid secretion in the ferret. Matson C, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):373-7

Modulation of luteinizing hormone immunoreactivity and bioactivity by dopamine but not norepinephrine in women. Barnes RB, et al. **Am J Obstet Gynecol** 1986 Feb;154(2):445-50

Norepinephrine inhibition of pulsatile LH release: receptor specificity. Bergen H, et al. **Am J Physiol** 1986 Feb;250(2 Pt 1):E205-11

Interpulse interval sequence of LH in normal men essentially constitutes a renewal process. Butler JP, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):E338-40

Estrogen inhibition of LH and FSH secretion: effects of a GnRH antagonist. Charlesworth MC, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):E341-5

Functional changes in luteinizing hormone-secreting cells from pre- and postpartum ewes. Wise ME, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):E282-7

Effects of estradiol and some antiestrogens (clomiphene, tamoxifen, and hydroxytamoxifen) on luteinizing hormone secretion by rat pituitary cells in culture. Emons G, et al. **Arch Gynecol** 1986;237(4):199-211

Coordinate actions of arachidonic acid and protein kinase C in gonadotropin-releasing hormone-stimulated secretion of luteinizing hormone. Chang JP, et al. **Biochem Biophys Res Commun** 1986 Jan 14:134(1):134-9

Recovery of pulsatile luteinizing hormone secretion following permanent disruption of the ascending noradrenergic fiber tract in the ovariectomized rat. Clifton DK, et al. **Biol Reprod** 1985 Nov; 33(4):808-14

Androgen and progesterone effects on follicle-stimulating hormone and luteinizing hormone secretion in anestrous mares. Thompson DL Jr, et al. **Biol Reprod** 1986 Feb;34(1):51-7

Ontogenesis of [3H]serotonin binding sites in the hypothalamus of the female rat: relation to serotonin-induced LH release in moxestrol-pretreated rats. Becú-Villalobos D, et al. **Brain Res** 1986 Feb;390(1):111-6

Sex differences in pituitary LH storage and release in LHRH-stimulated pubertal rats. A correlative immunohistochemical and radioimmunoassay study. Watanabe YG. **Cell Tissue Res** 1986; 243(3):509-15

Seasonal variation in plasma testosterone, luteinizing hormone concentrations and LH-RH responsiveness in mature, male rusa deer (Cervus rusa timorensis). van Mourik S, et al. **Comp Biochem Physiol** [A] 1986;83(2):347-51

Induction of ovulation in primate models. Kenigsberg D, et al. **Endocr Rev** 1986 Feb;7(1):34-43 (45 ref.)

Biphasic stimulatory effects of estrogen on gonadotropin surges induced by continuous administration of gonadotropin-releasing hormone in women. Araki S, et al. **Endocrinol Jpn** 1985 Oct;32(5):595-605

Modulation of luteinizing hormone(LH) release by clonidine and opioid peptides in castrated male rats. Koh T, et al. **Endocrinol Jpn** 1985 Oct; 32(5):653-9

Qualitative and quantitative differences in hLH species in the first and second LH release induced by continuous stimulation with synthetic LHRH in normal menstrual cycle as assessed by isoelectrofocusing. Suginami H, et al. **Endocrinol Jpn** 1985 Oct;32(5):583-93

Evidence that pulsatile follicle-stimulating hormone secretion is independent of endogenous luteinizing hormone-releasing hormone. Culler MD, et al. **Endocrinology** 1986 Feb;118(2):609-12

Prolactin (PRL), follicle-stimulating hormone, and luteinizing hormone are regulators of testicular PRL receptors in golden hamsters. Klemcke HG, et al. **Endocrinology** 1986 Feb;118(2):773-82

Comparison of the time courses of luteinizing hormone (LH) secretion rates during continuous stimulation by LH-releasing hormone (LH-RH) in vivo and in vitro. de Koning J, et al. **Experientia** 1986 Jan 15; 42(1):60-2

Activity of gonadotropin-releasing hormone neurons during the preovulatory luteinizing hormone surge. Steele PA, et al. **Fertil Steril** 1986 Feb;45(2):179-84

Relationship between release of LH and incorporation of tritiated thymidine in the anterior pituitary gland of the castrated male rat: effect of LHRH and its highly active analogue buserelin. Romano MI, et al. **Horm Metab Res** 1986 Jan;18(1):31-3

Temporal relationship between the onset of daily gonadotrophin surges and of puberty in female golden hamsters. Donham RS, et al. **J Endocrinol** 1986 Feb;108(2):219-24

Effect of LHRH immunoneutralization on follicular development, the LH surge and luteal function in the stumptailed macaque monkey (Macaca arctoides). Fraser HM, et al. **J Reprod Fertil** 1986 Jan; 76(1):299-309

Effects and interactions of LH and LHRH agonist on testicular morphology and function in hypophysectomized rats. Kerr JB, et al. **J Reprod Fertil** 1986 Jan;76(1):175-92

Sulfated LH subunits and a tyrosine-sulfated secretory protein (secretogranin II) in female rat adenohypophyses: changes with age and stimulation of release by LHRH. Cozzi MG, et al. **Mol Cell Endocrinol** 1986 Jan;44(1):47-54

Morphological characterization of LH secretory granule response to LHRH and calmodulin inhibitor. Nakamura F, et al. **Mol Cell Endocrinol** 1986 Jan;44(1):11-5

Androgenic and estrogenic control of the self-priming effect of LHRH in the castrated male rat. Nazian SJ. **Neuroendocrinology** 1986; 42(2):112-9

Evaluation of the OvuSTICK urinary luteinizing hormone kit in normal and stimulated menstrual cycles. Elkind-Hirsch K, et al. **Obstet Gynecol** 1986 Mar;67(3):450-3

Stimulation of gonadotropin release by a non-GnRH peptide sequence of the GnRH precursor. Millar RP, et al. **Science** 1986 Apr 4; 232(4746):68-70

[Dose-effect study of Berlin-Chemie's GnRHvet in castrated heifers by luteinizing hormone detection] Schneider F, et al. **Arch Exp Veterinarmed** 1985 Nov;39(6):894-900 (Eng. Abstr.) **(Ger)**

[Study on the central action of catecholestrogen: effect of 2-hydroxyestrogens on the preovulatory LH surge] Okatani Y. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 Feb;38(2):151-60 (Eng. Abstr.) **(Jpn)**

[Episode secretion of LH releasing hormone and LH in peripheral plasma of women with and without ovulatory disturbances] Okuda K, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Dec;37(12):2799-805 (Eng. Abstr.) **(Jpn)**

LH-FSH RELEASING HORMONE

Effects of oestradiol-17 beta and LRH upon the two fractions of pituitary follicle-stimulating hormone separated by concanavalin-A chromatography. Ulloa-Aguirre A, et al. **Acta Endocrinol (Copenh)** 1985 Dec;110(4):475-82

Estrogen inhibition of LH and FSH secretion: effects of a GnRH antagonist. Charlesworth MC, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):E341-5

Testicular steroid response to continuous and pulsatile intravenous luteinizing hormone-releasing hormone administration in normal men. Fauser BC, et al. **Andrologia** 1986 Jan-Feb;18(1):89-96

Luteinizing hormone-releasing hormone [letter] Glass AR. **Arch Intern Med** 1986 Mar;146(3):603, 607

Coordinate actions of arachidonic acid and protein kinase C in gonadotropin-releasing hormone-stimulated secretion of luteinizing hormone. Chang JP, et al. **Biochem Biophys Res Commun** 1986 Jan 14;134(1):134-9

Gonadotropin releasing hormone enhances polyphosphoinositide hydrolysis in rat pituitary cells. Kiesel L, et al. **Biochem Biophys Res Commun** 1986 Jan 29,134(2):861-7

Gonadotropin-releasing hormone release by superfused hypothalami in response to norepinephrine. Nowak FV, et al. **Biol Reprod** 1985 Nov; 33(4):790-6

Gonadotropin-releasing hormone effects on placental hormones during gestation: II. Progesterone, estrone, estradiol and estriol. Siler-Khodr TM, et al. **Biol Reprod** 1986 Mar;34(2):255-64

Gonadotropin-releasing hormone effects on placental hormones during gestation: I. Alpha-human chorionic gonadotropin, human chorionic gonadotropin and human chorionic somatomammotropin. Siler-Khodr TM, et al. **Biol Reprod** 1986 Mar;34(2):245-54

Diacylglycerol and phorbol esters enhance LHRH and prostaglandin E2 secretion from median eminence nerve terminals in vitro. Valenca MM, et al. **Brain Res Bull** 1985 Dec;15(6):657-9

Sex differences in pituitary LH storage and release in LHRH-stimulated pubertal rats. A correlative immunohistochemical and radioimmunoassay study. Watanabe YG. **Cell Tissue Res** 1986; 243(3):509-15

Enzyme immunoassay for the determination of des-Gly10-NH2-LH-RH-ethylamide (fertirelin) in bovine plasma. Okada J, et al. **Chem Pharm Bull (Tokyo)** 1985 Oct;33(10):4464-70

Seasonal variation in plasma testosterone, luteinizing hormone concentrations and LH-RH responsiveness in mature, male rusa deer (Cervus rusa timorensis). van Mourik S, et al. **Comp Biochem Physiol** [A] 1986;83(2):347-51

Ovulation inhibition with nafarelin acetate nasal administration for six months. Brenner PF, et al. **Contraception** 1985 Dec;32(6):531-51

Pharmacokinetics of gonadotropin-releasing hormone and its analogs. Handelsman DJ, et al. **Endocr Rev** 1986 Feb;7(1):95-105 (106 ref.)

Biphasic stimulatory effects of estrogen on gonadotropin surges induced by continuous administration of gonadotropin-releasing hormone in women. Araki S, et al. **Endocrinol Jpn** 1985 Oct;32(5):595-605

The time interval effect on two consecutive LHRH-TRH tests on adult female baboons. Su JH, et al. **Endocrinol Jpn** 1985 Aug;32(4):455-62

Qualitative and quantitative differences in hLH species in the first and second LH release induced by continuous stimulation with synthetic LHRH in normal menstrual cycle as assessed by isoelectrofocusing. Suginami H, et al. **Endocrinol Jpn** 1985 Oct;32(5):583-93

Gonadotropin-releasing hormone stimulates mass changes in phosphoinositides and diacylglycerol accumulation in purified gonadotrope cell cultures. Andrews WV, et al. **Endocrinology** 1986 Mar; 118(3):1148-58

Ovarian gonadotropin-releasing hormone-like protein(s): demonstration and characterization. Aten RF, et al. **Endocrinology** 1986 Mar; 118(3):961-7

Evidence that pulsatile follicle-stimulating hormone secretion is independent of endogenous luteinizing hormone-releasing hormone. Culler MD, et al. **Endocrinology** 1986 Feb;118(2):609-12

Transient changes in the in vitro activity of the luteinizing hormone-releasing hormone pulse generator after ovariectomy in rats. Dluzen DE, et al. **Endocrinology** 1986 Mar;118(3):1110-3

Localization of cells containing LHRH-like mRNA in rat forebrain using in situ hybridization. Shivers BD, et al. **Endocrinology** 1986 Feb; 118(2):883-5

Leukotriene C4 is a potent stimulator of LHRH secretion. Gerozissis K, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):159-60

Studies on the prolactin-releasing capacity of luteinizing hormone releasing hormone in male subjects. Gooren LJ, et al. **Exp Clin Endocrinol** 1985 Dec;86(3):300-4

Comparison of the time courses of luteinizing hormone (LH) secretion rates during continuous stimulation by LH-releasing hormone (LH-RH) in vivo and in vitro. de Koning J, et al. **Experientia** 1986 Jan 15; 42(1):60-2

Studies on the modulation of the desensitization of the pituitary gland by luteinizing hormone-releasing hormone in the ovariectomized rat. Koiter TR, et al. **Experientia** 1986 Mar 15;42(3):304-7

Increased frequency of pulsatile luteinizing hormone-releasing hormone administration selectively decreases follicle-stimulating hormone levels in men with idiopathic azoospermia. Gross KM, et al. **Fertil Steril** 1986 Mar;45(3):392-6

Inhibition of estradiol-induced gonadotropin release in ovariectomized rhesus macaques by a gonadotropin-releasing hormone antagonist. Norman RL, et al. **Fertil Steril** 1986 Feb;45(2):288-91

The economics of inducing ovulation with human menopausal gonadotropins versus pulsatile subcutaneous gonadotropin-releasing hormone. Sueldo CE, et al. **Fertil Steril** 1986 Jan;45(1):128-9

Ontogeny of neuropeptidergic systems: luteinizing hormone releasing hormone (LHRH); somatostatin (SRIF) and neurophysin (NF) in the hypothalamus of the domestic pig by immunocytochemistry. Polkowska J, et al. **Folia Histochem Cytobiol** 1985;23(4):193-200

Multiple forms of gonadotropin-releasing hormone in amphibian brains. Sherwood NM, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):313-22

Relationship between release of LH and incorporation of tritiated thymidine in the anterior pituitary gland of the castrated male rat: effect of LHRH and its highly active analogue buserelin. Romano MI, et al. **Horm Metab Res** 1986 Jan;18(1):31-3

Antagonistic analogs of luteinizing hormone-releasing hormone are mast cell secretagogues. Morgan JE, et al. **Int Arch Allergy Appl Immunol** 1986;80(1):70-5

Hypothalamic releasing factor in primary and situational depression. Dekeyser YF. **Int J Neurol** 1980;14(2-4):269-72

Elevation of serum testosterone during chronic LHRH agonist treatment in the bull. Melson BE, et al. **J Anim Sci** 1986 Jan;62(1):199-207

Ovulation inhibition by administration of weekly gonadotropin-releasing hormone antagonist. Kenigsberg D, et al. **J Clin Endocrinol Metab** 1986 Apr;62(4):734-8

Gonadotropin-releasing hormone neurosecretion in the human hypothalamus: in vitro regulation by dopamine. Rasmussen DD, et al. **J Clin Endocrinol Metab** 1986 Mar;62(3):479-83

Follicular stimulation versus ovulation induction in juvenile primates: importance of gonadotropin-releasing hormone dose. Sopelak VM, et al. **J Clin Endocrinol Metab** 1986 Mar;62(3):557-62

Immunocytochemical localization of luteinizing hormone-releasing hormone (LHRH) pathways in the sheep brain during anestrus and the mid-luteal phase of the estrous cycle. Lehman MN, et al. **J Comp Neurol** 1986 Feb 1;244(1):19-35

Testosterone maintains pituitary and serum FSH and spermatogenesis in gonadotrophin-releasing hormone antagonist-suppressed rats. Rea MA, et al. **J Endocrinol** 1986 Jan;108(1):101-7

Luteinizing hormone releasing hormone (LHRH): II. A new contraceptive agent. Rojanasakul A, et al. **J Med Assoc Thai** 1986 Jan;69(1):16-21

LHRH therapy for cryptorchidism [letter] de Vries JD. **J Pediatr** 1986 Jan;108(1):162

Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. Sennello LT, et al. **J Pharm Sci** 1986 Feb;75(2):158-60

Effect of short photoperiod on hypothalamic methionine-enkephalin and LHRH content and serum beta-endorphin-like immunoreactivity (beta-end LI) levels in golden hamsters. Kumar MS, et al. **J Pineal Res** 1984;1(2):197-205

Effect of LHRH immunoneutralization on follicular development, the LH surge and luteal function in the stumptailed macaque monkey (Macaca arctoides). Fraser HM, et al. **J Reprod Fertil** 1986 Jan;76(1):299-309

Suppression of follicular development after chronic LHRH immunoneutralization in the ewe. McNeilly AS, et al. **J Reprod Fertil** 1986 Jan;76(1):481-90

Double-blind, placebo-controlled study of luteinising-hormone-releasing-hormone nasal spray in treatment of undescended testes. deMuinck Keizer-Schrama SM, et al. **Lancet** 1986 Apr 19;1(8486):876-80

Characterization of luteinizing hormone-releasing hormone receptor binding in rat pituitary cell monolayer cultures; influence of intercellular communication. Andries M, et al **Mol Cell Endocrinol** 1986 Feb;44(2):147-58

Morphological characterization of LH secretory granule response to LHRH and calmodulin inhibitor. Nakamura F, et al. **Mol Cell Endocrinol** 1986 Jan;44(1):11-5

LHRH stimulates plasminogen activator and inhibits steroid production by granulosa cells of adult rat Graafian follicles. Wang C, et al. **Mol Cell Endocrinol** 1986 Jan;44(1):61-8

LHRH neurons in the female C57BL/6J mouse brain during reproductive aging: no loss up to middle age. Hoffman GE, et al. **Neurobiol Aging** 1986 Jan-Feb;7(1):45-8

Hypothalamic LHRH in aging rats: effects of ovariectomy and steroid replacement. Rubin BS, et al. **Neurobiol Aging** 1985 Winter;6(4):309-15

On the short-loop feedback regulation of the hypothalamic luteinizing hormone releasing hormone 'pulse generator' in the rhesus monkey. Kesner JS, et al. **Neuroendocrinology** 1986;42(2):109-11

Androgenic and estrogenic control of the self-priming effect of LHRH in the castrated male rat. Nazian SJ. **Neuroendocrinology** 1986;42(2):112-9

Influence of monoamines on content of luteinizing hormone-releasing hormone in different regions of the hypothalamus of male rats. Markaryan RL, et al. **Neurosci Behav Physiol** 1985 Sep-Oct;15(5):407-10

Axovascular relationships in developing median eminence of perinatal rats with special reference to luteinizing hormone-releasing hormone projections. Ugrumov MV, et al. **Neuroscience** 1985 Dec;16(4):897-906

Chronic gonadotropin-releasing hormone agonist treatment suppresses ovulation and sexual behavior in group-living female rhesus monkeys. Wallen K, et al. **Physiol Behav** 1986;36(2):369-75

Decapeptides as effective agonists from L-amino acids biologically equivalent to the luteinizing hormone-releasing hormone. Folkers K, et al. **Proc Natl Acad Sci USA** 1986 Feb;83(4):1070-4

Structure-activity studies on gonadotropin-releasing hormone in teleosts, amphibians, reptiles and mammals. Peter RE. **Prog Clin Biol Res** 1986;205:75-93 (66 ref.)

Hormonal treatment of undescended testis. Toublanc JE. **Prog Clin Biol Res** 1985;203:207-11

Stimulation of gonadotropin release by a non-GnRH peptide sequence of the GnRH precursor. Millar RP, et al. **Science** 1986 Apr 4;232(4746):68-70

Human luteinizing hormone-releasing hormone gene (LHRH) is located on short arm of chromosome 8 (region 8p11.2----p21). Yang-Feng TL, et al. **Somatic Cell Mol Genet** 1986 Jan;12(1):95-100

[Ovulation induction by an LH-RH pump] Fenichel P. **Rev Fr Gynecol Obstet** 1985 Nov;80(11):849-55 (Eng. Abstr.) **(Fre)**

[Episode secretion of LH releasing hormone and LH in peripheral plasma of women with and without ovulatory disturbances] Okuda K, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Dec;37(12):2799-805 (Eng. Abstr.) **(Jpn)**

[Stimulatory effect of a traditional herbal medicine, Unkeito on LH-RH release] Tasaka K, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1985 Dec;37(12):2821-6 (Eng. Abstr.) **(Jpn)**

[The state of gametes and the type of maturation of follicular oocytes in rats neonatally androgenized by LH-RH-induced ovulation] Kitaev EM, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):78-9 (Eng. Abstr.) **(Rus)**

LITHIUM

Modifications in the phagocytosis of human neutrophils induced by vinblastine and cytochalasin B: the effects of lithium. Carulli G, et al. **Acta Haematol (Basel)** 1985;74(2):81-5

Kidney function in a selected lithium population. A prospective, controlled, lithium-withdrawal study. Bendz H. **Acta Psychiatr Scand** 1985 Nov;72(5):451-63

Is lithium justified after one manic episode? Mander AJ. **Acta Psychiatr Scand** 1986 Jan;73(1):60-7

Visually stimulated saccadic eye movements in patients treated with lithium. Opgenoorth E, et al. **Acta Psychiatr Scand** 1986 Jan;73(1):54-9

Longitudinal evaluation of glomerular filtration rate during long-term lithium therapy. Vaamonde CA, et al. **Am J Kidney Dis** 1986 Mar;7(3):213-6

A possible synergistic effect of alprazolam and lithium carbonate [letter] Cerra D, et al. **Am J Psychiatry** 1986 Apr;143(4):552

Lithium-antidepressant combinations in the treatment of depressed, physically ill geriatric patients. Kushnir SL. **Am J Psychiatry** 1986 Mar;143(3):378-9

Lithium augmentation in psychotic depression refractory to combined drug treatment. Nelson JC, et al. **Am J Psychiatry** 1986 Mar;143(3):363-6

Lithium ion transport by erythrocytes of randomly selected blood donors and manic-depressive patients: lack of association with affective illness. Richelson E, et al. **Am J Psychiatry** 1986 Apr;143(4):457-62

Use of lithium and flupenthixol in a patient with pervasive developmental disorder [letter] Shafey H. **Am J Psychiatry** 1986 May;143(5):681

Ion selective liquid membrane electrode for the assay of lithium in blood serum. Metzger E, et al. **Anal Chem** 1986 Jan;58(1):132-5

Lithium Information Center. One model of a computer-based psychiatric information service. Carroll JA, et al. **Arch Gen Psychiatry** 1986 May;43(5):483-5

Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Keller MB, et al. **Arch Gen Psychiatry** 1986 May;43(5):458-66

Renal function of patients in long-term treatment with lithium citrate alone or in combination with neuroleptics and antidepressant drugs. Lassen E, et al. **Arch Gen Psychiatry** 1986 May;43(5):481-2

Acute and short-term effects of lithium on glutamate metabolism in rat brain. Marcus SR, et al. **Biochem Pharmacol** 1986 Feb 1;35(3):365-9

Lii-Nao countertransport and Li leak in erythrocytes are differentially affected by membrane enrichment with cholesteryl hemisuccinate. Levy

R, et al. **Biochim Biophys Acta** 1986 Jan 29;854(2):325-8

Effect of lithium on RBC water permeability [letter] Ballast CL, et al. **Biol Psychiatry** 1986 Apr;21(4):426-7

Lithium stimulation of in vitro granulopoiesis: evidence for mediation via sodium transport pathways. Gallicchio VS. **Br J Haematol** 1986 Mar;62(3):455-66

Lymphocytes from patients receiving lithium do not inhibit CFU-C growth. Irvine AE, et al. **Br J Haematol** 1986 Mar;62(3):467-77

Synergism of spironolactone and lithium in mania. Gillman MA, et al. **Br Med J [Clin Res]** 1986 Mar 8;292(6521):661-2

Determination of lithium in blood serum--a comparison between molecular absorption spectrophotometry and emission flame spectrometry. Popov P, et al. **Clin Chim Acta** 1986 Feb 15; 154(3):223-5

Effect of ibuprofen on lithium plasma and red blood cell concentrations. Kristoff CA, et al. **Clin Pharm** 1986 Jan;5(1):51-5

Influence of intravenous acetylsalicylic acid and sodium salicylate on human renal function and lithium clearance. Reimann IW, et al. **Eur J Clin Pharmacol** 1985;29(4):435-41

Effect of lithium on stem cell and stromal cell proliferation in vitro. Doukas MA, et al. **Exp Hematol** 1986 Mar;14(3):215-21

Deuterium NMR study of head-group deuterated phosphatidylserine in pure and binary phospholipid bilayers. Interactions with monovalent cations Na+ and Li+. Roux M, et al. **FEBS Lett** 1986 Apr 7; 199(1):33-8

Effects of prenatal exposure to lithium on indoleamines in maturing mouse brain. Hoff KM, et al. **Gen Pharmacol** 1986;17(1):101-3

Lignocaine induces lithium transport across bimolecular lipid membrane. Rajaji D, et al. **Indian J Biochem Biophys** 1984 Dec;21(6):392-3

Effect of lithium therapy on inflammatory response. O'Riordan JW, et al. **Inflammation** 1986 Mar;10(1):49-57

Lithium intoxication. Bazilinski N, et al. **Int J Artif Organs** 1986 Jan; 9(1):5-6

Use of lithium and flupenthixol in a patient with pervasive developmental disorder [letter] Shafey H. **J Am Acad Child Psychiatry** 1986 Jan; 25(1):137-8

Lithium dosage guide for prepubertal children: a preliminary report. Weller EB, et al. **J Am Acad Child Psychiatry** 1986 Jan;25(1):92-5

Li+ as substrate of the synaptosomal Na+/H+ antiporter. Schmalzing G, et al. **J Biol Chem** 1986 Feb 25;261(6):2759-67

Prediction of lithium dose: a mathematical alternative to the test-dose method. Zetin M, et al. **J Clin Psychiatry** 1986 Apr;47(4):175-8

Dental caries prevalence in Texas schoolchildren using water supplies with high and low lithium and fluoride. Curzon ME, et al. **J Dent Res** 1986 Mar;65(3):421-3

A kinetic analysis of Na-Li countertransport in human red blood cells. Hannaert PA, et al. **J Gen Physiol** 1986 Mar;87(3):353-68

Interactions of lithium and protons with the sodium-proton exchanger of dog red blood cells. Parker JC. **J Gen Physiol** 1986 Feb; 87(2):189-200

Effects of chronic lithium treatment on brain monoamine metabolism and amphetamine-induced locomotor stimulation in rats. Berggren U. **J Neural Transm** 1985;64(3-4):239-50

Lithium distribution in the brain of normal mice and of 'quaking' dysmyelinating mutants. Heurteaux C, et al. **J Neurochem** 1986 Apr; 46(4):1317-21

Indirect dopaminergic effects of tofisopam, a 2,3-benzodiazepine, and their inhibition by lithium. Chopin P, et al. **J Pharm Pharmacol** 1985 Dec;37(12):917-9

A potentiometric study of lithium complexation with catecholamines. Sandmann BJ, et al. **J Pharm Sci** 1986 Jan;75(1):73-7

Toxicokinetics of lithium intoxication treated by hemodialysis. Jaeger A, et al. **J Toxicol Clin Toxicol** 1985-86;23(7-8):501-17

Lithium and mitotic index [letter] Genest P, et al. **Lancet** 1971 Dec 11; 2(7737):1325

Behavioral and receptor binding studies of phencyclidine (PCP) and lithium interaction in the rat. Mattia A, et al. **Life Sci** 1986 Mar 17; 38(11):975-84

In vivo measurement of lithium in the body by a neutron activation analysis technique. Glaros D, et al. **Med Phys** 1986 Jan-Feb; 13(1):45-9

Results of genotoxicity testing of mazindol (degonan), lithium carbonicum (contemnol) and dropropizine (ditustat) in Chinese hamster V79 and human EUE cells. Slameňová D, et al. **Mutat Res** 1986 Mar; 169(3):171-7

The effect of lithium on cultured nervous tissue. Gajkowska B, et al. **Neuropatol Pol** 1985;23(3):315-33

Conditioned taste aversions and changes in motor activity in lithium-treated rats. Mediating role of the area postrema. Ladowsky RL, et al. **Neuropharmacology** 1986 Jan;25(1):71-7

Therapeutic experience with lithium in childhood aggressivity. Vetró A, et al. **Neuropsychobiology** 1985;14(3):121-7

On the mechanism of lithiation of uridine derivatives with lithium dialkylamides. Hayakawa H, et al. **Nucleic Acids Symp Ser** 1985; (16):109-12

Interstrain correlation between behavioural effects of lithium and effects on cortical cyclic AMP. Hamburger-Bar R, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):9-13

Lithium and twenty-four hour rhythms of serum corticosterone, prolactin and growth hormone in pigmented eye rats. Seggie J, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):755-8

Effects of lithium and rubidium on shock-induced changes in open-field activity. Hines G. **Psychopharmacology (Berlin)** 1986;88(2):209-12

The prophylactic lithium treatment in affective disorders and the possibilities of the outcome prediction. Hanuš H, et al. **Sb Ved Pr Lek Fak Univ Karlovy** 1984;27(1):5-75

[Lithium and other preventive agents in affective disorders in 1984] Souček K. **Cesk Psychiatr** 1985 Dec;81(6):363-6 **(Cze)**

[Lithium poisoning. 2 unpublished interactions: acetazolamide and niflumic acid] Gay C, et al. **Encephale** 1985 Nov-Dec;11(6):261-2 (Eng. Abstr.) **(Fre)**

[Lithium in psychiatry. Review and advice to nonpsychiatrists] Schou M. **Rev Med Liege** 1986 Feb 1;41(3):92-6 **(Fre)**

[Course and form variations of cyclothymic phases in lithium therapy] Banzhaf M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Dec; 37(12):718-21 (Eng. Abstr.) **(Ger)**

[Lithium and the kidney. Acute effects on ADH secretion and enzymuria] Palla R, et al. **Minerva Med** 1986 Feb 28;77(7-8):205-8 (Eng. Abstr.) **(Ita)**

[Effect of lithium oxybutyrate on the serotonin and 5-hydroxyindoleacetic acid content in the brain of rabbits] Saratikov AS, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):312-5 (Eng. Abstr.) **(Rus)**

LORAZEPAM

Benzodiazepines, but not antidepressants or neuroleptics, induce dose-dependent development of tolerance to lorazepam in psychiatric patients. Aranko K, et al. **Acta Psychiatr Scand** 1985 Nov; 72(5):436-46

Psychomotor tasks and recovery from anesthesia [letter] Millar K. **Anesth Analg** 1986 May;65(5):543-4

Relative bioavailability in humans for oral tablets and solutions of lormetazepam. Zecca L, et al. **Arzneimittelforschung** 1985; 35(12):1870-2

Intramuscular lorazepam to restrain violent patients [letter] Bick PA, et al. **Lancet** 1986 Jan 25;1(8474):206

Lorazepam in resistant mania [letter] Jobling M, et al. **Lancet** 1986 Mar 1;1(8479):510

Cognitive-behavioural treatment for benzodiazepine dependence [letter] Sanchez-Craig M, et al. **Lancet** 1986 Feb 15;1(8477):388

Acute treatment of manic agitation with lorazepam. Lenox RH, et al. **Psychosomatics** 1986 Jan;27(1 Suppl):28-32

Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. Salzman C, et al. **Psychosomatics** 1986 Jan; 27(1 Suppl):17-22

[Simple-blind clinical study with sublingual lorazepam vs. injectable diazepam as premedication in colonoscopies] Costas CD, et al. **Acta Gastroenterol Latinoam** 1985;15(1):43-8 (Eng. Abstr.) **(Spa)**

MALATES

The role of malate in hormone-induced enhancement of mitochondrial respiration. Bobyleva-Guarriero V, et al. **Arch Biochem Biophys** 1986 Mar;245(2):477-82

The role of malate in exercise-induced enhancement of mitochondrial respiration. Bobyleva-Guarriero V, et al. **Arch Biochem Biophys** 1986 Mar;245(2):470-6

MANIC DISORDER

Is lithium justified after one manic episode? Mander AJ. **Acta Psychiatr Scand** 1986 Jan;73(1):60-7

How does verapamil exert an antimanic effect? [letter] Sandyk R, et al. **Am J Psychiatry** 1986 Mar;143(3):388

Synergism of spironolactone and lithium in mania. Gillman MA, et al. **Br Med J [Clin Res]** 1986 Mar 8;292(6521):661-2

Clonazepam: a novel therapeutic adjunct. Freinhar JP, et al. **Int J Psychiatry Med** 1985-86;15(4):321-8

Verapamil treatment of acute mania. Brotman AW, et al. **J Clin Psychiatry** 1986 Mar;47(3):136-8

Antimanic effects of clonazepam. Chouinard G. **Psychosomatics** 1985 Dec; 26(12 Suppl):7-12

Acute treatment of manic agitation with lorazepam. Lenox RH, et al. **Psychosomatics** 1986 Jan;27(1 Suppl):28-32

MATERNAL BEHAVIOR

Thermal control of mother-young contact in Norway rats: factors mediating the chronic elevation of maternal temperature. Adels LE, et al. **Physiol Behav** 1986 Jan;36(1):183-96

Maternal aggression in rats: lack of interaction between chlordiazepoxide and fluprazine. Olivier B, et al. **Psychopharmacology (Berlin)** 1986; 88(1):40-3

MEMORY

Deficits in spatial-memory tasks following lesions of septal dopaminergic terminals in the rat. Simon H, et al. **Behav Brain Res** 1986 Jan; 19(1):7-16
The effects of physostigmine and scopolamine on recognition memory in monkeys. Aigner TG, et al. **Behav Neural Biol** 1986 Jan; 45(1):81-7
Substance P facilitation of memory: effects in an appetitively motivated learning task. Schlesinger K, et al. **Behav Neural Biol** 1986 Mar; 45(2):230-9
Leu-enkephalin impairs memory of an appetitive maze response in mice. Linden D, et al. **Behav Neurosci** 1986 Feb;100(1):33-8
Pilocarpine and physostigmine attenuate spatial memory impairments produced by lesions of the nucleus basalis magnocellularis. Murray CL, et al. **Behav Neurosci** 1986 Feb;100(1):23-32
Behavioral changes following central injection of cysteamine in rats. Bakhit C, et al. **Brain Res** 1986 Feb 12;365(1):159-63
Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. Liang KC, et al. **Brain Res** 1986 Mar 12;368(1):125-33
Effects of bifemelane hydrochloride (MCI-2016) on experimental amnesia (passive avoidance failure) in rodents. Tobe A, et al. **Jpn J Pharmacol** 1985 Oct;39(2):153-61
Difference in learning and retention by Albino-Swiss mice. Part 2. Effect of some anxiolytic drugs. Valzelli L, et al. **Methods Find Exp Clin Pharmacol** 1985 Nov;7(11):569-72
Conformational changes in muscarinic receptors may produce diminished cholinergic neurotransmission and memory deficits in aged rats. Lippa AS, et al. **Neurobiol Aging** 1985 Winter;6(4):317-23
A psychopharmacological perspective of cognitive functions. I. Theoretical overview and methodological considerations. Wolkowitz OM, et al. **Neuropsychobiology** 1985;14(2):88-96 (73 ref.)
Effects of phencyclidine, N-allyl-N-normetazocine (SKF-10,047), and verapamil on performance in a radial maze. McCann DJ, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):187-91

MEMORY, SHORT-TERM

Effect of stress-related hormones on short term memory. Gibbs ME, et al. **Behav Brain Res** 1986 Jan;19(1):1-6
Drug effects on memory: assessment of a combined active and passive avoidance task. Sahgal A, et al. **Behav Brain Res** 1985 Oct; 17(3):251-5

MENTAL DISORDERS

Benzodiazepines, but not antidepressants or neuroleptics, induce dose-dependent development of tolerance to lorazepam in psychiatric patients. Aranko K, et al. **Acta Psychiatr Scand** 1985 Nov; 72(5):436-46
The use of psychotropic drugs in the treatment of compulsive opiate abusers: the rationale for their use. Kleber HD. **Adv Alcohol Subst Abuse** 1985 Fall-1986 Winter;5(1-2):103-19 (65 ref.)
Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. Gawin FH, et al. **Arch Gen Psychiatry** 1986 Feb; 43(2):107-13
Reliability of adverse drug reaction assessment in psychiatric inpatients. Grohmann R, et al. **Eur Arch Psychiatry Neurol Sci** 1985; 235(3):158-63
Changes in psychological diagnosis and prescription in a practice employing a counsellor. Martin E, et al. **Fam Pract** 1985 Dec; 2(4):241-3
Drugs in nursing homes [letter] Sandifer MG. **Hosp Community Psychiatry** 1986 Mar;37(3):291-2
Hope for the chronic mentally ill. Macinick CG, et al. **Issues Ment Health Nurs** 1984;6(3-4):255-9
Extended EMIT-DAU phencyclidine screen. Ragan FA Jr, et al. **J Clin Psychiatry** 1986 Apr;47(4):194-5
Interhemispheric fusion. Mandell AJ. **J Psychoactive Drugs** 1985 Oct-Dec; 17(4):257-66
Oral liquid neuroleptics: administer with care. Kerr LE. **J Psychosoc Nurs Ment Health Serv** 1986 Mar;24(3):33-5
Current scope of psychopharmacological research in Europe. Copenhagen, May 2-3, 1985. **Pharmacopsychiatry** 1986 Jan; 19(1):1-54
Nosological developments in European psychiatry and psychopharmacology. Pichot P. **Pharmacopsychiatry** 1986 Jan; 19(1):23-5
Neuropeptides in the cerebrospinal fluid (CSF) in psychiatric disorders. Rafaelsen OJ, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):533-8
Rating scales and checklists for child psychopharmacology. Conners CK, et al. **Psychopharmacol Bull** 1985;21(4):809-43
DSM-III-R and pediatric psychopharmacology. Rapoport JL. **Psychopharmacol Bull** 1985;21(4):803-6
Measurement of compliance. Sleator EK. **Psychopharmacol Bull** 1985; 21(4):1089-93
The inpatient care of the chronically mentally ill. Talbott JA, et al. **Schizophr Bull** 1986;12(1):129-40
[Biologic therapy in psychiatry] Vencovský E. **Cesk Psychiatr** 1986 Feb; 82(1):9-14 (Eng. Abstr.) **(Cze)**
[Lithium in psychiatry. Review and advice to nonpsychiatrists] Schou M. **Rev Med Liege** 1986 Feb 1;41(3):92-6 **(Fre)**
[The neurobiologic model. Contribution of drugs] Benkefat C, et al. **Soins Psychiatr** 1986 Jan;(63):15-20 **(Fre)**
[Pharmacologic intervention in psychogeriatrics] Brunet A. **Union Med Can** 1986 Jan;115(1):28-34 (Eng. Abstr.) **(Fre)**
[The new biological revolution in psychiatry: a Latin American point of view (1st part)] Alarcón R. **Acta Psiquiatr Psicol Am Lat** 1985 Jun; 31(2):131-42 (Eng. Abstr.) **(Spa)**

MENTAL PROCESSES

Humoral-hormonal control of functions in expert chess players. Kassil GN, et al. **Hum Physiol** 1985 Jul-Aug;11(4):285-90

MEPROBAMATE

Pesticide-drug interaction in rats. Fenyvesi G, et al. **Arch Toxicol [Suppl]** 1985;8:269-71
A possible role of endogenous adenosine in the sedative action of meprobamate. DeLong RE, et al. **Eur J Pharmacol** 1985 Dec 3; 118(3):359-62

MESORIDAZINE

Priapism and psychotropic drug therapy [letter] Lazarus A. **J Clin Psychopharmacol** 1986 Feb;6(1):60-1

METHOTRIMEPRAZINE

Action of antidepressant neuroleptics, chlorprothixene and levomepromazine, on the central noradrenergic system: comparison with other antidepressants. Antkiewicz-Michaluk L. **Pol J Pharmacol Pharm** 1985 Sep-Oct;37(5):673-83
Effect of chemical immobilisation on the heart rate and haematological values in captive gazelles. Furley CW. **Vet Rec** 1986 Feb 15; 118(7):178-80

METHYLPHENIDATE

Methylphenidate treatment of cocaine abusers without attention deficit disorder: a negative report. Gawin F, et al. **Am J Drug Alcohol Abuse** 1985;11(3-4):193-7
Prediction of methylphenidate (Ritalin) responsiveness through sensory integrative testing. Kimball JG. **Am J Occup Ther** 1986 Apr; 40(4):241-8
Behavioral effects of low-dose methylphenidate in childhood attention deficit disorder: implications for a mechanism of stimulant drug action. Solanto MV. **J Am Acad Child Psychiatry** 1986 Jan;25(1):96-101
Short term effects of methylphenidate on the cognitive, learning and academic performance of children with attention deficit disorder in the laboratory and the classroom. Douglas VI, et al. **J Child Psychol Psychiatry** 1986 Mar;27(2):191-211
Gradual vs. abrupt withdrawal of methylphenidate in two older dependent males. Keeley KA, et al. **J Subst Abuse Treat** 1985;2(2):123-5
Effects of methylphenidate and pentobarbital on the spontaneous activity levels of rats with selective hippocampal system damage. Shull RN, et al. **Life Sci** 1986 Mar 24;38(12):1135-41
Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. Sebrechts MM, et al. **Pediatrics** 1986 Feb;77(2):222-8

MOTIVATION

Interaction of the cholinergic and catecholaminergic systems of the brain during a change in the motivational behavior of animals. Sadykhova EF, et al. **Neurosci Behav Physiol** 1985 Nov-Dec;15(6):471-6
[Effect of psychotropic substances on the development of alcoholic motivation in noninbred white rats] Burov IuV, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):289-91 (Eng. Abstr.) **(Rus)**

MOTOR ACTIVITY

Interaction between nootropic drugs and methamphetamine on avoidance acquisition but not on locomotor activity in mice. Sansone M, et al. **Arch Int Pharmacodyn Ther** 1985 Dec;278(2):229-35
Effect of forebrain commissurotomy on recovery from unilateral 6-OHDA lesions of the substantia nigra and circling induced by apomorphine. Steiner H, et al. **Behav Brain Res** 1985 Oct; 17(3):245-9
Relationship of limbic dopamine levels to amphetamine- and anticholinergic-induced hyperactivity in the rat. Carey RJ. **Biol Psychiatry** 1986 Mar;21(3):317-21

Behavioral changes following central injection of cysteamine in rats. Bakhit C, et al. **Brain Res** 1986 Feb 12;365(1):159-63

Conditioned rotational behavior in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra. Carey RJ. **Brain Res** 1986 Feb 19;365(2):379-82

Further behavioral analysis of GABA-mediated inhibition in the early chick embryo. Maderdrut JL, et al. **Brain Res** 1986 Feb; 390(1):157-60

Differential effects of striatal injections of dopaminergic, cholinergic and GABAergic drugs upon swimming behavior of rats. Vrijmoed-de Vries MC, et al. **Brain Res** 1986 Jan 29;364(1):77-90

Differences in amphetamine and morphine sensitivity in lateralized and non-lateralized rats: locomotor activity and drug self-administration. Glick SD, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):239-44

Alterations in motor behaviour produced by the isomers of 3-PPP in the MPTP-treated marmoset. Nomoto M, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):123-8

Typical and atypical antidepressant drug effects on locomotor activity after intra-accumbens injections in the rat. Oosterloo SK, et al. **Eur J Pharmacol** 1985 Nov 26;118(1-2):45-51

The effects of chronic bromocriptine treatment on behaviour and dopamine receptor binding in the rat striatum. Traub M, et al. **Eur J Pharmacol** 1985 Nov 26;118(1-2):147-54

Study on the mechanism of the long-lasting antagonistic effect of caerulein on amphetamine-induced hyperactivity in rats. Matsubara K, et al. **Gen Pharmacol** 1986;17(1):13-7

Sub-chronic administration of (-)-3-PPP and central dopamine receptor sensitivity changes. Hjorth S, et al. **J Neural Transm** 1985; 64(3-4):187-98

Monoamine neurotransmitter metabolism and locomotor activity during chemical hypoxia. Freeman GB, et al. **J Neurochem** 1986 Mar; 46(3):733-8

Possible involvement of the central nervous system in long-term effect of caerulein on amphetamine-induced hyperactivity in rats. Matsubara K, et al. **Jpn J Pharmacol** 1985 Nov;39(3):317-21

Effect of subchronic treatment with methamphetamine on apomorphine-induced changes in locomotor activity in mice. Watanabe H, et al. **Jpn J Pharmacol** 1986 Jan;40(1):185-7

A comparative study of the locomotor activity effects of apomorphine and the 'atypical dopamine agonists' (piribedil and S3608). Offermeier J, et al. **Life Sci** 1986 Mar 10;38(10):895-903

Effects of methylphenidate and pentobarbital on the spontaneous activity levels of rats with selective hippocampal system damage. Shull RN, et al. **Life Sci** 1986 Mar 24;38(12):1135-41

Neuropathology and amphetamine-induced turning resulting from AF64A injections into the striatum of the rat. Stwertka SA, et al. **Life Sci** 1986 Mar 24;38(12):1105-10

Dissociation between circling behaviour and striatal dopamine activity following unilateral deltamethrin administration to rats. Brodie ME, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Dec;331(4):341-6

Biochemical correlates of motor changes caused by the manipulation of dopamine function in the substantia nigra of the mouse. Bradbury AJ, et al. **Neuropharmacology** 1985 Dec;24(12):1155-61

The effects of yohimbine on exploratory and locomotor behaviour are attributable to its effects at noradrenaline and not at benzodiazepine receptors. Chopin P, et al. **Neuropharmacology** 1986 Jan;25(1):53-7

Conditioned taste aversions and changes in motor activity in lithium-treated rats. Mediating role of the area postrema. Ladowsky RL, et al. **Neuropharmacology** 1986 Jan;25(1):71-7

Central noradrenaline depletion attenuates amphetamine-induced locomotor behavior. Mohammed AK, et al. **Neurosci Lett** 1986 Feb 28;64(2):139-44

Lateralized and compulsive exteroceptive orientation in rats treated with apomorphine. Pisa M, et al. **Neurosci Lett** 1986 Feb 14;64(1):41-6

Locomotor depression in mice by norcocaine does not involve central alpha 2-adrenergic or presynaptic dopamine receptors. Reith ME, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):305-7

Antagonism by dopamine, but not noradrenaline receptor blockers of the anti-immobility activity of desipramine after different treatment schedules in the rat. Pulvirenti L, et al. **Pharmacol Res Commun** 1986 Jan;18(1):73-80

Effects of neuroleptics on hippocampal stimulation-induced 'wet-dog shaking' in rats. Araki H, et al. **Physiol Behav** 1986 Jan;36(1):69-74

Opioid benzodiazepine tifluadom and drug-induced hyperactivity in mice: lack of benzodiazepine-like effects. Sansone M, et al. **Pol J Pharmacol Pharm** 1985 Sep-Oct;37(5):585-90

Acute low-level formaldehyde behavioural and neurochemical toxicity in the rat. Boja JW, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):671-4

Comparison of the effects of amphetamine and a fluorinated analogue on locomotion and exploratory activity in the mouse. Dubin RE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):681-5

Lateralizing effects of apomorphine on taxis, postural support and rotation in rats. Pisa M, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):525-31

Central noradrenaline depletion antagonizes aspects of d-amphetamine-induced hyperactivity in the rat. Archer T, et al. **Psychopharmacology (Berlin)** 1986;88(2):141-6

Effects of lithium and rubidium on shock-induced changes in open-field activity. Hines G. **Psychopharmacology (Berlin)** 1986;88(2):209-12

Effects of amphetamine and apomorphine on locomotor activity after kainic acid lesion of the nucleus accumbens septi in the rat. Kafetzopoulos E. **Psychopharmacology (Berlin)** 1986;88(3):271-4

Locomotor activity and neurotensin: resolution of discrepancies in effects? Sahgal A, et al. **Psychopharmacology (Berlin)** 1986;88(1):131-2

Effects of insecticidal carbamates on brain acetylcholine content, acetylcholinesterase activity and behavior in mice. Kobayashi H, et al. **Toxicol Lett** 1985 Dec;29(2-3):153-9

[The effect of various new GABAergics on motor and oral stereotypes with apomorphine in the rat] Vamvakidès A, et al. **J Pharmacol** 1985 Oct-Dec;16(4):403-11 (Eng. Abstr.) **(Fre)**

[Effect of chronic psychogenic stress on a number of behavioral and neurochemical characteristics of rats] Danchev ND, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):57-9 (Eng. Abstr.) **(Rus)**

[Neurochemical aspects of the emotional reactivity and motor activity of rats in new circumstances] Kulagin DA, et al. **Usp Fiziol Nauk** 1986 Jan-Mar;17(1):92-109 (99 ref.) **(Rus)**

MSH

D-2 dopaminergic agonists and adenosine 3',5'-monophosphate directly regulate the synthesis of alpha-melanocyte-stimulating hormone-like peptides by cultured rat melanotrophs. Beaulieu M, et al. **Endocrinology** 1986 Mar;118(3):1032-9

Stimulation of adenosine 3',5'-monophosphate production in rat Sertoli cells by alpha-melanotropin-stimulating hormone (alpha MSH) and des-acetyl alpha MSH. Boitani C, et al. **Endocrinology** 1986 Apr; 118(4):1513-8

A diurnal rhythm in proopiomelanocortin messenger ribonucleic acid that varies concomitantly with the content and secretion of beta-endorphin in the intermediate lobe of the rat pituitary. Millington WR, et al. **Endocrinology** 1986 Feb;118(2):829-34

In vitro study of frog (Rana ridibunda Pallas) interrenal function by use of a simplified perifusion system. VIII. Structure-activity relationship of synthetic ACTH fragments and gamma-MSH. Leboulenger F, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):187-96

Comparative effects of corticotropin-releasing factor, arginine vasopressin, and related neuropeptides on the secretion of ACTH and alpha-MSH by frog anterior pituitary cells and neurointermediate lobes in vitro. Tonon MC, et al. **Gen Comp Endocrinol** 1986 Mar; 61(3):438-45

The size of enzymes acetylating alpha-melanocyte-stimulating hormone and beta-endorphin. Chappell MC, et al. **J Biol Chem** 1986 Jan 25; 261(3):1088-91

The hypothalamo-hypophyseal rat explant in vitro: endocrinological studies of the pars intermedia dopaminergic neural input. Davis MD. **J Physiol (Lond)** 1986 Jan;370:381-93

ACTH-(1-24) and alpha-MSH antagonize dopamine receptor-mediated inhibition of striatal dopamine and acetylcholine release. Versteeg DH, et al. **Life Sci** 1986 Mar 3;38(9):835-40

Modulation by Leu-enkephalin of peptide release from perifused neurointermediate pituitary. II. Inhibition of calcium-mediated secretion of alpha-MSH and beta-endorphin. Al Zein M, et al. **Neuroendocrinology** 1986;42(3):248-54

[Role of alpha-MSH and related peptides in the central nervous system] Delbende C, et al. **Rev Neurol (Paris)** 1985;141(6-7):429-39 (117 ref.) (Eng. Abstr.) **(Fre)**

NEUROREGULATORS

GABAA receptors and opioid receptors as examples of multiple site receptor proteins. Barnard E. **Alcohol Drug Res** 1985-86;6(2-3):63-5

Inhibitory neuromodulation of release of amino acid neurotransmitters. Peris J, et al. **Alcohol Drug Res** 1985-86;6(4):253-64 (61 ref.)

Neurotransmitters of the cochlea and cochlear nucleus: immunocytochemical evidence. Altschuler RA, et al. **Am J Otolaryngol** 1986 Mar-Apr;7(2):100-6 (59 ref.)

Deficits in inhibitory avoidance after neurotoxic lesions of the ventral striatum are neurochemically and behaviorally selective. Schwarting R, et al. **Behav Brain Res** 1985 Dec;18(3):279-83

Influences of amino acids on the circadian rhythms of brain neurotransmitters. Angelova C, et al. **Bibl Nutr Dieta** 1986; (38):72-81

Effects of dietary vanadium exposure on levels of regional brain neurotransmitters and their metabolites. Sharma RP, et al. **Biochem Pharmacol** 1986 Feb 1;35(3):461-5

External calcium, intrasynaptosomal free calcium and neurotransmitter release. Ashley RH. **Biochim Biophys Acta** 1986 Jan 29; 854(2):207-12

Presynaptic calcium diffusion from various arrays of single channels. Implications for transmitter release and synaptic facilitation. Fogelson AL, et al. **Biophys J** 1985 Dec;48(6):1003-17

Long-term potentiation is associated with an increase in calcium-dependent, potassium-stimulated release of [14C]glutamate from hippocampal slices: an ex vivo study in the rat. Feasey KJ, et al. **Brain Res** 1986 Jan 29;364(1):39–44

Tryptamine enhancement of neurotransmitter release under conditions that normally depress calcium influx. Friedman RN, et al. **Brain Res** 1986 Jan 29;364(1):172–6

Comparative effects of the neurotoxins N-chloroethyl-N-ethyl-2-bromobenzylamine hydrochloride (DSP4) and 6-hydroxydopamine on hypothalamic noradrenergic, dopaminergic and 5-hydroxytryptaminergic neurons in the male rat. Lookingland KJ, et al. **Brain Res** 1986 Feb 19;365(2):228–34

Mechanism of the calcium-dependent stimulation of transmitter release by 4-aminopyridine in synaptosomes. Tapia R, et al. **Brain Res** 1985 Dec 30;361(1–2):373–82

Neurotransmitter phenotypic plasticity in the mammalian embryo. Jonakait GM, et al. **Curr Top Dev Biol** 1986;20:165–75 (60 ref.)

Changes in gamma-aminobutyrate, glutamate, aspartate, glycine, and taurine contents in the striatum after unilateral nigrostriatal lesions in rats. Tanaka Y, et al. **Exp Neurol** 1986 Feb;91(2):259–68

Temperature dependence of neurotransmitter release in the antarctic fish Pagothenia borchgrevinki. Pockett S, et al. **Experientia** 1986 Apr 15; 42(4):414–5

Amino acid neurotransmitters in the CNS. Characteristics of the acidic amino acid exchange. Erecińska M, et al. **FEBS Lett** 1986 Apr 7; 199(1):95–9

Acute cyanide intoxication and central transmitter systems. Persson SA, et al. **Fundam Appl Toxicol** 1985 Dec;5(6 Pt 2):S150–9

Evidence for an excitatory amino acid as the transmitter of the auditory nerve in the in vitro mouse cochlear nucleus. Martin MR. **Hear Res** 1985;20(3):215–20

Effects of L-aspartate and oxaloacetic acid on click-evoked cochlear potentials. Sun YW, et al. **Hear Res** 1986;21(1):83–6

Calcium and transmitter release. Cohen I, et al. **Int Rev Neurobiol** 1985; 27:299–336 (103 ref.)

Retinal neurochemistry of three elasmobranch species: an immunohistochemical approach. Brunken WJ, et al. **J Comp Neurol** 1986 Jan 1;243(1):1–12

Biochemical and morphological correlates of transmitter type in C2, an identified histaminergic neuron in Aplysia. Schwartz JH, et al. **J Comp Neurol** 1986 Mar 15;245(3):401–21

Excitatory amino acid transmitters in neuronal circuits of the cat visual cortex. Tsumoto T, et al. **J Neurophysiol** 1986 Mar;55(3):469–83 (61 ref.)

L-glutamate: a neurotransmitter candidate for cone photoreceptors in the monkey retina. Sarthy PV, et al. **J Neurosci** 1986 Mar;6(3):637–43

The bag cells of Aplysia as a multitransmitter system: identification of alpha bag cell peptide as a second neurotransmitter. Sigvardt KA, et al. **J Neurosci** 1986 Mar;6(3):803–13

Effect of some centrally administered putative amino acid neurotransmitters on carrageenan-induced paw oedema in rats. Bhattacharya SK, et al. **J Pharm Pharmacol** 1986 Feb;38(2):144–6

Inhibitors of calcium buffering depress evoked transmitter release at the squid giant synapse. Adams DJ, et al. **J Physiol (Lond)** 1985 Dec; 369:145–59

Effects of neurotransmitters or drugs on the in vivo release of dopamine and its metabolites. Kito S, et al. **Jpn J Pharmacol** 1986 Jan; 40(1):57–67

Effect of 450191-S, a 1H-1,2,4-triazolyl benzophenone derivative, on cerebral content of neuroactive amino acids. Tomono S, et al. **Jpn J Pharmacol** 1985 Dec;39(4):558–61

Studies of neurotransmitter chemistry of central nervous system neurons in primary tissue culture. Thomas WE. **Life Sci** 1986 Jan 27; 38(4):297–308 (87 ref.)

GTP-binding proteins mediate transmitter inhibition of voltage-dependent calcium channels. Holz GG 4th, et al. **Nature** 1986 Feb 20–26;319(6055):670–2

Single channels and ionic currents in peptidergic nerve terminals. Lemos JR, et al. **Nature** 1986 Jan 30–Feb 5;319(6052):410–2

Modifying channel function [news] Stevens CF. **Nature** 1986 Feb 20–26; 319(6055):622

Facilitation of transmitter release through available transmitter regulation. An explanation not involving residual calcium theory. Sarrazin C. **Neurol Res** 1985 Dec;7(4):194–8

Adenosine modulation of striatal neurotransmitter release monitored in vivo using voltammetry. O'Neill RD. **Neurosci Lett** 1986 Jan 2; 63(1):11–6

Effects of amino acid neurotransmitter candidates on an identified insect motoneurone. Wafford KA, et al. **Neurosci Lett** 1986 Jan 16; 63(2):135–40

Model peptidergic systems at the insect neuromuscular junction. O'Shea M, et al. **Peptides** 1985;6 Suppl 3:417–24

Neurotransmitter release and its facilitation in crayfish. VII. Another voltage dependent process beside Ca entry controls the time course of phasic release. Parnas H, et al. **Pflugers Arch** 1986 Feb; 406(2):121–30

Neurotransmitter release and its facilitation in crayfish. VIII. Modulation of release by hyperpolarizing pulses. Parnas I, et al. **Pflugers Arch** 1986 Feb;406(2):131–7

Neurotransmitter regulation of anterior pituitary hormones. Tuomisto J, et al. **Pharmacol Rev** 1985 Sep;37(3):249–332 (1515 ref.)

Neurotransmitter metabolites and endocrine responses in depression. Hasey GM, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5–6):613–7

Postmortem neurochemistry in schizophrenia. Bracha HS, et al. **Psychiatr Clin North Am** 1986 Mar;9(1):133–41 (38 ref.)

Neurohumoral interactions in the posttraumatic period and possibilities of their correction. Bazarevitch GJ, et al. **Resuscitation** 1986 Jan; 13(2):115–21

Mechanism of transmitter release: voltage hypothesis and calcium hypothesis. Zucker RS, et al. **Science** 1986 Feb 7;231(4738):574–9

Neurobiochemical alterations induced by the artificial sweetener aspartame (NutraSweet). Coulombe RA Jr, et al. **Toxicol Appl Pharmacol** 1986 Mar 30;83(1):79–85

Excitatory amino acid analogs evoke release of endogenous amino acids and acetyl choline from chick retina in vitro. Campochiaro P, et al. **Vision Res** 1985;25(10):1375–86

The signature hypothesis: co-localizations of neuroactive substances as anatomical probes for circuitry analyses. Lam DM, et al. **Vision Res** 1985;25(10):1353–64 (48 ref.)

[Comparison of effects of electroacupuncture stimulations of two different intensities and frequencies on monoamine neurotransmitters in rat brain regions] Wang YJ, et al. **Chen Tzu Yen Chiu** 1985;10(1):24–9 (Eng. Abstr.) **(Chi)**

[Influence of monoamines on the dl-tetrahydropalmatine-induced inhibition of single-unit activity in the nucleus accumbens] Liu GO, et al. **Yao Hsueh Hsueh Pao** 1985 Jul;20(7):500–4 (Eng. Abstr.) **(Chi)**

[Hydergine: interaction with the neurotransmitter systems of the central nervous system] Markstein R. **J Pharmacol** 1985;16 Suppl 3:1–19 (60 ref.) (Eng. Abstr.) **(Fre)**

[Principles of transmembranous signal transduction in the action of hormones and neurotransmitters] Schultz G, et al. **Arzneimittelforschung** 1985;35(12A):1879–85 (72 ref.) (Eng. Abstr.) **(Ger)**

[Possible general mechanism of the presynaptic action of mediators] Abramets II, et al. **Dokl Akad Nauk SSSR** 1986 Mar–Apr; 287(1):245–8 **(Rus)**

NEUROTENSIN

Isolated canine ileal mucosal cells in short-term culture: a model for study of neurotensin release. Barber DL, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):G374–84

Regulation of neurotensin release from canine enteric primary cell cultures. Barber DL, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):G385–90

Neurotensin excites neurons in the arcuate nucleus of the rat hypothalamus in vitro. Herbison AE, et al. **Brain Res** 1986 Feb 5;364(2):391–5

Neurotensinlike immunoreactive neurons in the hedgehog (Erinaceus europaeus) and the sheep (Ovis aries) central nervous system. Papadopoulos GC, et al. **J Comp Neurol** 1986 Feb 8;244(2):193–203

Binding of [3H]neurotensin in human brain: properties and distribution. Kanba KS, et al. **J Neurochem** 1986 Mar;46(3):946–52

Autoradiographic localization of [3H]neurotensin-binding sites in the hippocampal region of the rat and primate brain. Köhler C, et al. **Neuroscience** 1985 Nov;16(3):577–87

Hyperthermic effect of neurotensin in the rabbit. Vybíral S, et al. **Pflugers Arch** 1986 Mar;406(3):312–4

Central nervous system neurotensin and feeding. Hawkins MF. **Physiol Behav** 1986 Jan;36(1):1–8

Further evidence that central neurotensin inhibits pituitary prolactin secretion by stimulating dopamine release from the hypothalamus. Tojo K, et al. **Proc Soc Exp Biol Med** 1986 Apr;181(4):517–22

Locomotor activity and neurotensin: resolution of discrepancies in effects? Sahgal A, et al. **Psychopharmacology (Berlin)** 1986;88(1):131–2

Action of neurotensin on size, composition, and growth of pancreas and stomach in the rat. Feurle GE, et al. **Regul Pept** 1985 Dec; 13(1):53–62

Neurotensin-like immunoreactivity released into the portal vein by duodenal acidification in the dog. Mogard M, et al. **Scand J Gastroenterol** 1986 Jan;21(1):97–103

[Endocrine impact of resections of the small intestine] De Graef J, et al. **Acta Gastroenterol Belg** 1985 May–Jun;48(3):286–8 (Eng. Abstr.) **(Fre)**

NEUROTIC DISORDERS

[Participation of the cholinergic system in central mechanisms of the cortico-limbic regulation of visceral functions] Beller NN, et al. **Fiziol Zh SSSR** 1986 Jan;72(1):61–8 **(Rus)**

[Stages in the development of neuroses in the dog and effects of preparations with antidepressive and tranquilizing properties] Mekhedova AIa, et al. **Zh Vyssh Nerv Deiat** 1985 Nov–Dec; 35(6):1147–55 (Eng. Abstr.) **(Rus)**

NIALAMIDE

Effect of nialamide on the metabolism of dopamine injected into the nucleus accumbens of old rats. Cousin KM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):25-30

NITRAZEPAM

Residual effect of single and repeated doses of midazolam and nitrazepam in relation to their plasma concentrations. Godtlibsen OB, et al. **Eur J Clin Pharmacol** 1986;29(5):595-600

Prescribing and dispensing of benzodiazepines by pharmacists. Newgreen DB, et al. **Med J Aust** 1986 Mar 31;144(7):370-1

NOMIFENSINE

Successful treatment of bulimia with nomifensine. Nassr DG. **Am J Psychiatry** 1986 Mar;143(3):373-4

Treatment of bulimia with nomifensine. Pope HG Jr, et al. **Am J Psychiatry** 1986 Mar;143(3):371-3

Disposition of nomifensine after acute and prolonged dosing. Lindberg RL, et al. **Clin Pharmacol Ther** 1986 Apr;39(4):384-8

Metabolism of nomifensine after oral and intravenous administration. Lindberg RL, et al. **Clin Pharmacol Ther** 1986 Apr;39(4):378-83

Cognitive symptoms in late-life depression and their treatment. Siegfried K. **J Affective Disord** 1985;Suppl 1:S33-40

Gas chromatographic-mass spectrometric determination of nomifensine using a stable isotope-labeled analogue as an internal standard. Bagchi SP, et al. **J Chromatogr** 1985 Nov 8;344:362-6

Haemolytic anaemia caused by nomifensine [letter] Woodliff HJ, et al. **Med J Aust** 1986 Feb 3;144(3):163

[The circulatory system in patients with depression during treatment with antidepressive drugs. II. Effect of therapeutic doses of thymoleptics on ECG records in patients with endogenous depression] Rajewska J. **Psychiatr Pol** 1985 Jul-Aug;19(4):278-84 (Eng. Abstr.) **(Pol)**

NOREPINEPHRINE

Effects of morphine on hypothalamic corticotropin-releasing factor (CRF), norepinephrine and dopamine in non-stressed and stressed rats. Suemaru S, et al. **Acta Med Okayama** 1985 Dec;39(6):463-70

Noradrenaline evokes an alpha-adrenoceptor-mediated inotropic effect in human ventricular myocardium. Aass H, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Jan;58(1):88-90

Effect of long-term application of Oxyphenon on biogenic amine levels in female rat brain. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:295-301

Comparison of the effect of single and repeated administration of Oxyphenon on norepinephrine and dopamine levels in female rat brains. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:309-12

Effect of Oxyphenon on norepinephrine and dopamine levels in male rat brain. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985; 112:303-8

Cardiovascular haemodynamics and the response of vasopressin, aldosterone, plasma renin activity and plasma catecholamines to head-up tilt in young and old healthy subjects. Vargas E, et al. **Age Ageing** 1986 Jan;15(1):17-28

Modulation of luteinizing hormone immunoreactivity and bioactivity by dopamine but not norepinephrine in women. Barnes RB, et al. **Am J Obstet Gynecol** 1986 Feb;154(2):445-50

Norepinephrine inhibition of pulsatile LH release: receptor specificity. Bergen H, et al. **Am J Physiol** 1986 Feb;250(2 Pt 1):E205-11

Role of protein kinase C in inhibition of renin release caused by vasoconstrictors. Kurtz A, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):C563-71

Effects of diet and photoperiod on NE turnover and GDP binding in Siberian hamster brown adipose tissue. McElroy JF, et al. **Am J Physiol** 1986 Mar;250(3 Pt 2):R383-8

Effect of amine on temperature-responsive neuron in slice preparation of rat brain stem. Watanabe T, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 2):R553-9

An association between norepinephrine-to-epinephrine ratio and suicidal ideation in depression [letter] **Am J Psychiatry** 1986 May; 143(5):683-4

The role of intracellular sodium activity in the inotropy potentiation among high [Ca]o' norepinephrine and strophanthidin. Abete P, et al. **Arch Int Pharmacodyn Ther** 1985 Nov;278(1):87-96

Catecholaminergic and serotoninergic brain structures in European green frogs: an autoradiographical study. *Diederen JH, et al.* **Basic Appl Histochem** 1985;29(4):297-308

6-Hydroxydopamine treatment does not affect the young rat's ability to modify its response when changing from food to water deprivation. Brenner E, et al. **Behav Brain Res** 1986 Jan;19(1):89-92

Influences of amino acids on the circadian rhythms of brain neurotransmitters. Angelova C, et al. **Bibl Nutr Dieta** 1986; (38):72-81

Inactivation of the early calcium uptake and noradrenaline release evoked by potassium in cultured chromaffin cells. Artalejo CR, et al. **Biochem Biophys Res Commun** 1986 Jan 14;134(1):1-7

Phosphopeptide analysis of phenylalanine hydroxylase isolated from liver cells exposed to hormonal stimuli. Fisher MJ, et al. **Biochem J** 1986 Jan 15;233(2):507-11

Urinary excretion of free tyramine and of norepinephrine and its metabolites in unipolar depressed patients. Roy A, et al. **Biol Psychiatry** 1986 Feb;21(2):221-4

Recovery of pulsatile luteinizing hormone secretion following permanent disruption of the ascending noradrenergic fiber tract in the ovariectomized rat. Clifton DK, et al. **Biol Reprod** 1985 Nov; 33(4):808-14

Gonadotropin-releasing hormone release by superfused hypothalami in response to norepinephrine. Nowak FV, et al. **Biol Reprod** 1985 Nov; 33(4):790-6

Effects of noradrenaline on 45Ca2+ efflux from isolated rat islets of Langerhans. Morgan NG, et al. **Biosci Rep** 1985 Dec;5(12):1053-60

Noradrenergic stimulation of supraoptic neuronal activity and vasopressin release in vitro: mediation by an alpha 1-receptor. Armstrong WE, et al. **Brain Res** 1986 Feb 12;365(1):192-7

Cardiovascular and neuroendocrine responses to behavioral stress after central or peripheral barodenervation in rats. Buchholz RA, et al. **Brain Res** 1986 Feb 19;365(2):360-4

Activation of the locus coeruleus induced by selective stimulation of the ventral tegmental area. Deutch AY, et al. **Brain Res** 1986 Jan 22; 363(2):307-14

Locus coeruleus neurons in culture have a developmentally transient alpha 1 adrenergic response. Finlayson PG, et al. **Brain Res** 1986 Mar; 390(2):292-5

Specific detection of noradrenaline in the rat brain by using antibodies. Geffard M, et al. **Brain Res** 1986 Jan 22;363(2):395-400

Responses of adrenal catecholamine secretion to lateral hypothalamic stimulation and lesion in rats. Katafuchi T, et al. **Brain Res** 1986 Jan 15;363(1):141-4

Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. Liang KC, et al. **Brain Res** 1986 Mar 12;368(1):125-33

Effects of intrahypothalamically administered norepinephrine, serotonin and bombesin on thermoregulation in the deermouse (Peromyscus maniculatus). Lin LH, et al. **Brain Res** 1986 Feb 5;364(2):212-9

Locus coeruleus norepinephrine-containing neurons: effects produced by acute and subchronic treatment with antipsychotic drugs and amphetamine. Ramirez OA, et al. **Brain Res** 1986 Jan 1; 362(1):165-70

Blockade of norepinephrine-induced long-lasting potentiation in the hippocampal dentate gyrus by an inhibitor of protein synthesis. Stanton PK, et al. **Brain Res** 1985 Dec 30;361(1-2):276-83

Noradrenaline modifies sympathetic preganglionic neuron spike and afterpotential. Yoshimura M, et al. **Brain Res** 1986 Jan 8; 362(2):370-4

Effects of dopamine and norepinephrine on neuronal activity of the olfactory tubercle. Guevara-Aguilar R, et al. **Brain Res Bull** 1985 Dec; 15(6):665-8

Alterations in noradrenergic innervation of the brain following dorsal bundle lesions in neonatal rats. Klisans-Fuenmayor D, et al. **Brain Res Bull** 1986 Jan;16(1):47-54

Adrenergic mechanisms of barbital dependence in mice. Germany A, et al. **Cell Mol Biol** 1985;31(5):369-71

Adrenergic coronary tone during submaximal exercise in the dog is produced by circulating catecholamines. Evidence for adrenergic denervation supersensitivity in the myocardium but not in coronary vessels. Chilian WM, et al. **Circ Res** 1986 Jan;58(1):68-82

Plasma noradrenaline and its relationship to plasma oestradiol in normal women during the menstrual cycle. Davidson L, et al. **Clin Exp Pharmacol Physiol** 1985 Sep-Oct;12(5):489-93

Treatment of childhood hyperactivity with desipramine: plasma drug concentration, cardiovascular effects, plasma and urinary catecholamine levels, and clinical response. Donnelly M, et al. **Clin Pharmacol Ther** 1986 Jan;39(1):72-81

Lymphatic transport rate of noradrenaline during adrenergic thermogenesis. Pácha J, et al. **Comp Biochem Physiol [C]** 1986; 83(1):161-4

Plasma catecholamines and vascular reactivity in acute and chronic renal failure. Campese VM, et al. **Contrib Nephrol** 1985;49:128-33

Relationship between plasma noradrenaline and blood pressure in uremia. Zuccalà A, et al. **Contrib Nephrol** 1985;49:134-9

Catecholamine-mediated injury to endothelium in rabbit *perfused aorta: a quantitat*ive analysis by scanning electron microscopy. Makhmudov RM, et al. **Cor Vasa** 1985;27(6):456-63

Human aqueous humor catecholamines. Autzen T, et al. **Curr Eye Res** 1985 Dec;4(12):1269-71

Desensitization of reticular neurons after ionophoretically applied noradrenalin in rats. Hricovíni M, et al. **Endocrinol Exp (Bratisl)** 1985 Dec;19(4):291-6

Acute influence of cigarette smoke in platelets, catecholamines and neurophysins in the normal conditions of daily life. de Lorgeril M, et

al. **Eur Heart J** 1985 Dec;6(12):1063-8

Reproducibility of plasma catecholamine concentrations at rest and during exercise in man. Péronnet F, et al. **Eur J Appl Physiol** 1986; 54(6):555-8

Noradrenergic-serotonergic interactions and nociception in the rat. Archer T, et al. **Eur J Pharmacol** 1986 Jan 29;120(3):295-307

Supersensitivity of alpha 2-adrenoceptors modulating [3H]5-HT release after noradrenergic denervation with DSP4. Benkirane S, et al. **Eur J Pharmacol** 1985 Dec 10;119(1-2):131-3

Reserpine-resistant responses to nerve stimulation in the cat nictitating membrane involve the release of newly synthesized noradrenaline. Duval N, et al. **Eur J Pharmacol** 1986 Mar 11;122(1):93-101

Plasma catecholamines and glucose during moderate exercise in the trout: comparison with bursts of violent activity. Ristori MT, et al. **Exp Biol** 1985;44(4):247-53

Visual discrimination learning and interhemispheric transfer in the cat, as affected by 6-hydroxydopamine. Sprague JM, et al. **Exp Brain Res** 1985;61(1):43-53

On steroid noradrenergic system interaction during the hypothalamic differentiation period in the female rat. Vidal MJ, et al. **Exp Clin Endocrinol** 1985 Dec;86(2):165-70

Acute cold exposure increases the glucagon sensitivity of thermogenic metabolism in the rat. Howland RJ. **Experientia** 1986 Feb 15; 42(2):162-3

Norepinephrine with its precursors and their antagonists haloperidol and phentolamine interact with dye free radicals in opposite ways. Marinov BS. **FEBS Lett** 1986 Mar 17;198(1):130-4

Brain monoamines and peptides: role in the control of eating behavior. Leibowitz SF. **Fed Proc** 1986 Apr;45(5):1396-403

Alpha- and beta-adrenergic mechanisms mediate blood pressure control by norepinephrine and angiotensin in ducks. Butler DG, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):323-9

Three phase contractile response of rabbit pulmonary artery to norepinephrine: influence of ruthenium red and calcium. Howell RE, et al. **Gen Pharmacol** 1986;17(1):105-8

Are hypertensive effects of aldosterone, angiotensin, vasopressin, and norepinephrine chronically additive? Cowley AW Jr, et al. **Hypertension** 1986 Apr;8(4):332-43

Weight-reducing diets and sodium intake [letter] Strazzullo P. **Hypertension** 1986 Apr;8(4):357-9

Cardiac function and plasma catecholamines during upright exercise in healthy young subjects. Kelbaek H, et al. **Int J Cardiol** 1986 Mar; 10(3):223-35

Free plasma catecholamines, heart rates, lactate levels, and oxygen uptake in competition weight lifters, cyclists, and untrained control subjects. Lehmann M, et al. **Int J Sports Med** 1986 Feb;7(1):18-21

Plasma norepinephrine concentration reflects pharmacological alteration of sympathetic activity in the conscious cat. Hubbard JW, et al. **J Auton Nerv Syst** 1986 Jan;15(1):93-100

A study of the relationship between dopamine and noradrenaline content and transmural pressure in the mesenteric arteries of the dog. Azevedo I, et al. **J Auton Pharmacol** 1986 Mar;6(1):33-7

Comparison of the effects of labetalol and SCH 19927, the R1R isomer of labetalol, on the rat isolated right ventricle and aorta. Doggrell SA, et al. **J Auton Pharmacol** 1985 Dec;5(4):279-88

Perfusion with calcium free solution potentiates prazosin blockade of noradrenaline induced pressor responses in the mesenteric bed of the rat. Downing OA, et al. **J Auton Pharmacol** 1985 Dec;5(4):295-9

Norepinephrine decreases EGF binding in primary rat hepatocyte cultures. Cruise JL, et al. **J Cell Physiol** 1986 Apr;127(1):39-44

Noradrenergic and serotoninergic innervation of cortical, thalamic, and tectal visual structures in Old and New World monkeys. Morrison JH, et al. **J Comp Neurol** 1986 Jan 1;243(1):117-38

Unchanged pressor effect of norepinephrine in normal man following the oral administration of two angiotensin converting enzyme inhibitors, captopril and HOE 498. Vierhapper H, et al. **J Hypertens** 1986 Feb; 4(1):9-11

Urinary norepinephrine excretion in panic and phobic disorders. Dajas F, et al. **J Neural Transm** 1986;65(1):75-81

GABA-noradrenergic interaction: evidence for differential sites of action for GABA-A and GABA-B receptors. Suzdak PD, et al. **J Neural Transm** 1985;64(3-4):163-72

Stimulation of amino acid uptake and Na+,K+-ATPase activity by norepinephrine in superior cervical sympathetic ganglia excised from adult rats. Ando M, et al. **J Neurochem** 1986 May;46(5):1487-92

Stimulatory effect of ascorbic acid on norepinephrine biosynthesis in digitonin-permeabilized adrenal medullary chromaffin cells. Morita K, et al. **J Neurochem** 1986 Mar;46(3):939-45

Doses of 6-hydroxydopamine sufficient to deplete norepinephrine are not sufficient to decrease plasticity in the visual cortex. Trombley P, et al. **J Neurosci** 1986 Jan;6(1):266-73

Noradrenergic hyperinnervation of the motor trigeminal nucleus: alterations in membrane properties and responses to synaptic input. Vornov JJ, et al. **J Neurosci** 1986 Jan;6(1):30-7

Responses to norepinephrine resistant to inhibition by alpha and beta adrenoceptor antagonists. Bond RA, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):408-15

Contribution of Ca++ and calmodulin to the action of norepinephrine on renal prostaglandin synthesis and vascular tone. Cooper CL, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):424-31

Presynaptic alpha-2 adrenoceptor activation and coupling of the receptor-presynaptic effector system in the perfused rat heart: affinity and efficacy of phenethylamines and imidazoline derivatives. Fuder H, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):237-45

Effects of melatonin and control injections on pineal serotonin and norepinephrine: afternoon injections lower serotonin levels thirty-six percent at light-dark transition. Catalá MD, et al. **J Pineal Res** 1984; 1(1):75-82

Temporal effects of norepinephrine on pineal serotonin in vitro. Walker RF, et al. **J Pineal Res** 1986;3(1):33-40

Evidence for a noradrenergic transmission in the control of parturition in the rat. Legrand C, et al. **J Reprod Fertil** 1986 Jan;76(1):415-24

Effects of bifemelane hydrochloride (MCI-2016) on acetylcholine and norepinephrine release from cortical slices of bilaterally carotid-artery-ligated Mongolian gerbils. Saito K, et al. **Jpn J Pharmacol** 1985 Nov;39(3):406-9

A noradrenaline-induced inhibition from locus coeruleus of nucleus accumbens neuron receiving input from hippocampus. Unemoto H, et al. **Jpn J Pharmacol** 1985 Oct;39(2):233-9

Diurnal rhythm of alpha 2-noradrenergic receptors in the paraventricular nucleus and other brain areas: relation to circulating corticosterone and feeding behavior. Jhanwar-Uniyal M, et al. **Life Sci** 1986 Feb 3; 38(5):473-82

Effects of cocaine on the electrical activity of single noradrenergic neurons from locus coeruleus. Pitts DK, et al. **Life Sci** 1986 Mar 31; 38(13):1229-34

Epinephrine and norepinephrine stimulation of adenylate cyclase in bovine retina homogenate: evidence for interaction with the dopamine D1 receptor. Vanderheyden P, et al. **Life Sci** 1986 Mar 31; 38(13):1221-7

Stimulation of 3H-norepinephrine release by trifluoperazine from rat pineal glands. Yurko KA, et al. **Life Sci** 1986 Apr 14;38(15):1393-7

In vitro effects of betamethasone, adrenaline and noradrenaline on normal human T-lymphocyte rosettes. Kumar R, et al. **Mater Med Pol** 1985 Jul-Sep;17(3):170-1

Modulation of visual cortical plasticity by acetylcholine and noradrenaline. Bear MF, et al. **Nature** 1986 Mar 13-19; 320(6058):172-6

Islet-activating protein (pertussis toxin) diminishes alpha 2-adrenoceptor mediated effects on noradrenaline release. Allgaier C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):235-9

Effects of a monoamine oxidase A inhibitor, FLA 668 (+) on the adrenergic mechanisms of the dog saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):181-5

Further evidence for, and nature of, the facilitatory GABAergic influence on central noradrenergic transmission. Dennis T, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):225-34

Further characterization of brain 3,4-dihydroxyphenylethyleneglycol (DHPG) formation: dependence on noradrenergic activity and site of formation. Li PP, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):26-33

Opioid peptides decrease noradrenaline release and blood pressure in the rabbit at peripheral receptors. Szabo B, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):50-6

Release of [3H]noradrenaline by alpha 1-adrenoceptor agonists. Vizi ES, et al. **Neurochem Res** 1986 Jan;11(1):71-84

Interaction between corticosterone and alpha-2-noradrenergic system of the paraventricular nucleus in relation to feeding behavior. Roland CR, et al. **Neuroendocrinology** 1986;42(4):296-305

The neurotropic effect of pituitary somatotropin and a fragment of it. Bulatov AA, et al. **Neurosci Behav Physiol** 1985 Sep-Oct; 15(5):419-22

Stimulation of noradrenaline synthesis by the calcium ionophore A23187 and its modulation by presynaptic receptors. Birch PJ, et al. **Neurosci Lett** 1985 Dec 4;62(2):187-92

Comparison between the actions of avian pancreatic polypeptide, neuropeptide Y and norepinephrine on the excitability of rat supraoptic vasopressin neurons. Day TA, et al. **Neurosci Lett** 1985 Dec 4; 62(2):181-5

Norepinephrine depletion in the paraventricular nucleus inhibits the adrenocortical responses to neural stimuli. Feldman S, et al. **Neurosci Lett** 1986 Feb 28;64(2):191-5

Frequency- and *reserpine-dependent* chemical coding of sympathetic transmission: differential release of noradrenaline and neuropeptide Y from pig spleen. Lundberg JM, et al. **Neurosci Lett** 1986 Jan 2; 63(1):96-100

Central noradrenaline depletion attenuates amphetamine-induced locomotor behavior. Mohammed AK, et al. **Neurosci Lett** 1986 Feb 28;64(2):139-44

The norepinephrine and dopamine content of the cat carotid body in vivo under normoxic and hypoxic conditions. Starlinger H, et al. **Neurosci Lett** 1986 Feb 14;64(1):65-8

Different developmental schedules of dopaminergic and noradrenergic neurons in dissociation culture of fetal rat midbrain and hindbrain. Ahnert-Hilger G, et al. **Neuroscience** 1986;17(1):157-65

Serotoninergic but not noradrenergic neurons in rat central nervous system adapt to long-term treatment with monoamine oxidase inhibitors. Blier P, et al. **Neuroscience** 1985 Dec;16(4):949-55

Release and turnover of noradrenaline in isolated median eminence: lack of negative feedback modulation. Vizi ES, et al. **Neuroscience** 1985 Dec; 16(4):907-16

Alteration of fetal heart rate caused by extrauterine environmental changes. Masuyama I, et al. **Nippon Juigaku Zasshi** 1986 Feb; 48(1):61-8

An effect of noradrenaline on resting potential and Na activity in sheep cardiac Purkinje fibres. Glitsch HG, et al. **Pflugers Arch** 1986 Feb; 406(2):144-50

Effects of dopamine and noradrenaline on Ca channels of cultured sensory and sympathetic neurons of chick. Marchetti C, et al. **Pflugers Arch** 1986 Feb;406(2):104-11

Effects of preshock experience on enhancement of rat brain noradrenaline turnover induced by psychological stress. Tsuda A, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):115-9

Effects of an extract of Ginkgo biloba on noradrenergic systems of rat cerebral cortex. Brunello N, et al. **Pharmacol Res Commun** 1985 Nov; 17(11):1063-72

Antagonism by dopamine, but not noradrenaline receptor blockers of the anti-immobility activity of desipramine after different treatment schedules in the rat. Pulvirenti L, et al. **Pharmacol Res Commun** 1986 Jan;18(1):73-80

Norepinephrine and the antibody response. Sanders VM, et al. **Pharmacol Rev** 1985 Sep;37(3):229-48 (256 ref.)

Evidence for the site of action of glycerol trinitrate and diltiazem in inhibiting vasoconstrictor responses to norepinephrine in isolated renal arteries. Gross GJ, et al. **Pharmacology** 1986;32(1):1-10

Action of antidepressant neuroleptics, chlorprothixene and levomepromazine, on the central noradrenergic system: comparison with other antidepressants. Antkiewicz-Michaluk L. **Pol J Pharmacol Pharm** 1985 Sep-Oct;37(5):673-83

Possible relationship of the locus coeruleus--hippocampal noradrenergic neurons to depression and mode of action of antidepressant drugs. Kostowski W. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):727-43 (57 ref.)

The influence of beta-agonists on normal and clonidine-decelerated noradrenaline turnover in the rat brain. Nowak G, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):765-72

Studies on the utility of urinary 3,4-dihydroxyphenylethylene-glycol (DHPG) measurement. Li PP, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):717-20

Adrenergic stimulation of prostacyclin production in the rat tail artery. II. The role of calcium. Golub MS, et al. **Prostaglandins Leukotrienes Med** 1985 Dec;20(3):313-24

Effects of S-adenosyl-methionine on plasma norepinephrine, blood pressure, and heart rate in healthy volunteers. Sherer MA, et al. **Psychiatry Res** 1986 Feb;17(2):111-8

Central noradrenaline depletion antagonizes aspects of d-amphetamine-induced hyperactivity in the rat. Archer T, et al. **Psychopharmacology (Berlin)** 1986;88(2):141-6

Effects of antidepressant drugs, selective noradrenaline-or 5-hydroxytryptamine uptake inhibitors, on apomorphine-induced hypothermia in mice. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1986;88(2):240-6

Involvement of noradrenaline in potentiation of the head-twitch response by GABA-related drugs. Singh L, et al. **Psychopharmacology (Berlin)** 1986;88(3):315-9

Plasma catecholamines at rest and exercise in subjects with high- and low-trait anxiety. Péronnet F, et al. **Psychosom Med** 1986 Jan-Feb; 48(1-2):52-8

Presynaptic modulation by noradrenaline and an opioid of the substance P-induced release of [3H]acetylcholine from the myenteric plexus. Vizi ES, et al. **Regul Pept** 1985 Nov 28;12(4):317-25

Influence of serotinin and norepinephrine on flow capacity/pressure characteristics of feline isolated cerebral arteries. Lou HC, et al. **Stroke** 1986 Jan-Feb;17(1):91-4

Neurobiochemical alterations induced by the artificial sweetener aspartame (NutraSweet). Coulombe RA Jr, et al. **Toxicol Appl Pharmacol** 1986 Mar 30;83(1):79-85

[Difference in vasoconstrictor responses of the internal and external carotid arteries to norepinephrine] Kawai Y, et al. **Nippon Heikatsukin Gakkai Zasshi** 1985 Aug;21(4):274-6 **(Jpn)**

[Influence of noradrenaline denervation supersensitivity on urination] Wada T, et al. **Nippon Heikatsukin Gakkai Zasshi** 1985 Aug; 21(4):280-2 **(Jpn)**

[Selected elements of the physiology of physical exertion as the introduction to physiopathology in obstetrics and perinatology. II. Factors of physiological regulation of energy metabolism during physical exertion. Neurohormonal regulation: the adrenergic system] Brodziński W. **Ginekol Pol** 1985 Oct;56(10):585-91 (Eng. Abstr.) **(Pol)**

[Effect of adrenaline and noradrenaline on the vascular antiaggregation activity in cats] Gabrielian ES, et al. **Farmakol Toksikol** 1986 Jan-Feb; 49(1):56-8 (Eng. Abstr.) **(Rus)**

[Experience in analyzing the functional structure of thermogenesis based on pharmacologic testing] Iudanova LA, et al. **Fiziol Zh SSSR** 1986 Jan;72(1):109-15 (Eng. Abstr.) **(Rus)**

[Mechanism of action of noradrenaline on cutaneous thermoreceptors] Kozyreva TV, et al. **Fiziol Zh SSSR** 1985 Nov;71(11):1344-50 (Eng. Abstr.) **(Rus)**

[Role of brain noradrenergic mechanisms in disturbing the circadian rhythm of the functioning hypothalamo-hypophyseo-adrenal cortex system in white rats in early ontogeny] Maslova LN, et al. **Ontogenez** 1986 Jan-Feb;17(1):56-61 (Eng. Abstr.) **(Rus)**

NORTRIPTYLINE

Change in serum antidepressant level at a constant dose of medication [letter] Chisholm DD. **Am J Psychiatry** 1986 Mar;143(3):388

Amitriptyline metabolism: association with debrisoquin hydroxylation in nonsmokers. Mellström B, et al. **Clin Pharmacol Ther** 1986 Apr; 39(4):369-71

Cardiac antiarrhythmic effect of nortriptyline. Madakasira S. **Gen Hosp Psychiatry** 1986 Mar;8(2):123-5

OBSESSIVE-COMPULSIVE DISORDER

High-affinity imipramine binding and serotonin uptake in platelets of eight adolescent and ten adult obsessive-compulsive patients. Weizman A, et al. **Am J Psychiatry** 1986 Mar;143(3):335-9

DDAVP as a possible method to enhance positive benefit of behaviour therapy. Greenberg D, et al. **Br J Psychiatry** 1985 Dec;147:713-5

The Leyton Obsessional Inventory-Child Version. Berg CJ, et al. **J Am Acad Child Psychiatry** 1986 Jan;25(1):84-91

Fluoxetine in the treatment of obsessive compulsive disorder. Fontaine R, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):605-8

ORGANIC MENTAL DISORDERS

[Value of amineptin in the treatment of different depressive states. Apropos of 112 cases treated as part of a national multi-centric study] Marie-Cardine M, et al. **Encephale** 1985 Jul-Aug;11(4):175-7 (Eng. Abstr.) **(Fre)**

OXAZEPAM

The metabolic disposition of oxazepam in rats. Sisenwine SF, et al. **Drug Metab Dispos** 1986 Jan-Feb;14(1):41-5

The behavioral actions of diazepam and oxazepam are similar. Mewaldt SP, et al. **Psychopharmacology (Berlin)** 1986;88(2):165-71

PARASYMPATHOMIMETICS

Cholinergic stimulation of the hypothalamus and natriuresis in rats: role of the renal nerves. Silva-Netto CR, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 2):F322-8

Stimulatory cholinergic effect on the release of antiaggregatory activity into the circulation of cat and man and its modification by beta-adrenergic antagonists. Swies J, et al. **Eur J Clin Invest** 1985 Dec; 15(6):320-6

Phorbol esters mimic some cholinergic actions in hippocampal pyramidal neurons. Malenka RC, et al. **J Neurosci** 1986 Feb;6(2):475-80

Differences between negative chrono-, dromo- and inotropic actions of cholinomimetics in the dog isolated atrium. Kobayashi M, et al. **Jpn Heart J** 1985 Sep;26(5):801-5

Effects of cholinergic drugs on aversive operant behavior induced by dorsal central gray stimulation in rats. Moriyama M, et al. **Jpn J Pharmacol** 1985 Nov;39(3):339-47

Cerebral neocortical neurons in the aged rat: spontaneous activity, properties of pyramidal tract neurons and effect of acetylcholine and cholinergic drugs. Lamour Y, et al. **Neuroscience** 1985 Dec; 16(4):835-44

Microwave facilitation of methylatropine antagonism of central cholinomimetic drug effects. Quock RM, et al. **Radiat Res** 1986 Mar; 105(3):328-40

PARGYLINE

N-dealkylation and N-oxidation of two alpha-methyl-substituted pargyline analogues in rat liver microsomes. Weli AM, et al. **Acta Pharm Suec** 1985;22(5):249-64

Effects of pargyline, reserpine and neurotoxin lesions on [3H]tryptamine binding sites in rat brain. Cascio CS, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):101-5

PEMOLINE

Pemoline and urinary excretion of catecholamines and indoleamines in

children with attention deficit disorder. Zametkin AJ, et al. **Am J Psychiatry** 1986 Mar;143(3):359-62
Pemoline and the prostate [letter] Lindau W, et al. **Lancet** 1986 Mar 29; 1(8483):738

PENTOBARBITAL

Oxygen consumption in fetal lambs after maternal administration of sodium pentobarbital. Rurak DW, et al. **Am J Obstet Gynecol** 1986 Mar;154(3):674-8
Comparison of drug effects on fixed-ratio performance and chain performance maintained under a second-order fixed-ratio schedule. Winsauer PJ, et al. **J Exp Anal Behav** 1985 Nov;44(3):367-76
Sex differences in the induction of physical dependence on pentobarbital in the rat. Suzuki T, et al. **Jpn J Pharmacol** 1985 Dec;39(4):453-9
Effects of methylphenidate and pentobarbital on the spontaneous activity levels of rats with selective hippocampal system damage. Shull RN, et al. **Life Sci** 1986 Mar 24;38(12):1135-41
Effects of diazepam and pentobarbital on discrete lever-press avoidance response in mice: baseline-dependent changes. Kuribara H, et al. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):343-8

PEPTIDES

Cleavage at acyl-proline bonds with sodium in liquid ammonia: application with nanomolar amounts of peptides and separation of products by high-performance liquid chromatography for structural analysis. Hempel J, et al. **Anal Biochem** 1985 Dec;151(2):225-30
Epitope specific immunity elicited by totally synthetic monovalent or polyvalent vaccines. Chedid L, et al. **Ann Sclavo** 1984;1(2):77-85
A rapid, sensitive mass spectrometric method for investigating microscale chemical reactions of surface adsorbed peptides and proteins. Chait BT, et al. **Biochem Biophys Res Commun** 1986 Jan 14;134(1):420-6
Time-resolved fluorescence and 1H NMR studies of tyrosyl residues in oxytocin and small peptides: correlation of NMR-determined conformations of tyrosyl residues and fluorescence decay kinetics. Ross JB, et al. **Biochemistry** 1986 Feb 11;25(3):607-12
Gut peptides in lactation. Holst N, et al. **Br J Obstet Gynaecol** 1986 Feb, 93(2):188-93
Changes in dynorphin, enkephalin and cholecystokinin content of hippocampus and substantia nigra after amygdala kindling. Iadarola MJ, et al. **Brain Res** 1986 Feb 12;365(1):185-91
Interaction of neuropeptides and biogenic amines on cyclic adenosine monophosphate accumulation in hypothalamic nuclei. Redgate ES, et al. **Brain Res** 1986 Feb 12;365(1):61-9
The regulation of the corticomelanotropic cell activity in Aves--II. Effect of various peptides on the release of ACTH from dispersed, perfused duck pituitary cells. Castro MG, et al. **Comp Biochem Physiol** [A] 1986; 83(1):71-5
Opioid potentiated chromatophorotropin regulation of pigment migration in the land crab Gecarcinus lateralis. Martinez EA, et al. **Comp Biochem Physiol** [C] 1986;83(1):77-82
Peptide characterization of secretin preparations. Wolfe MM, et al. **Dig Dis Sci** 1986 Mar;31(3):257-64
Peptide histidine isoleucine amide stimulates thyroid hormone secretion and coexists with vasoactive intestinal polypeptide in intrathyroid nerve fibers from laryngeal ganglia. Grunditz T, et al. **Endocrinology** 1986 Feb;118(2):783-90
Peptides and histamine release from rat peritoneal mast cells. Devillier P, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):89-96
Binding sites for calcium, lipid and p11 on p36, the substrate of retroviral tyrosine-specific protein kinases. Johnsson N, et al. **FEBS Lett** 1986 Mar 31;198(2):361-4
Chemical characterization and opioid activity of an exorphin isolated from in vivo digests of casein. Meisel H. **FEBS Lett** 1986 Feb 17; 196(2):223-7
Effect of inhibition of acid secretion on the regulatory peptides in the rat stomach. Allen JM, et al. **Gastroenterology** 1986 Apr;90(4):970-7
Common patterns of neuroendocrine integration in vertebrates and invertebrates. Acher R. **Gen Comp Endocrinol** 1986 Mar;61(3):452-8
Comparative effects of corticotropin-releasing factor, arginine vasopressin, and related neuropeptides on the secretion of ACTH and alpha-MSH by frog anterior pituitary cells and neurointermediate lobes in vitro. Tonon MC, et al. **Gen Comp Endocrinol** 1986 Mar; 61(3):438-45
Circular dichroism and fluorescence spectroscopic analyses of a proline-rich glycoprotein from human parotid saliva. Loomis RE, et al. **Int J Pept Protein Res** 1985 Dec;26(6):621-9
Inhibitin: a specific inhibitor of sodium/sodium exchange in erythrocytes. Morgan K, et al. **J Clin Invest** 1986 Feb;77(2):538-44
Distribution of immunoreactive somatostatin (ISRIF) in the nervous system of the squid, Loligo pealei. Feldman SC. **J Comp Neurol** 1986 Mar 8;245(2):238-57
Ketomethylene pseudopeptide analogues of substance P: synthesis and biological activity. Ewenson A, et al. **J Med Chem** 1986 Feb; 29(2):295-9
Effects of peptide hormones in urate crystal inflammation. Denko CW, et al. **J Rheumatol** 1985 Oct;12(5):971-5
Stimulation by serotonin of immunoreactive peptide histidine isoleucine release from rat hypothalamus in vitro. Inoue T, et al. **Neurosci Lett** 1986 Feb 14;64(1):17-22
Coexistence of peptide immunoreactivity in sensory neurons of the cat. Leah JD, et al. **Neuroscience** 1985 Nov;16(3):683-90
Peptides of the APUD system in amphibian skins. de Magistris L, et al. **Peptides** 1985;6 Suppl 3:203-8
Peptides as modifiers of Na+-induced pinocytosis in starved Amoeba proteus. Josefsson JO, et al. **Peptides** 1985;6 Suppl 3:485-8
The fish neuropeptide urotensin I: its physiology and pharmacology. Lederis K, et al. **Peptides** 1985;6 Suppl 3:353-61
Effects of sauvagine, urotensin I and CRF on food intake in rats. Negri L, et al. **Peptides** 1985;6 Suppl 3:53-7
Synthesis and biological activity of highly potent octapeptide analogs of somatostatin. Cai RZ, et al. **Proc Natl Acad Sci USA** 1986 Mar; 83(6):1896-900
Pro-opiomelanocortin-related peptides in cerebrospinal fluid: a study of manic-depressive disorder. Berrettini WH, et al. **Psychiatry Res** 1985 Dec;16(4):287-302
Permeability of the blood-brain barrier to neuropeptides: the case for penetration. Banks WA, et al. **Psychoneuroendocrinology** 1985; 10(4):385-99
Generation of anaphylatoxin activity related to C3a, by treatment of human serum with the nitrogen nucleophile N2H4 or the chaotrope KSCN. von Zabern I, et al. **Scand J Immunol** 1985 Dec; 22(6):639-51
Stimulation of gonadotropin release by a non-GnRH peptide sequence of the GnRH precursor. Millar RP, et al. **Science** 1986 Apr 4; 232(4746):68-70
[Very high efficiency chromatography of peptides] Sasagawa T, et al. **Tanpakushitsu Kakusan Koso** 1985 Nov;30(12):1320-35 (167 ref.) **(Jpn)**
[Peptide factors of gonadal autoregulation] Neamţu C. **Rev Med Chir Soc Med Nat Iasi** 1985 Jul-Sep;89(3):542-4 (0 ref.) **(Rum)**
[Enzymatic synthesis of peptides] Mitin IuV. **Antibiot Med Biotekhnol** 1986 Feb;31(2):93-8 (Eng. Abstr.) **(Rus)**
[Response of the secretory glands of the stomach to peptide injection into the hypothalamus, caudate nucleus and amygdala] Barashkova GM, et al. **Fiziol Zh SSSR** 1985 Dec;71(12):1513-20 (Eng. Abstr.) **(Rus)**
[Hypothalamic monoamines and nonapeptides in the regulation of thyroid function in the early ontogeny of birds] Karpezo NA, et al. **Ontogenez** 1985 Nov-Dec;16(6):589-96 (Eng. Abstr.) **(Rus)**

PERPHENAZINE

Liquid chromatographic method for perphenazine and its sulfoxide in pharmaceutical dosage forms for determination of stability. Beaulieu N, et al. **J Assoc Off Anal Chem** 1986 Jan-Feb;69(1):167-9

PERSONALITY ASSESSMENT

Rating scales and checklists for child psychopharmacology. Conners CK, et al. **Psychopharmacol Bull** 1985;21(4):809-43

PERSONALITY DISORDERS

Positive effects of carbamazepine on behavioral dyscontrol in borderline personality disorder. Gardner DL, et al. **Am J Psychiatry** 1986 Apr; 143(4):519-22
Clonazepam: a novel therapeutic adjunct. Freinhar JP, et al. **Int J Psychiatry Med** 1985-86;15(4):321-8

PERSONALITY INVENTORY

The Leyton Obsessional Inventory-Child Version. Berg CJ, et al. **J Am Acad Child Psychiatry** 1986 Jan;25(1):84-91
Scales of potential use in the psychopharmacologic treatment of depressed children and adolescents. Petti TA. **Psychopharmacol Bull** 1985; 21(4):951-77

PHENCYCLIDINE

Place-aversion conditioned by phencyclidine in rats: development of tolerance and pharmacologic antagonism. Iwamoto ET. **Alcohol Drug Res** 1985-86;6(4):265-76
A caution against use of verapamil in phencyclidine intoxication [letter] McCann DJ, et al. **Am J Psychiatry** 1986 May;143(5):679
Identification of polypeptides of the phencyclidine receptor of rat hippocampus by photoaffinity labeling with [3H]azidophencyclidine. Haring R, et al. **Biochemistry** 1986 Feb 11;25(3):612-20
Right to healthy birth: medico-legal issues in phencyclidine ingestion. Kaufman KR, et al. **Child Abuse Negl** 1986;10(1):41-4
Phencyclidine-specific Fab fragments alter phencyclidine disposition in dogs. Owens SM, et al. **Drug Metab Dispos** 1986 Jan-Feb; 14(1):52-8
Anticonvulsant properties of phencyclidine-like drugs in mice. Hayes BA,

et al. **Eur J Pharmacol** 1985 Oct 29;117(1):121-5

Treatment of depression in chronic cocaine and phencyclidine abuse with desipramine. Giannini AJ, et al. **J Clin Pharmacol** 1986 Mar; 26(3):211-4

Extended EMIT-DAU phencyclidine screen. Ragan FA Jr, et al. **J Clin Psychiatry** 1986 Apr;47(4):194-5

Comparison of drug effects on fixed-ratio performance and chain performance maintained under a second-order fixed-ratio schedule. Winsauer PJ, et al. **J Exp Anal Behav** 1985 Nov;44(3):367-76

Acetylcholine synthesis and release by a sympathetic ganglion in the presence of 2-(4-phenylpiperidino) cyclohexanol (AH5183). Collier B, et al. **J Neurochem** 1986 Mar;46(3):822-30

A review of thirty cases of rhabdomyolysis-associated acute renal failure among phencyclidine users. Patel R, et al. **J Toxicol Clin Toxicol** 1985-86;23(7-8):547-56

Behavioral and receptor binding studies of phencyclidine (PCP) and lithium interaction in the rat. Mattia A, et al. **Life Sci** 1986 Mar 17; 38(11):975-84

Quinacrine and 2-(4-phenylpiperidino)cyclohexanol (AH5183) inhibit acetylcholine release and synthesis in rat brain slices. Jope RS, et al. **Mol Pharmacol** 1986 Jan;29(1):45-51

A parametric study of the behavioral effects of phencyclidine in adult cats. Levine MS, et al. **Neuropharmacology** 1985 Dec;24(12):1181-5

A comparison of the discriminative stimulus properties of phencyclidine, given intraperitoneally or intraventricularly in rats. Slifer BL, et al. **Neuropharmacology** 1985 Dec;24(12):1175-9

2-(4-phenylpiperidino) cyclohexanol (AH5183) decreases quantal size at the frog neuromuscular junction. Van der Kloot W. **Pflugers Arch** 1986 Jan;406(1):83-5

Effects of phencyclidine, N-allyl-N-normetazocine (SKF-10,047), and verapamil on performance in a radial maze. McCann DJ, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):187-91

Structure-activity relationships of phencyclidine derivatives in rat cerebellum. Pang K, et al. **Pharmacol Biochem Behav** 1986 Jan; 24(1):127-34

Demonstration of a receptor in Torpedo synaptic vesicles for the acetylcholine storage blocker L-trans-2-(4-phenyl[3,4-3H]-piperidino) cyclohexanol. Bahr BA, et al. **Proc Natl Acad Sci USA** 1986 Apr; 83(7):2267-70

[Phencyclidine: behavioral effects and molecular targets] Vignon J. **Biochimie** 1985 Sep;67(9):XI-XVI **(Fre)**

[Identification of psychotropic drugs. IV. Analysis of phencyclidine and its analogues] Shimamine M, et al. **Eisei Shikenjo Hokoku** 1985; (103):93-6 (Eng. Abstr.) **(Jpn)**

PHENCYCLIDINE ABUSE

Extended EMIT-DAU phencyclidine screen. Ragan FA Jr, et al. **J Clin Psychiatry** 1986 Apr;47(4):194-5

PHENELZINE

Phenelzine poisoning. Breheny FX, et al. **Anaesthesia** 1986 Jan; 41(1):53-6

Phenelzine overdose treated with dantrolene sodium. Kaplan RF, et al. **JAMA** 1986 Feb 7;255(5):642-4

PHENETHYLAMINES

Pemoline and urinary excretion of catecholamines and indoleamines in children with attention deficit disorder. Zametkin AJ, et al. **Am J Psychiatry** 1986 Mar;143(3):359-62

Determination of beta-phenylethylamine concentrations in human plasma, platelets, and urine and in animal tissues by high-performance liquid chromatography with fluorometric detection. Tsuji M, et al. **Anal Biochem** 1986 Feb 15;153(1):116-20

The effect of repeated administration of (-) deprenyl on the phenylethylamine-induced stereotypy in rats. Timár J, et al. **Arch Int Pharmacodyn Ther** 1986 Jan;279(1):50-60

Effects of substituted phenylethylamines on blowfly feeding behavior. Long TF, et al. **Comp Biochem Physiol [C]** 1986;83(1):201-9

In vivo voltammetry in the suprachiasmatic nucleus of the rat: effects of RU24969, methiothepin and ketanserin. Martin KF, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):135-9

Synthesis, identification, and acute toxicity of alpha-benzylphenethylamine and alpha-benzyl-N-methylphenethylamine. Contaminants in clandestine preparation of amphetamine and methamphetamine. Noggle FT Jr, et al. **J Assoc Off Anal Chem** 1985 Nov-Dec;68(6):1213-22

Clinical studies on the phenylethylamine hypothesis of affective disorder: urine and blood phenylacetic acid and phenylalanine dietary supplements. Sabelli HC, et al. **J Clin Psychiatry** 1986 Feb; 47(2):66-70

Presynaptic alpha-2 adrenoceptor activation and coupling of the receptor-presynaptic effector system in the perfused rat heart: affinity and efficacy of phenethylamines and imidazoline derivatives. Fuder H, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):237-45

Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. Young R, et al. **Med Res Rev** 1986 Jan-Mar; 6(1):99-130 (74 ref.)

Effects of a monoamine oxidase A inhibitor, FLA 668 (+) on the adrenergic mechanisms of the dog saphenous vein. Caramona MM, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):181-5

The functional consequences of inhibition of monoamine oxidase type B: comparison of the pharmacological properties of L-deprenyl and MDL 72145. Fozard JR, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):186-93

Selective inhibition of monoamine oxidase by p-aminosubstituted phenylalkylamines in catecholaminergic neurones. Ask AL, et al **Neuropharmacology** 1986 Jan;25(1):33-40

Inhibition of monoamine oxidase A-form and semicarbazide-sensitive amine oxidase by selective and reversible monoamine oxidase-A inhibitors, amiflamine and FLA 788(+). Morikawa F, et al. **Pharmacology** 1986;32(1):38-45

WHO Expert Committee on Drug Dependence. Twenty-second report. **WHO Tech Rep Ser** 1985;729:1-31

Metabolism of deprenyl, a selective monoamine oxidase (MAO) B inhibitor in rat: relationship of metabolism to MAO-B inhibitory potency. Yoshida T, et al. **Xenobiotica** 1986 Feb;16(2):129-36

[Baygon (2-isopropoxyphenyl-N-methyl carbamate) activation of enzymatic deamination of 2-phenyl-ethylamine] Zeinalov TA. **Vopr Med Khim** 1985 Sep-Oct;31(5):60-4 (Eng. Abstr.) **(Rus)**

PHENOBARBITAL

Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection. Nahata MC, et al. **Am J Hosp Pharm** 1986 Feb; 43(2):384-5

Effects of phenobarbital treatment on 3-methylindole toxicosis in ponies. Turk MA, et al. **Am J Vet Res** 1986 Apr;47(4):901-5

Effect of butalbital and phenobarbital pretreatment on antipyrine clearance in the rat. Tse FL, et al. **Arch Int Pharmacodyn Ther** 1986 Feb; 279(2):181-94

Substrate and phenobarbital induction of the biliary excretion of exogenous organic anions in rats. Fischer E, et al. **Arch Toxicol [Suppl]** 1985;8:345-7

Increased response of cytochrome P-450 dependent biotransformation reactions in rat liver to repeated administration of inducers. Kleeberg U, et al. **Arch Toxicol [Suppl]** 1985;8:361-5

Chronic treatment with phenobarbital decreases the expression of rat liver EGF and insulin receptors. Hwang DL, et al. **Biochem Biophys Res Commun** 1986 Mar 13;135(2):501-6

Induction of alpha 2u globulin mRNA by phenobarbital in rat liver: characterization of a cDNA clone. Osorio-Almeida ML, et al. **Biochem Biophys Res Commun** 1986 Feb 13;134(3):1182-9

Identification of human cytochromes P-450 analogous to forms induced by phenobarbital and 3-methylcholanthrene in the rat. Adams DJ, et al. **Biochem J** 1985 Dec 15;232(3):869-76

Studies on rat liver cytochrome P-450s involved in the metabolism of antipyrine: phenobarbital- and 3-methylcholanthrene-inducible isozymes possessing 4-hydroxylase activity. Buppodom P, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1404-6

Induction of UDP-glucuronyl transferase mRNA in embryonic chick livers by phenobarbital. Jackson MR, et al. **Biochem Pharmacol** 1986 Apr 1;35(7):1191-8

Effect of phenobarbital on the oligosaccharide structure of rat alpha-acid glycoprotein. Monnet D, et al. **Biochim Biophys Acta** 1986 Mar 19; 881(1):10-4

Effects of phenobarbital steady state levels on antipyrine clearance and distribution in the rat. Pei YY, et al. **Biopharm Drug Dispos** 1986 Jan-Feb;7(1):11-9

The phenotypic stability of altered hepatic foci: effect of the short-term withdrawal of phenobarbital and of the long-term feeding of purified diets after the withdrawal of phenobarbital. Glauert HP, et al. **Carcinogenesis** 1986 Jan;7(1):117-21

Results of spin immunoassay for simultaneous measurement of phenytoin and phenobarbital in serum compared with those of liquid chromatography. Sayo H, et al. **Chem Pharm Bull (Tokyo)** 1985 Jul; 33(7):2866-70

A comparison of the toxicity effects of the anticonvulsant eterobarb (antilon, DMMP) and phenobarbital in normal human volunteers. Smith DB, et al. **Epilepsia** 1986 Mar-Apr;27(2):149-55

Synthesis and pharmacological properties of N,N'-bis-acylderivatives of phenobarbital. Cid E, et al. **Farmaco [Prat]** 1986 Jan;41(1):36-40

Cytochrome P-450-dependent H2O2 production demonstrated in vivo. Influence of phenobarbital and allylisopropylacetamide. Premereur N, et al. **FEBS Lett** 1986 Apr 7;199(1):19-22

Complete amino acid sequence of a cytochrome P-450 isolated from beta-naphthoflavone-induced rabbit liver microsomes. Comparison with phenobarbital-induced and constitutive isozymes and identification of invariant residues. Ozols J. **J Biol Chem** 1986 Mar 25; 261(9):3965-79

Phenobarbitone enhances [35S]TBPS binding to extensively washed rat cortical membranes. Honoré T, et al. **J Pharm Pharmacol** 1985 Dec;

37(12):928-9

Rates of progesterone oxidation by rabbit liver microsomes before and after phenobarbitone treatment. Senciall IR, et al. **J Steroid Biochem** 1985 Dec;23(6A):1007-12

Effect of estrogen, testosterone, and phenobarbital on uterine weight and liver microsomal enzymes in prepuberal mice. Robl JM, et al. **Pediatr Pharmacol (New York)** 1985;5(3):157-64

Comparison of in vivo and in vitro methods for assessing the effects of phenobarbital on the hepatic drug-metabolizing enzyme system. Chadwick RW, et al. **Toxicol Lett** 1985 Dec;29(2-3):95-105

Induction of renal and hepatic mixed function oxidases in the hamster and guinea pig. Smith JH, et al. **Toxicology** 1986 Feb;38(2):209-18

[Effect of phenobarbital on the kinetics of the change in the level of paramagnetic metalloprotein complexes in dinitrophenol poisoning] Luk'ianchuk VD. **Farmakol Toksikol** 1985 Nov-Dec;48(6):102-4 (Eng. Abstr.) **(Rus)**

[Comparative study of the effect of zixoryn and phenobarbital on the toxicity of anthracycline antibiotics and liver monooxygenase activity in mice] Bogush TA, et al. **Vestn Akad Med Nauk SSSR** 1985;(11):82-6 (Eng. Abstr.) **(Rus)**

[Activity of the liver monooxygenase system after induction with phenobarbital in the early neonatal period] Guliaeva LF, et al. **Vopr Med Khim** 1985 Sep-Oct;31(5):49-53 (Eng. Abstr.) **(Rus)**

PHENOTHIAZINE TRANQUILIZERS

Flow injection analysis of three N-substituted phenothiazine drugs with amperometric detection at a carbon fibre array electrode. Belal F, et al. **Analyst** 1985 Dec;110(12):1493-6

Phenothiazine drugs and metabolites: molecular conformation and dopaminergic, alpha adrenergic and muscarinic cholinergic receptor binding. Dahl SG, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1263-9

Effects of phenothiazines on cultured retinal pigment epithelial cells. Matsumura M, et al. **Ophthalmic Res** 1986;18(1):47-54

PHENOTHIAZINES

Differential inotropic actions of ethmozine and ethacizin (diethylamine analog of ethmozine). Urthaler F, et al. **Am Heart J** 1986 Mar;111(3):462-5

[Quantitative determination of fluoracizine in biological material] Nikolaeva EG. **Sud Med Ekspert** 1986 Jan-Mar;29(1):46-7 (Eng. Abstr.) **(Rus)**

[Isolation and detection of fluoracizine in biological material] Nikolaeva G. **Sud Med Ekspert** 1986 Jan-Mar;29(1):42-3 (Eng. Abstr.) **(Rus)**

PHENOXYBENZAMINE

Recovery of pulsatile luteinizing hormone secretion following permanent disruption of the ascending noradrenergic fiber tract in the ovariectomized rat. Clifton DK, et al. **Biol Reprod** 1985 Nov;33(4):808-14

Phenoxybenzamine partially inhibits alpha 2-adrenoceptors without affecting their presynaptic function. McKernan RM, et al. **Neuropharmacology** 1986 Jan;25(1):47-52

PHENYLALANINE

The effects of amino acids on protein degradation and translocation of non-histone proteins to the nucleus in lymphocytes. Polet H, et al. **Biochim Biophys Acta** 1986 Apr 8;886(1):33-9

Formation of m-tyrosine and o-tyrosine from L-phenylalanine in various tissues of rats. Ishimitsu S, et al. **Chem Pharm Bull (Tokyo)** 1985 Sep;33(9):3887-92

Aromatic amino acid requirement of the lactating sow. Lellis WA, et al. **J Anim Sci** 1985 Dec;61(6):1448-53

Clinical studies on the phenylethylamine hypothesis of affective disorder: urine and blood phenylacetic acid and phenylalanine dietary supplements. Sabelli HC, et al. **J Clin Psychiatry** 1986 Feb;47(2):66-70

PHENYLPROPANOLAMINE

Elimination of labetalol-induced false positives in drug analyses [letter] Wu A, et al. **Clin Chem** 1986 Feb;32(2):407

Phenylpropanolamine and blood pressure [letter] Morgan JP, et al. **Clin Pharmacol Ther** 1986 Jan;39(1):102-3

Clinical response and urethral pressure profile changes after phenylpropanolamine in dogs with primary sphincter incompetence. Richter KP, et al. **J Am Vet Med Assoc** 1985 Sep 15;187(6):605-11

Leukocytosis following intravenous phenylpropanolamine use--possible association. Paulman PM, et al. **Nebr Med J** 1986 Feb;71(2):40-1

PHENYTOIN

Metabolic effects of phenytoin toxicity [letter] Wagner KJ, et al. **Ann Emerg Med** 1986 Apr;15(4):509-10

Inability of ibuprofen to alter single dose phenytoin disposition. Bachmann KA, et al. **Br J Clin Pharmacol** 1986 Feb;21(2):165-9

Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. Cohen AF, et al. **Br J Clin Pharmacol** 1985 Dec;20(6):619-29

Antipyrine metabolite kinetics in healthy human volunteers during multiple dosing of phenytoin and carbamazepine. Shaw PN, et al. **Br J Clin Pharmacol** 1985 Dec;20(6):611-8

Results of spin immunoassay for simultaneous measurement of phenytoin and phenobarbital in serum compared with those of liquid chromatography. Sayo H, et al. **Chem Pharm Bull (Tokyo)** 1985 Jul;33(7):2866-70

Influence of bile on the gastrointestinal absorption of phenytoin in rats. Shinkuma D, et al. **Chem Pharm Bull (Tokyo)** 1985 Nov;33(11):5023-7

Comparison of the effects of sesame oil and oleic acid as suspension vehicles on gastrointestinal absorption of phenytoin in rats. Shinkuma D, et al. **Chem Pharm Bull (Tokyo)** 1985 Nov;33(11):4989-94

Influence of vehicle on gastrointestinal absorption of phenytoin in rats. Shinkuma D, et al. **Chem Pharm Bull (Tokyo)** 1985 Nov;33(11):4981-8

The Ames Seralyzer Reagent Strip System evaluated for measuring serum phenytoin. Mace PF, et al. **Clin Chem** 1986 Feb;32(2):391

Alternative method for predicting phenytoin levels [letter] Jochsberger T. **Drug Intell Clin Pharm** 1986 Feb;20(2):155-6

Hypolipidemic activity of antiepileptic 5-phenylhydantoins in mice. Maguire JH, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):135-8

Gingival growths. Miller AS, et al. **Gen Dent** 1986 Jan-Feb;34(1):60, 62

Proteoglycans and glycosaminoglycans in phenytoin-induced gingival overgrowth. Dahllöf G, et al. **J Periodont Res** 1986 Jan;21(1):13-21

Storage of phenytoin capsules [letter] Martin ED, et al. **Med J Aust** 1985 Dec 9-23;143(12-13):634-5

Electrophysiological interactions between quinidine-lidocaine and quinidine-phenytoin in guinea-pig papillary muscle. Sánchez-Chapula J. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Dec;331(4):369-75

The pharmacokinetics of phenytoin in perfused human placenta. Shah YG, et al. **Pediatr Pharmacol (New York)** 1985;5(3):165-79

Perinatal induction of hepatic aminopyrine N-demethylase by maternal exposure to phenytoin. Shapiro BH, et al. **Pediatr Pharmacol (New York)** 1985;5(3):201-7

[Interaction between diazoxide and phenytoin (letter)] Turck D, et al. **Presse Med** 1986 Jan 11;15(1):31 **(Fre)**

[Cerebellar injury caused by phenytoin] Bechinger D, et al. **Dtsch Med Wochenschr** 1986 Feb 7;111(6):237-8 **(Ger)**

[Determination of the active substance of a rovral preparation in biosubstrates] Dzhagatspanian SA, et al. **Gig Sanit** 1986 Jan;(1):58-60 **(Rus)**

PHOBIC DISORDERS

Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks. A double-blind comparison of zimeldine, imipramine and placebo. Evans L, et al. **Acta Psychiatr Scand** 1986 Jan;73(1):49-53

CO2 inhalation in the treatment of panic attacks. Griez E, et al. **Behav Res Ther** 1986;24(2):145-50

The effect of phobic anxiety on plasma beta-endorphin: a single-subject experiment. Thyer BA, et al. **Behav Res Ther** 1986;24(2):237-41

DDAVP as a possible method to enhance positive benefit of behaviour therapy. Greenberg D, et al. **Br J Psychiatry** 1985 Dec;147:713-5

Agoraphobia: relative and combined effectiveness of therapist-assisted in vivo exposure and imipramine. Mavissakalian M, et al. **J Clin Psychiatry** 1986 Mar;47(3):117-22

Urinary norepinephrine excretion in panic and phobic disorders. Dajas F, et al. **J Neural Transm** 1986;65(1):75-81

Clonazepam for panic disorders and agitation. Fontaine R. **Psychosomatics** 1985 Dec;26(12 Suppl):13-8

Disabling fear of AIDS responsive to imipramine. Jenike MA, et al. **Psychosomatics** 1986 Feb;27(2):143-4

PHYSOSTIGMINE

On acute effects of some drugs on the higher nervous activity in man. Scopolamine (0.6 mg), physostigmine (1.0 mg) and their interaction. Part LIII. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:185-226

Effects of scopolamine (0.6 mg), physostigmine (1.0 mg), and their complex on the blood pressure, the body temperature and the heart rate in man. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:279-94

Effects of physostigmine doses (0.1 mg, 0.3 mg, 0.6 mg) on the blood pressure, the body temperature and the heart rate in man. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:263-77

On acute effects of some drugs on the higher nervous activity in man. Physostigmine (0.1 mg, 0.3 mg, 0.6 mg). Part LIV. Hrbek J, et al. **Acta Univ Palacki Olomuc Fac Med** 1985;112:227-62

Mechanism of antagonism by physostigmine of acute flunitrazepam intoxication. Vatashsky E, et al. **Anesthesiology** 1986 Feb; 64(2):248-52

Pharmacokinetics of biliary excretion of physostigmine in rat. Boyer AW, et al. **Arch Int Pharmacodyn Ther** 1985 Dec;278(2):180-92

The effects of physostigmine and scopolamine on recognition memory in monkeys. Aigner TG, et al. **Behav Neural Biol** 1986 Jan; 45(1):81-7

High-affinity hemicholinium-3 binding to brain membranes: reduction by treatment with physostigmine in vivo. Swann AC, et al. **Brain Res** 1986 Jan 22;363(2):401-3

Urinary pharmacokinetics of physostigmine in the rat. Somani SM, et al. **Eur J Drug Metab Pharmacokinet** 1985 Oct-Dec;10(4):343-7

Protection from quinidine or physostigmine against in vitro inhibition by sarin of acetylcholinesterase activity. Singh AK, et al. **Life Sci** 1986 Jan 13;38(2):165-72

Acute effects of physostigmine and neostigmine in man. Janowsky DS, et al. **Milit Med** 1986 Jan;151(1):48-51

[Physostigmine salicylate therapy of poisoning due to anticholinergic substances] Albrecht K, et al. **Anaesthesiol Reanim** 1985;10(3):145-54 (Eng. Abstr.) **(Ger)**

[A further therapeutic possibility in sudden deafness] Görisch I, et al. **Z Arztl Fortbild (Jena)** 1986;80(2):69-70 **(Ger)**

PILOCARPINE

Individual responsiveness to topical pilocarpine and the effects of variations in application technique. Berggren L. **Acta Ophthalmol (Copenh)** 1985 Dec;63(6):642-6

Stability of pilocarpine hydrochloride and pilocarpine nitrate ophthalmic solutions submitted by U.S. hospitals. Kreienbaum MA, et al. **Am J Hosp Pharm** 1986 Jan;43(1):109-17

Pilocarpine and physostigmine attenuate spatial memory impairments produced by lesions of the nucleus basalis magnocellularis. Murray CL, et al. **Behav Neurosci** 1986 Feb;100(1):23-32

The secretory activity of rat nasal glands and the effect of cholinergic drugs. Klaassen AB, et al. **Cell Tissue Res** 1986;243(3):655-9

Multiple agonist binding sites of muscarinic acetylcholine receptors and their relation to the negative inotropic action of agonists in guinea-pig heart. Mizushima A, et al. **Eur J Pharmacol** 1985 Dec 17; 119(3):177-82

Pilocarpine prodrugs I. Synthesis, physicochemical properties and kinetics of lactonization of pilocarpic acid esters. Bundgaard H, et al. **J Pharm Sci** 1986 Jan;75(1):36-43

[The effect of adrenaline, pilocarpine and timolol on axoplasmic transport in the optic nerve. I. Findings in normotensive eyes] Brožek B, et al. **Cesk Oftalmol** 1985 Feb;41(1):13-6 (Eng. Abstr.) **(Cze)**

[Determination of pilocarpine and isopilocarpine by high performance liquid chromatography in normal phase. The stability of eye drops with a pilocarpine base and comparison of this method with a colorimetric method using hydroxylamine] Balansard G, et al. **Pharm Acta Helv** 1986; 61(2):47-50 (Eng. Abstr.) **(Fre)**

[Metabolism of pilocarpine in the rabbit eye following local administration] Schmitz J, et al. **Fortschr Ophthalmol** 1985; 82(6):613-7 (Eng. Abstr.) **(Ger)**

PITUITARY HORMONE RELEASING HORMONES

Short-term effects of oestradiol and 4-hydroxyoestradiol on gonadotrophin-releasing hormone induced luteinizing hormone secretion by rat pituitary cells in culture. Emons G, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):312-20

Acute effects of GnRF-induced gonadotrophin secretion upon ovarian steroid secretion in the ferret. Matson C, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):373-7

Gonadotropin-releasing hormone in practice [letter] Ory SJ, et al. **Arch Intern Med** 1986 Apr;146(4):804

Mapping of gonadotropin-releasing hormone receptor binding site. Keinan D, et al. **Biochemistry** 1985 Dec 17;24(26):7728-32

The molecular basis of gonadotropin-releasing hormone action. Conn PM. **Endocr Rev** 1986 Feb;7(1):3-10 (71 ref.)

Induction of ovulation in primate models. Kenigsberg D, et al. **Endocr Rev** 1986 Feb;7(1):34-43 (45 ref.)

Gonadal regulation of hypothalamic gonadotropin-releasing hormone release in primates. Plant TM. **Endocr Rev** 1986 Feb;7(1):75-88 (103 ref.)

Plasma beta-endorphin levels in anovulatory states: changes after treatments for the induction of ovulation. Petraglia F, et al. **Fertil Steril** 1986 Feb;45(2):185-90

Activity of gonadotropin-releasing hormone neurons during the preovulatory luteinizing hormone surge. Steele PA, et al. **Fertil Steril** 1986 Feb;45(2):179-84

Primary structure of gonadotropin-releasing hormone from lamprey brain. Sherwood NM, et al. **J Biol Chem** 1986 Apr 15;261(11):4812-9

Testosterone maintains pituitary and serum FSH and spermatogenesis in gonadotrophin-releasing hormone antagonist-suppressed rats. Rea MA, et al. **J Endocrinol** 1986 Jan;108(1):101-7

Progesterone pretreatment has a direct effect on GnRH-induced preovulatory follicles to determine their ability to develop into normal corpora lutea in anoestrous ewes. Hunter MG, et al. **J Reprod Fertil** 1986 Jan;76(1):349-63

Effects of age and photoperiod on the responsiveness of the pituitary gland of the vole (Microtus agrestis) to stimulation by GnRH. Kinch RF, et al. **J Reprod Fertil** 1986 Jan;76(1):75-82

Relationship between pituitary GnRH-binding sites and pituitary release of gonadotrophins in post-partum beef cows. Leung K, et al. **J Reprod Fertil** 1986 Jan;76(1):53-63

Hormonal therapy of cryptorchidism. A randomized, double-blind study comparing human chorionic gonadotropin and gonadotropin-releasing hormone. Rajfer J, et al. **N Engl J Med** 1986 Feb 20;314(8):466-70

GnRH release from the mediobasal hypothalamus. In vitro regulation by oxytocin. Gambacciani M, et al. **Neuroendocrinology** 1986; 42(2):181-3

Monitoring gonadotropin-releasing hormone administration by measurement of urinary steroid conjugates. De Vane GW, et al. **Obstet Gynecol** 1986 May;67(5):710-7

Hormonal treatment of undescended testis. Toublanc JE. **Prog Clin Biol Res** 1985;203:207-11

[Dose-effect study of Berlin-Chemie's GnRHvet in castrated heifers by luteinizing hormone detection] Schneider F, et al. **Arch Exp Veterinarmed** 1985 Nov;39(6):894-900 (Eng. Abstr.) **(Ger)**

[Restoration of pituitary-ovarian function by pulsatile administration of GnRH during the early puerperium] Masaoka K, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Nov 20;61(11):1239-48 (Eng. Abstr.) **(Jpn)**

PITUITARY HORMONES

The effect of training on responses of beta-endorphin and other pituitary hormones to insulin-induced hypoglycemia. Mikines KJ, et al. **Eur J Appl Physiol** 1985;54(5):476-9

Alternative routes of peptide hormone administration. Pontiroli AE, et al. **Spec Top Endocrinol Metab** 1985;7:77-99 (120 ref.)

[Mechanisms of action of beta-endorphin on the secretion of hypophyseal hormones] Slavnov VN, et al. **Probl Endokrinol (Mosk)** 1986 Jan-Feb; 32(1):49-52 (Eng. Abstr.) **(Rus)**

PITUITARY HORMONES, ANTERIOR

Responses of plasma adrenocorticotropin and cortisol to intravenous injection of synthetic ovine corticotropin releasing factor in the morning and early evening in normal human subjects. Watabe T, et al. **Endocrinol Jpn** 1985 Oct;32(5):771-9

Effects of gamma-aminobutyric acid receptor agonists on the secretion of growth hormone, luteinizing hormone, adrenocorticotrophic hormone and thyroid-stimulating hormone from the rat pituitary gland in vitro. Anderson RA, et al. **J Endocrinol** 1986 Jan;108(1):1-8

Sulfated LH subunits and a tyrosine-sulfated secretory protein (secretogranin II) in female rat adenohypophyses: changes with age and stimulation of release by LHRH. Cozzi MG, et al. **Mol Cell Endocrinol** 1986 Jan;44(1):47-54

Neurotransmitter regulation of anterior pituitary hormones. Tuomisto J, et al. **Pharmacol Rev** 1985 Sep;37(3):249-332 (1515 ref.)

PROGESTERONE

Prepubertal rat ovary: hormonal modulation of beta-adrenergic receptors and of progesterone response to adrenergic stimulation. Aguado LI, et al. **Biol Reprod** 1986 Feb;34(1):45-50

Gonadotropin-releasing hormone effects on placental hormones during gestation: II. Progesterone, estrone, estradiol and estriol. Siler-Khodr TM, et al. **Biol Reprod** 1986 Mar;34(2):255-64

Androgen and progesterone effects on follicle-stimulating hormone and luteinizing hormone secretion in anestrous mares. Thompson DL Jr, et al. **Biol Reprod** 1986 Feb;34(1):51-7

Hypothalamic site of progesterone action on gonadotropin release. Hanker JP, et al. **Horm Metab Res** 1985 Dec;17(12):679-82

Serum inflammatory responses of transcortin binding activities and of total and free corticosterone and progesterone levels in developing rats: a kinetic approach. Savu L, et al. **Int J Tissue React** 1985;7(6):443-8

Serotonin-induced stimulation of progesterone production by cow luteal cells in vitro. Battista PJ, et al. **J Reprod Fertil** 1986 Jan; 76(1):231-8

Progesterone pretreatment has a direct effect on GnRH-induced preovulatory follicles to determine their ability to develop into normal corpora lutea in anoestrous ewes. Hunter MG, et al. **J Reprod Fertil** 1986 Jan;76(1):349-63

The antiprogesterone steroid RU-486 does not impair gonadotropin-stimulated luteal adenylyl cyclase activity or gonadotropin release by pituitary cells. Rojas FJ, et al. **J Steroid Biochem** 1985 Dec;23(6A):1053-8

Rates of progesterone oxidation by rabbit liver microsomes before and after phenobarbitone treatment. Senciall IR, et al.

J Steroid Biochem 1985 Dec;23(6A):1007-12

Effect of ovarian steroids to stimulate region-specific hypothalamic 5-hydroxytryptamine synthesis in ovariectomized rats. King TS, et al. **Neuroendocrinology** 1986;42(4):344-50

Regulating estrus and therapy of repeat-breeder and anestrous Holstein heifers using progesterone releasing intravaginal devices (PRIDs). Fukui Y, et al. **Nippon Juigaku Zasshi** 1985 Dec;47(6):943-50

[The effect of sex factors on the interaction of progesterone and glucocorticoids during increased tyrosine aminotransferase and tryptophane pyrrolase activity in the liver in rats] Németh S. **Bratisl Lek Listy** 1986 Jan;85(1):19-23 (Eng. Abstr.) **(Slo)**

PROLACTIN

Effects of prolactin administration on the zona glomerulosa of the rat adrenal cortex: stereology and plasma hormone concentrations. Mazzocchi G, et al. **Acta Endocrinol (Copenh)** 1986 Jan;111(1):101-5

ACTH and prolactin deficiency. Puig ML, et al. **Acta Endocrinol (Copenh)** 1986 Mar;111(3):296-9

Influence of sequential doses of 5-hydroxytryptophan on prolactin release. Sueldo CE, et al. **Am J Obstet Gynecol** 1986 Feb;154(2):424-7

A possible role of arachidonate metabolism in the mechanism of prolactin release. Judd AM, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):E288-95

Effect of amphetamine on brain catecholamines, brain beta-endorphin, serum prolactin, catechol-O-methyltransferase and monoamine oxidase of various organs in the rat. Agarwal DP, et al. **Arzneimittelforschung** 1985;35(11):1639-42

Changes in growth hormone and prolactin release after superior cervical ganglionectomy of rats. Cardinali DP, et al. **Brain Res** 1986 Jan 22; 363(2):350-3

T-cell dysregulation in patients with hyperprolactinemia: effect of bromocriptine treatment. Vidaller A, et al. **Clin Immunol Immunopathol** 1986 Mar;38(3):337-43

Effects of phorbol ester on GH, TSH and PRL release by superfused rat adenohypophysis. Ikeda H, et al. **Endocrinol Jpn** 1985 Oct; 32(5):759-65

Prolactin release after 5-hydroxytryptophan treatment requires an intact neurointermediate pituitary lobe. Johnston CA, et al. **Endocrinology** 1986 Feb;118(2):805-10

Maturation of the prolactin and proopiomelanocortin-derived peptide responses to ether stress and morphine: neurochemical analysis. Johnston CA, et al. **Endocrinology** 1986 Feb;118(2):797-804

Prolactin (PRL), follicle-stimulating hormone, and luteinizing hormone are regulators of testicular PRL receptors in golden hamsters. Klemcke HG, et al. **Endocrinology** 1986 Feb;118(2):773-82

Effects of hyperprolactinemia on estrous cyclicity, serum luteinizing hormone, prolactin, estradiol, and progesterone concentrations, and catecholamine activity in microdissected brain areas. Wise PM. **Endocrinology** 1986 Mar;118(3):1237-45

Synthetic human growth hormone releasing factor (h-GRF-1-44-NH2) dose response effect on growth hormone and prolactin secretion in healthy adult men. Boissel JP, et al. **Eur J Clin Pharmacol** 1986; 29(5):609-14

Pharmacokinetics of a long-acting bromocriptine preparation (Parlodel LA) and its effect on release of prolactin and growth hormone. del Pozo E, et al. **Eur J Clin Pharmacol** 1986;29(5):615-8

Studies on the prolactin-releasing capacity of luteinizing hormone releasing hormone in male subjects. Gooren LJ, et al. **Exp Clin Endocrinol** 1985 Dec;86(3):300-4

Antagonistic effects of prolactin and oxytocin on tail fin regression and acid phosphatase activity in metamorphosing Ambystoma tigrinum. Platt JE, et al. **Gen Comp Endocrinol** 1986 Mar;61(3):376-82

Effect of thyrotropin-releasing hormone and dopamine on the in vitro secretion of prolactin by the bullfrog pituitary gland. Seki T, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):197-202

Prolactin induces yawning and the stretch-yawning syndrome in young adult male rats. Laping NJ, et al. **Horm Behav** 1986 Mar; 20(1):49-59

Effect of adrenergic antagonism on the growth hormone, prolactin and cortisol response to a synthetic opioid agonist in man. Bouloux PM, et al. **Horm Res** 1986;23(2):83-90

The role of neuropeptides in modulating PRL and GH secretion. Lancranjan I, et al. **Int J Neurol** 1980;14(2-4):175-88 (60 ref.)

Angiotensin II and dopamine modulate both cAMP and inositol phosphate productions in anterior pituitary cells. Involvement in prolactin secretion. Enjalbert A, et al. **J Biol Chem** 1986 Mar 25; 261(9):4071-5

Increased dopaminergic activity inhibits basal and metoclopramide-stimulated prolactin and thyrotropin secretion. Agner T, et al. **J Clin Endocrinol Metab** 1986 Apr;62(4):778-82

Evaluation of hypothalamic dopaminergic function by neuropharmacologic means in aged women. Cocchi D, et al. **J Neural Transm** 1985;64(3-4):199-210

Inhibition of prolactin release and blockade of adenohypophyseal cell cyclic AMP accumulation are two dissociable effects of dopaminergic and non-dopaminergic drugs. Lafond J, et al. **Mol Cell Endocrinol** 1986 Mar;44(3):219-25

Increase of rat serum prolactin by adenosine analogs and their blockade by the methylxanthine aminophylline. Stewart SF, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):140-5

Reduction of motor behavioral deficits in senescent animals via chronic prolactin administration. I. Rotational behavior. Joseph JA, et al. **Neurobiol Aging** 1986 Jan-Feb;7(1):31-5

Indolealkylamines and prolactin secretion. A structure-activity study in the central nervous system of the rat. Seeman G, et al. **Neuropharmacology** 1985 Dec;24(12):1195-200

24-hour plasma levels of prolactin, cortisol, growth hormone and catecholamines in schizophrenic patients. Kemali D, et al. **Neuropsychobiology** 1985;14(3):109-14

Restricted feeding regimen affects the diurnal prolactin surge but not nocturnal surge in pseudopregnant rats. Murakami N, et al. **Nippon Juigaku Zasshi** 1986 Feb;48(1):29-34

Submaximal plasma prolactin response to TRH and dopamine activity in man. Spoov J. **Pharmacopsychiatry** 1985 Nov;18(6):330-2

Endocrine response to acute cold exposure by lactating and non-lactating Norway rats. Adels LE, et al. **Physiol Behav** 1986 Jan;36(1):179-81

Further evidence that central neurotensin inhibits pituitary prolactin secretion by stimulating dopamine release from the hypothalamus. Tojo K, et al. **Proc Soc Exp Biol Med** 1986 Apr;181(4):517-22

Changes in pituitary prolactin responsiveness to TRH during pregnancy. Voogt JL. **Proc Soc Exp Biol Med** 1986 May;182(1):58-62

Effect of normal aging on the prolactin response to graded doses of sulpiride and to arginine. Nair NP, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):633-7

Lithium and twenty-four hour rhythms of serum corticosterone, prolactin and growth hormone in pigmented eye rats. Seggie J, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):755-8

Immediate effects of intermittent administration of domperidone upon prolactin release in normal women. Ulloa-Aguirre A, et al. **Rev Invest Clin** 1985 Oct-Dec;37(4):341-5

Abnormalities in the regulation of prolactin in patients on maintenance hemodialysis. Leu ML, et al. **Taiwan I Hsueh Hui Tsa Chih** 1985 Sep; 84(9):1059-70

[Effect of chlorpromazine on the graft versus host reaction] Grin J, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(3):337-47 (Eng. Abstr.) **(Spa)**

PROMAZINE

Termini generated at the site of the DNA breakage mediated by photoexcited promazines. Decuyper J, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1345-50

Liquid chromatographic determination of identity, content, and content uniformity of desipramine, fluphenazine, and promazine. Beaulieu N, et al. **J Assoc Off Anal Chem** 1986 Jan-Feb;69(1):178-9

PROMETHAZINE

Pesticide-drug interaction in rats. Fenyvesi G, et al. **Arch Toxicol [Suppl]** 1985;8:269-71

Irreversible binding with biological macromolecules and effects in bacterial mutagenicity tests of the radical cation of promethazine and photoactivated promethazine. Comparison with chlorpromazine. De Mol NJ, et al. **Chem Biol Interact** 1986 Jan;57(1):73-83

No promethazine in Nyquil [letter] Lewis ET. **N Engl J Med** 1986 Apr 3;314(14):927

[The quantitative analysis of aminophylline 0.32 g cum promethazine SR suppositories] Vogel E. **Pharmazie** 1985 Nov;40(11):801 **(Ger)**

PROPANEDIOLS

Diol metabolism and diol dehydratase in Clostridium glycolicum. Hartmanis MG, et al. **Arch Biochem Biophys** 1986 Feb 15; 245(1):144-52

Results of genotoxicity testing of mazindol (degonan), lithium carbonicum (contemnol) and dropropizine (ditustat) in Chinese hamster V79 and human EUE cells. Slameňová D, et al. **Mutat Res** 1986 Mar; 169(3):171-7

Metabolism and disposition of propylene glycol monomethyl ether (PGME) beta isomer in male rats. Miller RR, et al. **Toxicol Appl Pharmacol** 1986 Mar 30;83(1):170-7

PROPRANOLOL

Pharmacodynamic interaction of gallopamil and propranolol in the conscious dog. Lehmann HD. **Arzneimittelforschung** 1985; 35(12):1795-801

Studies on the uptake and release of propranolol and the effects of propranolol on catecholamines in cultures of bovine adrenal chromaffin cells. Boksa P. **Biochem Pharmacol** 1986 Mar 1;35(5):805-15

Age-dependent propranolol clearance in perfused rat liver. Iwamoto K, et al. **Biochem Pharmacol** 1986 Apr 1;35(7):1149-52

Mechanism of cationic amphiphilic drug inhibition of purified lysosomal phospholipase A1. Kubo M, et al. **Biochemistry** 1985 Nov 5; 24(23):6515-20

The effect of propranolol and thioridazine on positive and negative symptoms of schizophrenia. Eccleston D, et al. **Br J Psychiatry** 1985 Dec;147:623-30

Changes of transition temperatures of phosphatidylcholine and phosphatidylglycerol in presence of amphiphilic drugs. Harder A, et al. **Chem Phys Lipids** 1986 Jan;39(1-2):65-71

Comparison of four beta-blockers as assessed by 24-hour ECG recording. Escoubet B, et al. **Clin Pharmacol Ther** 1986 Apr;39(4):361-8

Phenylpropanolamine and blood pressure [letter] Morgan JP, et al. **Clin Pharmacol Ther** 1986 Jan;39(1):102-3

Influence of vagal cooling on cardiac output in normal and beta-blocked exercising dogs. Versteeg PG, et al. **Eur J Appl Physiol** 1986; 54(6):617-23

Beta-adrenoceptor blocking effects and plasma levels of bornaprolol and propranolol in man. Thuillez C, et al. **Eur J Clin Pharmacol** 1985; 29(4):405-11

Theoretical Michaelis-Menten elimination model for propranolol. McAinsh J, et al. **Eur J Drug Metab Pharmacokinet** 1985 Jul-Sep; 10(3):241-5

Hepatic uptake of propranolol [letter] Forker EL, et al. **Hepatology** 1986 Mar-Apr;6(2):340-1

Effects of propranolol on the impulse activity of cardiovascular sympathetic afferent fibers. Lombardi F, et al. **Hypertension** 1986 Jan; 8(1):50-5

Determination of alpha-naphthoxylactic acid, a major metabolite of propranolol, in plasma by high-performance liquid chromatography [letter] Harrison PM, et al. **J Chromatogr** 1986 Jan 10;374(1):223-5

A modified, sensitive liquid chromatographic method for measurement of propranolol with fluorescence detection. Koshakji RP, et al. **J Pharm Sci** 1986 Jan;75(1):87-9

Influence of food on the intravenous and oral dose kinetics of propranolol in the dog. Bai SA, et al. **J Pharmacokinet Biopharm** 1985 Jun; 13(3):229-41

Propranolol inhibits the compensatory increase in androgen secretion after unilateral orchidectomy in rats. Moger WH, et al. **J Reprod Fertil** 1986 Jan;76(1):251-6

Glucagon for propranolol overdose [letter] Mofenson HC, et al. **JAMA** 1986 Apr 18;255(15):2025-6

Low incidence of shivering with chronic propranolol therapy [letter] Lee DS, et al. **Lancet** 1986 Mar 1;1(8479):500

Modification of cellular immune functions in humans by endurance exercise training during beta-adrenergic blockade with atenolol or propranolol. Watson RR, et al. **Med Sci Sports Exerc** 1986 Feb; 18(1):95-100

In vitro receptor occupancy allows to establish equieffective doses of beta-blockers with different pharmacodynamic profiles in man. Investigations with propranolol and bufuralol. Wellstein A, et al. **Methods Find Exp Clin Pharmacol** 1985 Dec;7(12):645-51

Mutagenic evaluation of propranolol in somatic and germ cells of mice. Aruna N, et al. **Mutat Res** 1986 Mar;173(3):207-10

Anticonvulsant effects of propranolol and their pharmacological modulation. Fischer W, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec; 37(6):883-96

Effects of propranolol and indomethacin on muscarinic airway reactivity in unanesthetized guinea pigs. Roum JH, et al. **Proc Soc Exp Biol Med** 1986 Apr;181(4):569-74

The coronary vasodilator mediator released by hypoxia and isoprenaline is not affected by cyclo-oxygenase inhibition. Broadley KJ, et al. **Prostaglandins** 1986 Feb;31(2):295-306

Effects of propranolol on conditioned suppression, discriminated punishment and discriminated non-reward in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1986;88(2):252-7

The effects of propranolol metipranolol, and pindolol on the cardiovascular system of rabbits in vivo. Geršl V. **Sb Ved Pr Lek Fak Univ Karlovy** 1984;27(1):103-15

[Bioavailability of propranolol administered by the rectal route in man] Cid E, et al. **Therapie** 1985 Nov-Dec;40(6):447-9 (Eng. Abstr.) **(Fre)**

[Effect of beta-receptor block on QT/QS2 behavior during isometric and dynamic exercise] De Caprio L, et al. **G Ital Cardiol** 1985 Oct; 15(10):960-4 (Eng. Abstr.) **(Ita)**

[Effects of propranolol on the hepato-portal and systemic hemodynamics. Experimental model] Ussia G, et al. **Minerva Chir** 1985 Nov 30; 40(22):1541-6 (Eng. Abstr.) **(Ita)**

[Experience in analyzing the functional structure of thermogenesis based on pharmacologic testing] Iudanova LA, et al. **Fiziol Zh SSSR** 1986 Jan;72(1):109-15 (Eng. Abstr.) **(Rus)**

PROSTAGLANDINS

Effect of intragastric pH, prostaglandins and prostaglandin synthesis inhibitors on the release of gastrin and somatostatin into the gastric lumen of anaesthetized rats. Alino SF, et al. **Acta Physiol Scand** 1986 Jan;126(1):1-8

Mechanism of action of vasoactive hormones on prostaglandin synthesis in the kidney. Cooper CL, et al. **Adv Prostaglandin Thromboxane Leukotriene Res** 1985;15:437-9

Role of the renal kinin-prostaglandin system in diltiazem-induced natriuresis. Seino M, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 2):F197-202

Role of endogenous prostaglandins in somatostatin-induced inhibition of gastrointestinal hormone secretion. Koop H, et al. **Hepatogastroenterology** 1985 Dec;32(6):288-92

Inhibition of prostaglandin generation in the rabbit brain in-vivo by AD-1590, a non-steroidal anti-inflammatory agent with potent antipyretic activity. Nakamura H, et al. **J Pharm Pharmacol** 1985 Dec; 37(12):894-8

Contribution of Ca++ and calmodulin to the action of norepinephrine on renal prostaglandin synthesis and vascular tone. Cooper CL, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):424-31

Comparative effects of glucocorticoids and prostaglandins on small intestine of infant rats. Neu J, et al. **Pediatr Res** 1986 Feb; 20(2):109-12

Dissociation of hyperreninemia and renal prostaglandin synthesis in the adrenalectomized rat. Boucher LD, et al. **Prostaglandins** 1986 Jan; 31(1):143-55

Role of prostacyclin on steroidogenesis by frog interrenal gland in vitro. Delarue C, et al. **Prostaglandins** 1986 Jan;31(1):5-17

[Contribution of prostaglandins to the activity of guinea-pig phrenic and chicken esophageal parasympathetic nerves] Takeuchi T, et al. **Nippon Yakurigaku Zasshi** 1985 Oct;86(4):261-8 (Eng. Abstr.) **(Jpn)**

PSYCHIATRIC STATUS RATING SCALES

Rating scales and assessment instruments for use in pediatric psychopharmacology research. **Psychopharmacol Bull** 1985; 21(4):714-1124

Behavioral and cognitive measures used in psychopharmacological studies of infantile autism. Campbell M, et al. **Psychopharmacol Bull** 1985; 21(4):1047-53

Rating scales and checklists for child psychopharmacology. Conners CK, et al. **Psychopharmacol Bull** 1985;21(4):809-43

Scales of potential use in the psychopharmacologic treatment of depressed children and adolescents. Petti TA. **Psychopharmacol Bull** 1985; 21(4):951-77

PSYCHIATRY

The uncertain future of clinical psychiatry. Lesse S. **Am J Psychother** 1986 Jan;40(1):4-16

Psychobiology and psychopharmacology: issues in clinical research training. Janowsky DS, et al. **J Clin Psychopharmacol** 1986 Feb; 6(1):1-7

DSM-III-R and pediatric psychopharmacology. Rapoport JL. **Psychopharmacol Bull** 1985;21(4):803-6

[The new biological revolution in psychiatry: a Latin American point of view (2)] Alarcón RD. **Acta Psiquiatr Psicol Am Lat** 1985 Sep; 31(3):173-90 (Eng. Abstr.) **(Spa)**

PSYCHOMOTOR AGITATION

Alternative approaches in the treatment of psychotic agitation. Campbell R, et al. **Psychosomatics** 1986 Jan;27(1 Suppl):23-7

Clonazepam for panic disorders and agitation. Fontaine R. **Psychosomatics** 1985 Dec;26(12 Suppl):13-8

Acute treatment of manic agitation with lorazepam. Lenox RH, et al. **Psychosomatics** 1986 Jan;27(1 Suppl):28-32

Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. Salzman C, et al. **Psychosomatics** 1986 Jan; 27(1 Suppl):17-22

PSYCHOMOTOR PERFORMANCE

The effect of antipsychotic drugs on driving and driving related psychomotor functions. Judd LL. **Accid Anal Prev** 1985 Aug; 17(4):319-22

Psychomotor tasks and recovery from anesthesia [letter] Millar K. **Anesth Analg** 1986 May;65(5):543-4

Physical performance during sustained converting enzyme inhibition with Hoe 498 in conscious dogs. Becker RH, et al. **Arch Int Pharmacodyn Ther** 1985 Dec;278(2):303-13

Comparison of midazolam and triazolam for residual effects. Wehli L, et al. **Arzneimittelforschung** 1985;35(11):1700-4

Reduction of motor behavioral deficits in senescent animals via chronic prolactin administration. I. Rotational behavior. Joseph JA, et al. **Neurobiol Aging** 1986 Jan-Feb;7(1):31-5

Effects of clorazepate dipotassium and placebo on psychomotor skills. Moodley P, et al. **Percept Mot Skills** 1985 Dec;61(3 Pt 2):1121-2

Reward, performance, and the response strength method in self-stimulating rats: validation and neuroleptics. Hamilton AL, et al. **Physiol Behav** 1985 Dec;35(6):897-904

Dose-dependent impairment in the performance of a go-no go successive discrimination by chlordiazepoxide. Cole SO, et al.

Psychopharmacology (Berlin) 1986;88(2):184–6
Chlorpromazine and pimozide alter reinforcement efficacy and motor performance. Heyman GM, et al. **Psychopharmacology (Berlin)** 1986; 88(3):346–53
Chronic effects of ethosuximide, phenytoin, clonazepam, and valproic acid on the delayed-matching-to-sample performance of pigeons. Poling A, et al. **Psychopharmacology (Berlin)** 1986;88(3):301–4
Hormonal and behavioral effects associated with intravenous L-tryptophan administration. Winokur A, et al. **Psychopharmacology (Berlin)** 1986;88(2):213–9
[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. II. Comparison of the effects of various thymoleptics on the psychopathological symptoms of endogenous depressive syndromes] Strzyżewski W, et al. **Psychiatr Pol** 1985 Sep–Oct;19(5):363–9 (Eng. Abstr.) **(Pol)**
[Psychopathological and neurophysiological indicators in endogenous depression and the therapeutic effect of thymoleptics. I. Analysis of the clinical effect of antidepressive drugs with various pharmacological profiles] Twarowska-Hauser J, et al. **Psychiatr Pol** 1985 Sep–Oct; 19(5):357–62 (Eng. Abstr.) **(Pol)**

PSYCHOPHARMACOLOGY

27th annual psychopharmacology meeting. Jeseník Spa, January 1985. Abstracts. **Act Nerv Super (Praha)** 1985 Dec;27(4):246–328
Psychobiology and psychopharmacology: issues in clinical research training. Janowsky DS, et al. **J Clin Psychopharmacol** 1986 Feb; 6(1):1–7
Perspectives in Canadian neuro-psychopharmacology. Proceedings of the eighth annual meeting of the Canadian College of Neuropsychopharmacology. May 5–8, 1985, London, Ontario. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):463–768
Rating scales and assessment instruments for use in pediatric psychopharmacology research. **Psychopharmacol Bull** 1985; 21(4):714–1124
Rating scales and checklists for child psychopharmacology. Conners CK, et al. **Psychopharmacol Bull** 1985;21(4):809–43
DSM-III-R and pediatric psychopharmacology. Rapoport JL. **Psychopharmacol Bull** 1985;21(4):803–6
Measurement of compliance. Sleator EK. **Psychopharmacol Bull** 1985; 21(4):1089–93
Measures of cognitive functioning appropriate for use in pediatric psychopharmacological research studies. Swanson JM. **Psychopharmacol Bull** 1985;21(4):887–90
[The new biological revolution in psychiatry: a Latin American point of view (2)] Alarcón RD. **Acta Psiquiatr Psicol Am Lat** 1985 Sep; 31(3):173–90 (Eng. Abstr.) **(Spa)**

PSYCHOPHYSIOLOGIC DISORDERS

Captopril in the treatment of psychogenic polydipsia [letter] Goldstein JA. **J Clin Psychiatry** 1986 Feb;47(2):99
Measures of cognitive functioning appropriate for use in pediatric psychopharmacological research studies. Swanson JM. **Psychopharmacol Bull** 1985;21(4):887–90
[Central nervous system control mechanisms and the development of disease--their significance for psychosomatic medicine] Weiner H. **Psychother Psychosom Med Psychol** 1985 Dec;35(12):310–4 (Eng. Abstr.) **(Ger)**

PSYCHOTHERAPY

Interpersonal psychotherapy adapted for ambulatory cocaine abusers. Rounsaville BJ, et al. **Am J Drug Alcohol Abuse** 1985; 11(3–4):171–91
Combined psychotherapy and pharmacotherapy for depression. A systematic analysis of the evidence. Conte HR, et al. **Arch Gen Psychiatry** 1986 May;43(5):471–9
Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Keller MB, et al. **Arch Gen Psychiatry** 1986 May;43(5):458–66
Changes in psychological diagnosis and prescription in a practice employing a counsellor. Martin E, et al. **Fam Pract** 1985 Dec; 2(4):241–3
A new perspective on intervention in heavy, chronic drug use. Spotts JV, et al. **Int J Addict** 1985 Oct;20(10):1545–65
Hope for the chronic mentally ill. Macinick CG, et al. **Issues Ment Health Nurs** 1984;6(3–4):255–9
[The prognosis of schizophrenia] Lungershausen E. **Fortschr Med** 1986 Feb 6;104(5):97–100 (Eng. Abstr.) **(Ger)**

PSYCHOTIC DISORDERS

Drugs and depression. Harris B. **Am J Nurs** 1986 Mar;86(3):292–3
Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? Arana GW, et al. **Am J Psychiatry** 1986 May;143(5):650–1
Neuroleptic dosage for Asians: a failure to replicate. Sramek JJ, et al. **Am J Psychiatry** 1986 Apr;143(4):535–6
Serine, glycine and carbohydrates in schizoaffective disorders. Bruinvels J, et al. **Bibl Nutr Dieta** 1986;(38):168–72
The oldest patient with Capgras syndrome? Burns A. **Br J Psychiatry** 1985 Dec;147:719–20
Neuroleptics in culture-bound syndromes [letter] Harrison-Read PE. **Br J Psychiatry** 1986 Jan;148:106–7
Eye movement dysfunctions and psychosis. Holzman PS. **Int Rev Neurobiol** 1985;27:179–205 (91 ref.)
Monosymptomatic hypochondriacal psychosis manifesting as delusions of infestation: case studies of treatment with haloperidol. Andrews E, et al. **J Clin Psychiatry** 1986 Apr;47(4):188–90
Stability of the postpsychotic depression syndrome. Siris SG, et al. **J Clin Psychiatry** 1986 Feb;47(2):86–8
Intramuscular lorazepam to restrain violent patients [letter] Bick PA, et al. **Lancet** 1986 Jan 25;1(8474):206
New pharmacologic approaches in the treatment of psychosis. Proceedings of a symposium. Philadelphia, June 29, 1985. **Psychosomatics** 1986 Jan;27(1 Suppl):1–38
Alternative approaches in the treatment of psychotic agitation. Campbell R, et al. **Psychosomatics** 1986 Jan;27(1 Suppl):23–7
Treatment of acute psychosis with non-neuroleptic agents. Cohen BM, et al. **Psychosomatics** 1986 Jan;27(1 Suppl):7–16
[Droleptan] Peutillot JF. et al. **Soins Psychiatr** 1985 Nov;(61):I–II**(Fre)**
[Psychiatric indications for beta-adrenergic inhibitors] Féline A, et al. **Therapie** 1985 Nov–Dec;40(6):413–6 (Eng. Abstr.) **(Fre)**
[EEG changes with leponex medication] Kursawe HK, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1985 Dec;37(12):705–12 (Eng. Abstr.) **(Ger)**
[Behavioral changes in rhesus monkeys induced by repeated administration of ephedrine] Kato S. **Seishin Shinkeigaku Zasshi** 1985; 87(8):583–94 (Eng. Abstr.) **(Jpn)**

QUINIDINE

Effects of quinidine on pharmacokinetics and pharmacodynamics of digitoxin achieving steady-state conditions. Kuhlmann J, et al. **Clin Pharmacol Ther** 1986 Mar;39(3):288–94
Analysis of nonlinear tissue distribution of quinidine in rats by physiologically based pharmacokinetics. Harashima H, et al. **J Pharmacokinet Biopharm** 1985 Aug;13(4):425–40
Comparative electropharmacology of mexiletine, lidocaine and quinidine in a canine Purkinje fiber model. Burke GH, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):232–6
Effects of quinidine on the transmembrane potentials of young and adult canine cardiac Purkinje fibers. Morikawa Y, et al. **J Pharmacol Exp Ther** 1986 Mar;236(3):832–7
An adult male patient with unexplained fever. Molitor L. **JEN** 1986 Jan–Feb;12(1):63–4
The pharmacodynamic response of the basal skin potential to quinidine gluconate. Ando HY, et al. **Life Sci** 1986 Feb 3;38(5):417–24
Protection from quinidine or physostigmine against in vitro inhibition by sarin of acetylcholinesterase activity. Singh AK, et al. **Life Sci** 1986 Jan 13;38(2):165–72
Electrophysiological interactions between quinidine-lidocaine and quinidine-phenytoin in guinea-pig papillary muscle. Sánchez-Chapula J. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Dec;331(4):369–75
Quinidine blockage of K+ channels in the basolateral membrane of larval bullfrog skin. Van Driessche W, et al. **Pflugers Arch** 1985; 405 Suppl 1:S77–82
[The in vitro liberation behavior of quinidine from drug forms with prolonged release by various liberation methods] Appelt B, et al. **Pharmazie** 1986 Jan;41(1):44–6 (Eng. Abstr.) **(Ger)**
[A relived case by plasma exchange in serious complications of quinidine induced thrombocytopenic purpura] Tani S, et al. **Nippon Naika Gakkai Zasshi** 1985 Nov;74(11):1567–72 **(Jpn)**
[Effects of Ca++ on A-V conduction. Comparison with the effects of quinidine] González-Morales MA, et al. **Arch Farmacol Toxicol** 1985 Dec;11(3):155–64 (Eng. Abstr.) **(Spa)**

REACTION TIME

Choice reaction time in workers exposed to styrene vapour. Mackay CJ, et al. **Hum Toxicol** 1986 Mar;5(2):85–9

RECEPTORS, ADRENERGIC

Norepinephrine inhibition of pulsatile LH release: receptor specificity. Bergen H, et al. **Am J Physiol** 1986 Feb;250(2 Pt 1):E205–11
Inhibition of monoamine oxidase in monoaminergic neurones in the rat brain by irreversible inhibitors. Fagervall I, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1381–7
Evidence that epinephrine acts preferentially as an antilipolytic agent in abdominal human subcutaneous fat cells: assessment by analysis of beta and alpha 2 adrenoceptor properties. Berlan M, et al. **Eur J Clin Invest** 1985 Dec;15(6):341–8

Down-regulation of dopamine D-2, 5-HT2 receptors and beta-adrenoceptors in rat brain after prolonged treatment with a new potential antidepressant, Lu 19-005. Nowak G, et al. **J Neural Transm** 1985;64(3-4):227-38

Antagonism by dopamine, but not noradrenaline receptor blockers of the anti-immobility activity of desipramine after different treatment schedules in the rat. Pulvirenti L, et al. **Pharmacol Res Commun** 1986 Jan;18(1):73-80

[Effect of changes in the catecholamine content in the brain on the chemoreactive properties of the sensorimotor cortex neurons of rats] Kruglikov RI, et al. **Izv Akad Nauk SSSR [Biol]** 1985 Nov-Dec;(6):832-40 (Eng. Abstr.) **(Rus)**

[Role of brain noradrenergic mechanisms in disturbing the circadian rhythm of the functioning hypothalamo-hypophyseo-adrenal cortex system in white rats in early ontogeny] Maslova LN, et al. **Ontogenez** 1986 Jan-Feb;17(1):56-61 (Eng. Abstr.) **(Rus)**

[Adrenergic reactivity of the heart and coronary vessels in hemotransfusion shock] Khomaziuk AI, et al. **Vestn Akad Med Nauk SSSR** 1985;(12):74-80 (Eng. Abstr.) **(Rus)**

RECEPTORS, ADRENERGIC, ALPHA

Noradrenaline evokes an alpha-adrenoceptor-mediated inotropic effect in human ventricular myocardium. Aass H, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Jan;58(1):88-90

Cortical beta- and alpha 2- adrenoceptor binding, hypothalamic noradrenaline and pineal melatonin concentrations measured at different times of the day after repeated treatment of rats with imipramine, zimeldine, alaproclate and amiflamine. Ask AL, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Jan;58(1):16-24

Phenothiazine drugs and metabolites: molecular conformation and dopaminergic, alpha adrenergic and muscarinic cholinergic receptor binding. Dahl SG, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1263-9

Noradrenergic stimulation of supraoptic neuronal activity and vasopressin release in vitro: mediation by an alpha 1-receptor. Armstrong WE, et al. **Brain Res** 1986 Feb 12;365(1):192-7

Locus coeruleus neurons in culture have a developmentally transient alpha 1 adrenergic response. Finlayson PG, et al. **Brain Res** 1986 Mar;390(2):292-5

Adrenergic coronary tone during submaximal exercise in the dog is produced by circulating catecholamines. Evidence for adrenergic denervation supersensitivity in the myocardium but not in coronary vessels. Chilian WM, et al. **Circ Res** 1986 Jan;58(1):68-82

Selective alpha 2 receptor blockade facilitates the insulin response to adrenaline but not to glucose in man. Struthers AD, et al. **Clin Endocrinol (Oxf)** 1985 Nov;23(5):539-46

Supersensitivity of alpha 2-adrenoceptors modulating [3H]5-HT release after noradrenergic denervation with DSP4. Benkirane S, et al. **Eur J Pharmacol** 1985 Dec 10;119(1-2):131-3

Antidepressant drugs given repeatedly increase binding to alpha 1-adrenoceptors in the rat cortex. Maj J, et al. **Eur J Pharmacol** 1985 Dec 10;119(1-2):113-6

Alpha 1-adrenergic activation of brown adipocytes leads to an increased formation of inositol polyphosphates. Nånberg E, et al. **FEBS Lett** 1986 Jan 20;195(1-2):319-22

Alpha- and beta-adrenergic mechanisms mediate blood pressure control by norepinephrine and angiotensin in ducks. Butler DG, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):323-9

Selectivities of some agonists acting at alpha 1- and alpha 2-adrenoreceptors in the rat vas deferens. Leedham JA, et al. **J Auton Pharmacol** 1986 Mar;6(1):39-46

Chronic treatment with the potential antidepressant drug rolipram: the effect on the behavioural responses to adrenergic and dopaminergic receptor agonists with some biochemical correlates. Przegaliński E, et al. **J Neural Transm** 1985;64(3-4):211-26

Presynaptic alpha-2 adrenoceptor activation and coupling of the receptor-presynaptic effector system in the perfused rat heart: affinity and efficacy of phenethylamines and imidazoline derivatives. Fuder H, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):237-45

Modulation of peripheral beta-1 and alpha-2 receptor sensitivities by the administration of the tricyclic antidepressant, imipramine, alone and in combination with alpha-2 antagonists to rats. Keith RA, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):356-63

Diurnal rhythm of alpha 2-noradrenergic receptors in the paraventricular nucleus and other brain areas: relation to circulating corticosterone and feeding behavior. Jhanwar-Uniyal M, et al. **Life Sci** 1986 Feb 3;38(5):473-82

Desensitization of epinephrine-initiated platelet aggregation does not alter binding to the alpha 2-adrenergic receptor or receptor coupling to adenylate cyclase. Motulsky HJ, et al. **Mol Pharmacol** 1986 Jan;29(1):1-6

Islet-activating protein (pertussis toxin) diminishes alpha 2-adrenoceptor mediated effects on noradrenaline release. Allgaier C, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov;331(2-3):235-9

Effects of combined administration of L-tryptophan and tricyclic antidepressants on alpha 2- and beta-adrenoceptors and monoamine levels in rat brain. Russell VA, et al. **Neurochem Res** 1985 Dec;10(12):1661-71

Interaction between corticosterone and alpha-2-noradrenergic system of the paraventricular nucleus in relation to feeding behavior. Roland CR, et al. **Neuroendocrinology** 1986;42(4):296-305

Locomotor depression in mice by norcocaine does not involve central alpha 2-adrenergic or presynaptic dopamine receptors. Reith ME, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):305-7

Excitatory amino acid recognition sites coupled with inositol phospholipid metabolism: developmental changes and interaction with alpha 1-adrenoceptors. Nicoletti F, et al. **Proc Natl Acad Sci USA** 1986 Mar;83(6):1931-5

[Epinephrine uptake and release and presynaptic alpha 2-adrenoceptic regulation in the guinea pig hypothalamus] Fujii Y, et al. **Nippon Yakurigaku Zasshi** 1986 Jan;87(1):11-7 (Eng. Abstr.) **(Jpn)**

RECEPTORS, ADRENERGIC, BETA

Cortical beta- and alpha 2- adrenoceptor binding, hypothalamic noradrenaline and pineal melatonin concentrations measured at different times of the day after repeated treatment of rats with imipramine, zimeldine, alaproclate and amiflamine. Ask AL, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Jan;58(1):16-24

Increase in the cardiotonic action and in the therapeutic margin of digoxin by the adrenergic beta-stimulant doxaminol in cats. Sponer G, et al. **Arzneimittelforschung** 1985;35(11):1663-7

Prepubertal rat ovary: hormonal modulation of beta-adrenergic receptors and of progesterone response to adrenergic stimulation. Aguado LI, et al. **Biol Reprod** 1986 Feb;34(1):45-50

Influence of vagal cooling on cardiac output in normal and beta-blocked exercising dogs. Versteeg PG, et al. **Eur J Appl Physiol** 1986;54(6):617-23

Alpha- and beta-adrenergic mechanisms mediate blood pressure control by norepinephrine and angiotensin in ducks. Butler DG, et al. **Gen Comp Endocrinol** 1986 Feb;61(2):323-9

Chronic treatment with the potential antidepressant drug rolipram: the effect on the behavioural responses to adrenergic and dopaminergic receptor agonists with some biochemical correlates. Przegaliński E, et al. **J Neural Transm** 1985;64(3-4):211-26

Possible involvement of beta 2-adrenoceptors in hyperthermic effect of l-ephedrine in rats. Yamahara J, et al. **J Pharmacobiodyn** 1985 Aug;8(8):591-6

Modulation of peripheral beta-1 and alpha-2 receptor sensitivities by the administration of the tricyclic antidepressant, imipramine, alone and in combination with alpha-2 antagonists to rats. Keith RA, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):356-63

Hamster and rat pineal gland beta-adrenoceptor characterization with iodocyanopindolol and the effect of decreased catecholamine synthesis on the receptor. Craft CM, et al. **J Pineal Res** 1985;2(1):51-66

Agonist interactions with beta-adrenergic receptors following chronic administration of desipramine or the atypical antidepressants, iprindole and mianserin. Hancock AA, et al. **J Recept Res** 1985;5(5-6):311-34

In vitro receptor occupancy allows to establish equieffective doses of beta-blockers with different pharmacodynamic profiles in man. Investigations with propranolol and bufuralol. Wellstein A, et al. **Methods Find Exp Clin Pharmacol** 1985 Dec;7(12):645-51

Effects of combined administration of L-tryptophan and tricyclic antidepressants on alpha 2- and beta-adrenoceptors and monoamine levels in rat brain. Russell VA, et al. **Neurochem Res** 1985 Dec;10(12):1661-71

Catecholamine excretion and beta-adrenergic responsiveness in estrogen-treated rats. Carlberg KA, et al. **Pharmacology** 1986;32(3):147-56

Variability of chronic antidepressant treatments on beta-adrenergic receptor sites. Suranyi-Cadotte BE, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):765-8

The modulation of head-twitch behaviour by drugs acting on beta-adrenoceptors: evidence for the involvement of both beta 1- and beta 2-adrenoceptors. Handley SL, et al. **Psychopharmacology (Berlin)** 1986;88(3):320-4

RECEPTORS, CHOLINERGIC

Acetylcholine receptors in the gastrulating chick embryo. Laasberg T, et al. **Experientia** 1986 Apr 15;42(4):439-40

Chlorpromazine inhibition of muscarinic-cholinergic responses in the rat parotid gland. Van der Ven PF, et al. **J Dent Res** 1986 Mar;65(3):382-6

Enhanced elevation of corticosterone following arecoline administration to rats selectively bred for increased cholinergic function. Overstreet DH, et al. **Psychopharmacology (Berlin)** 1986;88(1):129-30

[Reactivity of the cholinoceptive cortical neurons to the repeated action of acetylcholine] Kotliar BI, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):259-60 (Eng. Abstr.) **(Rus)**

RECEPTORS, DOPAMINE

Effect of prolonged dopamine receptor blockade on lactotroph activity in the rat pituitary gland. Prysor-Jones RA, et al. **Acta Endocrinol (Copenh)** 1985 Dec;110(4):469-74

Studies of neurotensin-dopamine receptor interactions in striatal membranes of the male rat. The influence of 6-hydroxydopamine-induced dopamine receptor supersensitivity. Fuxe K, et al. **Acta Physiol Scand** 1986 Jan;126(1):147-9

Effect of dithiocarbamate fungicides and thiurams on 3H-haloperidol binding in rat brain. Komulainen H, et al. **Arch Toxicol [Suppl]** 1985; 8:77-9

Phenothiazine drugs and metabolites: molecular conformation and dopaminergic, alpha adrenergic and muscarinic cholinergic receptor binding. Dahl SG, et al. **Biochem Pharmacol** 1986 Apr 15; 35(8):1263-9

Postnatal ontogeny of dopamine D2 receptors in rat striatum. Murrin LC, et al. **Biochem Pharmacol** 1986 Apr 1;35(7):1159-62

Guanine nucleotide effects on agonist binding at D2 dopamine receptors in bovine anterior pituitary. Simmonds SH, et al. **Biochem Pharmacol** 1986 Mar 1;35(5):731-5

Isolation and characterization of D2-dopamine receptors. Strange PG, et al. **Biochem Soc Trans** 1985 Dec;13(6):1099-100

Relationship of limbic dopamine levels to amphetamine- and anticholinergic-induced hyperactivity in the rat. Carey RJ. **Biol Psychiatry** 1986 Mar;21(3):317-21

Performance deficit induced by low doses of dopamine agonists in rats. Toward a model for approaching the neurobiology of negative schizophrenic symptomatology? Carnoy P, et al. **Biol Psychiatry** 1986 Jan;21(1):11-22

Carbamazepine and dopaminergic supersensitivity [letter] Csernansky JG, et al. **Biol Psychiatry** 1986 Feb;21(2):238-9

Chronic treatment with five different neuroleptics elicits behavioral supersensitivity to opiate infusion into the nucleus accumbens. Stinus L, et al. **Biol Psychiatry** 1986 Jan;21(1):34-48

Central dopamine hyperactivity in rats mimics abnormal acoustic startle response in schizophrenics. Swerdlow NR, et al. **Biol Psychiatry** 1986 Jan;21(1):23-33

B-HT 958 lowers blood pressure and heart rate in the rat through stimulation of dopamine receptors. Brown MJ, et al. **Br J Pharmacol** 1986 Feb;87(2):361-70

Asymmetry in D-2 binding in female rat striata. Drew KL, et al. **Brain Res** 1986 Jan 15;363(1):192-5

The sialagogue response of striatal dopamine receptors to L-dopa is not influenced by castration or chronic estrogen treatment. Pazo JH, et al. **Brain Res Bull** 1986 Jan;16(1):1-4

Inhibition of dopaminergic agonist-induced gnawing behavior by neuroleptic drugs in mice. Yen-Koo HC, et al. **Drug Chem Toxicol** 1985;8(6):495-502

D-2 dopaminergic agonists and adenosine 3',5'-monophosphate directly regulate the synthesis of alpha-melanocyte-stimulating hormone-like peptides by cultured rat melanotrophs. Beaulieu M, et al. **Endocrinology** 1986 Mar;118(3):1032-9

Some atypical neuroleptics inhibit [3H]SCH 23390 binding in vivo. Andersen PH, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):143-4

A central site of dopamine agonist action to modify gastric secretion in the rat. Costall B, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):61-9

Dopamine D1 receptor mediation of the discriminative stimulus properties of SKF 38393. Cunningham KA, et al. **Eur J Pharmacol** 1985 Dec 10; 119(1-2):121-5

A novel long-lasting dopamine receptor blocker: haloperidol-bovine serum albumin conjugate. Garrigues AM, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):313-9

Guanine nucleotide regulation of agonist interactions at [3H]SCH23390-labeled D1 dopamine receptors in rat striatum. Hess EJ, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):31-8

Evidence for a functional role of dopamine type-1 (D-1) receptors in the substantia nigra of rats. Matthews RT, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):87-93

[3H]SCH 23390 binding sites increase after chronic blockade of D-1 dopamine receptors. Porceddu ML, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):367-70

Dopamine receptors mediating yawning: are they autoreceptors? Serra G, et al. **Eur J Pharmacol** 1986 Jan 21;120(2):187-92

Dopaminergic modulation of ACTH-induced grooming. Spruijt BM, et al. **Eur J Pharmacol** 1986 Jan 29;120(3):249-56

The effects of chronic bromocriptine treatment on behaviour and dopamine receptor binding in the rat striatum. Traub M, et al. **Eur J Pharmacol** 1985 Nov 26;118(1-2):147-54

[3H]spiperone and [3H]quinuclidinyl benzilate binding in striatal membranes from rats chronically treated with manganese chloride throughout development and for over two years. Leung TK, et al. **Gen Pharmacol** 1986;17(1):121-3

Selective antagonism of the hypotensive effects of dopamine agonists in spontaneously hypertensive rats. McCoy CE, et al. **Hypertension** 1986 Apr;8(4):298-302

Ganglionic dopamine receptors as mediators of the inhibition of neurogenic vasoconstriction produced by fenoldopam. Lokhandwala MF, et al. **J Auton Pharmacol** 1985 Dec;5(4):301-5

D-2 dopamine receptor-mediated inhibition of pro-opiomelanocortin synthesis in rat intermediate lobe. Abolition by pertussis toxin or activators of adenylate cyclase. Cote TE, et al. **J Biol Chem** 1986 Apr 5;261(10):4555-61

In vivo displacement by 3-PPP enantiomers of N,N-dipropyl-5,6-ADTN from dopamine receptor-binding sites in rat striatum. Carlsson A, et al. **J Neural Transm** 1985;64(3-4):173-85

Sub-chronic administration of (-)-3-PPP and central dopamine receptor sensitivity changes. Hjorth S, et al. **J Neural Transm** 1985; 64(3-4):187-98

Down-regulation of dopamine D-2, 5-HT2 receptors and beta-adrenoceptors in rat brain after prolonged treatment with a new potential antidepressant, Lu 19-005. Nowak G, et al. **J Neural Transm** 1985;64(3-4):227-38

A homologous series of N-alkylated cis-(+)-(1 S, 2 R)-5-methoxy-1-methyl-2-aminotetralins: central dopamine receptor antagonists showing profiles ranging from classical antagonism to selectivity for autoreceptors. Svensson K, et al. **J Neural Transm** 1986; 65(1):29-38

(+)-UH 232 and (+)-UH 242: novel stereoselective dopamine receptor antagonists with preferential action on autoreceptors. Svensson K, et al. **J Neural Transm** 1986;65(1):1-27

Dopaminergic regulation of cone retinomotor movement in isolated teleost retinas: I. Induction of cone contraction is mediated by D2 receptors. Dearry A, et al. **J Neurochem** 1986 Apr;46(4):1006-21

[3H]Fluphenazine binding to brain membranes: simultaneous measurement of D-1 and D-2 receptor sites. Morgan DG, et al. **J Neurochem** 1986 May;46(5):1623-31

Identification of dopamine 'D3' and 'D4' binding sites, labelled with [3H]2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene, as high agonist affinity states of the D1 and D2 dopamine receptors, respectively. Urwyler S, et al. **J Neurochem** 1986 Apr;46(4):1058-67

Evidence for dopamine release and metabolism beyond the control of nerve impulses and dopamine receptors in rat substantia nigra. Nissbrandt H, et al. **J Pharm Pharmacol** 1985 Dec;37(12):884-9

Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: studies in vivo. Galloway MP, et al. **J Pharmacol Exp Ther** 1986 Mar;236(3):689-98

Characterization of dopaminergic receptor sites in bovine pineal gland. Govitrapong P, et al. **J Pineal Res** 1984;1(3):215-26

Elevation of acetylcholine levels in striatum of rat brain by LY163502, trans-(-)-5,5a,6,7,8,9a,10-octahydro-6-propylpyrimido less than 4,5-g greater than quinolin-2-amine dihydrochloride, a potent and stereospecific dopamine (D2) agonist. Bymaster FP, et al. **Life Sci** 1986 Jan 27;38(4):317-22

Evidence for a D2 dopamine receptor in frog retina that decreases cyclic AMP accumulation and serotonin N-acetyltransferase activity. Iuvone PM. **Life Sci** 1986 Jan 27;38(4):331-42

Pharmacological profile of the abeorphine 201-678, a potent orally active and long lasting dopamine agonist. Jaton AL, et al. **Life Sci** 1986 Jan 13;38(2):155-63

Epinephrine and norepinephrine stimulation of adenylate cyclase in bovine retina homogenate: evidence for interaction with the dopamine D1 receptor. Vanderheyden P, et al. **Life Sci** 1986 Mar 31; 38(13):1221-7

ACTH-(1-24) and alpha-MSH antagonize dopamine receptor-mediated inhibition of striatal dopamine and acetylcholine release. Versteeg DH, et al. **Life Sci** 1986 Mar 3;38(9):835-40

Dopamine, acting through D-2 receptors, inhibits rat striatal adenylate cyclase by a GTP-dependent process. Cooper DM, et al. **Mol Pharmacol** 1986 Feb;29(2):113-9

[3H]-domperidone labels only a single population of receptors which convert from high to low affinity for dopamine in rat brain. Grigoriadis D, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan; 332(1):21-5

Analysis of [3H]spiperone binding sites in the rat striatum and frontoparietal cortex by means of quantitative receptor autoradiography after inactivation of dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vivo: selective protection by sulpiride in the striatum. Fuxe K, et al. **Neurosci Lett** 1986 Feb 28;64(2):163-8

Locomotor depression in mice by norcocaine does not involve central alpha 2-adrenergic or presynaptic dopamine receptors. Reith ME, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):305-7

Different behavioural patterns induced by the dopamine agonist apomorphine analysed by multivariate statistics. Ståhle L, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):291-8

Dopaminergic activity of four analogs of butaclamol. Collu R, et al. **Pharmacol Res Commun** 1985 Dec;17(12):1153-7

Modulation by dopaminergic and serotonergic systems of cholinergic interneurons in nucleus accumbens and striatum. Bluth R, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):753-63

Effect of DA1 receptor blockade with SCH 23390 on the renal response

to electrical stimulation of the renal nerves. Bradley T, et al. **Proc Soc Exp Biol Med** 1986 Apr;181(4):492-7

Persistence of low hypothalamic dopaminergic activity after removal of chronic estrogen treatment. Gottschall PE, et al. **Proc Soc Exp Biol Med** 1986 Jan;181(1):78-86

Neuroleptics, dopamine, and schizophrenia. Pickar D. **Psychiatr Clin North Am** 1986 Mar;9(1):35-48

RECEPTORS, DRUG

A common structural model for central nervous system drugs and their receptors. Lloyd EJ, et al. **J Med Chem** 1986 Apr;29(4):453-62

Effects of antidepressants on uptake and receptor systems in the brain. Fuller RW, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):485-90 (22 ref.)

[Ergot alkaloids and central monoaminergic receptors] Goldstein M. **J Pharmacol** 1985;16 Suppl 3:21-7 (Eng. Abstr.) **(Fre)**

RECEPTORS, ENDOGENOUS SUBSTANCES

Chronic treatment with phenobarbital decreases the expression of rat liver EGF and insulin receptors. Hwang DL, et al. **Biochem Biophys Res Commun** 1986 Mar 13;135(2):501-6

Mapping of gonadotropin-releasing hormone receptor binding site. Keinan D, et al. **Biochemistry** 1985 Dec 17;24(26):7728-32

Ontogeny of receptors for thyrotropin-releasing hormone in the rat brain. Blanchard L, et al. **Brain Res** 1986 Jan;389(1-2):35-8

Prolactin (PRL), follicle-stimulating hormone, and luteinizing hormone are regulators of testicular PRL receptors in golden hamsters. Klemcke HG, et al. **Endocrinology** 1986 Feb;118(2):773-82

Corticotropin-releasing factor binding to the anterior pituitary receptor is modulated by divalent cations and guanyl nucleotides. Perrin MH, et al. **Endocrinology** 1986 Mar;118(3):1171-9

Covalent cross-linking of growth hormone-releasing factor to pituitary receptors. Veliçelebi G, et al. **Endocrinology** 1986 Apr; 118(4):1278-83

Glucocorticoids increase cholecystokinin receptors and amylase secretion in pancreatic acinar AR42J cells. Logsdon CD. **J Biol Chem** 1986 Feb 15;261(5):2096-101

Phorbol ester or diacylglycerol modulates somatostatin binding to its receptors on rat pancreatic acinar cell membranes. Matozaki T, et al. **J Biol Chem** 1986 Jan 25;261(3):1414-20

Norepinephrine decreases EGF binding in primary rat hepatocyte cultures. Cruise JL, et al. **J Cell Physiol** 1986 Apr;127(1):39-44

A study of the cerebral cortex cholecystokinin receptor using two radiolabelled probes: evidence for a common CCK 8 and CCK 4 cholecystokinin receptor binding site. Clark CR, et al. **J Neurochem** 1986 Apr;46(4):1094-101

A search for receptors modulating the release of gamma-[3H]aminobutyric acid in rabbit caudate nucleus slices. Limberger N, et al. **J Neurochem** 1986 Apr;46(4):1109-17

Relationship between pituitary GnRH-binding sites and pituitary release of gonadotrophins in post-partum beef cows. Leung K, et al. **J Reprod Fertil** 1986 Jan;76(1):53-63

Characterization of luteinizing hormone-releasing hormone receptor binding in rat pituitary cell monolayer cultures; influence of intercellular communication. Andries M, et al. **Mol Cell Endocrinol** 1986 Feb; 44(2):147-58

Study of species specificity in growth hormone-releasing factor (GRF) interaction with vasoactive intestinal peptide (VIP) receptors using GRF and intestinal VIP receptors from rat and human: evidence that Ac-Tyr1hGRF is a competitive VIP antagonist in the rat. Laburthe M, et al. **Mol Pharmacol** 1986 Jan;29(1):23-7

Cholecystokinin and its receptors in vertebrates and invertebrates. Vigna SR. **Peptides** 1985;6 Suppl 3:283-7

Distribution of corticotropin-releasing factor receptors in primate brain. Millan MA, et al. **Proc Natl Acad Sci USA** 1986 Mar;83(6):1921-5

Excitatory amino acid recognition sites coupled with inositol phospholipid metabolism: developmental changes and interaction with alpha 1-adrenoceptors. Nicoletti F, et al. **Proc Natl Acad Sci USA** 1986 Mar; 83(6):1931-5

[Thyroliberin receptors in the brain of ground squirrels (Citellus undulatus) during winter hibernation] Iarygin KN, et al. **Dokl Akad Nauk SSSR** 1986;286(5):1268-71 **(Rus)**

RECEPTORS, ENDORPHIN

GABAA receptors and opioid receptors as examples of multiple site receptor proteins. Barnard E. **Alcohol Drug Res** 1985-86;6(2-3):63-5

Identification of distinct binding site subunits of mu and delta opioid receptors. Howard AD, et al. **Biochemistry** 1986 Jan 28;25(2):357-60

Examination of spinal monoamine receptors through which brainstem opiate-sensitive systems act in the rat. Jensen TS, et al. **Brain Res** 1986 Jan 15;363(1):114-27

Interaction between growth hormone releasing factor (GRF) and somatostatin analogue (SMS 201-995) in normal subjects. Losa M, et al. **Clin Endocrinol (Oxf)** 1985 Dec;23(6):715-20

The stimulation of food intake by selective agonists of mu, kappa and delta opioid receptors. Gosnell BA, et al. **Life Sci** 1986 Mar 24; 38(12):1081-8

Pharmacology of opioids. Part 1. Basic aspects. Mather LE. **Med J Aust** 1986 Apr 14;144(8):424-7

Proposals for the mu-active conformation of the enkephalin analog Tyr-cyclo[(-N gamma-D-A2-bu-Gly-Phe-Leu-). Maigret B, et al. **Mol Pharmacol** 1986 Mar;29(3):314-20

Opioid peptides decrease noradrenaline release and blood pressure in the rabbit at peripheral receptors. Szabo B, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):50-6

Behavioural and spectrum power effects of opioid peptides in chicks. Nisticò G, et al. **Peptides** 1985;6 Suppl 3:137-41

Developmental, behavioral, and opiate receptor changes after prenatal or postnatal beta-endorphin, CRF, or Tyr-MIF-1. Zadina JE, et al. **Psychoneuroendocrinology** 1985;10(4):367-83

[The role of mu- and delta-opiate receptors in the realization of the autonomic effects of opioid peptides] Martynova ER, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):60-3 (Eng. Abstr.) **(Rus)**

RECEPTORS, GABA-BENZODIAZEPINE

[3H]muscimol and [3H]quinuclidinyl benzilate binding in rat cortex in the abstinence after long-term barbital treatment. Nordberg A, et al. **Acta Physiol Scand** 1986 Jan;126(1):153-6

GABAA receptors and opioid receptors as examples of multiple site receptor proteins. Barnard E. **Alcohol Drug Res** 1985-86;6(2-3):63-5

Diazepam inhibits potassium-induced aldosterone secretion in adrenal glomerulosa cell. Shibata H, et al. **Biochem Biophys Res Commun** 1986 Mar 28;135(3):994-9

The gamma-aminobutyrate/benzodiazepine receptor from pig brain. Purification and characterization of the receptor complex from cerebral cortex and cerebellum. Kirkness EF, et al. **Biochem J** 1986 Jan 1; 233(1):265-70

Isolation of the gamma-aminobutyric acid/benzodiazepine receptor. Stephenson FA. **Biochem Soc Trans** 1985 Dec;13(6):1097-9

Effect of single or repeated estrogen administration on tuberoinfundibular GABA neurons and anterior pituitary GABA receptors: biochemical and functional studies. Apud JA, et al. **Brain Res** 1985 Dec 30; 361(1-2):146-53

Dark-rearing affects the development of benzodiazepine receptors in the central visual structures of rat brain. Schliebs R, et al. **Brain Res** 1986 Jan;389(1-2):179-85

Ontogeny of the GABA receptor complex in chick brain: studies in vivo and in vitro. Tehrani MH, et al. **Brain Res** 1986 Feb;390(1):91-8

Enhancement of GABA binding by the benzodiazepine partial agonist CGS9896. Meiners BA, et al. **Eur J Pharmacol** 1985 Dec 10; 119(1-2):61-5

GABAB receptors in the rabbit uterus may mediate contractile responses. Riesz M, et al. **Eur J Pharmacol** 1985 Dec 17;119(3):199-204

Long-term exposure of cortical cell cultures to clonazepam reduces benzodiazepine receptor binding. Sher PK. **Exp Neurol** 1986 May; 92(2):360-8

Benzodiazepine receptors resolved. Richards JG, et al. **Experientia** 1986 Feb 15;42(2):121-6 (56 ref.)

Presence of gamma-aminobutyric acid and its specific receptor binding sites in the human term placenta. Erdö SL, et al. **Gynecol Obstet Invest** 1985;20(4):199-203

Computer-controlled large scale production of high specific activity [11C]RO 15-1788 for PET studies of benzodiazepine receptors. Suzuki K, et al. **Int J Appl Radiat Isot** 1985 Dec;36(12):971-6

The postganglionic excitatory innervation of the mouse urinary bladder and its modulation by prejunctional GABAB receptors. Santicioli P, et al. **J Auton Pharmacol** 1986 Mar;6(1):53-66

Diazepam in blood of Danish drivers: occurrence as shown by gas-liquid chromatographic assay following radioreceptor screening. Worm K, et al. **J Forensic Sci Soc** 1985 Nov-Dec;25(6):407-12

GABA-noradrenergic interaction: evidence for differential sites of action for GABA-A and GABA-B receptors. Suzdak PD, et al. **J Neural Transm** 1985;64(3-4):163-72

Is GABA-stimulated [3H]flunitrazepam binding modulated by benzodiazepine receptor ligands? [letter] Mennini T. **J Neurochem** 1986 Apr;46(4):1326-7

Autoradiographic localization of benzodiazepine receptor binding in dissociated cultures of fetal mouse cerebral cortex. Sher PK, et al. **J Neurochem** 1986 Mar;46(3):899-904

Antibodies recognising the GABAA/benzodiazepine receptor including its regulatory sites. Stephenson FA, et al. **J Neurochem** 1986 Mar; 46(3):854-61

In vitro uptake of benzodiazepines by rat pineal gland. Lowenstein PR, et al. **J Pineal Res** 1984;1(3):207-13

Characterization of benzodiazepine binding sites after short-wave photo-affinity labeling with flunitrazepam. Herblin WF. **Life Sci** 1986 Feb 10;38(6):507-14

Discriminative and aversive properties of beta-carboline-3-carboxylic acid ethyl ester, a benzodiazepine receptor inverse agonist, in rhesus monkeys. Takada K, et al. **Life Sci** 1986 Mar 17;38(11):1049-56

A comparison of methods for removal of endogenous GABA from brain membranes prepared for binding assays. Fisher TE, et al. **Neurochem Res** 1986 Jan;11(1):1-8

Modulation of the GABA-benzodiazepine receptor complex by taurine in rat brain membranes. Malminen O, et al. **Neurochem Res** 1986 Jan; 11(1):85-94

The effects of yohimbine on exploratory and locomotor behaviour are attributable to its effects at noradrenaline and not at benzodiazepine receptors. Chopin P, et al. **Neuropharmacology** 1986 Jan;25(1):53-7

Septal driving of hippocampal theta rhythm: role of gamma-aminobutyrate-benzodiazepine receptor complex in mediating effects of anxiolytics. Quintero S, et al. **Neuroscience** 1985 Dec; 16(4):875-84

Benzodiazepine binding sites in mice forebrain and kidneys: evidence for similar regulation by GABA agonists. Rägo LK, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):1-3

Benzodiazepine-like effects of inosine on punished behavior of pigeons. Witkin JM, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):121-5

Effects of the benzodiazepine receptor ligands midazolam, Ro 15-1788, and Ro 5-4864, alone and in combinations, on platelet serotonin uptake. Lingjaerde O. **Pharmacopsychiatry** 1986 Jan;19(1):15-8

The effects of compounds related to gamma-aminobutyrate and benzodiazepine receptors on behavioural responses to anxiogenic stimuli in the rat: extinction and successive discrimination. Buckland C, et al. **Psychopharmacology (Berlin)** 1986;88(3):285-95

Effects of chlordiazepoxide training dose on the mixed agonist-antagonist properties of benzodiazepine receptor antagonist Ro 15-1788, in a drug discrimination procedure. De Vry J, et al. **Psychopharmacology (Berlin)** 1986;88(2):177-83

A comparison between chlordiazepoxide and CL 218,872, a synthetic non-benzodiazepine ligand for benzodiazepine receptors, on serotonin and catecholamine turnover in brain. McElroy JF, et al. **Psychopharmacology (Berlin)** 1986;88(1):105-8

The neonatal development of benzodiazepine receptor subtypes in the rat cerebral cortex and cerebellum. Watanabe Y, et al. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):335-42

[GABA receptor function and manic depressive disease] Hetmar O, et al. **Nord Med** 1986;101(2):62-5 (Eng. Abstr.) **(Dan)**

[Gamma-aminobutyric acid (GABA) activates three types of receptor-ionophore complex] Akaike N. **Yakugaku Zasshi** 1985 Oct; 105(10):926-36 (Eng. Abstr.) **(Jpn)**

[Interaction of piracetam with 3H-imipramine binding sites and the GAMA-benzodiazepine receptor complex of brain membranes] Rozhanets VV, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):40-2 (Eng. Abstr.) **(Rus)**

RECEPTORS, SEROTONIN

Serotonin receptor involvement in the avoidance learning deficit caused by p-chloroamphetamine-induced serotonin release. Ogren SO. **Acta Physiol Scand** 1986 Mar;126(3):449-62

Clonazepam-induced up-regulation of serotonin1 and serotonin2 binding sites in rat frontal cortex. Wagner HR, et al. **Adv Neurol** 1986; 43:645-51

Inhibition of monoamine oxidase in monoaminergic neurones in the rat brain by irreversible inhibitors. Fagervall I, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1381-7

Increased tryptophan hydroxylase activity in serotonergic nerve terminals spared by 5,7-dihydroxytryptamine. Stachowiak MK, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1241-8

5-Carboxamidotryptamine is a selective agonist at 5-hydroxytryptamine receptors mediating vasodilatation and tachycardia in anaesthetized cats. Connor HE, et al. **Br J Pharmacol** 1986 Feb;87(2):417-26

Characterization and localization of serotonin receptors in human brain postmortem. Biegon A, et al. **Brain Res** 1986 Jan 15;363(1):91-8

Effects of pargyline, reserpine and neurotoxin lesions on [3H]tryptamine binding sites in rat brain. Cascio CS, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):101-5

Inhibition of forskolin-stimulated adenylate cyclase activity by 5-HT receptor agonists. Devivo M, et al. **Eur J Pharmacol** 1985 Dec 17; 119(3):231-4

Effects of antidepressant drug combinations on cortical 5-HT2 receptors and wet-dog shakes in rats. Koshikawa F, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):273-81

Presynaptic serotonin receptors regulate [3H]serotonin release from rat spinal cord synaptosomes. Stauderman KA, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):107-9

[3H]DOB: a specific agonist radioligand for 5-HT2 serotonin receptors. Titeler M, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):145-6

Subtypes of the 5-HT receptor mediating the behavioural responses to 5-methoxy-N,N-dimethyltryptamine in the rat. Tricklebank MD, et al. **Eur J Pharmacol** 1985 Oct 29;117(1):15-24

Down-regulation of dopamine D-2, 5-HT2 receptors and beta-adrenoceptors in rat brain after prolonged treatment with a new potential antidepressant, Lu 19-005. Nowak G, et al. **J Neural Transm** 1985;64(3-4):227-38

Identification of multiple binding sites for [3H]5-hydroxytryptamine in the rat CNS. Blurton PA, et al. **J Neurochem** 1986 May; 46(5):1392-8

Stimulation of the serotonin autoreceptor prevents the calcium-calmodulin-dependent increase of serotonin biosynthesis in rat raphe slices. Sawada M, et al. **J Neurochem** 1986 Mar;46(3):963-7

Stereoselective blockade at the 5-HT autoreceptor and inhibition of radioligand binding to central 5-HT recognition sites by the optical isomers of methiothepin. Hibert M, et al. **Neuropharmacology** 1986 Jan; 25(1):1-4

Effects of MK-212 (6-chloro-2[1-piperazinyl]pyrazine) on schedule-controlled behavior and their reversal by 5-HT antagonists in the pigeon. Mansbach RS, et al. **Neuropharmacology** 1986 Jan; 25(1):13-9

Modulation by dopaminergic and serotonergic systems of cholinergic interneurons in nucleus accumbens and striatum. Bluth R, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):753-63

Head-twitch response induced by ergometrine in mice: behavioural evidence for direct stimulation of central 5-hydroxytryptamine receptors by ergometrine. Balsara JJ, et al. **Psychopharmacology (Berlin)** 1986;88(3):275-8

Evidence that serotonin receptors are involved in the anticonvulsant effect of yohimbine in mice. Ludvig N, et al. **Psychopharmacology (Berlin)** 1986;88(1):82-5

1-(1-Naphthyl)piperazine, a central serotonin agonist. Fuller RW, et al. **Res Commun Chem Pathol Pharmacol** 1986 Jan;51(1):37-45

Dependence of the antagonism at human platelet 5-HT2 receptors by ketanserin on the reaction pH. De Clerck F, et al. **Thromb Res** 1985 Dec 1;40(5):581-96

[In vivo study of central serotoninergic receptors in man using positron tomography] Baron JC, et al. **Rev Neurol (Paris)** 1985; 141(8-9):537-45 (Eng. Abstr.) **(Fre)**

REFLEX

Effects of graded changes in reflex renal nerve activity on renal function. Beers ET, et al. **Am J Physiol** 1986 Mar;250(3 Pt 2):F559-65

Cardiovascular and neuroendocrine responses to behavioral stress after central or peripheral barodenervation in rats. Buchholz RA, et al. **Brain Res** 1986 Feb 19;365(2):360-4

Inhibition of the swallowing reflex by local application of serotonergic agents into the nucleus of the solitary tract. Kessler JP, et al. **Eur J Pharmacol** 1985 Nov 26;118(1-2):77-85

Effects of antidepressant drug combinations on cortical 5-HT2 receptors and wet-dog shakes in rats. Koshikawa F, et al. **Eur J Pharmacol** 1985 Dec 3;118(3):273-81

Dopamine receptors mediating yawning: are they autoreceptors? Serra G, et al. **Eur J Pharmacol** 1986 Jan 21;120(2):187-92

Supraspinal depressant action of diazepam on the crossed extensor reflex. Kawasaki K, et al. **Neurosci Lett** 1986 Jan 16;63(2):175-9

[Attack of yawning, case report] Miyazaki M, et al. **Rinsho Shinkeigaku** 1985 Sep;25(9):1007-9 (Eng. Abstr.) **(Jpn)**

REINFORCEMENT SCHEDULE

Brief exposure to contingent reinforcement produces a sustained increment in the strength of an elicited response. Hutchinson RR, et al. **J Exp Anal Behav** 1986 Mar;45(2):189-94

Effects of chlorpromazine on fixed-ratio responding: modification by fixed-interval discriminative stimuli. Witkin JM. **J Exp Anal Behav** 1986 Mar;45(2):195-205

RESERPINE

Ultrastructural alterations of the egg chambers of Galleria mellonella L. (Lepidoptera) developing after reserpine administration. Głowacka SK, et al. **Acta Biol Hung** 1985;36(1):25-44

Modification of reserpine induced rigidity by dopaminergic and alpha-adrenergic drugs. Anderson RJ. **Acta Neurol Scand** 1985 Dec; 72(6):584-9

The effect of reserpine treatment on choline acetyltransferase activity in rat submaxillary glands. Ekström J. **Acta Physiol Scand** 1986 Jan; 126(1):103-6

NPY--a mediator of reserpine-resistant, non-adrenergic vasoconstriction in cat spleen after preganglionic denervation? Lundberg JM, et al. **Acta Physiol Scand** 1986 Jan;126(1):151-2

Stability of reserpine injections and tablets submitted by U.S. hospitals. Coffman HD, et al. **Am J Hosp Pharm** 1986 Jan;43(1):103-9

Effect of denervation and/or reserpine-induced changes on adrenomedullary catecholamines in pigeon: a fluorescence histochemical study. Mahata SK, et al. **Basic Appl Histochem** 1985;29(4):331-6

Studies on the effect of reserpine on the peroxidase activity of submaxillary gland. Chakraborty R, et al. **Biochem Pharmacol** 1986 Apr 15; 35(8):1235-9

Reserpine-induced effects in the adrenergic neuron as studied with cytofluorimetric scanning. Larsson PA, et al. **Brain Res Bull** 1986 Jan; 16(1):63-74

Effects of pargyline, reserpine and neurotoxin lesions on [3H]tryptamine binding sites in rat brain. Cascio CS, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):101-5

Reserpine-resistant responses to nerve stimulation in the cat nictitating membrane involve the release of newly synthesized noradrenaline. Duval N, et al. **Eur J Pharmacol** 1986 Mar 11;122(1):93-101

Metorphamide levels in chromaffin cells increase after treatment with reserpine. Eiden LE, et al. **J Neurochem** 1986 May;46(5):1651-4

Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. Parker EM, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):179-92

Frequency- and reserpine-dependent chemical coding of sympathetic transmission: differential release of noradrenaline and neuropeptide Y from pig spleen. Lundberg JM, et al. **Neurosci Lett** 1986 Jan 2; 63(1):96-100

Reserpine and the monoaminergic regulation of adrenal dopamine beta-hydroxylase activity. Lima L, et al. **Neuroscience** 1986; 17(1):235-45

[Histoenzymatic studies of the kidneys of albino rats after experimental administration of serpasil and deslanoside] Zarebska A. **Patol Pol** 1985 Apr-Jun;36(2):200-7 (Eng. Abstr.) **(Pol)**

RUBIDIUM

Modulation of Ca2+-dependent K+ transport by modifications of the NAD+/NADH ratio in intact human red cells. Alvarez J, et al. **Biochim Biophys Acta** 1986 Apr 14;856(2):408-11

Influence of medium amino acids on the ouabain sensitive and insensitive 86Rb+-fluxes in HeLa cells. Schaefer A, et al. **Experientia** 1986 Apr 15;42(4):436-7

Effects of lithium and rubidium on shock-induced changes in open-field activity. Hines G. **Psychopharmacology (Berlin)** 1986;88(2):209-12

SCHIZOPHRENIA

Enkephalin analogue in schizophrenia. Double blind cross-over trial. Joergensen A, et al. **Acta Psychiatr Scand** 1986 Jan;73(1):45-8

Social skills training for schizophrenic individuals at risk for relapse. Liberman RP, et al. **Am J Psychiatry** 1986 Apr;143(4):523-6

Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. Berman KF, et al. **Arch Gen Psychiatry** 1986 Feb;43(2):126-35

Dopamine agonist treatment of schizophrenia with N-propylnorapomorphine. Tamminga CA, et al. **Arch Gen Psychiatry** 1986 Apr;43(4):398-402

Vitamin C status in schizophrenia. Subotičanec K. **Bibl Nutr Dieta** 1986;(38):173-81

Central dopamine hyperactivity in rats mimics abnormal acoustic startle response in schizophrenics. Swerdlow NR, et al. **Biol Psychiatry** 1986 Jan;21(1):23-33

Acute schizophrenia. Johnstone EC. **Br J Hosp Med** 1985 Oct; 34(4):198-201

Chronic schizophrenia. Morgan R. **Br J Hosp Med** 1985 Oct; 34(4):202-5

The effect of propranolol and thioridazine on positive and negative symptoms of schizophrenia. Eccleston D, et al. **Br J Psychiatry** 1985 Dec;147:623-30

Homovanillic acid (HVA) urinary excretion and day/night rhythm of chronic schizophrenic patients. Preliminary observations. Mathieu P, et al. **Encephale** 1985 Sep-Oct;11(5):199-202

The universal enervating triad: psychopharmaceutical considerations of anxiety, schizophrenia, and depression. Miller TW, et al. **Issues Ment Health Nurs** 1984;6(3-4):275-91

Stability of the postpsychotic depression syndrome. Siris SG, et al. **J Clin Psychiatry** 1986 Feb;47(2):86-8

A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrenic patients. Tuason VB. **J Clin Psychiatry** 1986 Mar;47(3):126-9

The natural course of schizophrenia and effective maintenance drug treatment. Davis JM, et al. **J Clin Psychopharmacol** 1986 Feb; 6(1 Suppl):2S-10S (79 ref.)

Dosage strategies with long-acting injectable neuroleptics, including haloperidol decanoate. Kane JM. **J Clin Psychopharmacol** 1986 Feb; 6(1 Suppl):20S-23S

Drug-behavior therapy outcomes with chronic schizophrenics [letter] Liberman RP, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):52-3

The efficacy of antipsychotic drugs and family therapies in the maintenance treatment of schizophrenia. Schooler NR. **J Clin Psychopharmacol** 1986 Feb;6(1 Suppl):11S-19S (29 ref.)

A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety, and dosage equivalence. Vasavan Nair NP, et al. **J Clin Psychopharmacol** 1986 Feb;6(1 Suppl):30S-37S

Treatment of uncooperative psychiatric patients in the community: Mental Health Act in need of reform. Brahams, D. **Lancet** 1986 Apr 12; 1(8485):863-4

Postmortem central catecholamines and antemortem cognitive impairment in elderly schizophrenics and controls. Bridge TP, et al. **Neuropsychobiology** 1985;14(2):57-61

24-hour plasma levels of prolactin, cortisol, growth hormone and catecholamines in schizophrenic patients. Kemali D, et al. **Neuropsychobiology** 1985;14(3):109-14

Pharmacotherapy of chronic hospitalized schizophrenics: prescription practices. Wilson WH, et al. **Neuropsychobiology** 1985;14(2):75-82

Approaches to the assessment of schizophrenia in Europe. Berner P, et al. **Pharmacopsychiatry** 1986 Jan;19(1):33-6

A German multicentre study on the long-term treatment of schizophrenic outpatients. Pietzcker A. **Pharmacopsychiatry** 1985 Nov;18(6):333-8

Early treatment events and prediction of response to neuroleptics in schizophrenia. Awad AG, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):585-8

The assessment of a psychosocial treatment with chronic schizophrenic patients using neuropsychopharmacological indices. Bütter HJ, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):593-7

Cholecystokinin peptides, dopamine and schizophrenia--a review. Nair NP, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985; 9(5-6):515-24 (60 ref.)

Postmortem neurochemistry in schizophrenia. Bracha HS, et al. **Psychiatr Clin North Am** 1986 Mar;9(1):133-41 (38 ref.)

Integrating treatments in schizophrenia. Carpenter WT Jr, et al. **Psychiatr Clin North Am** 1986 Mar;9(1):153-64 (46 ref.)

The two-syndrome concept and neuroendocrinology of schizophrenia. Crow TJ, et al. **Psychiatr Clin North Am** 1986 Mar;9(1):99-113 (74 ref.)

Neuroleptics, dopamine, and schizophrenia. Pickar D. **Psychiatr Clin North Am** 1986 Mar;9(1):35-48

Cerebrospinal fluid studies of monoamine metabolism in schizophrenia. van Kammen DP, et al. **Psychiatr Clin North Am** 1986 Mar; 9(1):81-97 (94 ref.)

CSF dopamine turnover and positive schizophrenic symptoms after withdrawal of long-term neuroleptic treatment. Frecska E, et al. **Psychiatry Res** 1985 Nov;16(3):221-6

Neuroleptic withdrawal in chronic schizophrenia: CT and endocrine variables relating to psychopathology. Naber D, et al. **Psychiatry Res** 1985 Nov;16(3):207-19

Neuronal cholecystokinin and schizophrenia: pathogenic and therapeutic studies. Tamminga CA, et al. **Psychopharmacology (Berlin)** 1986; 88(3):387-91

A controlled trial of prostaglandin E1 precursor in chronic neuroleptic resistant schizophrenic patients. Vaddadi KS, et al. **Psychopharmacology (Berlin)** 1986;88(3):362-7

[Catamnestic evaluation of the treatment of schizophrenia using insulin coma] Pavlovský P, et al. **Cesk Psychiatr** 1985 Dec;81(6):391-6 (Eng. Abstr.) **(Cze)**

[Fluspirilene in schizophrenia maintenance therapy and its interaction with dexetimide] Skopová J, et al. **Cesk Psychiatr** 1985 Dec;81(6):414-9 (Eng. Abstr.) **(Cze)**

[Contribution of contingent negative variation (CNV) to the study of schizophrenia] Timsit-Berthier M, et al. **Acta Psychiatr Belg** 1985; 85:712-33 (Eng. Abstr.) **(Fre)**

[Benzamides, a therapeutic response adapted to 2 sides, paranoid and hebephrenic, of schizophrenia] Cassan P. **Ann Med Psychol (Paris)** 1985 Jul;143(7):677-82 **(Fre)**

[The prognosis of schizophrenia] Lungershausen E. **Fortschr Med** 1986 Feb 6;104(5):97-100 (Eng. Abstr.) **(Ger)**

[Psychopathologic changes in chronic schizophrenic patients following withdrawal of neuroleptics: relation to therapeutic, neuroendocrine and computer tomography variables] Albus M, et al. **Fortschr Neurol Psychiatr** 1986 Jan;54(1):15-20 (Eng. Abstr.) **(Ger)**

[Proportion of schizophrenia in inpatient treatment morbidity of a defined catchment area] Degenhardt T. **Psychiatr Neurol Med Psychol (Leipz)** 1986 Jan;38(1):20-4 (Eng. Abstr.) **(Ger)**

[Ambulatory treatment and rehabilitation in schizophrenia] Hubschmid T. **Ther Umsch** 1986 Jan;43(1):43-9 (Eng. Abstr.) **(Ger)**

[Monoamine metabolite levels in cerebrospinal fluid of schizophrenic patients] Imazu Y, et al. **Seishin Shinkeigaku Zasshi** 1985; 87(9):634-42 **(Jpn)**

[Monitored supportive treatment of chronic schizophrenia with delayed-action clopenthixol] Welbel L, et al. **Psychiatr Pol** 1985 Mar-Apr;19(2):109-14 (Eng. Abstr.) **(Pol)**

[Features of remissions in adolescents with paroxysmal schizophrenia who have suffered catatono-oneiroid episodes] Simashkova NV. **Zh Nevropatol Psikhiatr** 1986;86(1):86-91 (Eng. Abstr.) **(Rus)**

[Regression analysis of clinical data for purposes of predicting the efficacy of psychopharmacotherapy of episodes of schizophrenia] Zaitsev SG, et al. **Zh Nevropatol Psikhiatr** 1986;86(1):91-7 (Eng. Abstr.) **(Rus)**

[Chronic treatment of schizophrenia with injectable bromperidol decanoate] Suárez Richards M. **Acta Psiquiatr Psicol Am Lat** 1985 Sep; 31(3):222-8 (Eng. Abstr.) **(Spa)**

SCHIZOPHRENIA, PARANOID

Clonazepam: a novel therapeutic adjunct. Freinhar JP, et al. **Int J Psychiatry Med** 1985-86;15(4):321-8

Comparing the effects of pimozide and placebo in a single case experiment. Klieser E, et al. **Pharmacopsychiatry** 1985 Nov;18(6):339-42

Effects of haloperidol on somatostatin-like immunoreactivity in the CSF of Schizophrenic patients. Gattaz WF, et al. **Psychiatry Res** 1986 Jan; 17(1):1-6

[Comparison of the effects of chlorprothixene and haloperidol on hypothalamic function in patients with paranoid schizophrenia] Horodnicki JM, et al. **Psychiatr Pol** 1985 May-Jun;19(3):181-7 (Eng. Abstr.) **(Pol)**

[Changes in the serum thioridazine level after administration of pridinol] Sidorowicz S, et al. **Psychiatr Pol** 1985 Sep-Oct;19(5):423-4 **(Pol)**

SELF STIMULATION

Lateralized decrease in self-stimulation induced by haloperidol in rats with unilateral 6-hydroxydopamine lesions. Carey RJ. **Behav Brain Res** 1985 Dec;18(3):215-22

Pharmaco-ontogeny of reward: enhancement of self-stimulation by D-amphetamine and cocaine in 3- and 10-day-old rats. Barr GA, et al. **Brain Res** 1986 Jan;389(1-2):193-202

Auto-titration technique using intracranial self-stimulation and effects of antianxiety drugs. Ichimaru Y, et al. **Jpn J Pharmacol** 1985 Nov; 39(3):331-8

Antagonism of the effects of the atypical benzodiazepine, Ro 5-4864 on intracranial self-stimulation in the rat. Pellow S, et al. **Pharmacol Biochem Behav** 1986 Feb;24(2):193-7

Reward, performance, and the response strength method in self-stimulating rats: validation and neuroleptics. Hamilton AL, et al. **Physiol Behav** 1985 Dec;35(6):897-904

SENSORY DEPRIVATION

Visual behavior of monocularly deprived kittens treated with 6-hydroxydopamine. Gordon B, et al. **Brain Res** 1986 Jan; 389(1-2):21-9

Effects of neonatal monocular enucleation on the number of GAD-positive puncta in rat visual cortex. Ribak CE, et al. **Exp Brain Res** 1986;62(1):203-6

SEROTONIN

Ablation of serotonergic nerves in the rat pancreas. Lack of effects on hormone secretion and intrinsic blood flow. Jansson L, et al. **Acta Endocrinol (Copenh)** 1985 Dec;110(4):515-21

Mechanisms by which 5HT stimulates ovulation in the immature rat treated with pregnant mare serum gonadotrophin. Wilson CA, et al. **Acta Endocrinol (Copenh)** 1986 Feb;111(2):235-40

Serotonin-containing nerve fibers in the rat spinal cord: electron microscopic immunohistochemistry. Mizukawa K, et al. **Acta Med Okayama** 1986 Feb;40(1):1-10

Evidence for a modulatory influence of centrally administered substance P on a 5-hydroxytryptamine-mediated behavioural response in the male rat. Ogren SO, et al. **Acta Physiol Scand** 1985 Dec;125(4):743-5

Serotonin receptor involvement in the avoidance learning deficit caused by p-chloroamphetamine-induced serotonin release. Ogren SO. **Acta Physiol Scand** 1986 Mar;126(3):449-62

Evidence for a role of brain serotonergic neurotransmission in avoidance learning. Ogren SO. **Acta Physiol Scand [Suppl]** 1985;544:1-71

Bufotenine reconsidered. McLeod WR, et al. **Acta Psychiatr Scand** 1985 Nov;72(5):447-50

Reengineering the brain serotonin system: localized application of specific neurotoxins and fetal serotonergic neurons into the adult CNS. Azmitia EC. **Adv Neurol** 1986;43:493-507

The primate serotonergic system: a review of human and animal studies and a report on Macaca fascicularis. Azmitia EC, et al. **Adv Neurol** 1986;43:407-68 (83 ref.)

Biochemical pharmacology of the serotonin system. Fuller RW. **Adv Neurol** 1986;43:469-80 (76 ref.)

Biochemical mechanisms in 5-hydroxytryptamine-induced human platelet aggregation. de Clerck F, et al. **Agents Actions** 1985 Dec; 17(2):220-8

Substance P, 5-hydroxytryptamine, and bradykinin stimulate abdominal visceral afferents. Lew WY, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 2):R465-73

Effect of amine on temperature-responsive neuron in slice preparation of rat brain stem. Watanabe T, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 2):R553-9

High-affinity imipramine binding and serotonin uptake in platelets of eight adolescent and ten adult obsessive-compulsive patients. Weizman A, et al. **Am J Psychiatry** 1986 Mar;143(3):335-9

Pemoline and urinary excretion of catecholamines and indoleamines in children with attention deficit disorder. Zametkin AJ, et al. **Am J Psychiatry** 1986 Mar;143(3):359-62

Effect of luminally administered serotonin and substance P on jejunal handling of water and electrolytes. McFadden D, et al. **Am J Surg** 1986 Jan;151(1):81-6

Serotonin transport by platelet plasma and granule membranes. Rudnick G, et al. **Ann NY Acad Sci** 1985;456:277-8

Neurochemical effects of buspirone in rat hippocampus: evidence for selective activation of 5HT neurons. Mennini T, et al. **Arch Int Pharmacodyn Ther** 1986 Jan;279(1):40-9

Catecholaminergic and serotoninergic brain structures in European green frogs: an autoradiographical study. Diederen JH, et al. **Basic Appl Histochem** 1985;29(4):297-308

The behavioral effects of depletions of brain serotonin induced by 5,7-dihydroxytryptamine vary with time after administration. Gately PF, et al. **Behav Neural Biol** 1986 Jan;45(1):31-42

Influences of amino acids on the circadian rhythms of brain neurotransmitters. Angelova C, et al. **Bibl Nutr Dieta** 1986; (38):72-81

Uptake of tryptophan into the brain: dietary influences on serotoninergic function. Bender DA. **Bibl Nutr Dieta** 1986;(38):82-6

Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Reith ME, et al. **Biochem Pharmacol** 1986 Apr 1; 35(7):1123-9

Recent advances in high-performance liquid chromatographic analysis of small molecules. Application of high-performance liquid chromatography with electrochemical detection to the study of neurotransmitters in vivo. Routledge C, et al. **Biochem Soc Trans** 1985 Dec;13(6):1058-61

Human serotonectin: a blood glycoprotein that binds serotonin. Chemical and physiological characterization. Mella A, et al. **Biochim Biophys Acta** 1986 Feb 19;880(2-3):139-46

Seasonal variation of platelet serotonin uptake and 3H-imipramine binding in normal and depressed subjects. Egrise D, et al. **Biol Psychiatry** 1986 Mar;21(3):283-92

The inhibitory action of 5-hydroxytryptamine on gastric secretory function in rats. Cho CH, et al. **Br J Pharmacol** 1986 Feb; 87(2):371-7

5-Carboxamidotryptamine is a selective agonist at 5-hydroxytryptamine receptors mediating vasodilatation and tachycardia in anaesthetized cats. Connor HE, et al. **Br J Pharmacol** 1986 Feb;87(2):417-26

Serotonergic innervation of the forebrain in the North American opossum. Martin GF, et al. **Brain Behav Evol** 1985;26(3-4):196-228

Ontogenesis of [3H]serotonin binding sites in the hypothalamus of the female rat: relation to serotonin-induced LH release in moxestrol-pretreated rats. Becú-Villalobos D, et al. **Brain Res** 1986 Feb;390(1):111-6

Brain serotonin synthesis and Na+,K+-ATPase activity are increased postnatally after prenatal administration of L-tryptophan. Hernández-Rodriguez J, et al. **Brain Res** 1986 Mar;390(2):221-6

Altered responsiveness to substance P and 5-hydroxytryptamine in cat dorsal horn neurons after 5-HT depletion with p-chlorophenylalanine. Jeftinija S, et al. **Brain Res** 1986 Mar 12;368(1):107-15

Synaptic connections between serotoninergic axon terminals and tyrosine hydroxylase-immunoreactive neurons in the arcuate nucleus of the rat hypothalamus. A combination of electron microscopic autoradiography and immunocytochemistry. Kiss J, et al. **Brain Res** 1986 Feb 5; 364(2):284-94

Modulatory action of serotonin on glutamate-induced excitation of cerebellar Purkinje cells. Lee M, et al. **Brain Res** 1985 Dec 30; 361(1-2):107-13

Distribution of enkephalin-immunoreactive cell bodies in relation to serotonin-containing neurons in the raphe nuclei of the cat: immunohistochemical evidence for the coexistence of enkephalins and serotonin in certain cells. Léger L, et al. **Brain Res** 1986 Jan 1; 362(1):63-73

Effects of intrahypothalamically administered norepinephrine, serotonin and bombesin on thermoregulation in the deermouse (Peromyscus maniculatus). Lin LH, et al. **Brain Res** 1986 Feb 5;364(2):212-9

Excitation of lateral horn neurons of the neonatal rat spinal cord by 5-hydroxytryptamine. Ma RC, et al. **Brain Res** 1986 Jan; 389(1-2):89-98

Studies on serotonin-accumulating cells in rabbit retinal cultures. Osborne NN, et al. **Brain Res** 1986 Jan 8;362(2):287-98

Serotonergic mechanisms in brains of suicide victims. Owen F, et al. **Brain Res** 1986 Jan 1;362(1):185-8

Serotonin decreases a background current and increases calcium and calcium-activated current in pedal neurons of Hermissenda. Jacklet JW, et al. **Cell Mol Neurobiol** 1985 Dec;5(4):407-12

The organization of serotonin-immunoreactive neuronal systems in the brain of the crested newt, Triturus cristatus carnifex Laur. Fasolo A, et al. **Cell Tissue Res** 1986;243(2):239-47

Ultrastructural localization of serotonin in the intrapulmonary neuroepithelial bodies of neonatal rabbits by use of immunoelectron microscopy. Lauweryns JM, et al. **Cell Tissue Res** 1986;243(3):455-9

Distributional pattern of serotonin-immunoreactive nerve fibers in the lateral geniculate nucleus of the rat, cat and monkey (Macaca fuscata). Ueda S, et al. **Cell Tissue Res** 1986;243(2):249-53

Determination of serotonin and melatonin in rat pineal gland by high-performance liquid chromatography with ultraviolet and fluorometric dual detection. Wakabayashi H, et al

Chem Pharm Bull (Tokyo) 1985 Sep;33(9):3875-80

Tolbutamide increases hypothalamic serotonin activity in the rat. Grunstein HS, et al. **Diabetes** 1986 Apr;35(4):475-80

Noradrenergic-serotonergic interactions and nociception in the rat. Archer T, et al. **Eur J Pharmacol** 1986 Jan 29;120(3):295-307

8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) elicits eating in free-feeding rats by acting on central serotonin neurons. Bendotti C, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):147-50

Supersensitivity of alpha 2-adrenoceptors modulating [3H]5-HT release after noradrenergic denervation with DSP4. Benkirane S, et al. **Eur J Pharmacol** 1985 Dec 10;119(1-2):131-3

d- and l-isomers of fenfluramine differ markedly in their interaction with brain serotonin and catecholamines in the rat. Invernizzi R, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):9-15

Central serotonergic responses and behavioural adaptation to repeated immobilisation: the effect of the corticosterone synthesis inhibitor metyrapone. Kennett GA, et al. **Eur J Pharmacol** 1985 Dec 17; 119(3):143-52

Inhibition of the swallowing reflex by local application of serotonergic agents into the nucleus of the solitary tract. Kessler JP, et al. **Eur J Pharmacol** 1985 Nov 26;118(1-2):77-85

Presynaptic serotonin receptors regulate [3H]serotonin release from rat spinal cord synaptosomes. Stauderman KA, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):107-9

Enhancement of cerebellar Purkinje cell complex discharge activity by microiontophoretic serotonin. Strahlendorf JC, et al. **Exp Brain Res** 1986;61(3):614-24

Lack of inhibition of thrombin-induced rise in intracellular Ca2+ levels and 5-hydroxytryptamine secretion by 1-oleoyl-2-acetylglycerol in human platelets. Krishnamurthi S, et al. **FEBS Lett** 1986 Feb 17; 196(2):365-9

Verapamil reversal of serotonin-induced jejunal secretion of water and electrolytes in awake dogs. Zinner MJ, et al. **Gastroenterology** 1986 Mar;90(3):515-9

Effects of prenatal exposure to lithium on indoleamines in maturing mouse brain. Hoff KM, et al. **Gen Pharmacol** 1986;17(1):101-3

Effects of serotonin on the internal anal sphincter: in vivo manometric study in rats. Goldberg M, et al. **Gut** 1986 Jan;27(1):49-54

Effect of whole body irradiation on urinary 5-HT metabolites under the influence of newly synthesized chemical radioprotector. Thakur DK. **Indian J Med Sci** 1985 Oct;39(10):236-9

Pre- and postnatal development of 5-hydroxytryptamine-immunoreactive cells in the superior cervical ganglion of the rat. Häppölä O, et al. **J Auton Nerv Syst** 1986 Jan;15(1):21-31

Inositol 1,4,5-trisphosphate induces aggregation and release of 5-hydroxytryptamine from saponin-permeabilized human platelets. Watson SP, et al. **J Biol Chem** 1986 Apr 25;261(12):5368-72

Automated method to estimate catecholamine and indoleamine content and turnover rates. Freeman GB, et al. **J Chromatogr** 1986 Jan 24; 374(2):239-49

Serotonin syndrome: a case report. Price WA, et al. **J Clin Pharmacol** 1986 Jan;26(1):77-8

Therapeutic effects of serotonin uptake inhibitors in depression. Asberg M, et al. **J Clin Psychiatry** 1986 Apr;47 Suppl:23-35 (199 ref.)

Reversibility of serotonin irritation syndrome with atmospheric anions. Giannini AJ, et al. **J Clin Psychiatry** 1986 Mar;47(3):141-3

Use of serotonergic agents in the clinical assessment of central serotonin function. Murphy DL, et al. **J Clin Psychiatry** 1986 Apr; 47 Suppl:9-15 (77 ref.)

Postnatal development of serotonin nerve fibers in the somatosensory cortex of mice studied by immunohistochemistry. Fujimiya M, et al. **J Comp Neurol** 1986 Apr 8;246(2):191-201

Noradrenergic and serotoninergic innervation of cortical, thalamic, and tectal visual structures in Old and New World monkeys. Morrison JH, et al. **J Comp Neurol** 1986 Jan 1;243(1):117-38

New approaches to the study of bulbospinal (B3) serotonergic neurons in the control of blood pressure. Chalmers JP, et al. **J Hypertension [Suppl]** 1985 Dec;3(4):S5-9

Enzyme-linked immunosorbent assay (ELISA) for detection of antibodies to protein-reactive drugs and metabolites: criteria for identification of antibody activity. Detection and hapten specificity of anti-DNP, anti-captopril and anti-sulphanilamidobenzoic acid. Coleman JW, et al. **J Immunol Methods** 1986 Apr 3;88(1):37-44

Oxidation of 5-hydroxytryptamine and 5,7-dihydroxytryptamine. A new oxidation pathway and formation of a novel neurotoxin. Wrona MZ, et al. **J Med Chem** 1986 Apr;29(4):499-505

Identification of multiple binding sites for [3H]5-hydroxytryptamine in the rat CNS. Blurton PA, et al. **J Neurochem** 1986 May; 46(5):1392-8

Dopaminergic regulation of cone retinomotor movement in isolated teleost retinas: II. Modulation by gamma-aminobutyric acid and serotonin. Dearry A, et al. **J Neurochem** 1986 Apr;46(4):1022-31

Monoamine neurotransmitter metabolism and locomotor activity during chemical hypoxia. Freeman GB, et al. **J Neurochem** 1986 Mar; 46(3):733-8

Brain dialysis: in vivo metabolism of dopamine and serotonin by monoamine oxidase A but not B in the striatum of unrestrained rats. Kato T, et al. **J Neurochem** 1986 Apr;46(4):1277-82

Effect of intrastriatal injection of diisopropylfluorophosphate on acetylcholine, dopamine, and serotonin metabolism. Robinson SE, et al. **J Neurochem** 1986 May;46(5):1632-8

Stimulation of the serotonin autoreceptor prevents the calcium-calmodulin-dependent increase of serotonin biosynthesis in rat raphe slices. Sawada M, et al. **J Neurochem** 1986 Mar;46(3):963-7

VIP neurons as prime synaptic targets for serotonin afferents in rat suprachiasmatic nucleus: a combined radioautographic and immunocytochemical study. Bosler O, et al. **J Neurocytol** 1985 Oct; 14(5):749-63

Influence of long-term immobilization stress on regional blood-brain barrier permeability, cerebral blood flow and 5-HT level in conscious normotensive young rats. Sharma HS, et al. **J Neurol Sci** 1986 Jan; 72(1):61-76

Serotonin decreases the duration of action potentials recorded from tetraethylammonium-treated bullfrog dorsal root ganglion cells. Holz GG 4th, et al. **J Neurosci** 1986 Mar;6(3):620-6

Regulation of the circadian clock in the Aplysia eye: mimicry of neural action by serotonin. Nadakavukaren JJ, et al. **J Neurosci** 1986 Jan; 6(1):14-21

Serotonin enhances the excitatory acetylcholine response in the RB cell cluster of Aplysia californica. Simmons LK, et al. **J Neurosci** 1986 Mar; 6(3):774-81

Prostaglandin D2-induced potentiation of hexobarbitone hypnosis in rats: role of 5-hydroxytryptamine. Bhattacharya SK, et al. **J Pharm Pharmacol** 1985 Dec;37(12):915-6

Mechanisms of the relaxations induced by 5-hydroxytryptamine on the rat isolated caecum. Uguru MO, et al. **J Pharm Pharmacol** 1986 Feb; 38(2):140-3

Influence of chlorpromazine on the accumulation of 5-hydroxytryptamine by interaction with ATP. Gasco MR, et al. **J Pharm Sci** 1985 Nov; 74(11):1188-91

In vivo actions of a calcium channel blocker (nimodipine) on the cerebrovascular response to infused 5-hydroxytryptamine. McCalden TA, et al. **J Pharmacol Exp Ther** 1986 Apr;237(1):36-9

Effects of melatonin and control injections on pineal serotonin and norepinephrine: afternoon injections lower serotonin levels thirty-six percent at light-dark transition. Catalá MD, et al. **J Pineal Res** 1984; 1(1):75-82

Studies on the kinetics of melatonin and N-acetylserotonin in the rat at mid-light and mid-dark. Chan MY, et al. **J Pineal Res** 1984; 1(3):227-36

Differential effect of carbidopa on the concentration of rat pineal and hypothalamic indoleamines. Oxenkrug GF, et al. **J Pineal Res** 1984; 1(4):349-53

Melatonin and N-acetylserotonin stress responses: effects of type of stimulation and housing conditions. Seggie J, et al. **J Pineal Res** 1985; 2(1):39-49

Temporal effects of norepinephrine on pineal serotonin in vitro. Walker RF, et al. **J Pineal Res** 1986;3(1):33-40

Serotonin-induced stimulation of progesterone production by cow luteal cells in vitro. Battista PJ, et al. **J Reprod Fertil** 1986 Jan; 76(1):231-8

Different sensitivities of vasoconstrictor responses to serotonin and KCl of isolated and perfused dog mesenteric arteries with and without endothelia. Chiba S, et al. **Jpn J Pharmacol** 1985 Oct;39(2):271-3

Do antipsychotic drugs and serotonin down regulate [3H]-spiroperidol binding sites in human cortex? Andorn AC. **Life Sci** 1986 Apr 7; 38(14):1251-60

Biochemical characterization of serotonin stimulated phosphoinositide turnover. Conn PJ, et al. **Life Sci** 1986 Feb 17;38(7):663-9

Serotonin content of rabbit lung and small intestine during perinatal development. de Bock V, et al. **Life Sci** 1986 Feb 3;38(5):431-5

Liquid chromatographic assay for cerebrospinal fluid serotonin. Linnoila M, et al. **Life Sci** 1986 Feb 24;38(8):687-94

3H-5-hydroxytryptamine accumulation by rat brain synaptic vesicles in a membrane-impermeant medium, and selective reduction by 5,7-dihydroxytryptamine. Ruth JA, et al. **Life Sci** 1986 Mar 31; 38(13):1193-201

High affinity [3H]imipramine binding and serotonin uptake to platelets of adolescent females suffering from anorexia nervosa. Weizman R, et al. **Life Sci** 1986 Mar 31;38(13):1235-42

Investigations of nerve populations influencing ion transport that can be stimulated electrically, by serotonin and by a nicotinic agonist. Keast JR, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Nov; 331(2-3):260-6

Catecholaminergic-serotonergic balance in the CNS and reproductive cycling in aging rats. Cooper RL, et al. **Neurobiol Aging** 1986 Jan-Feb; 7(1):9-15

Immunocytochemical changes in serotonin in the forebrain and pituitary of aging fish. Margolis-Nunno H, et al. **Neurobiol Aging** 1986 Jan-Feb; 7(1):17-21

Effect of ovarian steroids to stimulate region-specific hypothalamic 5-hydroxytryptamine synthesis in ovariectomized rats. King TS, et al.

Neuroendocrinology 1986;42(4):344-50

Serotonin and dopamine independently regulate pituitary beta-endorphin release in vivo. Sapun-Malcolm D, et al. **Neuroendocrinology** 1986; 42(3):191-6

Indolealkylamines and prolactin secretion. A structure-activity study in the central nervous system of the rat. Seeman G, et al. **Neuropharmacology** 1985 Dec;24(12):1195-200

Descending serotonergic fibers in the dorsolateral and ventral funiculi of cat spinal cord. Hylden JL, et al. **Neurosci Lett** 1985 Dec 18; 62(3):299-304

Stimulation by serotonin of immunoreactive peptide histidine isoleucine release from rat hypothalamus in vitro. Inoue T, et al. **Neurosci Lett** 1986 Feb 14;64(1):17-22

Serotonin immunoreactivity in the circumesophageal nervous system of Hermissenda crassicornis. Land PW, et al. **Neurosci Lett** 1985 Dec 4; 62(2):199-205

Immunohistochemical demonstration of serotonin nerve fibers in the subthalamic nucleus of the rat, cat and monkey. Mori S, et al. **Neurosci Lett** 1985 Dec 18;62(3):305-9

Changes in brain serotonin levels affect leukocytes, lymphocytes, T-cell subpopulations and natural killer cell activity in rats. Steplewski Z, et al. **Neurosci Lett** 1985 Dec 4;62(2):277-82

Serotonin-immunoreactive projections to the hippocampus from the interpeduncular nucleus in the rat. Wirtshafter D, et al. **Neurosci Lett** 1986 Mar 14;64(3):259-62

Serotoninergic but not noradrenergic neurons in rat central nervous system adapt to long-term treatment with monoamine oxidase inhibitors. Blier P, et al. **Neuroscience** 1985 Dec;16(4):949-55

Neurons reactive to antibodies against serotonin in the stomatogastric nervous system and in the alimentary canal of locust and crickets (Orthoptera, Insecta). Klemm N, et al. **Neuroscience** 1986; 17(1):247-61

Neuropeptides and 5-HT immunoreactivity in the gastric nerves of the dogfish (Scyliorhinus stellaris). Cimini V, et al. **Peptides** 1985; 6 Suppl 3:373-7

TFMPP may produce its stimulus effects via a 5-HT1B mechanism. McKenney JD, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):43-7

Alteration of the turnover of dopamine and 5-hydroxytryptamine in rat brain associated with hypothermia. Okuda C, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):79-83

Effects of the benzodiazepine receptor ligands midazolam, Ro 15-1788, and Ro 5-4864, alone and in combinations, on platelet serotonin uptake. Lingjaerde O. **Pharmacopsychiatry** 1986 Jan;19(1):15-8

The effect of insulin on the central serotonergic system of the rat. Juszkiewicz M. **Pol J Pharmacol Pharm** 1985 Sep-Oct;37(5):591-600

Serotonergic regulation of the brain and gut beta-endorphin and dynorphin content in the rat. Majeed NH, et al. **Pol J Pharmacol Pharm** 1985 Nov-Dec;37(6):909-18

Implication of the serotoninergic system in the decreased ACTH response to stress after lesion of the amygdaloid central nucleus. Beaulieu S, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):665-9

Serotonin, septal lesions, and shock-escape learning in rats. Mattingly BA, et al. **Psychol Rep** 1986 Feb;58(1):3-9

A comparison between chlordiazepoxide and CL 218,872, a synthetic non-benzodiazepine ligand for benzodiazepine receptors, on serotonin and catecholamine turnover in brain. McElroy JF, et al. **Psychopharmacology (Berlin)** 1986;88(1):105-8

Effects of peripheral 5-HT on consumption of flavoured solutions. Montgomery AM, et al. **Psychopharmacology (Berlin)** 1986; 88(2):262-6

Effects of antidepressant drugs, selective noradrenaline-or 5-hydroxytryptamine uptake inhibitors, on apomorphine-induced hypothermia in mice. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1986;88(2):240-6

The effect of radioprotective compounds on brain serotonine metabolisation of irradiated experimental animals. Bodó K, et al. **Radiobiol Radiother (Berl)** 1985;26(5):589-97

1-(1-Naphthyl)piperazine, a central serotonin agonist. Fuller RW, et al. **Res Commun Chem Pathol Pharmacol** 1986 Jan;51(1):37-45

Neurohumoral interactions in the posttraumatic period and possibilities of their correction. Bazarevitch GJ, et al. **Resuscitation** 1986 Jan; 13(2):115-21

Exogenous serotonin and gastric mucosal blood flow in conscious dogs. Bech K, et al. **Scand J Gastroenterol** 1985 Dec;20(10):1285-90

Influence of serotinin and norepinephrine on flow capacity/pressure characteristics of feline isolated cerebral arteries. Lou HC, et al. **Stroke** 1986 Jan-Feb;17(1):91-4

The inhibitory effects of ferriprotoporphyrin IX on platelet aggregation and release of serotonin. Essien EM. **Thromb Res** 1985 Dec 1; 40(5):609-22

Unsaturated platelet-activating factor: influence on aggregation, serotonin release and thromboxane synthesis of human thrombocytes. Korth R, et al. **Thromb Res** 1986 Mar 1;41(5):699-706

[Fluorohistochemical changes of serotonin in the APUD cells after injection of 6-hydroxydopamine intraperitoneally] Peng JY, et al. **Chen Tzu Yen Chiu** 1985;10(4):298-303 (Eng. Abstr.) **(Chi)**

[The effect of vagus nerve stimulation and various drugs on chemical mediator release in anesthetized dogs] Kitamura S, et al. **Nippon Kyobu Shikkan Gakkai Zasshi** 1985 Dec;23(12):1449-55 (Eng. Abstr.) **(Jpn)**

[Catecholamine and serotonin content in the lymph nodes following deafferentation] Izranov VA. **Biull Eksp Biol Med** 1986 Mar; 101(3):276-7 (Eng. Abstr.) **(Rus)**

[Effect of lithium oxybutyrate on the serotonin and 5-hydroxyindoleacetic acid content in the brain of rabbits] Saratikov AS, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):312-5 (Eng. Abstr.) **(Rus)**

[Effect of serotonin on thermoregulation in normothermic hibernators and during arousal from deep hypothermia] Sitnikov VD, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):5-7 (Eng. Abstr.) **(Rus)**

[Role of the pituitary in modulating the effect of the dopaminergic and serotoninergic systems on the immune response] Al'perina EL, et al. **Fiziol Zh SSSR** 1985 Nov;71(11):1428-32 (Eng. Abstr.) **(Rus)**

[Effect of activation of the cholinergic system of the small intestine on its contractile responses induced by serotonin] Ovsiannikov VI, et al. **Fiziol Zh SSSR** 1985 Nov;71(11):1413-8 (Eng. Abstr.) **(Rus)**

[Method for the separate determination of total, thrombocyte and free serotonin in the blood plasma] Rabinovich NL, et al. **Lab Delo** 1985; (12):729-31 (Eng. Abstr.) **(Rus)**

[Effect of synaptic activation and serotonin application on the calcium current in Helix neurons] Kononenko NI, et al. **Neirofiziologiia** 1986; 18(1):77-85 (Eng. Abstr.) **(Rus)**

SEX BEHAVIOR, ANIMAL

Altered endocrine and behavioral responses with reproductive aging in the male Japanese quail. Ottinger MA, et al. **Horm Behav** 1986 Mar; 20(1):83-94

Effect of bicuculline on sexual activity in castrated male rats. Fernandez-Guasti A, et al. **Physiol Behav** 1986;36(2):235-7

Chronic gonadotropin-releasing hormone agonist treatment suppresses ovulation and sexual behavior in group-living female rhesus monkeys. Wallen K, et al. **Physiol Behav** 1986;36(2):369-75

SLEEP

Hypnotic activity of an imidazo-pyridine (zolpidem). Nicholson AN, et al. **Br J Clin Pharmacol** 1986 Feb;21(2):205-11

Effect of timiperone, a new antipsychotic drug, on the sleep-wakefulness cycle in cats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Nov; 39(3):391-4

Effects of ECT on sleep and CSF biogenic amines in affective illness. Hoffmann G, et al. **Psychiatry Res** 1985 Nov;16(3):199-206

Effects of repeated zimelidine administration on sleep parameters in the rat. Reyes RB, et al. **Psychopharmacology (Berlin)** 1986;88(1):54-7

SLEEP DEPRIVATION

Effect of midazolam and sleep deprivation on day-time sleep propensity. Borbély AA, et al. **Arzneimittelforschung** 1985;35(11):1696-9

Abstinence from night sleep as a treatment for endogenous depressions. The earliest observations in a Danish mental hospital (1954) and an analysis of the causal mechanism. Ostenfeld I. **Dan Med Bull** 1986 Feb; 33(1):45-9

Effect of 24-hour sleep deprivation on biogenic amine turnover. Bol'shakova TD, et al. **Hum Physiol** 1985 Jul-Aug;11(4):291-5

SLEEP, REM

Sleep, depression and the effects of antidepressant drugs. Gaillard JM, et al. **Acta Psychiatr Belg** 1985 Sep-Oct;85(5):561-7

SLEEP STAGES

Influence of proopiomelanocortin-derived peptides on the sleep-waking cycle of the rat. Chastrette N, et al. **Neurosci Lett** 1985 Dec 18; 62(3):365-70

Effect of hypoxia on ventilatory and arousal responses to CO2 during NREM sleep with and without flurazepam in young adults. Gothe B, et al. **Sleep** 1986;9(1):24-37

SOCIAL ADJUSTMENT

Social skills training for schizophrenic individuals at risk for relapse. Liberman RP, et al. **Am J Psychiatry** 1986 Apr;143(4):523-6

SODIUM

Changes in intracellular sodium with chloride secretion in dog tracheal epithelium. Shorofsky SR, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):C646-50

Body sodium in rats: response to DOCA, adrenalectomy, changes in salt intake, and a salt load. Simpson FO, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 2):F551-8

Effects of sodium depletion and angiotensin II on osmotic regulation of vasopressin. Wade CE, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 2):R287-91

Interference with central actions of angiotensin II suppresses sodium appetite. Weiss ML, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 2):R250-9

Glucose and sodium transport in brush-border membrane vesicles from fetal rabbit kidney. Beck JC. **Ann NY Acad Sci** 1985;456:457-9

Different temperature sensitivity and cation specificity of two distinct D-glucose/Na+ cotransport systems in the intestinal brush-border membrane. Brot-Laroche E, et al. **Ann NY Acad Sci** 1985;456:47-50

Ion-coupled neurotransmitter transport across the synaptic plasma membrane. Kanner BI, et al. **Ann NY Acad Sci** 1985;456:153-61 (40 ref.)

The duck red cell model of volume-sensitive chloride-dependent cation transport. McManus TJ, et al. **Ann NY Acad Sci** 1985;456:183-6

The role of intracellular sodium activity in the inotropy potentiation among high [Ca]o' norepinephrine and strophanthidin. Abete P, et al. **Arch Int Pharmacodyn Ther** 1985 Nov;278(1):87-96

An unusual pattern of Na+ and K+ movements across the horse erythrocyte membrane. Contreras A, et al. **Biochim Biophys Acta** 1986 Apr 14;856(2):388-91

Lii-Nao countertransport and Li leak in erythrocytes are differentially affected by membrane enrichment with cholesteryl hemisuccinate. Levy R, et al. **Biochim Biophys Acta** 1986 Jan 29;854(2):325-8

Sodium current and gating current experiments on the node of Ranvier. Meves H. **Biomed Biochim Acta** 1986;45(1-2):S33-8

Lithium stimulation of in vitro granulopoiesis: evidence for mediation via sodium transport pathways. Gallicchio VS. **Br J Haematol** 1986 Mar;62(3):455-66

Elevation of sodium levels in the cerebral ventricles of anaesthetized dogs triggers the release of an inhibitor of ouabain-sensitive sodium, potassium-ATPase into the circulation. Jandhyala BS, et al. **Clin Sci** 1986 Jan;70(1):103-10

Deuterium NMR study of head-group deuterated phosphatidylserine in pure and binary phospholipid bilayers. Interactions with monovalent cations Na+ and Li+. Roux M, et al. **FEBS Lett** 1986 Apr 7; 199(1):33-8

Plasma levels and cardiovascular, endocrine, and excretory effects of atrial natriuretic peptide during different sodium intakes in man. Weidmann P, et al. **J Clin Endocrinol Metab** 1986 May;62(5):1027-36

Inhibitin: a specific inhibitor of sodium/sodium exchange in erythrocytes. Morgan K, et al. **J Clin Invest** 1986 Feb;77(2):538-44

Sodium transport by rat cortical collecting tubule. Effects of vasopressin and desoxycorticosterone. Reif MC, et al. **J Clin Invest** 1986 Apr; 77(4):1291-8

Changes in body water and plasma constituents during bullfrog development: effects of temperature and hormones. Brown SC, et al. **J Exp Zool** 1986 Jan;237(1):25-33

Unusual responses of cultured Fundulus heteroclitus melanophores to epinephrine and ions, paradox of K+ versus Na+. Clark CR, et al. **J Exp Zool** 1985 Dec;236(3):361-4

A kinetic analysis of Na-Li countertransport in human red blood cells. Hannaert PA, et al. **J Gen Physiol** 1986 Mar;87(3):353-68

Interactions of lithium and protons with the sodium-proton exchanger of dog red blood cells. Parker JC. **J Gen Physiol** 1986 Feb; 87(2):189-200

Methylation of critical carboxyl groups in the vicinity of the sodium channel of guinea-pig atrium. Freeman SE, et al. **J Mol Cell Cardiol** 1986 Jan;18(1):99-108

Characterization of sodium-dependent [3H]GBR-12935 binding in brain: a radioligand for selective labelling of the dopamine transport complex. Janowsky A, et al. **J Neurochem** 1986 Apr;46(4):1272-6

An effect of noradrenaline on resting potential and Na activity in sheep cardiac Purkinje fibres. Glitsch HG, et al. **Pflugers Arch** 1986 Feb; 406(2):144-50

Supersensitivity of the renal tubule to catecholamines in the chronically denervated canine kidney. Szénási G, et al. **Pflugers Arch** 1986 Jan; 406(1):57-9

SOMATOFORM DISORDERS

Forms of atypical depression and their response to antidepressant drugs. Davidson J, et al. **Psychiatry Res** 1986 Feb;17(2):87-95

SOMATOSTATIN

Effect of intragastric pH, prostaglandins and prostaglandin synthesis inhibitors on the release of gastrin and somatostatin into the gastric lumen of anaesthetized rats. Alino SF, et al. **Acta Physiol Scand** 1986 Jan;126(1):1-8

Effect and mechanism of vagal nerve stimulation on somatostatin secretion in dogs. Ahrén B, et al. **Am J Physiol** 1986 Feb;250(2 Pt 1):E212-7

Somatostatin induces ectopic activity fronts via a local intestinal mechanism during fed state or pentagastrin. Schippers E, et al. **Am J Physiol** 1986 Feb;250(2 Pt 1):G149-54

Inhibition of gastrin release by gastric inhibitory peptide mediated by somatostatin. Wolfe MM, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 1):G331-5

The structure and hormone content of the endocrine pancreas of the one-humped camel (Camelus dromedarius). Khatim MS, et al. **Anat Anz** 1985;159(1-5):181-6

Somatostatin, insulin and glucagon secretion by the perfused pancreas from the cysteamine-treated rat. Silvestre RA, et al. **Biochem Biophys Res Commun** 1986 Feb 13;134(3):1291-7

Conversion of somatostatin-28 to somatostatin-14 during maturation of epithelial cells in the porcine jejunum. Schäfer G, et al. **Biochim Biophys Acta** 1986 Mar 14;885(3):240-7

Inhibition by somatostatin of the release of growth hormone induced by lysine-vasopressin in normal subjects. Chiodera P, et al. **Biomed Pharmacother** 1985;39(6):334-7

Behavioral changes following central injection of cysteamine in rats. Bakhit C, et al. **Brain Res** 1986 Feb 12;365(1):159-63

Neuropeptides in cerebral cortex of macaque monkey (Macaca fuscata fuscata): regional distribution and ontogeny. Hayashi M, et al. **Brain Res** 1986 Feb 5;364(2):360-8

Influence of a benzodiazepine, midazolam, and gamma-aminobutyric acid (GABA) on basal somatostatin secretion from cerebral and diencephalic neurons in dispersed cell culture. Stryker TD, et al. **Brain Res** 1986 Jan 8;362(2):339-43

Effects of hibernation on somatostatin-like immunoreactivity in the brain of the ground squirrel (Spermophilus richardsonii) and European hedgehog (Erinaceus europaeus). Nürnberger F, et al. **Cell Tissue Res** 1986;243(2):263-71

Interaction between growth hormone releasing factor (GRF) and somatostatin analogue (SMS 201-995) in normal subjects. Losa M, et al. **Clin Endocrinol (Oxf)** 1985 Dec;23(6):715-20

Coexpression of somatostatin-like immunoreactivity and catecholaminergic properties in neural crest derivatives: comodulation of peptidergic and adrenergic differentiation in cultured neural crest. García-Arrarás JE, et al. **Dev Biol** 1986 Mar;114(1):247-57

Differential regulation of cholinergic and peptidergic development in the rat striatum in culture. Kessler JA. **Dev Biol** 1986 Jan;113(1):77-89

Modulatory effect of glucose, amino acids, and secretin on CCK-8-induced somatostatin and pancreatic polypeptide release in dogs. Schusdziarra V, et al. **Diabetes** 1986 May;35(5):523-9

Somatostatin release from freshly isolated and cultured rat islets in response to rat insulin and to anti-insulin serum. Schäfer G, et al. **Diabetes Res** 1985 Jul;2(4):201-5

The effect of adding albumin to solutions of somatostatin (SST-14) on inhibiting pentagastrin-stimulated acid secretion in man. Whitehouse I, et al. **Digestion** 1986;33(2):69-73

The role of growth hormone-releasing factor and somatostatin on somatic growth in rats. Wehrenberg WB. **Endocrinology** 1986 Feb; 118(2):489-94

In vivo synthesis and processing of rat hypothalamic prosomatostatin. Camier M, et al. **FEBS Lett** 1986 Feb 3;196(1):14-8

Somatostatin and alpha 2-adrenergic agonists selectively inhibit vasopressin-induced cyclic AMP accumulation in MDCK cells. Friedlander G, et al. **FEBS Lett** 1986 Mar 17;198(1):38-42

Ontogeny of neuropeptidergic systems: luteinizing hormone releasing hormone (LHRH); somatostatin (SRIF) and neurophysin (NF) in the hypothalamus of the domestic pig by immunocytochemistry. Polkowska J, et al. **Folia Histochem Cytobiol** 1985;23(4):193-200

Effect of somatostatin and its analogs on histamine-stimulated cAMP production in isolated guinea pig gastric glands. Nishihara S, et al. **Gastroenterol Jpn** 1985 Dec;20(6):543-7

Endogenous somatostatin and the gut. Lucey MR. **Gut** 1986 Apr; 27(4):457-67 (94 ref.)

Inhibition of pentagastrin-stimulated acid secretion after subcutaneous administration of a new somatostatin analogue. Whitehouse I, et al. **Gut** 1986 Feb;27(2):141-6

Role of endogenous prostaglandins in somatostatin-induced inhibition of gastrointestinal hormone secretion. Koop H, et al. **Hepatogastroenterology** 1985 Dec;32(6):288-92

Antigenic specificity of a new and potent somatostatin antiserum. Tamarit-Rodriguez J, et al. **Horm Metab Res** 1985 Dec;17(12):623-5

Somatostatin actions in primary dissociated cell cultures of mammalian spinal cord neurons. Macdonald RL, et al. **Int J Neurol** 1980; 14(2-4):221-32

Somatostatin immunocytochemistry in the rabbit retina. Sagar SM, et al. **Invest Ophthalmol Vis Sci** 1986 Mar;27(3):316-22

Phorbol ester or diacylglycerol modulates somatostatin binding to its receptors on rat pancreatic acinar cell membranes. Matozaki T, et al. **J Biol Chem** 1986 Jan 25;261(3):1414-20

Distribution of immunoreactive somatostatin (ISRIF) in the nervous system of the squid, Loligo pealei. Feldman SC. **J Comp Neurol** 1986 Mar 8;245(2):238-57

Somatostatin-like immunoreactivity in neurons, nerve terminals, and fibers of the cat spinal cord. Krukoff TL, et al. **J Comp Neurol** 1986 Jan 1;243(1):13-22

Glutamic acid decarboxylase and somatostatin immunoreactivities in rat visual cortex. Lin CS, et al. **J Comp Neurol** 1986 Feb 15; 244(3):369-83

Somatostatinlike immunoreactive neurons in the hedgehog (Erinaceus europaeus) and the sheep (Ovis aries) central nervous system. Papadopoulos GC, et al. **J Comp Neurol** 1986 Feb 8;244(2):174–92

The capability for regulation of insulin secretion by somatostatin in purified pancreatic islet B cells during aging. Magal E, et al. **Mech Ageing Dev** 1986 Jan;33(2):139–46

On the actions of substance P, somatostatin, and vasoactive intestinal polypeptide on rat peritoneal mast cells and in human skin. Piotrowski W, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Dec; 331(4):364–8

Regulation of growth hormone and thyrotropin secretion by somatostatin systems in rat brain. Terry LC, et al. **Neuroendocrinology** 1986; 42(3):218–25

Relationship between cerebrospinal fluid somatostatin and peripheral thyroid hormones with carbamazepine treatment. Joffe RT, et al. **Neuropsychobiology** 1985;14(3):115–7

Correlation of mitochondrial swelling after capsaicin treatment and substance P and somatostatin immunoreactivity in small neurons of dorsal root ganglion in the rat. Chiba T, et al. **Neurosci Lett** 1986 Mar 14;64(3):311–6

Pancreatic peptides regulate Cl– secretion in the marine teleost gill. Davis MS, et al. **Peptides** 1985;6 Suppl 3:379–82

Synthesis and biological activity of highly potent octapeptide analogs of somatostatin. Cai RZ, et al. **Proc Natl Acad Sci USA** 1986 Mar; 83(6):1896–900

Effects of haloperidol on somatostatin–like immunoreactivity in the CSF of Schizophrenic patients. Gattaz WF, et al. **Psychiatry Res** 1986 Jan; 17(1):1–6

Permeability of epidural somatostatin and morphine into the intrathecal space of dogs. Chrubasik J, et al. **Regul Pept** 1986 Jan;13(2):119–24

Effect of atropine on plasma gastrin and somatostatin concentrations during sham feeding in man. Feldman M, et al. **Regul Pept** 1985 Nov 28;12(4):345–52

Gonadotroph–specific expression of metallothionein fusion genes in pituitaries of transgenic mice. Low MJ, et al. **Science** 1986 Feb 28; 231(4741):1002–4

[Somatostatin and gastric acid secretion] Chevalier T, et al. **Gastroenterol Clin Biol** 1986 Jan;10(1):34–40 (75 ref.) **(Fre)**

[Structural and hormonal alterations in the pancreas after hepatectona in dogs] Shobu R, et al. **Nippon Geka Gakkai Zasshi** 1986 Jan; 87(1):61–6 (Eng. Abstr.) **(Jpn)**

[Effects of somatostatin and its analog on gastric secretion. An application of the secretagogues to gastric secretion] Nomura M, et al. **Nippon Yakurigaku Zasshi** 1985 Sep;86(3):189–95 (Eng. Abstr.) **(Jpn)**

SOMATOTROPIN RELEASING HORMONE

Growth hormone releasing factor–like immunoreactivity in human milk. Werner H, et al. **Biochem Biophys Res Commun** 1986 Mar 28; 135(3):1084–9

Total DNA synthesis and cloning in Escherichia coli of a gene coding for the human growth hormone releasing factor. Cravador A, et al. **Biochimie** 1985 Jul–Aug;67(7–8):829–34

Interaction between growth hormone releasing factor (GRF) and somatostatin analogue (SMS 201–995) in normal subjects. Losa M, et al. **Clin Endocrinol (Oxf)** 1985 Dec;23(6):715–20

The inter– and intra–subject variabilities of plasma GH response to human growth hormone–releasing hormone (1–44) NH2 in men. Hotta M, et al. **Endocrinol Jpn** 1985 Oct;32(5):673–80

Effects of age on GH responses to growth hormone–releasing factor in rats. Niimi M, et al. **Endocrinol Jpn** 1985 Aug;32(4):559–62

Electrical stimulation of several limbic areas suppressed the growth hormone (GH) release induced by human pancreatic GH–releasing factor in pentobarbital–anesthetized rats. Kato M, et al. **Endocrinology** 1986 Mar;118(3):955–60

hpGRF–44–NH2, lot no. 92–81–5G–41–47, is (human) growth hormone–releasing factor containing no trace of (ovine) corticotropin–releasing factor. Ling N, et al. **Endocrinology** 1986 Mar; 118(3):1249–51

Identification of a putative GH–releasing factor (GRF) batch as predominantly ovine CRF with a small quantity of human GRF. Tannenbaum GS, et al. **Endocrinology** 1986 Mar;118(3):1246–8

Covalent cross–linking of growth hormone–releasing factor to pituitary receptors. Veliçelebi G, et al **Endocrinology** 1986 Apr; 118(4):1278–83

The role of growth hormone–releasing factor and somatostatin on somatic growth in rats. Wehrenberg WB. **Endocrinology** 1986 Feb; 118(2):489–94

Synthetic human growth hormone releasing factor (h–GRF–1–44–NH2) dose response effect on growth hormone and prolactin secretion in healthy adult men. Boissel JP, et al. **Eur J Clin Pharmacol** 1986; 29(5):609–14

Growth hormone–releasing factor (somatocrinin) stimulates epithelial cell proliferation in the rat digestive tract. Lehy T, et al. **Gastroenterology** 1986 Mar;90(3):646–53

Suppression of the growth hormone (GH) response to clonidine and GH–releasing hormone by exogenous GH. Nakamoto JM, et al. **J Clin Endocrinol Metab** 1986 May;62(5):822–6

Responses of growth hormone (GH) and somatomedin–C to GH–releasing hormone in healthy aging men. Pavlov EP, et al. **J Clin Endocrinol Metab** 1986 Mar;62(3):595–600

Exogenous growth hormone inhibits growth hormone–releasing factor–induced growth hormone secretion in normal men. Rosenthal SM, et al. **J Clin Invest** 1986 Jan;77(1):176–80

Stimulation and inhibition of food intake in sheep by centrally–administered hypothalamic releasing factors. Ruckebusch Y, et al. **Life Sci** 1986 Mar 10;38(10):929–34

Study of species specificity in growth hormone–releasing factor (GRF) interaction with vasoactive intestinal peptide (VIP) receptors using GRF and intestinal VIP receptors from rat and human: evidence that Ac–Tyr1hGRF is a competitive VIP antagonist in the rat. Laburthe M, et al. **Mol Pharmacol** 1986 Jan;29(1):23–7

Relative potencies of human, rat, bovine/caprine, porcine and ovine hypothalamic growth hormone–releasing factors to release growth hormone by the rat anterior pituitary in vitro. Baird A, et al. **Neuroendocrinology** 1986;42(4):273–6

Coexistence of tyrosine hydroxylase and growth hormone–releasing factor in a subpopulation of tubero–infundibular neurons of the rat. Meister B, et al. **Neuroendocrinology** 1986;42(3):237–47

Immunohistochemical localization of GRF–containing neurons in rat brain. VandePol CJ, et al. **Neuroendocrinology** 1986;42(2):143–7

The molecular weight forms of rat growth hormone secreted in response to growth hormone–releasing factor. Wehrenberg WB, et al. **Proc Soc Exp Biol Med** 1986 May;182(1):107–11

[Hormonal growth factors] Chatelain P, et al. **Rev Prat** 1985 Oct 11; 35(45):2725–31 (Eng. Abstr.) **(Fre)**

[Hypothalamic factors: current findings] Sizonenko PC. **Schweiz Med Wochenschr** 1986 Mar 1;116(9):271–4 (Eng. Abstr.) **(Fre)**

[Effect of hypo– and hyperthyroidism, and hypothalamic ventromedial lesions on the plasma growth hormone response to human growth hormone–releasing factor in rats] Tonegawa Y. **Nippon Ika Daigaku Zasshi** 1985 Dec;52(6):624–32 (Eng. Abstr.) **(Jpn)**

SPACE PERCEPTION

Deficits in spatial–memory tasks following lesions of septal dopaminergic terminals in the rat. Simon H, et al. **Behav Brain Res** 1986 Jan; 19(1):7–16

SPATIAL BEHAVIOR

Pesticide–drug interaction in rats. Fenyvesi G, et al. **Arch Toxicol [Suppl]** 1985;8:269–71

Dopamine depletion, stimulation or blockade in the rat disrupts spatial navigation and locomotion dependent upon beacon or distal cues. Whishaw IQ, et al. **Behav Brain Res** 1985 Oct–Nov;18(1):11–29

Disturbances in exploratory behavior and functional recovery in the Y and radial mazes following dopamine depletion of the lateral septum. Taghzouti K, et al. **Behav Neural Biol** 1986 Jan;45(1):48–56

Lateralized and compulsive exteroceptive orientation in rats treated with apomorphine. Pisa M, et al. **Neurosci Lett** 1986 Feb 14;64(1):41–6

STARTLE REACTION

Central dopamine hyperactivity in rats mimics abnormal acoustic startle response in schizophrenics. Swerdlow NR, et al. **Biol Psychiatry** 1986 Jan;21(1):23–33

STEREOTYPED BEHAVIOR

The effect of repeated administration of (–) deprenyl on the phenylethylamine–induced stereotypy in rats. Timár J, et al. **Arch Int Pharmacodyn Ther** 1986 Jan;279(1):50–60

Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Reith ME, et al. **Biochem Pharmacol** 1986 Apr 1; 35(7):1123–9

Oscillations in apomorphine–induced stereotypies during 1 year of apomorphine administration. Csernansky JG, et al. **Biol Psychiatry** 1986 Apr;21(4):402–5

Inhibition of dopaminergic agonist–induced gnawing behavior by neuroleptic drugs in mice. Yen–Koo HC, et al. **Drug Chem Toxicol** 1985;8(6):495–502

The effect of antimuscarinic agents on haloperidol induced behavioral hypersensitivity. Carvey PM, et al. **Eur J Pharmacol** 1986 Jan 21; 120(2):193–9

Behavior performed at onset of drug action and apomorphine stereotypy. Szechtman H. **Eur J Pharmacol** 1986 Feb 11;121(1):49–56

The effects of chronic bromocriptine treatment on behaviour and dopamine receptor binding in the rat striatum. Traub M, et al. **Eur J Pharmacol** 1985 Nov 26;118(1–2):147–54

Prolactin induces yawning and the stretch–yawning syndrome in young adult male rats. Laping NJ, et al. **Horm Behav** 1986 Mar; 20(1):49-59

Behavioral effects of substance P in rats. Barbeau A, et al. **Int J Neurol** 1980;14(2-4):239-52

Amphetamine-induced circling behaviour in MPTP-lesioned mice. Fung YK, et al. **J Pharm Pharmacol** 1985 Dec;37(12):922-3

Effects of unilateral microinjections of sulpiride into the medial prefrontal cortex on circling behavior of rats. Morency MA, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):735-8

Head-twitch response induced by ergometrine in mice: behavioural evidence for direct stimulation of central 5-hydroxytryptamine receptors by ergometrine. Balsara JJ, et al. **Psychopharmacology (Berlin)** 1986;88(3):275-8

The modulation of head-twitch behaviour by drugs acting on beta-adrenoceptors: evidence for the involvement of both beta 1- and beta 2-adrenoceptors. Handley SL, et al. **Psychopharmacology (Berlin)** 1986;88(3):320-4

Inhibition of head twitch response to quipazine in rats by chronic amitriptyline but not fluvoxamine or citalopram. Pawlowski L, et al. **Psychopharmacology (Berlin)** 1986;88(3):279-84

Involvement of noradrenaline in potentiation of the head-twitch response by GABA-related drugs. Singh L, et al. **Psychopharmacology (Berlin)** 1986;88(3):315-9

[The effect of various new GABAergics on motor and oral stereotypes with apomorphine in the rat] Vamvakidès A, et al. **J Pharmacol** 1985 Oct-Dec;16(4):403-11 (Eng. Abstr.) **(Fre)**

[Behavioral and pharmacological studies of methamphetamine-induced stereotypy of mice by the open field method] Nakamura K, et al. **Yakugaku Zasshi** 1985 Aug;105(8):775-83 (Eng. Abstr.) **(Jpn)**

STRESS, PSYCHOLOGICAL

Emotional trauma and thyroxine [letter] Jackson GL. **Ann Intern Med** 1986 Feb;104(2):289

Cardiovascular and neuroendocrine responses to behavioral stress after central or peripheral barodenervation in rats. Buchholz RA, et al. **Brain Res** 1986 Feb 19;365(2):360-4

Stress: physiological aspects (2). Speirs RL. **Dent Update** 1985 Nov-Dec; 12(10):617-8, 620-3

Effects of essential fatty acid administration on cardiovascular responses to stress in the rat. Mills DE, et al. **Lipids** 1986 Feb;21(2):139-42

Stressor-provoked response patterns in a swim task: modification by diazepam. Prince CR, et al. **Pharmacol Biochem Behav** 1986 Feb; 24(2):323-8

Effects of preshock experience on enhancement of rat brain noradrenaline turnover induced by psychological stress. Tsuda A, et al. **Pharmacol Biochem Behav** 1986 Jan;24(1):115-9

Selective breeding of chickens for corticosterone response to social stress. Gross WB, et al. **Poult Sci** 1985 Dec;64(12):2230-3

Effects of eicosapentaenoic acid (20:5 omega 3) on stress reactivity in rats. Mills DE, et al. **Proc Soc Exp Biol Med** 1986 May; 182(1):127-31

Implication of the serotoninergic system in the decreased ACTH response to stress after lesion of the amygdaloid central nucleus. Beaulieu S, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):665-9

High sensitivity of brain octopamine levels to stress. Ennaceur A, et al. **Psychopharmacology (Berlin)** 1986;88(3):305-9

Stress-induced inhibition of reproductive functions: role of endogenous corticotropin-releasing factor. Rivier C, et al. **Science** 1986 Feb 7; 231(4738):607-9

[Catecholamines and mental stress] Christensen NJ. **Ugeskr Laeger** 1986 Jan 27;148(5):233-7 (Eng. Abstr.) **(Dan)**

[Differential diagnosis and treatment of the professional burnout syndrome] Grantham H. **Ann Med Psychol (Paris)** 1985 Sep-Oct; 143(8):776-81 **(Fre)**

[Biology of states of burnout] Poirier MF. **Ann Med Psychol (Paris)** 1985 Sep-Oct;143(8):761-8 **(Fre)**

[Effect of chronic psychogenic stress on a number of behavioral and neurochemical characteristics of rats] Danchev ND, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):57-9 (Eng. Abstr.) **(Rus)**

[Genetical aspects of hormonal modification of the stress reactivity. II. Modification in early ontogenesis of the stress reactivity of adult gray rats selected for behavior toward man] Dygalo NN, et al. **Genetika** 1986 Mar;22(3):500-6 (Eng. Abstr.) **(Rus)**

[Activity of the sympathetic-adrenal system in monkeys under acute and chronic emotional stress] Bol'shakova TD, et al. **Izv Akad Nauk SSSR [Biol]** 1985 Nov-Dec;(6):822-31 (Eng. Abstr.) **(Rus)**

[Effect of intensive operator activity on lipid peroxidation processes in the human body] Ivanova SM, et al. **Kosm Biol Aviakosm Med** 1986 Jan-Feb;20(1):20-2 (Eng. Abstr.) **(Rus)**

[Effect of adaptation to brief stress exposure on the realization of the stress reaction, impairment of metabolism and myocardial contraction caused by prolonged emotional-pain stress] Meerson FZ, et al. **Vopr Med Khim** 1986 Jan-Feb;32(1):76-81 (Eng. Abstr.) **(Rus)**

SUBSTANCE P

Complementary action of substance P and vasoactive intestinal peptide on the rat parotid secretion. Ekström J, et al. **Acta Physiol Scand** 1986 Jan;126(1):25-31

Release of substance-P-like immunoreactivity in dog paw lymph after scalding injury. Jonsson CE, et al. **Acta Physiol Scand** 1986 Jan; 126(1):21-4

Evidence for a modulatory influence of centrally administered substance P on a 5-hydroxytryptamine-mediated behavioural response in the male rat. Ogren SO, et al. **Acta Physiol Scand** 1985 Dec;125(4):743-5

Electrophysiological effects of substance P and VIP in the denervated rat parotid gland. Thesleff P. **Acta Physiol Scand** 1986 Mar; 126(3):377-83

Histamine involvement in the local and systemic microvascular effects produced by intradermal substance P. Woodward DF, et al. **Agents Actions** 1985 Dec;17(2):126-30

Substance P, 5-hydroxytryptamine, and bradykinin stimulate abdominal visceral afferents. Lew WY, et al. **Am J Physiol** 1986 Mar; 250(3 Pt 2):R465-73

Effect of luminally administered serotonin and substance P on jejunal handling of water and electrolytes. McFadden D, et al. **Am J Surg** 1986 Jan;151(1):81-6

Nerve fibers in the urethral mucosa of canine penis are immunoreactive for both substance P and calcitonin gene-related peptide. Iwanaga T, et al. **Arch Histol Jpn** 1985 Dec;48(5):547-52

The distribution and origin of substance P-like immunoreactivity in the rat molar pulp and periodontal tissues. Wakisaka S, et al. **Arch Oral Biol** 1985;30(11-12):813-8

Localization of substance P- and enkephalin-like immunoreactivity in the human paravertebral sympathetic ganglia. Del Fiacco M, et al. **Basic Appl Histochem** 1985;29(4):309-20

Substance P facilitation of memory: effects in an appetitively motivated learning task. Schlesinger K, et al. **Behav Neural Biol** 1986 Mar; 45(2):230-9

Self-association and solubility of peptides: solvent-titration study of N alpha-protected C-terminal sequences of substance P. Toniolo C, et al. **Biopolymers** 1986 Feb;25(2):281-9

An examination of the pharmacology of two substance P antagonists and the evidence for tachykinin receptor subtypes. Bailey SJ, et al. **Br J Pharmacol** 1986 Jan;87(1):79-85

Axonal transport of substance P-like immunoreactivity in regenerating rat sciatic nerve. Bisby MA, et al. **Brain Res** 1985 Dec 30; 361(1-2):396-9

Regeneration of primary afferent neurons containing substance P-like immunoreactivity. Bisby MA, et al. **Brain Res** 1986 Feb 12; 365(1):85-95

Selective activation of mesolimbic and mesocortical dopamine metabolism in rat brain by infusion of a stable substance P analogue into the ventral tegmental area. Elliott PJ, et al. **Brain Res** 1986 Jan 15;363(1):145-7

Neuropeptides in cerebral cortex of macaque monkey (Macaca fuscata fuscata): regional distribution and ontogeny. Hayashi M, et al. **Brain Res** 1986 Feb 5;364(2):360-8

Altered responsiveness to substance P and 5-hydroxytryptamine in cat dorsal horn neurons after 5-HT depletion with p-chlorophenylalanine. Jeftinija S, et al. **Brain Res** 1986 Mar 12;368(1):107-15

Facilitation of nicotinic response in the guinea pig prevertebral neurons by substance P. Jiang ZG, et al. **Brain Res** 1986 Jan 15; 363(1):196-8

Coexistence of pancreatic polypeptide and substance P in the chicken retina. Katayama-Kumoi Y, et al. **Brain Res** 1985 Dec 30; 361(1-2):25-35

Comparison of the substance P- and dynorphin-containing projections to the substantia nigra: a radioimmunocytochemical and biochemical study. McLean S, et al. **Brain Res** 1985 Dec 30;361(1-2):185-92

Substance P augments a persistent slow inward calcium-sensitive current in voltage-clamped spinal dorsal horn neurons of the rat. Murase K, et al. **Brain Res** 1986 Feb 19;365(2):369-76

Early postnatal administration of 5,7-dihydroxytryptamine: effects on substance P and thyrotropin-releasing hormone neurons and terminals in rat brain. Towle AC, et al. **Brain Res** 1986 Jan 15;363(1):38-46

Differential regulation of cholinergic and peptidergic development in the rat striatum in culture. Kessler JA. **Dev Biol** 1986 Jan;113(1):77-89

Preferential conformation of substance P in solution. Chassaing G, et al. **Eur J Biochem** 1986 Jan 2;154(1):77-85

Interaction of substance P with tubulin. Maccioni RB, et al. **Eur J Biochem** 1986 Jan 15;154(2):427-35

Multiple-copy genes: production and modification of monomeric peptides from large multimeric fusion proteins. Kempe T, et al. **Gene** 1985; 39(2-3):239-45

Comparison of the histamine-releasing action of substance P on mast cells and basophils from different species and tissues. Ali H, et al. **Int Arch Allergy Appl Immunol** 1986;79(4):413-8

Behavioral effects of substance P in rats. Barbeau A, et al. **Int J Neurol** 1980;14(2-4):239-52

The role of substance P in the nigrostriatal system. Borison RL, et al.

Int J Neurol 1980;14(2-4):189-94

Multiple modes of communication by substance P. Harkins JA, et al. **Int J Neurol** 1980;14(2-4):233-8 (37 ref.)

Response of splanchnic-driven neurons to substance P and eledoisin-related peptide. Felpel LP, et al. **J Auton Nerv Syst** 1986 Mar; 15(3):269-74

Hydrolysis of substance P and its analogs by angiotensin-converting enzyme from rat lung. Characterization of endopeptidase activity of the enzyme. Yokosawa H, et al. **J Biochem (Tokyo)** 1985 Nov; 98(5):1293-9

Interactions of bombesin and substance P at the feline lower esophageal sphincter. Reynolds JC, et al. **J Clin Invest** 1986 Feb;77(2):436-40

Vasoactive intestinal polypeptide and substance P in primary afferent pathways to the sacral spinal cord of the cat. Kawatani M, et al. **J Comp Neurol** 1985 Nov 15;241(3):327-47

Stimulation of cellular proliferation and differentiation in the intact and regenerating planarian Dugesia(G) tigrina by the neuropeptide substance P. Saló E, et al. **J Exp Zool** 1986 Jan;237(1):129-35

Ketomethylene pseudopeptide analogues of substance P: synthesis and biological activity. Ewenson A, et al. **J Med Chem** 1986 Feb; 29(2):295-9

Distribution of substance P neurons in the epithalamus of the rat: an immunohistochemical investigation. Rønnekleiv OK, et al. **J Pineal Res** 1984;1(4):355-70

On the actions of substance P, somatostatin, and vasoactive intestinal polypeptide on rat peritoneal mast cells and in human skin. Piotrowski W, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1985 Dec; 331(4):364-8

Synaptosomal degradation of substance P and some other neuropeptides. Arzumanyan AM, et al. **Neurochem Res** 1985 Dec;10(12):1623-34

Estrous cycle variations in cholecystokinin and substance P concentrations in discrete areas of the rat brain. Frankfurt M, et al. **Neuroendocrinology** 1986;42(3):226-31

Correlation of mitochondrial swelling after capsaicin treatment and substance P and somatostatin immunoreactivity in small neurons of dorsal root ganglion in the rat. Chiba T, et al. **Neurosci Lett** 1986 Mar 14;64(3):311-6

Neuropeptide immunoreactivity of pericellular baskets in the guinea pig trigeminal ganglion. Kuwayama Y, et al. **Neurosci Lett** 1986 Feb 28; 64(2):169-72

Simultaneous release of several tachykinins and calcitonin gene-related peptide from rat spinal cord slices. Saria A, et al. **Neurosci Lett** 1986 Jan 30;63(3):310-4

Antagonism of non-cholinergic excitatory junction potentials in the guinea-pig ileum by a substance P analogue antagonist. Taylor GS, et al. **Neurosci Lett** 1986 Jan 2;63(1):23-6

Sexual differences in the distribution of substance P immunoreactive fibers in the ventral horn of the rat lumbar spinal cord. Uda K, et al. **Neurosci Lett** 1986 Feb 28;64(2):157-62

Inputs to motoneurones in the hypoglossal nucleus of the rat: light and electron microscopic immunocytochemistry for choline acetyltransferase, substance P and enkephalins using monoclonal antibodies. Connaughton M, et al. **Neuroscience** 1986;17(1):205-24

Characterization of substance P-like immunoreactivity in submammalian species by high performance liquid chromatography. Lembeck F, et al. **Peptides** 1985;6 Suppl 3:231-6

Non-cholinergic inotropic responses evoked by electric field stimulation in the isolated rat urinary bladder. Possible participation of substance P. Dveksler G, et al. **Pharmacol Res Commun** 1985 Dec; 17(12):1109-19

Multiple tachykinins (neurokinin A, neuropeptide K and substance P) in capsaicin-sensitive sensory neurons in the guinea-pig. Hua XY, et al. **Regul Pept** 1985 Dec;13(1):1-19

Presynaptic modulation by noradrenaline and an opioid of the substance P-induced release of [3H]acetylcholine from the myenteric plexus. Vizi ES, et al. **Regul Pept** 1985 Nov 28;12(4):317-25

A technique for decalcification and demonstration of substance P-like immunoreactivity. Wakisaka S, et al. **Stain Technol** 1986 Jan; 61(1):39-42

SUBSTANCE USE DISORDERS

Proposed changes in DSM-III substance use disorders: description and rationale. Rounsaville BJ, et al. **Am J Psychiatry** 1986 Apr; 143(4):463-8

SYMPATHOMIMETICS

Potassium secretion by rabbit descending colon: effects of adrenergic stimuli. Smith PL, et al. **Am J Physiol** 1986 Apr; 250(4 Pt 1):G432-9

Arousal and stability: the effects of five new sympathomimetic drugs suggest a new principle for the prevention of space motion sickness. Kohl RL, et al. **Aviat Space Environ Med** 1986 Feb;57(2):137-43

Sympathomimetic drugs and lung surfactant factor [letter] Gerner R. **J Perinat Med** 1985;13(6):317-8

[Effects and cardiovascular dangers of betamimetics] Beaune J, et al. **Rev Fr Gynecol Obstet** 1985 Dec;80(12):905-7 **(Fre)**

[Fetal effects of betamimetics] Domenichini Y. **Rev Fr Gynecol Obstet** 1985 Dec;80(12):907-11 **(Fre)**

[Pharmacological studies on the pressor response in adrenal-enucleated rats] Tomori M. **Nippon Yakurigaku Zasshi** 1986 Jan;87(1):67-76 (Eng. Abstr.) **(Jpn)**

SYNAPTIC RECEPTORS

Studies of neurotensin-dopamine receptor interactions in striatal membranes of the male rat. The influence of 6-hydroxydopamine-induced dopamine receptor supersensitivity. Fuxe K, et al. **Acta Physiol Scand** 1986 Jan;126(1):147-9

Identification of polypeptides of the phencyclidine receptor of rat hippocampus by photoaffinity labeling with [3H]azidophencyclidine. Haring R, et al. **Biochemistry** 1986 Feb 11;25(3):612-20

Seasonal variation of platelet serotonin uptake and 3H-imipramine binding in normal and depressed subjects. Egrise D, et al. **Biol Psychiatry** 1986 Mar;21(3):283-92

An examination of the pharmacology of two substance P antagonists and the evidence for tachykinin receptor subtypes. Bailey SJ, et al. **Br J Pharmacol** 1986 Jan;87(1):79-85

Examination of spinal monoamine receptors through which brainstem opiate-sensitive systems act in the rat. Jensen TS, et al. **Brain Res** 1986 Jan 15;363(1):114-27

Evidence for an excitatory amino acid as the transmitter of the auditory nerve in the in vitro mouse cochlear nucleus. Martin MR. **Hear Res** 1985;20(3):215-20

Behavioral and receptor binding studies of phencyclidine (PCP) and lithium interaction in the rat. Mattia A, et al. **Life Sci** 1986 Mar 17; 38(11):975-84

Stimulation of noradrenaline synthesis by the calcium ionophore A23187 and its modulation by presynaptic receptors. Birch PJ, et al. **Neurosci Lett** 1985 Dec 4;62(2):187-92

[Antidepressant drugs and central monoaminergic receptors] Asakura M, et al. **Yakubutsu Seishin Kodo** 1985 Dec;5(4):303-19 (143 ref.) (Eng. Abstr.) **(Jpn)**

[Interaction of piracetam with 3H-imipramine binding sites and the GAMA-benzodiazepine receptor complex of brain membranes] Rozhanets VV, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):40-2 (Eng. Abstr.) **(Rus)**

[Possible general mechanism of the presynaptic action of mediators] Abramets II, et al. **Dokl Akad Nauk SSSR** 1986 Mar-Apr; 287(1):245-8 **(Rus)**

[Problems of drug recognition. Imipramine receptors] Shimanovskiĭ NL, et al. **Farmakol Toksikol** 1986 Jan-Feb;49(1):103-7 (36 ref.) **(Rus)**

TESTOSTERONE

Androgens and imprinting: differential effects of testosterone on filial preference in the domestic chick. Bolhuis JJ, et al. **Behav Neurosci** 1986 Feb;100(1):51-6

In vitro interactions between Sertoli cells and steroidogenic cells. Perrard-Sapori MH, et al. **Biochem Biophys Res Commun** 1986 Jan 29; 134(2):957-62

High-affinity binding of testosterone in serum from normal developing chick embryos and during the graft-versus-host reaction. Savu L, et al. **Biochim Biophys Acta** 1986 Mar 19;881(1):15-21

Failure of high-dose sustained release luteinizing hormone releasing hormone agonist (buserelin) plus oral testosterone to suppress male fertility. Michel E, et al. **Clin Endocrinol (Oxf)** 1985 Dec; 23(6):663-75

Seasonal variation in plasma testosterone, luteinizing hormone concentrations and LH-RH responsiveness in mature, male rusa deer (Cervus rusa timorensis). van Mourik S, et al. **Comp Biochem Physiol** [A] 1986;83(2):347-51

Hormonal effects of ketoconazole in vivo in the male rat: mechanism of action. Bhasin S, et al. **Endocrinology** 1986 Mar;118(3):1229-32

Stress-induced elevation of testosterone concentration in high ranking baboons: role of catecholamines. Sapolsky RM. **Endocrinology** 1986 Apr; 118(4):1630-5

Suppression of annual plasma testosterone and thyroxine cycles in the edible dormouse Glis glis under constant photoperiod at 24 degrees C. Jallageas M, et al. **Experientia** 1986 Feb 15;42(2):171-3

Elevation of serum testosterone during chronic LHRH agonist treatment in the bull. Melson BE, et al. **J Anim Sci** 1986 Jan;62(1):199-207

Testosterone maintains pituitary and serum FSH and spermatogenesis in gonadotrophin-releasing hormone antagonist-suppressed rats. Rea MA, et al. **J Endocrinol** 1986 Jan;108(1):101-7

Gonadotropin and testosterone response in prepubertal boys with hypospadias. Shima H, et al. **J Urol** 1986 Mar;135(3):539-42

Influence of neonatal injection of estradiol and testosterone on hypothalamo-hypophyseal-gonadal interrelationships and fertility in male rats. Baranov VG, et al. **Neurosci Behav Physiol** 1985 Sep-Oct; 15(5):404-7

Effect of estrogen, testosterone, and phenobarbital on uterine weight and liver microsomal enzymes in prepuberal mice. Robl JM, et al.

Pediatr Pharmacol (New York) 1985;5(3):157–64

Effect of bicuculline on sexual activity in castrated male rats. Fernandez–Guasti A, et al. **Physiol Behav** 1986;36(2):235–7

[The state of gametes and the type of maturation of follicular oocytes in rats neonatally androgenized by LH–RH–induced ovulation] Kitaev EM, et al. **Biull Eksp Biol Med** 1986 Jan;101(1):78–9 (Eng. Abstr.) **(Rus)**

[Effect of RL–175 on testosterone and corticosterone levels in the plasma of male albino rats] Lokhov RE, et al. **Vopr Med Khim** 1985 Nov–Dec; 31(6):86–8 (Eng. Abstr.) **(Rus)**

THIORIDAZINE

The effect of propranolol and thioridazine on positive and negative symptoms of schizophrenia. Eccleston D, et al. **Br J Psychiatry** 1985 Dec;147:623–30

Thioridazine enhances lysosomal accumulation of epidermal growth factor and toxicity of conjugates of epidermal growth factor with Pseudomonas exotoxin. Kuratomi Y, et al. **Exp Cell Res** 1986 Feb; 162(2):436–48

[Changes in the serum thioridazine level after administration of pridinol] Sidorowicz S, et al. **Psychiatr Pol** 1985 Sep–Oct;19(5):423–4 **(Pol)**

THYROID HORMONES

Serum thyroid hormones in the patient under intermittent peritoneal dialysis. Pérez A, et al. **Arch Invest Med (Mex)** 1985 Jul–Sep; 16(3):255–60 **(Eng, Spa)**

Structural and functional impairment of adrenergic input to intraocular cerebellar grafts during thyroid hormone deficiency. Granholm AC, et al. **Cent Nerv Syst Trauma** 1984 Winter;1(2):105–15

Thyroid labeling error [letter] Heflin KC. **Drug Intell Clin Pharm** 1985 Dec;19(12):945

Peptide histidine isoleucine amide stimulates thyroid hormone secretion and coexists with vasoactive intestinal polypeptide in intrathyroid nerve fibers from laryngeal ganglia. Grunditz T, et al. **Endocrinology** 1986 Feb;118(2):783–90

Glucocorticoids and thyroid hormones stimulate biochemical and morphological differentiation of human fetal lung in organ culture. Gonzales LW, et al. **J Clin Endocrinol Metab** 1986 Apr; 62(4):678–91

Effect of hypothyroidism on pituitary cytoplasmic concentrations of messenger RNA encoding thyrotrophin beta and alpha subunits, prolactin and growth hormone. Franklyn JA, et al. **J Endocrinol** 1986 Jan;108(1):43–7

Thyroid hormones modulate the toxicity of 2,3,7,8–tetrachlorodibenzo–p–dioxin (TCDD). Rozman K, et al. **J Toxicol Environ Health** 1985;16(3–4):481–91

Trials of culturing of Mycobacterium leprae using media enriched with thyroid hormones. Massalski W, et al. **Mater Med Pol** 1983 Jan–Jun; 15(1–2):13–4

Decrease in resting metabolic rate during rapid weight loss is reversed by low dose thyroid hormone treatment. Welle SL, et al. **Metabolism** 1986 Apr;35(4):289–91

Relationship between cerebrospinal fluid somatostatin and peripheral thyroid hormones with carbamazepine treatment. Joffe RT, et al. **Neuropsychobiology** 1985;14(3):115–7

Alternative routes of peptide hormone administration. Pontiroli AE, et al. **Spec Top Endocrinol Metab** 1985;7:77–99 (120 ref.)

[Determination of thyroid hormones in the plasma of laying hens using a modified radioimmunoassay] Schäfer K, et al. **DTW** 1985 Nov 26; 92(11–12):459–61 (Eng. Abstr.) **(Ger)**

[Possible regulation of the basic metabolism by thyroid hormones through changes in the sensitivity of mitochondria to cytoplasmic glycopeptide which induces electrogenic anion transport] Galnutdinov MKh, et al. **Dokl Akad Nauk SSSR** 1986 Mar–Apr;287(1):220–2 **(Rus)**

THYROTROPIN

Plasma thyrotrophin (TSH) response to intrahypothalamic injection of an alpha 2–adrenergic receptor agonist (clonidine). Ishikawa K, et al. **Acta Endocrinol (Copenh)** 1986 Jan;111(1):25–9

Pituitary gland: one site of ultrashort–feedback regulation for control of thyrotropin. Kakita T, et al. **Am J Physiol** 1986 Feb; 250(2 Pt 1):E121–4

The effect of maneb, zineb, and ethylenethiourea on the humoral activity of the pituitary–thyroid axis in rat. Laisi A, et al. **Arch Toxicol [Suppl]** 1985;8:253–8

Reparative growth in the rat thyroid: effect of TSH suppression. Stringer BM, et al. **Cell Tissue Kinet** 1986 Jan;19(1):49–56

Stimulatory effect of PMRPamide (Phe–Met–Arg–Phe–NH2) on thyrotropin secretion in rats. Mitsuma T, et al. **Endocrinol Exp (Bratisl)** 1985 Dec;19(4):205–11

Effects of phorbol ester on GH, TSH and PRL release by superfused rat adenohypophysis. Ikeda H, et al. **Endocrinol Jpn** 1985 Oct; 32(5):759–65

Dopamine and L–dopa: inhibition of thyrotropin–stimulated thyroidal thyroxine release. Maayan ML, et al. **Endocrinology** 1986 Feb; 118(2):632–6

Effect of 1,25(OH)2D3 on the TSH secretion from rat pituitary cells. Törnquist K, et al. **Horm Metab Res** 1986 Jan;18(1):69

Effects of histamine and related compounds on thyrotropin secretion in rats. Mitsuma T, et al. **Horm Res** 1986;23(2):99–105

Increased dopaminergic activity inhibits basal and metoclopramide–stimulated prolactin and thyrotropin secretion. Agner T, et al. **J Clin Endocrinol Metab** 1986 Apr;62(4):778–82

Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. Hamblin PS, et al. **J Clin Endocrinol Metab** 1986 Apr;62(4):717–22

Modulation of thyrotrophin release from an intracellular pool by pre–exposure to thyrotrophin–releasing hormone and dibutyryl cyclic AMP. Davis JR, et al. **J Endocrinol** 1986 Feb;108(2):211–7

Graded response in the individual thyroid follicle cell to increasing doses of TSH. Nilsson M, et al. **Mol Cell Endocrinol** 1986 Feb; 44(2):165–9

Regulation of thyrotropin secretion by the central epinephrine system. Studies in the chronically cannulated rat. Terry LC. **Neuroendocrinology** 1986;42(2):102–8

Regulation of growth hormone and thyrotropin secretion by somatostatin systems in rat brain. Terry LC, et al. **Neuroendocrinology** 1986; 42(3):218–25

THYROXINE

The role of thyroid and adrenal cortical hormones in the modulation of the gonadal function in birds. Péczely P. **Acta Biol Hung** 1985; 36(1):45–70

Antler cycle and thermolabile and thermostable alkaline phosphatase in white–tailed deer; circannual and circadian rhythms and variation after thyroxine, dexamethasone and ACTH administration. Sempéré AJ, et al. **Acta Endocrinol (Copenh)** 1986 Jan;111(1):133–9

Plasma thyroxine through parturition and early lactation in goats fed silage of grass and rape. Emre Z, et al. **Acta Vet Scand** 1985;26(3):417–8

Effects of thyrotropin–releasing hormone on serum concentrations of thyroxine and triiodothyronine in healthy, thyroidectomized, thyroxine–treated, and propylthiouracil–treated dogs. Li WI, et al. **Am J Vet Res** 1986 Jan;47(1):163–9

Emotional trauma and thyroxine [letter] Jackson GL. **Ann Intern Med** 1986 Feb;104(2):289

Salinity adaptation in fish: interaction of thyroxine with fish gill mitochondria. Shivakumar K, et al. **Arch Biochem Biophys** 1986 Mar; 245(2):356–62

The effect of maneb, zineb, and ethylenethiourea on the humoral activity of the pituitary–thyroid axis in rat. Laisi A, et al. **Arch Toxicol [Suppl]** 1985;8:253–8

Preliminary data on an immunoenzymatic assay of free thyroxin. Proença MT, et al. **Clin Chem** 1986 Apr;32(4):697

Concentration of free thyroxin in serum of a patient with euthyroid hyperthyroxinemia secondary to increased thyroxin–binding prealbumin: results by various methods compared. Skiest D, et al. **Clin Chem** 1986 Apr;32(4):687–9

Effect of heparin on free thyroxin as measured by equilibrium dialysis and ultrafiltration. Wang YS, et al. **Clin Chem** 1986 Apr;32(4):700

The nonequivalence of levothyroxine products [letter] Dong BJ, et al. **Drug Intell Clin Pharm** 1986 Jan;20(1):77–8

Dopamine and L–dopa: inhibition of thyrotropin–stimulated thyroidal thyroxine release. Maayan ML, et al. **Endocrinology** 1986 Feb; 118(2):632–6

Suppression of annual plasma testosterone and thyroxine cycles in the edible dormouse Glis glis under constant photoperiod at 24 degrees C. Jallageas M, et al. **Experientia** 1986 Feb 15;42(2):171–3

Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. Hamblin PS, et al. **J Clin Endocrinol Metab** 1986 Apr;62(4):717–22

A novel enzyme immunoassay for total thyroxine using immobilized antibodies and hydrophobic chromatography purified thyroxine–peroxidase conjugate. Ferrua B, et al. **J Immunol Methods** 1986 Mar 13;87(2):137–43

Levothyroxine loses potency with age [letter] Stoffer SS, et al. **JAMA** 1986 Apr 11;255(14):1881–2

Modulation of thyroid parameters by exogenous thyroxine in familial dysalbuminemic hyperthyroxinemia. Premachandra BN, et al. **Metabolism** 1986 Mar;35(3):283–8

Endocrine response to acute cold exposure by lactating and non–lactating Norway rats. Adels LE, et al. **Physiol Behav** 1986 Jan;36(1):179–81

Effect of sodium molybdate on the thyroxine–binding affinity of transport cytosol proteins. Svobodová V, et al. **Physiol Bohemoslov** 1985; 34(6):481–7

Increased clearance rate of plasma thyroxine accompanies estradiol–induced vitellogenesis in male Japanese quail. Robinson GA, et al. **Poult Sci** 1985 Dec;64(12):2397–9

Daily variation of corticosterone and thyroid hormones in broiler cockerels. Smoak KD, et al. **Poult Sci** 1986 Jan;65(1):197–8

Cold exposure and mammary exchanges of circulating thyroxine and

oestrone sulphate in the goat. Goode J, et al. **Q J Exp Physiol** 1986 Jan;71(1):93-8
[Effect of hypo- and hyperthyroidism, and hypothalamic ventromedial lesions on the plasma growth hormone response to human growth hormone-releasing factor in rats] Tonegawa Y. **Nippon Ika Daigaku Zasshi** 1985 Dec;52(6):624-32 (Eng. Abstr.) **(Jpn)**
[The biocellular effect of thyroid hormone on functional differentiation of porcine granulosa cells in culture] Hayashi M, et al. **Nippon Naibunpi Gakkai Zasshi** 1985 Oct 20;61(10):1189-96 (Eng. Abstr.) **(Jpn)**
[Acute negative chronotropic effect of L-thyroxine on the everted sinus-atrium preparation of the bullfrog] Tamura T. **Nippon Seirigaku Zasshi** 1985;47(12):756-66 (Eng. Abstr.) **(Jpn)**
[Structural state of rat liver mitochondrial and microsomal membranes in aging and after treatment with thyroxine] Lemeshko VV, et al. **Ukr Biokhim Zh** 1986 Jan-Feb;58(1):63-8 (Eng. Abstr.) **(Rus)**
[Concentrations of thyroxine, beta carotene, vitamin A and pregnancy in heifers after administration of beta carotene] Bekeová E, et al. **Vet Med (Praha)** 1985 Dec;30(12):715-24 (Eng. Abstr.) **(Slo)**

TRANQUILIZING AGENTS

Influence of tranquilisers on ionic permeability of bimolecular lipid membranes. Rajaji D, et al. **Indian J Biochem Biophys** 1984 Dec;21(6):369-72
Bacterial mutagenicity of the tranquilizing constituents of Valerianaceae roots. von der Hude W, et al. **Mutat Res** 1986 Jan-Feb;169(1-2):23-7
[Mechanism of the tranquilizing action of electron structural analogs of nicotinamide] Akhundov RA, et al. **Biull Eksp Biol Med** 1986 Mar;101(3):329-31 (Eng. Abstr.) **(Rus)**

TRANQUILIZING AGENTS, MAJOR

The effect of antipsychotic drugs on driving and driving related psychomotor functions. Judd LL. **Accid Anal Prev** 1985 Aug;17(4):319-22
Drugs and depression. Harris B. **Am J Nurs** 1986 Mar;86(3):292-3
A cybernetic theory of how psychotropic drugs work [letter] Klein DF. **Am J Psychiatry** 1986 May;143(5):685-6
Lithium augmentation in psychotic depression refractory to combined drug treatment. Nelson JC, et al. **Am J Psychiatry** 1986 Mar;143(3):363-6
Neuroleptic dosage for Asians: a failure to replicate. Sramek JJ, et al. **Am J Psychiatry** 1986 Apr;143(4):535-6
Renal function of patients in long-term treatment with lithium citrate alone or in combination with neuroleptics and antidepressant drugs. Lassen E, et al. **Arch Gen Psychiatry** 1986 May;43(5):481-2
Performance deficit induced by low doses of dopamine agonists in rats. Toward a model for approaching the neurobiology of negative schizophrenic symptomatology? Carnoy P, et al. **Biol Psychiatry** 1986 Jan;21(1):11-22
Chronic treatment with five different neuroleptics elicits behavioral supersensitivity to opiate infusion into the nucleus accumbens. Stinus L, et al. **Biol Psychiatry** 1986 Jan;21(1):34-48
Acute schizophrenia. Johnstone EC. **Br J Hosp Med** 1985 Oct;34(4):198-201
Chronic schizophrenia. Morgan R. **Br J Hosp Med** 1985 Oct;34(4):202-5
Neuroleptics in culture-bound syndromes [letter] Harrison-Read PE. **Br J Psychiatry** 1986 Jan;148:106-7
Differential effects of selective and non-selective neuroleptics on intracellular and extracellular cyclic AMP accumulation in rat striatal slices. Lazareno S, et al. **Brain Res** 1985 Dec 30;361(1-2):91-8
Locus coeruleus norepinephrine-containing neurons: effects produced by acute and subchronic treatment with antipsychotic drugs and amphetamine. Ramirez OA; et al. **Brain Res** 1986 Jan 1;362(1):165-70
Inhibition of dopaminergic agonist-induced gnawing behavior by neuroleptic drugs in mice. Yen-Koo HC, et al. **Drug Chem Toxicol** 1985;8(6):495-502
Some atypical neuroleptics inhibit [3H]SCH 23390 binding in vivo. Andersen PH, et al. **Eur J Pharmacol** 1986 Jan 14;120(1):143-4
Guanine nucleotide regulation of agonist interactions at [3H]SCH23390-labeled D1 dopamine receptors in rat striatum. Hess EJ, et al. **Eur J Pharmacol** 1986 Feb 11;121(1):31-8
The natural course of schizophrenia and effective maintenance drug treatment. Davis JM, et al. **J Clin Psychopharmacol** 1986 Feb;6(1 Suppl):2S-10S (79 ref.)
Dosage strategies with long-acting injectable neuroleptics, including haloperidol decanoate. Kane JM. **J Clin Psychopharmacol** 1986 Feb;6(1 Suppl):20S-23S
Drug-behavior therapy outcomes with chronic schizophrenics [letter] Liberman RP, et al. **J Clin Psychopharmacol** 1986 Feb;6(1):52-3
The efficacy of antipsychotic drugs and family therapies in the maintenance treatment of schizophrenia. Schooler NR. **J Clin Psychopharmacol** 1986 Feb;6(1 Suppl):11S-19S (29 ref.)
Oral liquid neuroleptics: administer with care. Kerr LE. **J Psychosoc Nurs Ment Health Serv** 1986 Mar;24(3):33-5
Do antipsychotic drugs and serotonin down regulate [3H]-spiroperidol binding sites in human cortex? Andorn AC. **Life Sci** 1986 Apr 7;38(14):1251-60
The benzazepine SCH 23390 increases plasma levels of cortisol in the conscious dog. Goiny M, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Jan;332(1):111-2
Laterality of dopamine function and neuroleptic action in the amygdala in the rat. Bradbury AJ, et al. **Neuropharmacology** 1985 Dec;24(12):1163-70
A German multicentre study on the long-term treatment of schizophrenic outpatients. Pietzcker A. **Pharmacopsychiatry** 1985 Nov;18(6):333-8
Effects of neuroleptics on hippocampal stimulation-induced 'wet-dog shaking' in rats. Araki H, et al. **Physiol Behav** 1986 Jan;36(1):69-74
Reward, performance, and the response strength method in self-stimulating rats: validation and neuroleptics. Hamilton AL, et al. **Physiol Behav** 1985 Dec;35(6):897-904
Early treatment events and prediction of response to neuroleptics in schizophrenia. Awad AG, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):585-8
Gamma-type endorphins: neurolepticum-like and antipsychotic action. Van Ree JM, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5-6):561-7
Neuroleptics, dopamine, and schizophrenia. Pickar D. **Psychiatr Clin North Am** 1986 Mar;9(1):35-48
CSF dopamine turnover and positive schizophrenic symptoms after withdrawal of long-term neuroleptic treatment. Frecska E, et al. **Psychiatry Res** 1985 Nov;16(3):221-6
Neuroleptic withdrawal in chronic schizophrenia: CT and endocrine variables relating to psychopathology. Naber D, et al. **Psychiatry Res** 1985 Nov;16(3):207-19
Homovanillic acid in caudate and pre-frontal cortex following acute and chronic neuroleptic administration. Bowers MB Jr, et al. **Psychopharmacology (Berlin)** 1986;88(1):63-5
Maternal aggression in rats: lack of interaction between chlordiazepoxide and fluprazine. Olivier B, et al. **Psychopharmacology (Berlin)** 1986;88(1):40-3
A controlled trial of prostaglandin E1 precursor in chronic neuroleptic resistant schizophrenic patients. Vaddadi KS, et al. **Psychopharmacology (Berlin)** 1986;88(3):362-7
[Influence of monoamines on the dl-tetrahydropalmatine-induced inhibition of single-unit activity in the nucleus accumbens] Liu GQ, et al. **Yao Hsueh Hsueh Pao** 1985 Jul;20(7):500-4 (Eng. Abstr.) **(Chi)**
[Benzamides, a therapeutic response adapted to 2 sides, paranoid and hebephrenic, of schizophrenia] Cassan P. **Ann Med Psychol (Paris)** 1985 Jul;143(7):677-82 **(Fre)**
[The prognosis of schizophrenia] Lungershausen E. **Fortschr Med** 1986 Feb 6;104(5):97-100 (Eng. Abstr.) **(Ger)**
[Psychopathologic changes in chronic schizophrenic patients following withdrawal of neuroleptics: relation to therapeutic, neuroendocrine and computer tomography variables] Albus M, et al. **Fortschr Neurol Psychiatr** 1986 Jan;54(1):15-20 (Eng. Abstr.) **(Ger)**
[Behavioral and pharmacological studies of methamphetamine-induced stereotypy of mice by the open field method] Nakamura K, et al. **Yakugaku Zasshi** 1985 Aug;105(8):775-83 (Eng. Abstr.) **(Jpn)**
[Effect of neuroleptics, narcotic analgesics and narcotic agents on the absorptive activity of the small intestine] Koval'skaia KS, et al. **Farmakol Toksikol** 1986 Jan-Feb;49(1):63-6 (Eng. Abstr.) **(Rus)**

TRANQUILIZING AGENTS, MINOR

Neurochemical effects of buspirone in rat hippocampus: evidence for selective activation of 5HT neurons. Mennini T, et al. **Arch Int Pharmacodyn Ther** 1986 Jan;279(1):40-9
Evidence that the beta-carboline, ZK 91296, can reduce anxiety in animals at doses well below those causing sedation. Pellow S, et al. **Brain Res** 1986 Jan 15;363(1):174-7
Comment: Addiction liability of benzodiazepines and buspirone [letter] Nelson RC. **Drug Intell Clin Pharm** 1986 Mar;20(3):233-4
Capillary gas chromatographic-mass spectrometric determination of buspirone in plasma. Gammans RE, et al. **J Chromatogr** 1985 Dec 13;345(2):285-97
Behavioral studies with anxiolytic drugs. II. Interactions of zopiclone with ethyl-beta-carboline-3-carboxylate and Ro 15-1788 in squirrel monkeys. Barrett JE, et al. **J Pharmacol Exp Ther** 1986 Feb;236(2):313-9
Auto-titration technique using intracranial self-stimulation and effects of antianxiety drugs. Ichimaru Y, et al. **Jpn J Pharmacol** 1985 Nov;39(3):331-8
Effect of 450191-S, a 1H-1,2,4-triazolyl benzophenone derivative, on cerebral content of neuroactive amino acids. Tomono S, et al. **Jpn J Pharmacol** 1985 Dec;39(4):558-61
Difference in learning and retention by Albino-Swiss mice. Part 2. Effect of some anxiolytic drugs. Valzelli L, et al. **Methods Find Exp Clin Pharmacol** 1985 Nov;7(11):569-72

Resistance to the anti-anxiety effect of buspirone in patients with a history of benzodiazepine use [letter] Schweizer E, et al. **N Engl J Med** 1986 Mar 13;314(11):719–20

Septal driving of hippocampal theta rhythm: role of gamma-aminobutyrate-benzodiazepine receptor complex in mediating effects of anxiolytics. Quintero S, et al. **Neuroscience** 1985 Dec; 16(4):875–84

Buspirone: anxiolytic? Pecknold JC, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1985;9(5–6):639–42

Effects of propranolol on conditioned suppression, discriminated punishment and discriminated non-reward in the rat. Salmon P, et al. **Psychopharmacology (Berlin)** 1986;88(2):252–7

[Quantitative evaluation of the anxiolytic and nootropic effects of potassium orotate in a wide range of doses] Karkishchenko NN, et al. **Farmakol Toksikol** 1986 Jan–Feb;49(1):14–6 (Eng. Abstr.) **(Rus)**

TRANSFER (PSYCHOLOGY)

Visual discrimination learning and interhemispheric transfer in the cat, as affected by 6-hydroxydopamine. Sprague JM, et al. **Exp Brain Res** 1985;61(1):43–53

TRANYLCYPROMINE

Determination of tranylcypromine in plasma using gas chromatography-chemical-ionization mass spectrometry. Edwards DJ, et al. **J Chromatogr** 1985 Nov 8;344:356–61

Discussion of 'Fatal malignant hyperthermia as a result of ingestion of tranylcypromine (Parnate) combined with white wine and cheese' [letter] Reid WH. **J Forensic Sci** 1986 Jan;31(1):8–10

Tranylcypromine and chlordiazepoxide intoxication [letter] Young S, et al. **Med J Aust** 1986 Feb 3;144(3):166–7

TRIAZOLAM

Comparison of midazolam and triazolam for residual effects. Wehli L, et al. **Arzneimittelforschung** 1985;35(11):1700–4

Treatment of triazolam dependence with a tapering withdrawal regimen. Singh AN, et al. **Can Med Assoc J** 1986 Feb 1;134(3):243–5

Hyperphagic and anorectic effects of beta-carbolines in a palatable food consumption test: comparisons with triazolam and quazepam. Cooper SJ. **Eur J Pharmacol** 1986 Jan 29;120(3):257–65

Enhanced bioavailability of triazolam following sublingual versus oral administration. Scavone JM, et al. **J Clin Pharmacol** 1986 Mar; 26(3):208–10

Temporal variation in triazolam pharmacokinetics and pharmacodynamics after oral administration. Smith RB, et al. **J Clin Pharmacol** 1986 Feb; 26(2):120–4

TRIFLUOPERAZINE

Trifluoperazine inhibits Sendai virus-induced hemolysis. MacDonald RI. **Biochim Biophys Acta** 1986 Apr 14;856(2):337–47

Effective short-term treatment of generalized anxiety disorder with trifluoperazine. Mendels J, et al. **J Clin Psychiatry** 1986 Apr; 47(4):170–4

Radioimmunoassay for the 7-hydroxy metabolite of trifluoperazine and its application to a kinetic study in human volunteers. Aravagiri M, et al. **J Pharm Sci** 1985 Nov;74(11):1196–202

Stimulation of 3H-norepinephrine release by trifluoperazine from rat pineal glands. Yurko KA, et al. **Life Sci** 1986 Apr 14;38(15):1393–7

TRIFLUPROMAZINE

[New methods for synthesis of trifluoromethyl compounds directed for medicinal applications] Kumadaki I. **Yakugaku Zasshi** 1985 Aug; 105(8):713–23 (24 ref.) (Eng. Abstr.) **(Jpn)**

TRYPTAMINES

Tryptamine enhancement of neurotransmitter release under conditions that normally depress calcium influx. Friedman RN, et al. **Brain Res** 1986 Jan 29;364(1):172–6

Indole ring binds to 7-methylguanine base by pi-pi stacking interaction. Crystal structure of 7-methylguanosine 5'-monophosphate-tryptamine complex. Kamiichi K, et al. **FEBS Lett** 1986 Jan 20;195(1–2):57–60

11C-labeling of indolealkylamine alkaloids and the comparative study of their tissue distributions. Takahashi T, et al. **Int J Appl Radiat Isot** 1985 Dec;36(12):965–9

Quantification of tryptamine in brain using high-performance liquid chromatography. Larson AA, et al. **J Chromatogr** 1986 Feb 14; 375(1):37–47

Autoradiographic localization of tryptamine binding sites in the rat and dog central nervous system. McCormack JK, et al. **J Neurosci** 1986 Jan;6(1):94–101

An investigation of demethylation in the metabolism of methoxytryptamine and methoxytryptophol. Leone RM, et al. **J Pineal Res** 1985;2(1):87–94

Relative efficacy of melatonin and 5-methoxytryptamine in terms of their antigonadotrophic and counterantigonadotrophic actions in male Syrian hamsters. Reiter RJ, et al. **J Pineal Res** 1984;1(1):91–8

Temperature-sensitive high affinity [3H]tryptamine binding sites in rat brain. Karasawa A, et al. **Life Sci** 1986 Apr 7;38(14):1331–7

Indolealkylamines and prolactin secretion. A structure-activity study in the central nervous system of the rat. Seeman G, et al. **Neuropharmacology** 1985 Dec;24(12):1195–200

Autoradiographic localization and pharmacology of unique [3H]tryptamine binding sites in rat brain. Altar CA, et al. **Neuroscience** 1986;17(1):263–73

TRYPTOPHAN

Direct plasma injection method for the analysis of tryptophan metabolites by high-performance liquid chromatography coupled with precolumn deproteinization. Morita I, et al. **Anal Biochem** 1985 Dec; 151(2):358–64

Recovery of tryptophan from 25-minute acid hydrolysates of protein. Yokote Y, et al. **Anal Biochem** 1986 Feb 1;152(2):245–9

Structure-function relationships in heparin cofactor II: chemical modification of arginine and tryptophan and demonstration of a two-domain structure. Church FC, et al. **Arch Biochem Biophys** 1986 Apr;246(1):175–84

Influences of amino acids on the circadian rhythms of brain neurotransmitters. Angelova C, et al. **Bibl Nutr Dieta** 1986; (38):72–81

Uptake of tryptophan into the brain: dietary influences on serotoninergic function. Bender DA. **Bibl Nutr Dieta** 1986;(38):82–6

Complex photophysics of the single tryptophan of porcine pancreatic phospholipase A2, its zymogen, and an enzyme/micelle complex. Ludescher RD, et al. **Biochemistry** 1985 Dec 3;24(25):7240–9

Tryptophan fluorescence of terminal deoxynucleotidyl transferase: effects of quenchers on time-resolved emission spectra. Robbins DJ, et al. **Biochemistry** 1985 Dec 3;24(25):7250–7

Evidence from pulse radiolysis and flash photolysis of the environment of tryptophan and tyrosine in the coat protein of fd phage. Ghiron CA, et al. **Biochim Biophys Acta** 1986 Feb 14;869(3):363–6

The effects of amino acids on protein degradation and translocation of non-histone proteins to the nucleus in lymphocytes. Polet H, et al. **Biochim Biophys Acta** 1986 Apr 8;886(1):33–9

A new method for decay-associated fluorescence spectroscopy. Application to the tryptophan zwitterion. Privat JP, et al. **Biochimie** 1985 Sep;67(9):949–58

Levels of total and free tryptophan in maternal and in umbilical blood of infants born by vaginal delivery and by elective cesarean section. Zanardo V, et al. **Biol Neonate** 1985;48(6):346–50

The environment of the tryptophan residue in Pseudomonas aeruginosa azurin and its fluorescence properties. Turoverov KK, et al. **Biophys Chem** 1985 Nov;23(1–2):79–89

Brain serotonin synthesis and Na+,K+-ATPase activity are increased postnatally after prenatal administration of L-tryptophan. Hernández-Rodríguez J, et al. **Brain Res** 1986 Mar;390(2):221–6

Effect of scalding on tryptophan catabolism in rats. Guo JS, et al. **Chin Med J [Engl]** 1985 Aug;98(8):587–90

Effect of scalding on tryptophan contents in rat plasma, urine and tissues. Guo JS, et al. **Chin Med J [Engl]** 1985 Aug;98(8):582–6

Production of a novel tryptophan analog, beta-1-indazole-L-alanine with tryptophan synthase of Escherichia coli. Tanaka H, et al. **FEBS Lett** 1986 Feb 17;196(2):357–60

Escherichia coli tryptophan operon directs the in vivo synthesis of a leader peptide. Dekel-Gorodetsky L, et al. **J Bacteriol** 1986 Mar; 165(3):1046–8

Tryptophan degradation in mice initiated by indoleamine 2,3-dioxygenase. Takikawa O, et al. **J Biol Chem** 1986 Mar 15;261(8):3648–53

Selective and differential medium for the primary isolation of members of the Proteeae. Hawkey PM, et al. **J Clin Microbiol** 1986 Mar; 23(3):600–3

Serotonin syndrome: a case report. Price WA, et al. **J Clin Pharmacol** 1986 Jan;26(1):77–8

Motor activity increases tryptophan, 5-hydroxyindoleacetic acid, and homovanillic acid in ventricular cerebrospinal fluid of the conscious rat. Chaouloff F, et al. **J Neurochem** 1986 Apr;46(4):1313–6

Amino acid analysis demonstrates that increased plasma free tryptophan causes the increase of brain tryptophan during exercise in the rat. Chaouloff F, et al. **J Neurochem** 1986 May;46(5):1647–50

Effects of combined administration of L-tryptophan and tricyclic antidepressants on alpha 2- and beta-adrenoceptors and monoamine levels in rat brain. Russell VA, et al. **Neurochem Res** 1985 Dec; 10(12):1661–71

The photolysis of tryptophan with 337.1 nm laser radiation. Borkman RF, et al. **Photochem Photobiol** 1986 Jan;43(1):13–9

Alkaline quenching of bacteriorhodopsin tryptophanyl fluorescence: evidence for aqueous accessibility or a hydrogen-bonded chain. Palmer PL, et al. **Photochem Photobiol** 1985 Nov;42(5):541–7

Photochemical modifications of lac repressor: effect of effectors binding on tryptophan photooxidation. Spodheim-Maurizot M, et al.

Photochem Photobiol 1985 Oct;42(4):353-9

Plasma tryptophan and tyrosine ratios to competing amino acids in relation to antidepressant response to citalopram and maprotiline. A preliminary study. Møller SE, et al. **Psychopharmacology (Berlin)** 1986; 88(1):96-100

Hormonal and behavioral effects associated with intravenous L-tryptophan administration. Winokur A, et al. **Psychopharmacology (Berlin)** 1986;88(2):213-9

[The tryptophan operon of the facultative methylotrophic bacteria Pseudomonas sp. M. III. Characteristics of regulatory 5-MTR mutants] Maksimova NP, et al. **Genetika** 1986 Feb;22(2):194-9 (Eng. Abstr.) **(Rus)**

[Karyological and morphological analysis of bovine kidney cells resistant to tryptophan analogs--inhibitors of tryptophanyl-tRNA synthetase] Palei EL, et al. **Genetika** 1986 Mar;22(3):473-80 (Eng. Abstr.) **(Rus)**

[Determination of tryptophan in protein hydrolysates using ion exchange chromatography] Izatullaev EA, et al. **Lab Delo** 1986;(2):118-9 **(Rus)**

[Selection of cell lines resistant to tryptophan analogs] Palei EL, et al. **Mol Biol (Mosk)** 1986 Jan-Feb;20(1):208-18 (Eng. Abstr.) **(Rus)**

TRYPTOPHAN HYDROXYLASE

Antidepressant effect of a tryptophan hydroxylase activation inhibitor, AGN 2979 [letter] Clerc G, et al. **Am J Psychiatry** 1986 Feb; 143(2):264-5

Increased tryptophan hydroxylase activity in serotonergic nerve terminals spared by 5,7-dihydroxytryptamine. Stachowiak MK, et al. **Biochem Pharmacol** 1986 Apr 15;35(8):1241-8

[Tryptophan-5-hydroxylase activity in the rabbit brain synaptosomes at different times after the single administration of the opioid peptide Tyr-D-Ala-Gly-Phe-NH2] Uzbekov MG. **Biull Eksp Biol Med** 1986 Feb;101(2):159-60 (Eng. Abstr.) **(Rus)**

TYROSINE

Phosphotyrosine as a substrate of acid and alkaline phosphatases. Apostol I, et al. **Acta Biochim Pol** 1985;32(3):187-97

Involvement of tyrosyl residues in the structure-function relationships of D-beta-hydroxybutyrate dehydrogenase: a phospholipid-requiring enzyme. el Kebbaj MS, et al. **Arch Biochem Biophys** 1986 Feb 1; 244(2):671-7

The use of dithionite reduction to identify the essential tyrosine residue in the F1-ATPase from the thermophilic bacterium, PS3, that reacts with 7-chloro-4-nitrobenzofurazan. Verburg JG, et al. **Arch Biochem Biophys** 1986 Feb 15;245(1):8-13

The effect of short-term immunotherapy with Pollinex on anti-IgE and antigen-induced histamine release from sensitive human basophils. Chyrek-Borowska S, et al. **Arch Immunol Ther Exp (Warsz)** 1985; 33(6):777-82

Influences of amino acids on the circadian rhythms of brain neurotransmitters. Angelova C, et al. **Bibl Nutr Dieta** 1986; (38):72-81

Catecholamine synthesis: physiological coupling to precursor supply. Milner JD, et al. **Biochem Pharmacol** 1986 Mar 15;35(6):875-81

Tyrosine motions in relation to the ferric spin equilibrium of cytochrome P-450cam. Fisher MT, et al. **Biochemistry** 1985 Nov 5; 24(23):6696-701

Time-resolved fluorescence and 1H NMR studies of tyrosine and tyrosine analogues: correlation of NMR-determined rotamer populations and fluorescence kinetics. Laws WR, et al. **Biochemistry** 1986 Feb 11; 25(3):599-607

Time-resolved fluorescence and 1H NMR studies of tyrosyl residues in oxytocin and small peptides: correlation of NMR-determined conformations of tyrosyl residues and fluorescence decay kinetics. Ross JB, et al. **Biochemistry** 1986 Feb 11;25(3):607-12

Evidence from pulse radiolysis and flash photolysis of the environment of tryptophan and tyrosine in the coat protein of fd phage. Ghiron CA, et al. **Biochim Biophys Acta** 1986 Feb 14;869(3):363-6

Formation of m-tyrosine and o-tyrosine from L-phenylalanine in various tissues of rats. Ishimitsu S, et al. **Chem Pharm Bull (Tokyo)** 1985 Sep; 33(9):3887-92

Is the C-terminal flanking peptide of rat cholecystokinin double sulphated? Adrian TE, et al. **FEBS Lett** 1986 Feb 3;196(1):5-8

Complete tyrosine O-sulfation of gastrin in adult and neonatal cat pancreas. Cantor P, et al. **FEBS Lett** 1986 Jan 20;195(1-2):272-4

Kinetics of acetylation-deacetylation of angiotensin II. Intramolecular interactions of the tyrosine and histidine side-chains. Moore GJ. **Int J Pept Protein Res** 1985 Nov;26(5):469-81

Evidence for the steric proximity of Tyr 174 and Lys 111 in bovine growth hormone. Nowicki C, et al. **Int J Pept Protein Res** 1985 Dec; 26(6):568-74

Aromatic amino acid requirement of the lactating sow. Lellis WA, et al. **J Anim Sci** 1985 Dec;61(6):1448-53

Exposed tyrosine residues of lambda cro repressor protein evidenced by nitration and photo CIDNP experiments. Shirakawa M, et al. **J Biochem (Tokyo)** 1985 Sep;98(3):799-805

Identification of the site of sulfation of the fourth component of human complement. Hortin G, et al. **J Biol Chem** 1986 Feb 5; 261(4):1786-93

Localization of the structural difference between bovine blood coagulation factors X1 and X2 to tyrosine 18 in the activation peptide. Morita T, et al. **J Biol Chem** 1986 Mar 25;261(9):4008-14

Distribution of tyrosinated and nontyrosinated alpha-tubulin during mitosis. Gundersen GG, et al. **J Cell Biol** 1986 Mar;102(3):1118-26

Sensitive determination of tyrosine metabolites, p-hydroxyphenylacetic acid, 4-hydroxy-3-methoxyphenyl-acetic acid and 4-hydroxy-3-methoxymandelic acid, by gas chromatography-negative-ion chemical-ionization mass spectrometry. Application to a stable isotope-labelled tracer experiment to investigate their metabolism in man. Shimamura M, et al. **J Chromatogr** 1986 Jan 10;374(1):17-26

Selective and differential medium for the primary isolation of members of the Proteeae. Hawkey PM, et al. **J Clin Microbiol** 1986 Mar; 23(3):600-3

Acute effects of oral or parenteral aspartame on catecholamine metabolism in various regions of rat brain. Yokogoshi H, et al. **J Nutr** 1986 Mar; 116(3):356-64

Mechanism of nasal absorption of drugs. II: Absorption of L-tyrosine and the effect of structural modification on its absorption. Huang CH, et al. **J Pharm Sci** 1985 Dec;74(12):1298-301

Phosphorylation of tyrosine in the carboxyl-terminal tryptic peptide of pp60c-src. Laudano AP, et al. **Proc Natl Acad Sci USA** 1986 Feb; 83(4):892-6

Interaction of vanadate with phenol and tyrosine: implications for the effects of vanadate on systems regulated by tyrosine phosphorylation. Tracey AS, et al. **Proc Natl Acad Sci USA** 1986 Feb;83(3):609-13

Plasma tryptophan and tyrosine ratios to competing amino acids in relation to antidepressant response to citalopram and maprotiline. A preliminary study. Møller SE, et al. **Psychopharmacology (Berlin)** 1986; 88(1):96-100

Tyrosine phosphorylation of platelet protein induced by phorbol ester. Ishihara N, et al. **Thromb Haemost** 1985 Oct 30;54(3):579-85

TYROSINE AMINOTRANSFERASE

Effect of acetaldehyde treatment in vivo on rat liver tryptophan oxygenase and tyrosine aminotransferase activities. Shiohara E, et al. **Arukoru Kenkyuto Yakubutsu Ison** 1985 Dec;20(4):388-94

Glucocorticoid regulation of hepatic cytosolic glucocorticoid receptors in vivo and its relationship to induction of tyrosine aminotransferase. Shirwany TA, et al. **Biochim Biophys Acta** 1986 Apr 8;886(1):162-8

The human tyrosine aminotransferase gene mapped to the long arm of chromosome 16 (region 16q22----q24) by somatic cell hybrid analysis and in situ hybridization. Barton DE, et al. **Hum Genet** 1986 Mar; 72(3):221-4

Assignment of the human tyrosine aminotransferase gene to chromosome 16. Natt E, et al. **Hum Genet** 1986 Mar;72(3):225-8

[The effect of sex factors on the interaction of progesterone and glucocorticoids during increased tyrosine aminotransferase and tryptophane pyrrolase activity in the liver in rats] Németh S. **Bratisl Lek Listy** 1986 Jan;85(1):19-23 (Eng. Abstr.) **(Slo)**

TYROSINE HYDROXYLASE

Activation of tyrosine hydroxylase by Ca2+-dependent neutral protease, calpain. Togari A, et al. **Biochem Biophys Res Commun** 1986 Jan 29; 134(2):749-54

Synaptic connections between serotoninergic axon terminals and tyrosine hydroxylase-immunoreactive neurons in the arcuate nucleus of the rat hypothalamus. A combination of electron microscopic autoradiography and immunocytochemistry. Kiss J, et al. **Brain Res** 1986 Feb 5; 364(2):284-94

Regulation of tyrosine hydroxylase-containing amacrine cell number in larval frog retina. Reh TA, et al. **Dev Biol** 1986 Apr;114(2):463-9

Relationship of age, sex, and reproductive status to the quantity of tyrosine hydroxylase in the median eminence and superior cervical ganglion of the rat. Porter JC. **Endocrinology** 1986 Apr;118(4):1426-32

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration to C57-black mice leads to parallel decrements in neostriatal dopamine content and tyrosine hydroxylase activity. Mayer RA, et al. **Eur J Pharmacol** 1986 Jan 29;120(3):375-7

Isolation and sequence of a cDNA clone which contains the complete coding region of rat phenylalanine hydroxylase. Structural homology with tyrosine hydroxylase, glucocorticoid regulation, and use of alternate polyadenylation sites. Dahl HH, et al. **J Biol Chem** 1986 Mar 25;261(9):4148-53

Effects of phorbol ester on tyrosine hydroxylase phosphorylation and activation in cultured bovine adrenal chromaffin cells. Pocotte SL, et al. **J Biol Chem** 1986 Feb 5;261(4):1873-7

Regulation of guanosine triphosphate cyclohydrolase and tetrahydrobiopterin levels and the role of the cofactor in tyrosine hydroxylation in primary cultures of adrenomedullary chromaffin cells. Abou-Donia MM, et al. **J Neurochem** 1986 Apr;46(4):1190-9

Tyrosine hydroxylase immunoreactive neurons throughout the hypothalamus receive glutamate decarboxylase immunoreactive synapses: a double pre-embedding immunocytochemical study with particulate silver and HRP. van den Pol AN. J **Neurosci** 1986 Mar; 6(3):877-91

Coexistence of tyrosine hydroxylase and growth hormone-releasing factor in a subpopulation of tubero-infundibular neurons of the rat. Meister B, et al. **Neuroendocrinology** 1986;42(3):237-47

Catecholaminergic neurites in senile plaques in prefrontal cortex of aged nonhuman primates. Kitt CA, et al. **Neuroscience** 1985 Nov; 16(3):691-9

VANILMANDELIC ACID

Modifications in a method for vanillylmandelic acid in urine [letter] Anderson GM, et al. **Clin Chem** 1986 Apr;32(4):709

Determination of vanillylmandelic acid with ion-pair chromatography and fluorescence detection. Lindgren K, et al. **Clin Chem** 1986 Apr; 32(4):693-6

Sensitive determination of tyrosine metabolites, p-hydroxyphenylacetic acid, 4-hydroxy-3-methoxyphenyl-acetic acid and 4-hydroxy-3-methoxymandelic acid, by gas chromatography-negative-ion chemical-ionization mass spectrometry. Application to a stable isotope-labelled tracer experiment to investigate their metabolism in man. Shimamura M, et al. **J Chromatogr** 1986 Jan 10;374(1):17-26

[Excretion of catecholamines and their various metabolites in children aged 10-12 years in relation to their mental development] Orgacka H, et al. **Endokrynol Pol** 1985;36(5):285-92 (Eng. Abstr.) **(Pol)**

VASOPRESSINS

Cardiovascular haemodynamics and the response of vasopressin, aldosterone, plasma renin activity and plasma catecholamines to head-up tilt in young and old healthy subjects. Vargas E, et al. **Age Ageing** 1986 Jan;15(1):17-28

Noradrenergic stimulation of supraoptic neuronal activity and vasopressin release in vitro: mediation by an alpha 1-receptor. Armstrong WE, et al. **Brain Res** 1986 Feb 12;365(1):192-7

Spontaneous and stimulated adrenocorticotropin and vasopressin pulsatile secretion in the pituitary venous effluent of the horse. Redekopp C, et al. **Endocrinology** 1986 Apr;118(4):1410-6

Immunoreactivity of hypothalamo-neurohypophysial neurons which secrete corticotropin-releasing hormone (CRH) and vasopressin (Vp): immunocytochemical evidence for a correlation with their functional state in colchicine-treated rats. Alonso G, et al. **Exp Brain Res** 1986; 61(3):497-505

Somatostatin and alpha 2-adrenergic agonists selectively inhibit vasopressin-induced cyclic AMP accumulation in MDCK cells. Friedlander G, et al. **FEBS Lett** 1986 Mar 17;198(1):38-42

Hormone-stimulated polyphosphoinositide breakdown in rat liver plasma membranes. Roles of guanine nucleotides and calcium. Uhing RJ, et al. **J Biol Chem** 1986 Feb 15;261(5):2140-6

Sodium transport by rat cortical collecting tubule. Effects of vasopressin and desoxycorticosterone. Reif MC, et al. **J Clin Invest** 1986 Apr; 77(4):1291-8

[Lithium and the kidney. Acute effects on ADH secretion and enzymuria] Palla R, et al. **Minerva Med** 1986 Feb 28;77(7-8):205-8 (Eng. Abstr.) **(Ita)**

VIOLENCE

Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. Salzman C, et al. **Psychosomatics** 1986 Jan; 27(1 Suppl):17-22

VISUAL PERCEPTION

Visual discrimination learning and interhemispheric transfer in the cat, as affected by 6-hydroxydopamine. Sprague JM, et al. **Exp Brain Res** 1985;61(1):43-53

Generation of end-inhibition in the visual cortex via interlaminar connections. Bolz J, et al. **Nature** 1986 Mar 27-Apr 2; 320(6060):362-5

The role of GABAergic inhibition in the response properties of neurones in cat visual area 18. Vidyasagar TR, et al. **Neuroscience** 1986; 17(1):49-55

WAKEFULNESS

Effect of timiperone, a new antipsychotic drug, on the sleep-wakefulness cycle in cats. Tanaka M, et al. **Jpn J Pharmacol** 1985 Nov; 39(3):391-4

ZIMELIDINE

Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks. A double-blind comparison of zimeldine, imipramine and placebo. Evans L, et al. **Acta Psychiatr Scand** 1986 Jan;73(1):49-53

The effects of fluoxetine and zimeldine on the behavior of olfactory bulbectomized rats. Joly D, et al. **Pharmacol Biochem Behav** 1986 Feb; 24(2):199-204

Effects of repeated zimelidine administration on sleep parameters in the rat. Reyes RB, et al. **Psychopharmacology (Berlin)** 1986;88(1):54-7

BIBLIOGRAPHY

ACEPROMAZINE

Effects of acetylpromazine on the hemodynamics of the equine metatarsal artery, as determined by two-dimensional real-time and pulsed Doppler ultrasonography. Walker M, et al. **Am J Vet Res** 1986 May; 47(5):1075-8

ACETYLCHOLINE

Neurochemical mechanisms of mood stabilization. Focus on electroconvulsive therapy. Lerer B, et al. **Ann NY Acad Sci** 1986; 462:366-75 (74 ref.)

Evidence that the acetylcholine binding site is not formed by the sequence alpha 127-143 of the acetylcholine receptor. Criado M, et al. **Biochemistry** 1986 May 20;25(10):2839-46

Acetylcholine receptor: characterization of the voltage-dependent regulatory (inhibitory) site for acetylcholine in membrane vesicles from Torpedo californica electroplax. Takeyasu K, et al. **Biochemistry** 1986 Apr 8;25(7):1770-6

Separation and quantification of choline and acetylcholine by thermospray liquid chromatography/mass spectrometry. Liberato DJ, et al. **Biomed Environ Mass Spectrom** 1986 Apr;13(4):171-4

Stimulative effect of glia maturation factor and acetylcholine on active amino acid uptake and Ca2+,Mg2+-ATPase activity in nodose ganglia excised from adult rats. Ando M, et al. **Brain Res** 1986 May 14; 373(1-2):359-64

Somatostatin and cholecystokinin octapeptide differentially modulate the release of [3H]acetylcholine from caudate nucleus but not cerebral cortex: role of dopamine receptor activation. Arnerić SP, et al. **Brain Res** 1986 May 21;374(1):153-61

Acetylcholine-induced hyperpolarization in identified neurones of the African giant snail (Achatina fulica Férussac). Furukawa Y, et al. **Brain Res** 1986 May 28;374(2):227-35

One perfusion mixture for immunocytochemical detection of noradrenaline, dopamine, serotonin and acetylcholine in the same rat brain. McRae-Degueurce A, et al. **Brain Res** 1986 Jun 18; 376(1):217-9

Inhibitory effects of acetylcholine on aggressive-defense reaction induced by electrical stimulation of the hypothalamus in cats. Kono R, et al. **Brain Res Bull** 1986 Apr;16(4):491-5

Choline analogues: their use in studies of acetylcholine synthesis, storage, and release. Collier B. **Can J Physiol Pharmacol** 1986 Mar; 64(3):341-6

Attenuation of the responses to repeated cholinergic interventions in the isolated dog atrium. Furukawa Y, et al. **Can J Physiol Pharmacol** 1986 Feb;64(2):206-12

Neurochemical effects of choline supplementation. Wecker L. **Can J Physiol Pharmacol** 1986 Mar;64(3):329-33

Absence of role of endothelium in the response of isolated porcine coronary arteries to acetylcholine. Gräser T, et al. **Cardiovasc Res** 1986 Apr;20(4):299-302

Characterization of substance P-induced bronchoconstriction in the guinea-pig: a comparison with acetylcholine. Stewart AG, et al. **Clin Exp Pharmacol Physiol** 1986 Mar;13(3):223-32

Acetylcholine- and inositol 1,4,5-trisphosphate-induced calcium mobilization in Xenopus laevis oocytes. Nadler E, et al. **FEBS Lett** 1986 Apr 21;199(2):208-12

Effects of cyclic nucleotides, betazole hydrochloride and acetylcholine on pepsinogen secretion from isolated rabbit gastric mucosa. Noguchi Y, et al. **Gastroenterol Jpn** 1986 Apr;21(2):129-34

GABA-induced hypothermia in rats: involvement of serotonergic and cholinergic mechanisms. Serrano JS, et al. **Gen Pharmacol** 1986; 17(3):327-32

Response of isolated uterus of rat, hamster and guinea pig to different uterine stimulants. Mehrotra PK, et al. **Indian J Exp Biol** 1985 Oct; 23(10):572-3

Cholinergic stimulation of phosphatidic acid formation by rat cornea in vitro. Proia AD, et al. **Invest Ophthalmol Vis Sci** 1986 Jun; 27(6):905-8

Translocation of cytosolic acetylcholine into synaptic vesicles and demonstration of vesicular release. Michaelson DM, et al. **J Biol Chem** 1986 May 25;261(15):6831-5

Cytochemical identification of cholinergic amacrine cells in cat retina. Pourcho RG, et al. **J Comp Neurol** 1986 May 22;247(4):497-504

Synergistic interaction in bovine pituitary cultures between growth hormone-releasing factor and other hypophysiotrophic factors. Ingram CD, et al. **J Endocrinol** 1986 Apr;109(1):67-74

Vasoactive intestinal polypeptide and acetylcholine are responsible for neurovasodilation in the head of the cat. Bevan JA, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S427-9

The effect of ascorbate on the acetylcholine release from guinea-pig ileal myenteric plexus. Hayashi E, et al. **J Pharm Pharmacol** 1986 Mar; 38(3):232-5

Extracellular calcium-dependent and -independent effects of methylmercury on spontaneous and potassium-evoked release of acetylcholine at the neuromuscular junction. Atchison WD. **J Pharmacol Exp Ther** 1986 May;237(2):672-80

Chronic effects of paraoxon on transmitter release and the synaptic

contribution to tolerance. Thomsen RH, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):689-94

Characterization of the acetylcholine-induced potassium current in rabbit cardiac Purkinje fibres. Carmeliet E, et al. **J Physiol (Lond)** 1986 Feb; 371:219-37

Desensitization of the acetylcholine-induced increase of potassium conductance in rabbit cardiac Purkinje fibres. Carmeliet E, et al. **J Physiol (Lond)** 1986 Feb;371:239-55

Changes by acetylcholine of membrane currents in rabbit cardiac Purkinje fibres. Carmeliet E, et al. **J Physiol (Lond)** 1986 Feb;371:201-17

Studies of qingyangshen (root of Cynanchum otophyllum). III. Effect of qingyangshen on acetylcholine concentration in mouse brain. Kuang PG, et al. **J Tradit Chin Med** 1985 Dec;5(4):267-70

L-methionine enhances the contractile responses of rat uterine smooth muscle to acetylcholine and high KCl. Ichida S. **Jpn J Pharmacol** 1986 Mar;40(3):469-71

Pharmacologic evidence for direct dopaminergic regulation of striatal acetylcholine release. Gorell JM, et al. **Life Sci** 1986 Jun 16; 38(24):2239-46

Functional antagonism of D-1 and D-2 dopaminergic mechanisms affecting striatal acetylcholine release. Gorell JM, et al. **Life Sci** 1986 Jun 16;38(24):2247-54

Autoradiographic distribution of high affinity muscarinic and nicotinic cholinergic receptors labeled with [3H]acetylcholine in rat brain. Schwartz RD. **Life Sci** 1986 Jun 9;38(23):2111-9

Location of a polypeptide sequence within the alpha-subunit of the acetylcholine receptor containing the cholinergic binding site. Oblas B, et al. **Mol Pharmacol** 1986 Jun;29(6):649-56

Involvement of dopaminergic, cholinergic, and glutamatergic mechanisms in the actions of phencyclidine-like drugs. Johnson KM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:52-66

Channel properties of an insect neuronal acetylcholine receptor protein reconstituted in planar lipid bilayers. Hanke W, et al. **Nature** 1986 May 8-14;321(6066):171-4

Influence of excitatory amino acid receptor antagonists and of baclofen on synaptic transmission in the optic nerve to the suprachiasmatic nucleus in slices of rat hypothalamus. Shibata S, et al. **Neuropharmacology** 1986 Apr;25(4):403-9

Ion channels activated by acetylcholine and gamma-aminobutyric acid in freshly dissociated sympathetic neurones of the rat. Cull-Candy SG, et al. **Neurosci Lett** 1986 May 23;66(3):275-80

M-current in human neocortical neurones. Halliwell JV. **Neurosci Lett** 1986 Jun 6;67(1):1-6

Developmental changes in the interactions of cholinergic and beta-adrenergic agonists on electrophysiologic properties of canine cardiac Purkinje fibers. Moak JP, et al. **Pediatr Res** 1986 Jul; 20(7):613-8

Cholinergic suppression: a postsynaptic mechanism of long-term associative learning. Morielli AD, et al. **Proc Natl Acad Sci USA** 1986 Jun;83(12):4556-60

Acetylcholine raises excitability by inhibiting the fast transient potassium current in cultured hippocampal neurons. Nakajima Y, et al. **Proc Natl Acad Sci USA** 1986 May;83(9):3022-6

Acetylcholine induces vasodilation and prostacyclin synthesis in rat lungs. Feddersen CO, et al. **Prostaglandins** 1986 May;31(5):973-87

[Analysis of the form of cortical neuron reaction to acetylcholine] Kotliar BI, et al. **Biol Nauki** 1986;(4):52-4 (Eng. Abstr.) **(Rus)**

[Reactivity of the cortical neurons to acetylcholine in rats] Kotliar BI, et al. **Zh Vyssh Nerv Deiat** 1986 Jan-Feb;36(1):156-62 (Eng. Abstr.) **(Rus)**

[Plastic reorganization in the synapses of the neocortex in the rat after combined microapplications of mediators] Kotliar BI, et al. **Zh Vyssh Nerv Deiat** 1986 Mar-Apr;36(2):397-9 **(Rus)**

ADJUSTMENT DISORDERS

Animal model of depression: imipramine, bromocriptine and lisuride alleviate motor depression. Golda V, et al. **Act Nerv Super (Praha)** 1986 Mar;28(1):26-7

[Comparative evaluation of the therapeutic efficacy of the antidepressants adepren, linamiphen and emovit] Guliamov MG. **Zh Nevropatol Psikhiatr** 1986;86(4):582-7 (Eng. Abstr.) **(Rus)**

AFFECT

Central nervous system mediation of positive and negative reinforcement in neonatal albino rats. Kehoe P, et al. **Brain Res** 1986 Jun; 392(1-2):69-75

Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. de Wit H, et al. **Drug Alcohol Depend** 1986 Feb;16(4):341-60

Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. Peloquin LJ, et al. **J Abnorm Psychol** 1986 Feb;95(1):88-98

[A good mood. What everyone can contribute to its success (I)] Demling L. **Fortschr Med** 1986 Feb 20;104(7):64-5 **(Ger)**

AFFECTIVE DISORDERS

Neurochemical mechanisms of mood stabilization. Focus on electroconvulsive therapy. Lerer B, et al. **Ann NY Acad Sci** 1986; 462:366-75 (74 ref.)

Current concepts in clinical therapeutics: major affective disorders, Part 1. Bryant SG, et al. **Clin Pharm** 1986 Apr;5(4):304-18 (165 ref.)

Neurotransmitter precursor therapies in affective disorders. von Lerber-Good WF. **Int J Vitam Nutr Res [Suppl]** 1986;29:69-82 (39 ref.)

Pharmacologic induction of cholinergic system up-regulation and supersensitivity in affective disorders research. Dilsaver SC. **J Clin Psychopharmacol** 1986 Apr;6(2):65-74 (167 ref.)

Neurochemical and neuroendocrine dysregulation in affective disorders. Golden RN, et al. **Psychiatr Clin North Am** 1986 Jun;9(2):313-27

AFFECTIVE DISORDERS, PSYCHOTIC

Symptom exacerbation in psychotically depressed adolescents due to high desipramine plasma concentrations. Conrad CD, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):161-4

[Diagnosis and treatment of affective psychosis at various times] Xu SH. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Oct; 18(5):302-5 (Eng. Abstr.) **(Chi)**

AFTERIMAGE

Effects of haloperidol and nomifensine on the visual aftereffects of tilt and movement. Harris JP, et al. **Psychopharmacology (Berlin)** 1986; 89(2):177-82

AGGRESSION

Beta-adrenergic blockers for the control of aggressive behaviors in patients with chronic schizophrenia. Sorgi PJ, et al. **Am J Psychiatry** 1986 Jun;143(6):775-6

Stimulation of the ventral tegmental area (A10 region) enhances the hypothalamic attack behavior in the cat. Piazza P, et al. **Behav Brain Res** 1986 Feb;19(2):179-82

Chemical lesions of the nucleus accumbens septi in rats: effects on muricide and apomorphine-induced aggression. Pucilowski O, et al. **Behav Brain Res** 1986 Feb;19(2):171-8

Elicitation of intraspecific defensive behaviors in the rat by microinjection of picrotoxin, a gamma-aminobutyric acid antagonist, into the midbrain periaqueductal gray matter. Depaulis A, et al. **Brain Res** 1986 Mar 5; 367(1-2):87-95

Inhibitory effects of acetylcholine on aggressive-defense reaction induced by electrical stimulation of the hypothalamus in cats. Kono R, et al. **Brain Res Bull** 1986 Apr;16(4):491-5

Propranolol treatment of assaultive patients with organic brain disease. A double-blind crossover, placebo-controlled study. Greendyke RM, et al. **J Nerv Ment Dis** 1986 May;174(5):290-4

Drugs as research tools in psychology: cholinergic drugs and aggression. Bell R, et al. **Neuropsychobiology** 1985;14(4):181-92 (84 ref.)

Effects of the potentiation of the GABAergic neurotransmission in the olfactory bulbs on mouse-killing behavior. Molina V, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):657-64

Effect of 6-OHDA injected into the locus coeruleus on apomorphine-induced aggression. Pucilowski O, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):773-5

Cholinergic agonists suppress play fighting in juvenile rats. Wilson LI, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1157-9

Testosterone removal in rats results in a decrease in social aggression and a loss of social dominance. Albert DJ, et al. **Physiol Behav** 1986; 36(3):401-7

Plasma catecholamines associated with hypothalamically-elicited defense behavior. Stoddard SL, et al. **Physiol Behav** 1986;36(5):867-73

Parachlorophenylalanine-induced serotonin depletion increases offensive but not defensive aggression in male rats. Vergnes M, et al. **Physiol Behav** 1986;36(4):653-8

[Synthesis and pharmacological studies of derivatives of 5- and 7-(O-hydroxyphenyl)-2,3-dihydro-1,4-diazepins] Kostka K, et al. **Acta Pol Pharm** 1985;42(5):442-7 (Eng. Abstr.) **(Pol)**

AMINO ACIDS

Effects of aspartame ingestion on the carbohydrate-induced rise in tryptophan hydroxylation rate in rat brain. Fernstrom JD, et al. **Am J Clin Nutr** 1986 Aug;44(2):195-205

Separation of amino acid phenylthiohydantoin derivatives by high-pressure liquid chromatography. Meuth JL, et al. **Anal Biochem** 1986 May 1;154(2):478-84

Biosynthesis of an unusual amino acyl moiety contained in bestatin. Okuyama A, et al. **Biochem Int** 1986 Apr;12(4):627-31

Basolateral amino acid transport systems in the perfused exocrine pancreas: sodium-dependency and kinetic interactions between influx and efflux mechanisms. Mann GE, et al. **Biochim Biophys Acta** 1986 Jun 26;858(2):263-74

Measurement of the amino acid metabolite of phencyclidine by selected ion monitoring. Syracuse CD, et al. **Biomed Environ Mass Spectrom** 1986 Mar;13(3):113-5

The response of muscle protein synthesis to nutrient intake in postabsorptive rats: the role of insulin and amino acids. Preedy VR, et al. **Biosci Rep** 1986 Feb;6(2):177-83

Stimulative effect of glia maturation factor and acetylcholine on active amino acid uptake and Ca2+,Mg2+-ATPase activity in nodose ganglia excised from adult rats. Ando M, et al. **Brain Res** 1986 May 14; 373(1-2):359-64

gamma-Endorphin and schizophrenia: amino acid composition of gamma-endorphin and nucleotide sequence of gamma-endorphin cDNA from pituitary glands of schizophrenic patients. Bovenberg RA, et al. **Brain Res** 1986 Jun 18;376(1):29-37

Effects of D-aspartate on excitatory amino acid-induced release of [3H]GABA from goldfish retina. Cha JH, et al. **Brain Res** 1986 Jun 18;376(1):140-8

Selective uptake of neuroactive amino acids by both oligodendrocytes and astrocytes in primary dissociated culture: a possible role for oligodendrocytes in neurotransmitter metabolism. Reynolds R, et al. **Brain Res** 1986 Apr 23;371(2):253-66

Sequential metabolic characteristics following portacaval shunt in rats. de Boer JE, et al. **Eur Surg Res** 1986;18(2):96-106

High-performance liquid chromatography of amino acids, peptides and proteins. LXVII. Evaluation of bandwidth relationships of peptides related to human beta-endorphin, separated by gradient-elution reversed-phase high-performance liquid chromatography. Hearn MT, et al. **J Chromatogr** 1986 Feb 21;352:35-66

Renal hemodynamics during separate and combined infusion of amino acids and dopamine. ter Wee PM, et al. **Kidney Int** 1986 Apr; 29(4):870-4

Hepatic microvascular regulatory mechanisms. V. Effects of lodoxamide tromethamine or phentolamine-HCl on vascular responses elicited by serotonin. Reilly FD, et al. **Microcirc Endothelium Lymphatics** 1984 Dec;1(6):671-89

Mutagenesis by normal metabolites in Escherichia coli: phenylalanine mutagenesis is dependent on error-prone DNA repair. Sargentini NJ, et al. **Mutat Res** 1986 Jul;161(2):113-8

Influence of excitatory amino acid receptor antagonists and of baclofen on synaptic transmission in the optic nerve to the suprachiasmatic nucleus in slices of rat hypothalamus. Shibata S, et al. **Neuropharmacology** 1986 Apr;25(4):403-9

Phencyclidine selectively blocks a spinal action of N-methyl-D-aspartate in mice. Aanonsen LM, et al. **Neurosci Lett** 1986 Jun 18;67(2):191-7

Met-enkephalin selectively increases the spontaneous release of amino acid neurotransmitters from rat striatal slices. Arnerić SP, et al. **Neurosci Lett** 1986 May 6;66(1):73-8

Chronic effects of perchloroethylene and trichloroethylene on the gerbil brain amino acids and glutathione. Briving C, et al. **Neurotoxicology** 1986 Spring;7(1):101-8

Somatostatin and CCK-8 modulate release of striatal amino acids: role of dopamine receptors. Arnerić SP, et al. **Peptides** 1986 Jan-Feb; 7(1):97-103

Norepinephrine and amino acids in prepyriform cortex of rats fed imbalanced amino acid diets. Gietzen DW, et al. **Physiol Behav** 1986; 36(6):1071-80

Effect of mealing on plasma and brain amino acid, and brain monoamine in rats after oral aspartame. Torii K, et al. **Physiol Behav** 1986; 36(4):759-64

AMITRIPTYLINE

Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. Soloff PH, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):691-7

Evaluation of amitriptyline in primary fibrositis. A double-blind, placebo-controlled study. Carette S, et al. **Arthritis Rheum** 1986 May; 29(5):655-9

Amitriptyline normalizes tetrabenazine-induced changes in cerebral microcirculation. Kent TA, et al. **Biol Psychiatry** 1986 May; 21(5-6):483-91

Changes in the behavioural response to a TRH analogue following chronic amitriptyline treatment and repeated electroconvulsive shock in the rat. Bennett GW, et al. **Br J Pharmacol** 1986 May;88(1):129-39

Quantitative homogeneous enzyme immunoassays for amitriptyline, nortriptyline, imipramine, and desipramine. Pankey S, et al. **Clin Chem** 1986 May;32(5):768-72

A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. Blackburn IM, et al. **J Affective Disord** 1986 Jan-Feb;10(1):67-75

Hypochondriacal fears and beliefs in DSM-III melancholia. Changes with amitriptyline. Kellner R, et al. **J Affective Disord** 1986 Jan-Feb; 10(1):21-6

A comparison of the effects of trazodone and amitriptyline on skills performance by geriatric subjects. Burns M, et al. **J Clin Psychiatry** 1986 May;47(5):252-4

Treating delusional depressives with amitriptyline. Spiker DG, et al. **J Clin Psychiatry** 1986 May;47(5):243-6

Long-term amitriptyline treatment alters the affinity state of alpha 2 adrenoceptors in rabbit hindbrain. Hamilton CA, et al. **Life Sci** 1986 Jun 30;38(26):2429-36

Amitriptyline for intractable hiccups [letter] Stalnikowicz R, et al. **N Engl J Med** 1986 Jul 3;315(1):64-5

Leu-enkephalin content in rat brain during prolonged treatment with imipramine or amitriptyline. Herman ZS, et al. **Neuropeptides** 1986 Feb-Mar;7(2):113-24

Weight changes in antidepressants: a comparison of amitriptyline and trazodone. Hecht Orzack M, et al. **Neuropsychobiology** 1986; 15 Suppl 1:28-30

Cognitive performance in geriatric subjects after acute treatment with antidepressants. Moskowitz H, et al. **Neuropsychobiology** 1986; 15 Suppl 1:38-43

Biotransformation of amitriptyline in man: interaction with phenothiazines. Vandel S, et al. **Neuropsychobiology** 1986;15(1):15-9

A double-blind comparative trial of zimelidine, amitriptyline, and placebo in patients with mixed anxiety and depression. Amsterdam JD, et al. **Pharmacopsychiatry** 1986 May;19(3):115-9

Acute effects of different antidepressant drugs on saliva secretion and accommodation range. Knorring L, et al. **Pharmacopsychiatry** 1986 May; 19(3):106-10

Amitriptyline and haloperidol in unstable and schizotypal borderline disorders. Soloff PH, et al. **Psychopharmacol Bull** 1986;22(1):177-82

Comparison of the metabolism of the three antidepressants amitriptyline, imipramine, and chlorimipramine in vitro in rat liver microsomes. Krüger R, et al. **Psychopharmacology (Berlin)** 1986;88(4):505-13

[Prediction of the effect of antidepressants in patients with endogenous depression] Litvinova NM, et al. **Zh Nevropatol Psikhiatr** 1986; 86(4):577-82 (Eng. Abstr.) **(Rus)**

[Changes in the wave composition of evoked potentials during treatment of endogenous depression] Loginov VV, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):431-5 (Eng. Abstr.) **(Rus)**

AMPHETAMINE

Studies on cyproheptadine-amphetamine interaction after pretreatment with 6-hydroxydopamine. Chodera A, et al. **Acta Physiol Pol** 1984 Sep-Dec;35(5-6):426-31

Neuroendocrine responses as a probe into the mechanisms of action of electroconvulsive therapy. Cowen PJ. **Ann NY Acad Sci** 1986; 462:163-71 (32 ref.)

Stereoselective accumulation of hydroxylated metabolites of amphetamine in rat striatum and hypothalamus. Dougan DF, et al. **Br J Pharmacol** 1986 May;88(1):285-90

Inhibition of amphetamine-induced locomotor activity by injection of carbachol into the anterior hypothalamic/preoptic area: pharmacological and electrophysiological studies in the rat. Brudzynski SM, et al. **Brain Res** 1986 Jun 18;376(1):47-56

Crus cerebri lesions abolish amphetamine-induced ascorbate release in the rat neostriatum. Wilson RL, et al. **Brain Res** 1986 Apr 9; 370(2):393-6

Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. de Wit H, et al. **Drug Alcohol Depend** 1986 Feb;16(4):341-60

Effects of dopamine and amphetamine on mouse caudate neurons recorded in vitro. Trulson ME, et al. **Eur J Pharmacol** 1986 May 13; 124(1-2):161-5

Desensitization of rat striatal dopamine-stimulated adenylate cyclase after acute amphetamine administration. Barnett JV, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):820-5

Comparison of amphetamine metabolism using isolated hepatocytes from five species including human. Green CE, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):931-6

Effect of glucose on amphetamine-induced motor behavior. White NM, et al. **Life Sci** 1986 Jun 16;38(24):2255-62

Clinical implications of behavioral pharmacology research on phencyclidine. Balster RL. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:148-62

Amphetamine-induced stereotypic responses in Roman high- and Roman low-avoidance rats. Driscoll P, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1329-32

Antagonistic behavioral effects of calcitonin and amphetamine in the rat. Twery MJ, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1203-7

The effects of prenatal morphine on the responsiveness to morphine and amphetamine. Wagner GC, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):757-9

AMPHETAMINES

Recommendations for demand reduction of amphetamines. Streit F. **Chem Depend** 1980;4(1-2):135-43

Effects of an i.v. lethal dose of 3,4-methylenedioxyamphetamine (MDA) in the dog and antagonism by chlorpromazine. Davis WM, et al. **Gen Pharmacol** 1986;17(2):179-83

Rapid determination of p-hydroxylated methamphetamine metabolites by column liquid chromatography-electrochemistry. Shimosato K, et al. **J Chromatogr** 1986 Apr 25;377:279-86

3,4-Methylenedioxymethamphetamine (MDMA): stereoselective interactions at brain 5-HT1 and 5-HT2 receptors. Lyon RA, et al. **Psychopharmacology (Berlin)** 1986;88(4):525-6

ANOREXIA NERVOSA

Anorexia nervosa and bulimia. Autry JH, et al. **Annu Rev Public Health** 1986;7:535-43

Responses to epinephrine in patients with anorexia nervosa. Nakagawa K, et al. **Endocrinol Jpn** 1985 Dec;32(6):845-9

ANTIDEPRESSIVE AGENTS

Globus hystericus syndrome responsive to antidepressants. Brown SR, et al. **Am J Psychiatry** 1986 Jul;143(7):917-8

Current antidepressants. Hollister LE. **Annu Rev Pharmacol Toxicol** 1986; 26:23-37 (30 ref.)

Synergistic action of alprazolam with tranylcypromine in drug-resistant atypical depression with panic attacks. Ries RK, et al. **Biol Psychiatry** 1986 May;21(5-6):522-6

Fluvoxamine--a baseline study of clinical response, long term tolerance and safety in a general practice population. Martin AJ, et al. **Br J Clin Pract** 1986 Mar;40(3):95-9

Differential effects of antidepressant drugs on [3H]dihydroalprenolol and [3H]imipramine ligand recognition sites in olfactory bulbectomized and sham-lesioned rats. Jesberger JA, et al. **Gen Pharmacol** 1986; 17(3):293-307

Dose effects of antidepressant medication in different populations. A World Health Organization Collaborative Study. **J Affective Disord** 1986;Suppl 2:S1-67

Unipolar depression in the elderly. Reoccurrence on discontinuation of tricyclic antidepressants. Cook BL, et al. **J Affective Disord** 1986 Mar-Apr;10(2):91-4

Quantitative determination of N-[trans-2-(dimethylamino)-cyclopentyl]-N-(3',4'-dichlorophenyl)propamide, its 2H5-labeled analogue and their N-dealkylated metabolites in dog serum by capillary gas chromatography-mass spectrometry. Theis DL, et al. **J Chromatogr** 1986 Mar 7;375(2):299-311

Antidepressant treatment for posttraumatic stress disorder (PTSD) [letter] Harris SE. **J Clin Psychiatry** 1986 May;47(5):275

Antidepressant drug therapy for bulimia: current status. Pope HG Jr, et al. **J Clin Psychiatry** 1986 Jul;47(7):339-45 (73 ref.)

Pharmacologic induction of cholinergic system up-regulation and supersensitivity in affective disorders research. Dilsaver SC. **J Clin Psychopharmacol** 1986 Apr;6(2):65-74 (167 ref.)

The effect of antidepressants on ethylmorphine and imipramine N-demethylation in rat liver microsomes. Daniel W, et al. **J Pharm Pharmacol** 1986 May;38(5):396-8

Effect of chronic administration of antidepressants on duration of immobility in rats forced to swim. Kawashima K, et al. **Jpn J Pharmacol** 1986 Feb;40(2):199-204

Diclofensine and imipramine. A double-blind comparative trial in depressive out-patients. Capponi R, et al. **Neuropsychobiology** 1985; 14(4):173-80

Effects of acute and chronic bupropion on locomotor activity and dopaminergic neurons. Nielsen JA, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):795-9

Effects of chronically administered antidepressant drugs on animal behavior. Vogel GW, et al. **Physiol Behav** 1986;36(4):659-66

Antidepressants and biochemical theories of depression. McNeal ET, et al. **Psychol Bull** 1986 May;99(3):361-74

Pharmacology of combined antidepressant/H2-blocking drug therapy. Curry SH, et al. **Psychopharmacol Bull** 1986;22(1):220-2

A review of controlled studies of adinazolam mesylate in patients with major depressive disorder. Feighner JP. **Psychopharmacol Bull** 1986; 22(1):186-91

Lithium and bupropion antagonise the phasic changes in locomotor activity caused by dopamine infused into the rat nucleus accumbens. Barnes JC, et al. **Psychopharmacology (Berlin)** 1986;89(3):311-6

Effects of repeated doses of fluvoxamine, mianserin and placebo on memory and measures of sedation. Curran HV, et al. **Psychopharmacology (Berlin)** 1986;89(3):360-3

Similar effects of antidepressant and non-antidepressant drugs on behavior under an interresponse-time greater than 72-s schedule. Pollard GT, et al. **Psychopharmacology (Berlin)** 1986;89(2):253-8

[Cardiovascular tolerability of indalpine in therapeutic doses] Jaillon P, et al. **Therapie** 1986 Jan-Feb;41(1):49-52 (Eng. Abstr.) **(Fre)**

[Pharmacokinetic aspects of the effects and interactions of various neuro- and psychotropic drugs] Melzacka M. **Postepy Hig Med Dosw** 1985 Nov-Dec;39(6):581-611 (204 ref.) (Eng. Abstr.) **(Pol)**

[Critical study of the clinical actions of 5-HTP] Teixeira M. **Actas Luso Esp Neurol Psiquiatr Cienc Afines** 1986 Mar-Apr; 14(2):104-12 **(Por)**

[Prolonged administration of antidepressants induces changes in the pulsed release but not in the reverse uptake of biogenic amines] Dolzhenko AT, et al. **Biull Eksp Biol Med** 1986 May;101(5):569-70 (Eng. Abstr.) **(Rus)**

[The role of GABA-benzodiazepine receptor complex in affecting the anxiolytic effect of 3-hydroxypyridines--new non-benzodiazepine tranquilizers] Voronina TA, et al. **Biull Eksp Biol Med** 1986 May; 101(5):571-3 (Eng. Abstr.) **(Rus)**

[Clinical aspects and significance of measuring concentrations of neuroleptics and antidepressants in the blood] Cheshkova E, et al. **Zh Nevropatol Psikhiatr** 1986;86(4):573-6 (Eng. Abstr.) **(Rus)**

[Comparative evaluation of the therapeutic efficacy of the antidepressants adepren, linamiphen and emovit] Guliamov MG. **Zh Nevropatol Psikhiatr** 1986;86(4):582-7 (Eng. Abstr.) **(Rus)**

ANXIETY

The effect of state anxiety on personality measurement. Reich J, et al. **Am J Psychiatry** 1986 Jun;143(6):760-3

Recent developments in 5HT-related pharmacology of animal models of anxiety. Gardner CR. **Pharmacol Biochem Behav** 1986 May; 24(5):1479-85

5-HT and anxiety: promises and pitfalls. Johnston AL, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1467-70

Are serotonergic neurons involved in the control of anxiety and in the anxiolytic activity of benzodiazepines? Thiebot MH. **Pharmacol Biochem Behav** 1986 May;24(5):1471-7

A double-blind comparative trial of zimelidine, amitriptyline, and placebo in patients with mixed anxiety and depression. Amsterdam JD, et al. **Pharmacopsychiatry** 1986 May;19(3):115-9

[Anxiety: a practical therapeutic approach] Turmel J, et al. **Union Med Can** 1986 Mar;115(3):175-7 (Eng. Abstr.) **(Fre)**

ANXIETY DISORDERS

How antipanic drugs might work [letter] Nesse RM, et al. **Am J Psychiatry** 1986 Jul;143(7):945

Lack of preference for diazepam in anxious volunteers. de Wit H, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):533-41

An interim multicentre report on 677 anxious geriatric out-patients treated with buspirone. Napoliello MJ. **Br J Clin Pract** 1986 Feb;40(2):71-3

Psychopharmacology and psychotherapy in the treatment of anxiety. Freedman AM. **Curr Psychiatr Ther** 1986;23:101-18 (47 ref.)

Alprazolam treatment for panic disorders. Alexander PE, et al. **J Clin Psychiatry** 1986 Jun;47(6):301-4

Pharmacotherapy of the panic disorders. Ballenger JC. **J Clin Psychiatry** 1986 Jun;47 Suppl:27-32 (55 ref.)

Nonsteroidal anti-inflammatory drugs and panic disorder [letter] Goldstein JA. **J Clin Psychiatry** 1986 May;47(5):277

Pharmacotherapeutic considerations in anxiety disorders. Hollister LE. **J Clin Psychiatry** 1986 Jun;47 Suppl:33-6 (21 ref.)

Current trends in clinical research on panic attacks, agoraphobia, and related anxiety disorders. Klerman GL. **J Clin Psychiatry** 1986 Jun; 47 Suppl:37-9 (10 ref.)

Early placebo response in anxious and depressed patients. Loebel AD, et al. **J Clin Psychiatry** 1986 May;47(5):230-3

Treatment of panic disorder and agoraphobia with clonazepam. Spier SA, et al. **J Clin Psychiatry** 1986 May;47(5):238-42

Cognitive processes in anxiety and depression: discussion paper. Mathews A. **J R Soc Med** 1986 Mar;79(3):158-61

[Alprazolam (Tafil) and bromazepam (Lexotan) in the treatment of anxiety. A randomized, double-blind comparison in psychiatric outpatients] Sonne LM, et al. **Ugeskr Laeger** 1986 Jun 2; 148(23):1392-5 (Eng. Abstr.) **(Dan)**

[Psychopharmacology of panic attacks] Dugas M, et al. **Ann Med Interne (Paris)** 1986;137(2):152-4 (Eng. Abstr.) **(Fre)**

[Rapid response of a disorder to the addition of lithium carbonate: panic resistant to tricyclic antidepressants] Cournoyer J. **Can J Psychiatry** 1986 May;31(4):335-8 (Eng. Abstr.) **(Fre)**

[Clinical methods for studying anxiolytic agents] Guelfi JD. **Therapie** 1986 Jan-Feb;41(1):37-41 (Eng. Abstr.) **(Fre)**

APOMORPHINE

Verapamil's lack of antidopaminergic properties in mice [letter] Renwart N, et al. **Am J Psychiatry** 1986 Jul;143(7):933-4

Neuroendocrine responses as a probe into the mechanisms of action of electroconvulsive therapy. Cowen PJ. **Ann NY Acad Sci** 1986; 462:163-71 (32 ref.)

Chemical lesions of the nucleus accumbens septi in rats: effects on muricide and apomorphine-induced aggression. Pucilowski O, et al. **Behav Brain Res** 1986 Feb;19(2):171-8

Aporphines 65: chemical, microbial synthesis and characterization by gas chromatography/mass spectrometry of (R)-(-)-10-hydroxy 11-methoxy-N-n-propylnoraporphine, a potential metabolite of N-n-propylnorapomorphine. Neumeyer JL, et al. **Biomed Environ Mass Spectrom** 1986 May;13(5):223-9

Differential effects of dopamine agonists on acoustically and electrically elicited startle responses: comparison to effects of strychnine. Davis

M, et al. **Brain Res** 1986 Apr 16;371(1):58-69

Dopaminergic control of male sex behavior in rats: effects of an intracerebrally-infused agonist. Hull EM, et al. **Brain Res** 1986 Apr 2;370(1):73-81

Denervation-like postsynaptic supersensitivity to dopamine agonists induced by microinjection of colchicine into the substantia nigra pars compacta. Kamata K, et al. **Brain Res** 1986 Mar 5;367(1-2):1-7

Effects of acute and chronic carbamazepine administration on apomorphine-elicited stereotypy. Barros HM, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):345-9

Apomorphine enantiomers' effects on dopamine metabolism: receptor and non-receptor related actions. Saller CF, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):181-8

The effect of apomorphine and pergolide on the potassium-evoked overflow of GABA in rat striatum studied by microdialysis. Tossman U, et al. **Eur J Pharmacol** 1986 Apr 16;123(2):295-8

Differential effects of apomorphine on spinal reflex activity following 6-hydroxydopamine or long-term haloperidol pretreatment. Jensen TS, et al. **J Neural Transm** 1986;65(2):125-34

Effects of apomorphine on morphine analgesia during the state of dopaminergic supersensitivity after chronic treatment with haloperidol. Kamata K, et al. **J Pharmacobiodyn** 1986 Jan;9(1):88-94

Reversal of supersensitive apomorphine-induced rotational behavior in mice by continuous exposure to apomorphine. Winkler JD, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):242-7

In vivo voltammetric study of dopamine release in the striatum following microinjection of apomorphine into the substantia nigra zona reticulata. Kamata K, et al. **Jpn J Pharmacol** 1986 Mar;40(3):472-7

Tracer and maximal specific binding of tritiated spiperone or N-n-propylnorapomorphine to quantify dopamine receptors in rat brain regions in vivo. Van der Werf JF, et al. **Life Sci** 1986 Jul 14; 39(2):155-60

Survival time in hypoxic mice: differentiation between apomorphine-induced hypothermia and antihypoxic properties. Saligaut C, et al. **Methods Find Exp Clin Pharmacol** 1986 Apr;8(4):207-12

Responsiveness to 'autoreceptor' doses of apomorphine inversely correlated with the firing rate of dopaminergic A9 neurons: action of baclofen. Mereu G, et al. **Neurosci Lett** 1986 Apr 11;65(2):161-6

Reduced apomorphine sensitivity of dopamine metabolism in rat striatum after repeated administration of methamphetamine. Kashihara K, et al. **Neurosci Res** 1986 May;3(4):351-5

Effect of 6-OHDA injected into the locus coeruleus on apomorphine-induced aggression. Puciłowski O, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):773-5

Comparison of motor depressant effects of caerulein and N-propylnorapomorphine in mice. Vasar E, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):469-78

Antagonism of apomorphine-induced yawning by SCH 23390: evidence against the autoreceptor hypothesis. Morelli M, et al. **Psychopharmacology (Berlin)** 1986;89(2):259-60

Involvement of different dopamine receptors in rat diphasic motility response to apomorphine. Vaccheri A, et al. **Psychopharmacology (Berlin)** 1986;89(3):265-8

Behavioral and biochemical studies of dopamine receptor sensitivity in differentially housed mice. Wilmot CA, et al. **Psychopharmacology (Berlin)** 1986;89(3):364-9

[Pharmacokinetic aspects of the effects and interactions of various neuro- and psychotropic drugs] Melzacka M. **Postepy Hig Med Dosw** 1985 Nov-Dec;39(6):581-611 (204 ref.) (Eng. Abstr.) **(Pol)**

APPETITE

Glucose regulates [3H](+)-amphetamine binding and Na+K+ ATPase activity in the hypothalamus: a proposed mechanism for the glucostatic control of feeding and satiety. Hauger R, et al. **Brain Res Bull** 1986 Feb;16(2):281-8 (41 ref.)

Aldosterone effects on salt appetite in adrenalectomized rats. McEwen BS, et al. **Neuroendocrinology** 1986;43(1):38-43

Amphetamine-induced anorexia: analysis with hypothalamic lesions and knife cuts. McCabe JT, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):1047-56

AROMATIC AMINO ACID DECARBOXYLASES

Inhibition of aromatic L-amino acid decarboxylase and tyrosine aminotransferase by the monoamine oxidase inhibitor phenelzine. Dyck LE, et al. **J Neurochem** 1986 Jun;46(6):1899-903

Dopaminergic and noradrenergic sympathetic nerves of the dog have different DOPA decarboxylase activities. Harris T, et al. **Neurosci Lett** 1986 Apr 11;65(2):155-60

AROUSAL

Ontogenesis of unit activity in the raphe dorsalis of the behaving kitten: its relationship with the states of vigilance. Adrien J, et al. **Brain Res** 1986 Feb 26;366(1-2):10-21

Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. de Wit H, et al. **Drug Alcohol Depend** 1986 Feb;16(4):341-60

Effect of sulpiride on vigilance in healthy subjects. Bartfai A, et al. **Int J Psychophysiol** 1986 May;4(1):1-5

Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. Peloquin LJ, et al. **J Abnorm Psychol** 1986 Feb;95(1):88-98

Contribution to the search for vigilance-indicative EEG variables. Results of a controlled, double-blind study with pyritinol in elderly patients with symptoms of mental dysfunction. Herrmann WM, et al. **Pharmacopsychiatry** 1986 Mar;19(2):75-83

Effects of repeated doses of fluvoxamine, mianserin and placebo on memory and measures of sedation. Curran HV, et al. **Psychopharmacology (Berlin)** 1986;89(3):360-3

Norepinephrine alterations under stress conditions following the regular practice of meditation. Morrell EM, et al. **Psychosom Med** 1986 Mar-Apr;48(3-4):270-7

[Refinement of an EEG diurnal vigilance index. Application to drug trials] Goidenberg F. **Rev Electroencephalogr Neurophysiol Clin** 1986 Mar; 16(1):39-48 (Eng. Abstr.) **(Fre)**

ATTENTION

Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. Peloquin LJ, et al. **J Abnorm Psychol** 1986 Feb;95(1):88-98

Impaired selective attention in methylazoxymethanol-induced microencephalic rats. Mohammed AK, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):975-81

Effects of chlordiazepoxide on cued radial maze performance in rats. Hodges H, et al. **Psychopharmacology (Berlin)** 1986;88(4):460-6

ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY

Vicissitudes of follow-up studies: differential effects of parent training and stimulant medication with hyperactives. Firestone P, et al. **Am J Orthopsychiatry** 1986 Apr;56(2):184-94

A neuropathic substrate for stimulant drug effects in hyperactive children. Evans RW, et al. **Clin Neuropharmacol** 1986;9(3):264-81

Measurement of whole blood serotonin as a guide in prescribing psychostimulant medication for children with attentional deficits. Saul RC, et al. **Clin Neuropharmacol** 1986;9(2):189-95

Plasma free tryptophan concentration in children with attention deficit disorder. Hoshino Y, et al. **Folia Psychiatr Neurol Jpn** 1985; 39(4):531-5

Attention deficit disorder in adolescents. Silver LB, et al. **Hosp Community Psychiatry** 1986 Jun;37(6):608-13

Comparing classroom and clinic measures of attention deficit disorder: differential, idiosyncratic, and dose-response effects of methylphenidate. Rapport MD, et al. **J Consult Clin Psychol** 1986 Jun;54(3):334-41

Methylphenidate and cognitive therapy in children with attention deficit disorder: a double-blind trial. Brown RT, et al. **J Dev Behav Pediatr** 1986 Jun;7(3):163-74

Fenfluramine treatment of childhood attention deficit disorder with hyperactivity: a preliminary report. Donnelly M, et al. **Psychopharmacol Bull** 1986;22(1):152-4

The therapeutic effect of clonidine in attention deficit disorder with hyperactivity: a comparison with placebo and methylphenidate. Hunt RD, et al. **Psychopharmacol Bull** 1986;22(1):229-36

Methylphenidate: rate-dependent effects on hyperactivity. Rapport MD, et al. **Psychopharmacol Bull** 1986;22(1):223-8

AUTISM

Short-term efficacy and safety of fenfluramine in hospitalized preschool-age autistic children: an open study. Campbell M, et al. **Psychopharmacol Bull** 1986;22(1):141-7

Fenfluramine treatment of autism: UCLA collaborative study of 81 patients at nine medical centers. Ritvo ER, et al. **Psychopharmacol Bull** 1986;22(1):133-40

AUTISM, INFANTILE

Long-term effects of combined vitamin B6-magnesium administration in an autistic child. Martineau J, et al. **Biol Psychiatry** 1986 May; 21(5-6):511-8

Effects of fenfluramine on eight outpatients with the syndrome of autism. Stubbs EG, et al. **Dev Med Child Neurol** 1986 Apr;28(2):229-35

Side effects of fenfluramine in autistic children. Piggott LR, et al. **J Am Acad Child Psychiatry** 1986 Mar;25(2):287-9

AVOIDANCE LEARNING

The use of avoidance training in studies of modulation of memory storage. Gold PE. **Behav Neural Biol** 1986 Jul;46(1):87-98

Long-term effects of leucine-enkephalin on active avoidance responding in mice. Dana RC, et al. **Behav Neurosci** 1986 Apr;100(2):185–9

Congener characteristics influence aversion conditioning to alcoholic beverages in rats. Franchina JJ, et al. **Behav Res Ther** 1986; 24(3):299–306

The course of the decrease of hypothalamic beta–endorphin induced by training, and the development of the effect of beta–endorphin on the retrieval of inhibitory avoidance in rats. Izquierdo I, et al. **Braz J Med Biol Res** 1985;18(3):391–5

Conditioning of aversion to alcohol orosensory cues in 5– and 10–day rats: subsequent reduction in alcohol ingestion. Molina JC, et al. **Dev Psychobiol** 1986 May;19(3):175–83

Conditioned aversions and their memories in 5–day–old rats during suckling. Kehoe P, et al. **J Exp Psychol [Anim Behav]** 1986 Jan; 12(1):40–7

Escape behavior produced by the blockade of glutamic acid decarboxylase (GAD) in mesencephalic central gray or medial hypothalamus. Brandao ML, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):497–501

Amphetamine–induced stereotypic responses in Roman high– and Roman low–avoidance rats. Driscoll P, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1329–32

Pharmacological evidence of catecholaminergic involvement in the behavioral effects of luteinizing hormone releasing hormone in rats. Mora S, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):433–8

Cholecystokinin octapeptide and lithium produce different effects on feeding and taste aversion learning. Ervin GN, et al. **Physiol Behav** 1986;36(3):507–12

Differential effect of chemical lesion and electrocoagulation of the central amygdaloid nucleus on active avoidance responses. Sanchez Riolobos A. **Physiol Behav** 1986;36(3):441–4

Disruption of conditioned taste aversion by ECS: the role of lithium chloride. Shaw N. **Physiol Behav** 1986;36(6):1193–5

Cholinergic suppression: a postsynaptic mechanism of long–term associative learning. Morielli AD, et al. **Proc Natl Acad Sci USA** 1986 Jun;83(12):4556–60

Taste/tactile cue discriminations in taste–aversion learning following depletion of noradrenaline. Archer T, et al. **Scand J Psychol** 1986; 27(1):39–51

[Comparison of the effect of serotonin administered into the dorsal hippocampus on conditioned passive and active avoidance in rats] Gasanov GG, et al. **Biull Eksp Biol Med** 1986 May;101(5):517–9 (Eng. Abstr.) **(Rus)**

[Dynamics of the latent periods of the avoidance response and its correlation with adaptive behavior in the rat] Arushanian EB, et al. **Zh Vyssh Nerv Deiat** 1986 Mar–Apr;36(2):343–50 (Eng. Abstr.) **(Rus)**

AZEPINES

Biochemical studies with the new thienotriazolo–diazepine brotizolam. Bechtel WD, et al. **Arzneimittelforschung** 1986 Mar;36(3A):534–40

Metabolic fate of [14C]–brotizolam in the rat, dog, monkey and man. Bechtel WD, et al. **Arzneimittelforschung** 1986 Mar;36(3A):578–86

Blood level, excretion, and metabolite pattern of [14C]–brotizolam in humans. Bechtel WD, et al. **Arzneimittelforschung** 1986 Mar; 36(3A):575–8

Blood level, distribution, excretion, and metabolite pattern of [14C]–brotizolam in the rat, dog, and rhesus monkey. Bechtel WD, et al. **Arzneimittelforschung** 1986 Mar;36(3A):568–74

Antiemotional and anticonvulsant activity of brotizolam and its effects on motor performance in animals. Böke–Kuhn K, et al. **Arzneimittelforschung** 1986 Mar;36(3A):528–31

General pharmacology of brotizolam in animals. Danneberg P, et al. **Arzneimittelforschung** 1986 Mar;36(3A):540–51

Pharmacological action of some known and possible metabolites of brotizolam. Danneberg P, et al. **Arzneimittelforschung** 1986 Mar; 36(3A):587–91

Effects of brotizolam on the sleep–waking cycle of the cat. Kuhn FJ. **Arzneimittelforschung** 1986 Mar;36(3A):522–7

Effects of brotizolam on cardiovascular functions and autonomic nervous system. Kushiku K, et al. **Arzneimittelforschung** 1986 Mar; 36(3A):552–9

Physical dependence capacity of brotizolam in rhesus monkeys. 2nd communication: primary dependence and barbital substitution. Stockhaus K. **Arzneimittelforschung** 1986 Mar;36(3A):601–5

Physical dependence capacity of brotizolam in rhesus monkeys. 1st communication: primary dependence studies. Stockhaus K, et al. **Arzneimittelforschung** 1986 Mar;36(3A):597–600

Chemistry of brotizolam and its metabolites. Weber KH, et al. **Arzneimittelforschung** 1986 Mar;36(3A):518–21

Evidence for a specific effect of BHT 920, an azepine derivative, on tyrosine hydroxylase in the dopaminergic system of the rat. Jennewein HM, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):363–9

[Synthesis and pharmacological studies of derivatives of 5– and 7–(O–hydroxyphenyl)–2,3–dihydro–1,4–diazepins] Kostka K, et al. **Acta Pol Pharm** 1985;42(5):442–7 (Eng. Abstr.) **(Pol)**

[Synthesis of derivatives of perhydroazepine, perhydro–1,5–oxazocine, morpholine and piperazine containing 3–(isopropylamino)–propan–2–ol group––compounds with potential effect on the circulatory system and central nervous system] Kotełko B, et al. **Acta Pol Pharm** 1985; 42(5):433–6 (Eng. Abstr.) **(Pol)**

[Characteristics of plasmid pBS271 controlling epsilon–caprolactam degradation by bacteria in the genus Pseudomonas] Boronin AM, et al. **Mikrobiologiia** 1986 Mar–Apr;55(2):231–6 (Eng. Abstr.) **(Rus)**

BEHAVIOR

Neuropeptides in behavior and psychiatric syndromes: an overview. Barchas JD, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986; 64:287–307 (129 ref.)

BEHAVIOR, ANIMAL

Development of tolerance to benzodiazepines. II. Baclofen effect on the activity of rats during tolerance to the sedative action of nitrazepam and oxazepam. Chodera A, et al. **Acta Physiol Pol** 1984 Jul–Aug; 35(4):301–9

Neurochemical and behavioral studies on the mode of action of oxypertine. Moroji T, et al. **Arzneimittelforschung** 1986 May; 36(5):804–8

Behavior and brain neurotransmitters: correlations in different strains of mice. Krehbiel D, et al. **Behav Neural Biol** 1986 Jul;46(1):30–45

Suppression of corticosterone synthesis alters the behavior of hippocampally lesioned rats. Ryan JP, et al. **Behav Neural Biol** 1985 Jul;44(1):47–59

Behavioral and physiological effects of chronic 2,450–MHz microwave irradiation of the rat at 0.5 mW/cm2. D'Andrea JA, et al. **Bioelectromagnetics** 1986;7(1):45–56

Changes in the behavioural response to a TRH analogue following chronic amitriptyline treatment and repeated electroconvulsive shock in the rat. Bennett GW, et al. **Br J Pharmacol** 1986 May;88(1):129–39

Reinnervation of the nucleus accumbens and frontal cortex of the rat by dopaminergic grafts and effects on hoarding behavior. Herman JP, et al. **Brain Res** 1986 May 7;372(2):210–6

Correlation between pentobarbital suppressed cerebellar cyclic GMP and performance of a swimming task. McCaslin PP, et al. **Brain Res** 1986 May 28;374(2):367–70

Evidence that serotonin mediates non–cholinergic neocortical low voltage fast activity, non–cholinergic hippocampal rhythmical slow activity and contributes to intelligent behavior. Vanderwolf CH, et al. **Brain Res** 1986 May 28;374(2):342–56

Involvement of neuronal cell bodies of the mesencephalic locomotor region in the initiation of locomotor activity of freely behaving rats. Brudzynski SM, et al. **Brain Res Bull** 1986 Mar;16(3):377–81

Effect of GABAergic drugs in the behavioral 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):265–8

Antagonism of drug–induced yawning and penile erections in rats. Gower AJ, et al. **Eur J Pharmacol** 1986 Mar 18;122(2):239–44

A system for assessing toxicity of chemicals by continuous monitoring of homecage behaviors. Evans HL, et al. **Fundam Appl Toxicol** 1986 May;6(4):721–32

Correlation of indices of stress with intensity of electrical shock for cows. Lefcourt AM, et al. **J Dairy Sci** 1986 Mar;69(3):833–42

The inhibition of the cage–leaving response––a model for studies of the serotonergic neurotransmission in the rat. Rényi L, et al. **J Neural Transm** 1986;65(3–4):193–210

5,7–Dihydroxytryptamine lesions of crayfish serotonin–containing neurons: effect on the lateral giant escape reaction. Glanzman DL, et al. **J Neurosci** 1986 Jun;6(6):1560–9

Effect of tryptamine on the behavior of mice. Sugimoto Y, et al. **J Pharmacobiodyn** 1986 Jan;9(1):68–73

Structural modifications of pro–opiomelanocortin–derived peptides alter their behavioral effects markedly. Hirsch MD, et al. **J Pharmacol Exp Ther** 1986 May;237(2):378–85

Reversal of supersensitive apomorphine–induced rotational behavior in mice by continuous exposure to apomorphine. Winkler JD, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):242–7

Behavioral and neurochemical evaluation of phenylpropanolamine. Woolverton WL, et al. **J Pharmacol Exp Ther** 1986 Jun; 237(3):926–30

An inhalational behavioral chamber. Pradhan SN, et al. **J Pharmacol Methods** 1986 Jun;15(3):189–99

The effect of thioridazine on haloperidol induced behavioral hypersensitivity. Klawans HL, et al. **Life Sci** 1986 May 12; 38(19):1707–14

Sex dependent behavioral response to frontal cortical suction lesions in the rat. Lipsey JR, et al. **Life Sci** 1986 Jun 16;38(24):2185–92

Neurobehavioral screening in rats: validation study. Alder S, et al. **Methods Find Exp Clin Pharmacol** 1986 May;8(5):279–89

Collaborative Behavioral Teratology Study: protocol design and testing procedures. Adams J, et al. **Neurobehav Toxicol Teratol** 1985 Nov–Dec; 7(6):579–86

Dopaminergic mediation of long–term behavioral effects of in utero drug exposure. Middaugh LD, et al. **Neurobehav Toxicol Teratol** 1985 Nov–Dec;7(6):685–9

Neurochemical and electrophysiological disturbances mediate developmental behavioral alterations produced by medicines. Mirmiran M, et al. **Neurobehav Toxicol Teratol** 1985 Nov–Dec;7(6):677–83

Collaborative Behavioral Teratology Study: statistical approach. Nelson CJ, et al. **Neurobehav Toxicol Teratol** 1985 Nov–Dec;7(6):587–90

Effect of chronic administration of the 6–aza analogue of mianserin (Org. 3770) and its enantiomers on behaviour and changes in noradrenaline metabolism of olfactory–bulbectomized rats in the 'open field' apparatus. O'Connor WT, et al. **Neuropharmacology** 1986 Mar;25(3):267–70

The anxiolytic but not the sedative properties of tracazolate are reversed by the benzodiazepine receptor antagonist, Ro 15–1788. File SE, et al. **Neuropsychobiology** 1985;14(4):193–7

Histidyl–proline, a rapidly degraded metabolite of thyrotropin releasing hormone, has behavioural activity. Coggins PJ, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1229–33

Serotonergic mechanisms in the behavioral effects of buspirone and gepirone. Eison AS, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):701–7

Phencyclidine–induced wet–dog shakes observed in rats after withdrawal from reserpine treatment. Nabeshima T, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1275–9

Effect of sodium pentobarbital on behavioral thermoregulation in rats and mice. Strek KS, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):1147–50

Effects of chronically administered antidepressant drugs on animal behavior. Vogel GW, et al. **Physiol Behav** 1986;36(4):659–66

The effects of a 5–HT1 receptor ligand isapirone (TVX Q 7821) on 5–HT synthesis and the behavioural effects of 5–HT agonists in mice and rats. Goodwin GM, et al. **Psychopharmacology (Berlin)** 1986;89(3):382–7

Antagonism of apomorphine–induced yawning by SCH 23390: evidence against the autoreceptor hypothesis. Morelli M, et al. **Psychopharmacology (Berlin)** 1986;89(2):259–60

Similar effects of antidepressant and non–antidepressant drugs on behavior under an interresponse–time greater than 72–s schedule. Pollard GT, et al. **Psychopharmacology (Berlin)** 1986;89(2):253–8

[A unique psychopharmacologic profile of adrafinil in mice] Rambert FA, et al. **J Pharmacol** 1986 Jan–Mar;17(1):37–52 (Eng. Abstr.) **(Fre)**

[The influence on labyrinth behavior of rats of anticonvulsant acting drugs: comparison of propranolol, phenobarbital, phenytoin and diazepam] Kluge S, et al. **Pharmazie** 1986 Apr;41(4):297–8 **(Ger)**

[Effects of central acting drugs on the mirror staircase test] Houri D. **Nippon Yakurigaku Zasshi** 1986 Feb;87(2):135–42 (Eng. Abstr.) **(Jpn)**

[Behavioral pharmacological properties of nicergoline. Effects on gross–behavior in rats and monkeys and on DRL response, CER, and CAR in rats] Yamamura M, et al. **Nippon Yakurigaku Zasshi** 1986 Feb; 87(2):209–21 (Eng. Abstr.) **(Jpn)**

[Effect of stress–inducing factors on monkey behavior. II. Hormonal indices and their relation to behavior in the modelling of emotional stress in hamadryas baboons] Butovskaia ML, et al. **Biol Nauki** 1986; (2):59–64 (Eng. Abstr.) **(Rus)**

BENZAZEPINES

Study on bradycardia induced by diltiazem in the rabbit sinoatrial node. Miyamoto J, et al. **Arzneimittelforschung** 1986 May;36(5):808–10

Effects of diltiazem on PR intervals in healthy young adults. Araki H, et al. **Clin Ther** 1986;8(2):196–202

The influence of diltiazem hydrochloride on trough serum digoxin concentrations. North DS, et al. **Drug Intell Clin Pharm** 1986 Jun; 20(6):500–3

Dopamine D1 receptors characterized with [3H]SCH 23390. Solubilization of a guanine nucleotide–sensitive form of the receptor. Niznik HB, et al. **J Biol Chem** 1986 Jun 25;261(18):8397–406

Dopamine receptor agonists: 3–allyl–6–chloro–2,3,4,5–tetrahydro–1–(4–hydroxyphenyl)–1H–3–benzazepine–7,8–diol and a series of related 3–benzazepines. Ross ST, et al. **J Med Chem** 1986 May;29(5):733–40

Effects of diltiazem on renal blood flow and renal function during angiotensin II infusion in anesthetized dogs. Yamaguchi I, et al. **J Pharmacobiodyn** 1986 Mar;9(3):257–64

Cardiotonic activity of a new inotropic agent, 3,4–dihydro–6–[4–(3,4–dimethoxybenzoyl)–1–piperazinyl]–2(1H)–quinolinone (OPC–8212), in the dog with and without beta–blocker and Ca++–antagonist pretreatment. Hori M, et al. **Jpn Circ J** 1986 Jan;50(1):37–44

Influence of diltiazem on cyclosporin clearance [letter] Griño JM, et al. **Lancet** 1986 Jun 14;1(8494):1387

Cyclosporin–diltiazem interaction [letter] Pochet JM, et al. **Lancet** 1986 Apr 26;1(8487):979

Specific binding of 3H–SCH 23390 to dopamine D1 receptors in vivo. Andersen PH, et al. **Life Sci** 1986 Apr 21;38(16):1507–14

Regulation of agonist and antagonist binding to striatal D–1 dopamine receptors: studies using the selective D–1 antagonist [3H]SK&F R–83566. Flaim KE, et al. **Life Sci** 1986 Jun 9;38(23):2087–96

Electrophysiological study of the effects of D1 and D2 dopamine antagonists on the interaction of converging inputs from the sensory–motor cortex and substantia nigra neurons in the rat. Vives F, et al. **Neuroscience** 1986 Feb;17(2):349–59

Reduction of the rewarding effect of brain stimulation by a blockade of dopamine D1 receptor with SCH 23390. Nakajima S, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):919–23

Antagonism of apomorphine–induced yawning by SCH 23390: evidence against the autoreceptor hypothesis. Morelli M, et al. **Psychopharmacology (Berlin)** 1986;89(2):259–60

[Physical performance capacity, metabolism and hormonal behavior as affected by diltiazem] Kindermann W, et al. **Z Kardiol** 1986 Feb; 75(2):99–106 (Eng. Abstr.) **(Ger)**

BENZODIAZEPINE TRANQUILIZERS

Metabolic interaction between morphine and various benzodiazepines. Pacifici GM, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Apr; 58(4):249–52

Ineffectiveness of clonidine in the treatment of the benzodiazepine withdrawal syndrome: report of three cases. Goodman WK, et al. **Am J Psychiatry** 1986 Jul;143(7):900–3

How antipanic drugs might work [letter] Nesse RM, et al. **Am J Psychiatry** 1986 Jul;143(7):945

Benzodiazepine sensitivity in normal human subjects. Hommer DW, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):542–51

Benzodiazepine antagonist Ro 15–1788 in self–poisoning [letter] Lheureux P, et al. **Arch Intern Med** 1986 Jun;146(6):1241

Patterns of benzodiazepine abuse and dependence. Busto U, et al. **Br J Addict** 1986 Feb;81(1):87–94

Management of benzodiazepine dependence––update 1986. Lader MH, et al. **Br J Addict** 1986 Feb;81(1):7–10

The behavior of 1,4–benzodiazepine drugs in acidic media. V. Kinetics of hydrolysis of flutazolam and haloxazolam in aqueous solution. Kuwayama T, et al. **Chem Pharm Bull (Tokyo)** 1986 Jan;34(1):320–6

Residual effects of zopiclone and benzodiazepine hypnotics on psychomotor performance related to car driving. Harrison C, et al. **Drugs Exp Clin Res** 1985;11(12):823–9

Alternative treatments for withdrawing the long–term benzodiazepine user: a pilot study. Nathan RG, et al. **Int J Addict** 1986 Feb; 21(2):195–211

Distribution of temazepam in body fluids and tissues in lethal overdose. Martin CD, et al. **J Anal Toxicol** 1986 Mar–Apr;10(2):77–8

A new method for the determination in blood and urine of a novel triazolobenzodiazepine (estazolam) by HPLC. Scotto di Tella A, et al. **J Anal Toxicol** 1986 Mar–Apr;10(2):65–7

LC/MS determination of bromazepam, clopenthixol, and reserpine in serum of a non–fatal case of intoxication. Tas AC, et al. **J Anal Toxicol** 1986 Mar–Apr;10(2):46–8

High–performance liquid chromatography systems for the separation of benzodiazepines and their metabolites. Gill R, et al. **J Chromatogr** 1986 Mar 28;356(1):37–46

Determination of lormetazepam in plasma by gas chromatography and electron–capture detection. Zecca L, et al. **J Chromatogr** 1986 Apr 25; 377:368–72

Pharmacokinetics and clinical effects of alprazolam following single and multiple oral doses in patients with panic disorder. Ciraulo DA, et al. **J Clin Pharmacol** 1986 Apr;26(4):292–8

Alprazolam treatment for panic disorders. Alexander PE, et al. **J Clin Psychiatry** 1986 Jun;47(6):301–4

Pharmacotherapy of the panic disorders. Ballenger JC. **J Clin Psychiatry** 1986 Jun;47 Suppl:27–32 (55 ref.)

Pharmacotherapeutic considerations in anxiety disorders. Hollister LE. **J Clin Psychiatry** 1986 Jun;47 Suppl:33–6 (21 ref.)

High dose alprazolam in schizophrenia [letter] Kulik FA, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):191–2

Benzodiazepine dependence in mice after ingestion of drug–containing food pellets. Gallaher EJ, et al. **J Pharmacol Exp Ther** 1986 May; 237(2):462–7

Does alprazolam, in contrast to diazepam, activate alpha 2–adrenoceptors involved in the regulation of rat growth hormone secretion? Eriksson E, et al. **Life Sci** 1986 Apr 21;38(16):1491–8

Does cimetidine inhibit the clearance of temazepam after an overdose? [letter] Dobb GJ, et al. **Med J Aust** 1986 Jul 7;145(1):58–9

Are serotonergic neurons involved in the control of anxiety and in the anxiolytic activity of benzodiazepines? Thiebot MH. **Pharmacol Biochem Behav** 1986 May;24(5):1471–7

The use of benzodiazepines for psychotic disorders: a literature review and preliminary clinical findings. Arana GW, et al. **Psychopharmacol Bull** 1986;22(1):77–87

Benzodiazepines for treatment of panic attacks: a new look. Rickels K, et al. **Psychopharmacol Bull** 1986;22(1):93–9

A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. Rizley R, et al. **Psychopharmacol Bull** 1986;22(1):167–72

Benzodiazepines: review and update. Byrne BE. **Va Dent J** 1986 Jan–Mar; 63(1):22–30

[Alprazolam (Tafil) and bromazepam (Lexotan) in the treatment of anxiety. A randomized, double–blind comparison in psychiatric outpatients] Sonne LM, et al. **Ugeskr Laeger** 1986 Jun 2; 148(23):1392–5 (Eng. Abstr.) **(Dan)**

[Fatigue. Drug therapy] Meunier H. **Arch Belg** 1985;43(11–12):501–10 **(Fre)**

best copy available

[Relations between the nervous and immune systems: a few examples] Lenfant M, et al. **Bull Acad Natl Med (Paris)** 1985 Oct; 169(7):1005-11 (Eng. Abstr.) **(Fre)**

[Current prospects for the benzodiazepines] Gut JP, et al. **Therapie** 1986 Jan-Feb;41(1):31-5 (Eng. Abstr.) **(Fre)**

[Treatment of depressive disorders. Clinical evaluation of the relative effectiveness of flupenthixol in comparison with bromazepam] Paulmann F. **Fortschr Med** 1986 Mar 13;104(10):218-22 (Eng. Abstr.) **(Ger)**

BENZODIAZEPINONES

Stimulatory effect of pirenzepine on mucosal bicarbonate secretion in rat duodenum in vivo. Säfsten B, et al. **Acta Physiol Scand** 1986 Jun; 127(2):267-8

Pirenzepine and propantheline effects on esophageal pressure responses to bethanechol. Hassan M, et al. **Am J Gastroenterol** 1986 May; 81(5):334-8

Clonazepam in bipolar affective disorder [letter] Zetin M, et al. **Am J Psychiatry** 1986 Aug;143(8):1055

Benzodiazepine antagonist Ro 15-1788 in self-poisoning [letter] Lheureux P, et al. **Arch Intern Med** 1986 Jun;146(6):1241

Biochemical pharmacology of pirenzepine. Similarities with tricyclic antidepressants in antimuscarinic effects only. Bechtel WD, et al. **Arzneimittelforschung** 1986 May;36(5):793-6

Difference in effects of pirenzepine and atropine on carbachol-induced pepsinogen secretion from isolated gastric glands. Sakamoto C, et al. **Biochem Biophys Res Commun** 1986 Apr 14;136(1):193-9

DNA sequence specificity of the pyrrolo[1,4]benzodiazepine antitumor antibiotics. Methidiumpropyl-EDTA-iron(II) footprinting analysis of DNA binding sites for anthramycin and related drugs. Hertzberg RP, et al. **Biochemistry** 1986 Mar 25;25(6):1249-58

Pharmacological analysis of the inhibition by pirenzepine and atropine of vagal-stimulated acid secretion in the isolated stomach of the mouse. Black JW, et al. **Br J Pharmacol** 1986 May;88(1):291-7

The behavior of 1,4-benzodiazepine drugs in acidic media. V. Kinetics of hydrolysis of flutazolam and haloxazolam in aqueous solution. Kuwayama T, et al. **Chem Pharm Bull (Tokyo)** 1986 Jan;34(1):320-6

Plasma and biliary disposition of pirenzepine in man. Lee SP, et al. **Clin Exp Pharmacol Physiol** 1986 Mar;13(3):241-8

Randomized, double-blind, placebo-controlled crossover trial of cimetidine and pirenzepine in nonulcer dyspepsia. Talley NJ, et al. **Gastroenterology** 1986 Jul;91(1):149-56

Alterations in biodistribution of [3H]Ro 15-1788 in mice by acute stress: possible changes in in vivo binding availability of brain benzodiazepine receptor. Inoue O, et al. **Int J Nucl Med Biol** 1985;12(5):369-74

Sensitive high-performance liquid chromatographic determination of pirenzepine in plasma. Meineke I, et al. **J Chromatogr** 1986 Mar 7; 375(2):369-75

Treatment of panic disorder and agoraphobia with clonazepam. Spier SA, et al. **J Clin Psychiatry** 1986 May;47(5):238-42

Clonazepam in the treatment of panic disorder [letter] Judd FK, et al. **Med J Aust** 1986 Jul 7;145(1):59

Gallamine binding to muscarinic M1 and M2 receptors, studied by inhibition of [3H]pirenzepine and [3H]quinuclidinylbenzilate binding to rat brain membranes. Burke RE. **Mol Pharmacol** 1986 Jul; 30(1):58-68

AHN 086: an irreversible ligand of 'peripheral' benzodiazepine receptors. Lueddens HW, et al. **Mol Pharmacol** 1986 Jun;29(6):540-5

The anxiolytic but not the sedative properties of tracazolate are reversed by the benzodiazepine receptor antagonist, Ro 15-1788. File SE, et al. **Neuropsychobiology** 1985;14(4):193-7

Differential interactions between chlordiazepoxide, pentobarbital and benzodiazepine antagonists Ro 15-1788 and CGS 8216 in a drug discrimination procedure. De Vry J, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):999-1005

The effects of Ro 15-1788 on anxiolytic self-administration in the rhesus monkey. Johanson CE, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):855-9

Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist. Chang RS, et al. **Proc Natl Acad Sci USA** 1986 Jul;83(13):4923-6

A late-appearing benzodiazepine-induced hypoactivity that is not reversed by a receptor antagonist. Lister RG, et al. **Psychopharmacology (Berlin)** 1986;88(4):520-4

[Dose-dependent telenzepine inhibition of the secretion of human gastric acid stimulated by sham feeding and saliva] Müller P, et al. **Z Gastroenterol** 1986 Mar;24(3):152-6 (Eng. Abstr.) **(Ger)**

BIOGENIC AMINES

Endothelial cell metabolism of biogenic amines. Shepro D, et al. **Annu Rev Physiol** 1986;48:335-45 (66 ref.)

Treatment with GM1 ganglioside increases rat spinal cord indole content. Hadjiconstantinou M, et al. **Brain Res** 1986 Feb 26;366(1-2):343-5

Analysis of temporal and dose-dependent effects of estrogen on monoamines in brain nuclei. Renner K, et al. **Brain Res** 1986 Feb 26; 366(1-2):64-71

The regionalization of [3H]dihydrotetrabenazine binding sites in the mouse brain and its relationship to the distribution of monoamines and their metabolites. Scherman D, et al. **Brain Res** 1986 Apr 2;370(1):176-81

Conjugates of biogenic amines in ventriculocisternal perfusates of conscious African green monkeys. Tyce GM, et al. **Brain Res** 1986 May 7;372(2):269-76

Topographical distribution of amines and major amine metabolites in the rat striatum. Widmann R, et al. **Brain Res** 1986 Mar 5; 367(1-2):244-9

Monoamine levels and turnover in brain: relationship to priming actions of estrogen. Renner KJ, et al. **Brain Res Bull** 1986 Apr; 16(4):469-75

The effects of desipramine, zimelidine, electroconvulsive treatment and lithium on rat brain biogenic amines: a comparison with peripheral changes. Karoum F, et al. **Eur J Pharmacol** 1986 Mar 4; 121(3):377-85

Effects of in-utero exposure to cadmium on the brain biogenic amine levels and tissue metal distribution in rats. Murthy RC, et al. **Ind Health** 1986;24(1):15-21

Determination of biogenic amines in cheese and some other food products by high-performance liquid chromatography in combination with thermo-sensitized reaction detection. Joosten HM, et al. **J Chromatogr** 1986 Apr 4;356(2):311-9

High-performance liquid chromatography of biogenic amines and metabolites in brain, cerebrospinal fluid, urine and plasma. Seegal RF, et al. **J Chromatogr** 1986 Apr 25;377:131-44

Influence of 2,5-hexanedione on rat brain amine synthesis and metabolism. Farr CH, et al. **J Environ Pathol Toxicol Oncol** 1986 Mar-Apr; 6(3-4):361-8

Effects of octopamine, dopamine, and serotonin on production of flight motor output by thoracic ganglia of Manduca sexta. Claassen DE, et al. **J Neurobiol** 1986 Jan;17(1):1-14

Aminergic modulation in lobster stomatogastric ganglion. II. Target neurons of dopamine, octopamine, and serotonin within the pyloric circuit. Flamm RE, et al. **J Neurophysiol** 1986 May;55(5):866-81

Aminergic modulation in lobster stomatogastric ganglion. I. Effects on motor pattern and activity of neurons within the pyloric circuit. Flamm RE, et al. **J Neurophysiol** 1986 May;55(5):847-65

Zolpidem, a novel nonbenzodiazepine hypnotic. II. Effects on cerebellar cyclic GMP levels and cerebral monoamines. Scatton B, et al. **J Pharmacol Exp Ther** 1986 May;237(2):659-65

Behavioral and neurochemical evaluation of phenylpropanolamine. Woolverton WL, et al. **J Pharmacol Exp Ther** 1986 Jun; 237(3):926-30

Concentrations of monoamine metabolites in the cerebrospinal fluid of twins and unrelated individuals--a genetic study. Oxenstierna G, et al. **J Psychiatr Res** 1986;20(1):19-29

Microbore HPLC of biogenic amines in small biological samples. Mefford IN, et al. **Methods Enzymol** 1986;124:402-12

Monoamines as immunomodulators: importance of suppressors and helpers of the bone marrow. Devoino L, et al. **Methods Find Exp Clin Pharmacol** 1986 Mar;8(3):175-81

Binding of psychoactive drugs to rat brain amine receptors, measured ex vivo, and their effects on the metabolism of biogenic amines. Burki HR. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar;332(3):258-66

Monoamines and their catabolites in the rabbit carotid body. Effects of reserpine, sympathectomy and carotid sinus nerve section. Leitner LM, et al. **Pflugers Arch** 1986 Jun;406(6):552-6

Norepinephrine and amino acids in prepyriform cortex of rats fed imbalanced amino acid diets. Gietzen DW, et al. **Physiol Behav** 1986; 36(6):1071-80

Effect of mealing on plasma and brain amino acid, and brain monoamine in rats after oral aspartame. Torii K, et al. **Physiol Behav** 1986; 36(4):759-64

Effects of Suanzaorentang on behavior changes and central monoamines. Hsieh MT, et al. **Proc Natl Sci Counc Repub China [B]** 1986 Jan; 10(1):43-8

[Influence of praziquantel on monoamine transmitters in the rat brain] Liu GQ, et al. **Yao Hsueh Hsueh Pao** 1985 Nov;20(11):807-10 (Eng. Abstr.) **(Chi)**

[The influence of central monoaminergic systems on the anticonvulsive action of propranolol] Lasek R, et al. **Pharmazie** 1986 Feb; 41(2):128-30 (Eng. Abstr.) **(Ger)**

[Prolonged administration of antidepressants induces changes in the pulsed release but not in the reverse uptake of biogenic amines] Dolzhenko AT, et al. **Biull Eksp Biol Med** 1986 May;101(5):569-70 (Eng. Abstr.) **(Rus)**

[Effect of splenin on the concentration of biogenic amines in the tissues and blood plasma of the rat] Doroshenko NM, et al. **Fiziol Zh** 1986 May-Jun;32(3):367-70 (Eng. Abstr.) **(Rus)**

[Bombesin and monoamine-containing cells of the rat stomach] Solov'eva IA, et al. **Fiziol Zh SSSR** 1986 Apr;72(4):503-12 (Eng. Abstr.) **(Rus)**

[Neurohistologic and histochemical characteristics of Loeschke's zone of the medulla in the cat] Chaikovskaia LA. **Neirofiziologiia** 1986; 18(2):219-26 (Eng. Abstr.) **(Rus)**

[Brain monoamines and the hypophyseo-gonadal system of adult rats after the androgenization of their mothers during pregnancy] Naumenko EV, et al. **Ontogenez** 1986 May-Jun;17(3):285-92 (Eng. Abstr.) **(Rus)**

BIOPHARMACEUTICS

A time to speak out on bioequivalence and therapeutic equivalence [editorial] Dettelbach HR. **J Clin Pharmacol** 1986 May-Jun; 26(5):307-8

BIPOLAR DISORDER

The management of resistant depression. Levine S. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):141-51

Renal function and lithium: a longitudinal study. DePaulo JR Jr, et al. **Am J Psychiatry** 1986 Jul;143(7):892-5

Safety of the combination of lithium and neuroleptic drugs. Goldney RD, et al. **Am J Psychiatry** 1986 Jul;143(7):882-4

Identifying lithium-responsive bipolar depressed patients using nuclear magnetic resonance. Rosenthal J, et al. **Am J Psychiatry** 1986 Jun; 143(6):779-80

Rapid reduction of mania by means of reserpine therapy [letter] Telner JI, et al. **Am J Psychiatry** 1986 Aug;143(8):1058

Clonazepam in bipolar affective disorder [letter] Zetin M, et al. **Am J Psychiatry** 1986 Aug;143(8):1055

Electroconvulsive therapy in the treatment of manic episodes. Small JG, et al. **Ann NY Acad Sci** 1986;462:37-49

Lithium counteracts carbamazepine-induced leukopenia while increasing its therapeutic effect. Brewerton TD. **Biol Psychiatry** 1986 Jun; 21(7):677-85

Lithium mechanisms in bipolar illness and altered intracellular calcium functions. Meltzer HL. **Biol Psychiatry** 1986 May;21(5-6):492-510

Regular 48-hour cycling of sleep duration and mood in a 35-year-old woman: use of lithium in time isolation. Welsh DK, et al. **Biol Psychiatry** 1986 May;21(5-6):527-37

Affective disorders and circadian rhythms. Hallonquist JD, et al. **Can J Psychiatry** 1986 Apr;31(3):259-72 (143 ref.)

Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic-depressive patients. Abdalla DS, et al. **Clin Chem** 1986 May;32(5):805-7

Who responds to prophylactic lithium? Abou-Saleh MT, et al. **J Affective Disord** 1986 Mar-Apr;10(2):115-25

Folic acid enhances lithium prophylaxis. Coppen A, et al. **J Affective Disord** 1986 Jan-Feb;10(1):9-13

Lymphocyte beta-adrenergic receptor density of patients with recurrent affective illness. Wood K, et al. **J Affective Disord** 1986 Jan-Feb; 10(1):3-8

Lithium-resistant adolescent mania. Hsu LK. **J Am Acad Child Psychiatry** 1986 Mar;25(2):280-3

Carbamazepine and ECT: a paradoxical combination [letter] Cantor C. **J Clin Psychiatry** 1986 May;47(5):276-7

The serotonin syndrome: case responsive to propranolol [letter] Guzé BH, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):119-20

An inverse relationship between mania and obsessive-compulsive disorder: a case report [letter] Keck PE Jr, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):123-4

Bipolar disorder: are there manic-prone and depressive-prone forms? Quitkin FM, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):167-72

Effects of bipolar affective disorder and lithium administration on the cholinergic system in human blood. Jope RS, et al. **J Psychiatr Res** 1986;20(1):9-18

Effects of lithium on visual perception in manic-depressive patients without acute symptomatology. Kropf D, et al. **Neuropsychobiology** 1986;15(1):34-42

Lithium treatment and blood pressure. Vestergaard P, et al. **Pharmacopsychiatry** 1986 Mar;19(2):73-4

Erythrocyte lithium transport during lithium treatment in patients with affective disorders. Zaremba D, et al. **Pharmacopsychiatry** 1986 Mar; 19(2):63-7

Clinical studies on norepinephrine metabolism: how to interpret the numbers. Linnoila M, et al. **Psychiatry Res** 1986 Mar;17(3):229-39

Effects of carbamazepine on serum electrolytes in affectively ill patients. Joffe RT, et al. **Psychol Med** 1986 May;16(2):331-5

Investigating opioid peptides in schizophrenia and depression. Berger PA, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986;64:309-33 (91 ref.)

[Diagnosis and treatment of affective psychosis at various times] Xu SH. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Oct; 18(5):302-5 (Eng. Abstr.) **(Chi)**

[Erythrocyte membrane transport of L-tyrosine and L-tryptophan in 66 patients with depressive syndromes. Preliminary results] Pringuey D, et al. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):131-40 (Eng. Abstr.) **(Fre)**

[Specific neurohumoral activity of the cerebrospinal fluid of patients with manic-depressive psychosis] Vartanian GA, et al. **Fiziol Cheloveka** 1986 Jan-Feb;12(1):167-70 **(Rus)**

[Changes in the wave composition of evoked potentials during treatment of endogenous depression] Loginov VV, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):431-5 (Eng. Abstr.) **(Rus)**

BLOOD-BRAIN BARRIER

Stimulation of tryptophan uptake into brain microvessels by D-glutamine. Gorgievski-Hrisoho M, et al. **Brain Res** 1986 Mar 5;367(1-2):395-7

Transport of ions across the blood-brain barrier. Betz AL. **Fed Proc** 1986 Jun;45(7):2050-4 (26 ref.)

Blood-CSF barrier to CCK and effect of centrally administered bombesin on release of brain CCK. Zhu XG, et al. **J Neurosci Res** 1986; 15(3):393-403

Blood--brain barrier sodium/potassium pump: modulation by central noradrenergic innervation. Harik SI. **Proc Natl Acad Sci USA** 1986 Jun; 83(11):4067-70

BOMBESIN

The periaqueductal gray: a prerequisite for ACTH-induced excessive grooming. Spruijt BM, et al. **Behav Brain Res** 1986 Apr;20(1):19-25

A substance P antagonist also inhibits specific binding and mitogenic effects of vasopressin and bombesin-related peptides in Swiss 3T3 cells. Zachary I, et al. **Biochem Biophys Res Commun** 1986 May 29; 137(1):135-41

Early events elicited by bombesin and structurally related peptides in quiescent Swiss 3T3 cells. II. Changes in Na+ and Ca2+ fluxes, Na+/K+ pump activity, and intracellular pH. Mendoza SA, et al. **J Cell Biol** 1986 Jun;102(6):2223-33

Blood-CSF barrier to CCK and effect of centrally administered bombesin on release of brain CCK. Zhu XG, et al. **J Neurosci Res** 1986; 15(3):393-403

Effect of vasoactive intestinal peptide, peptide histidine isoleucine and growth hormone-releasing factor-40 on bombesin-like immunoreactivity, somatostatin and gastrin release from the perfused rat stomach. Schusdziarra V, et al. **Peptides** 1986 Jan-Feb; 7(1):127-33

[Bombesin and monoamine-containing cells of the rat stomach] Solov'eva IA, et al. **Fiziol Zh SSSR** 1986 Apr;72(4):503-12 (Eng. Abstr.) **(Rus)**

BRADYKININ

Bradykinin and vasopressin stimulate Na+-K+-Cl- cotransport in cultured endothelial cells. Brock TA, et al. **Am J Physiol** 1986 Jun; 250(6 Pt 1):C888-95

BUTAPERAZINE

[Butaperazine blood level determination by radioimmunoassay following oral application of Tyrylen drug forms] Hergert I, et al. **Pharmazie** 1986 Apr;41(4):289 **(Ger)**

BUTYLAMINES

Terodiline in the treatment of women with urgency and motor urge incontinence. A clinical and urodynamic double-blind cross-over study. Gerstenberg TC, et al. **Br J Urol** 1986 Apr;58(2):129-33

Amines as inhibitors of iron transport in rabbit reticulocytes. Glass J, et al. **J Biol Chem** 1986 Jun 25;261(18):8298-302

Bladder training and terodiline in females with idiopathic urge incontinence and stable detrusor function. Klarskov P, et al. **Scand J Urol Nephrol** 1986;20(1):41-6

[Studies on the synthesis and structure-activity relationships of n-alpha, beta-disubstituted-4-chlorocinnamyl)-sec-butylamines] Peng SQ, et al. **Yao Hsueh Hsueh Pao** 1986 Jan;21(1):20-8 (Eng. Abstr.) **(Chi)**

BUTYROPHENONES

3H-spiperone binding in platelet membranes: a possible biological marker for schizophrenia. Sethi BB, et al. **Acta Psychiatr Scand** 1986 Feb; 73(2):186-90

Effect of azaperone on cardiovascular responsiveness in stress-sensitive pigs. Gregory NG, et al. **J Vet Pharmacol Ther** 1986 Jun; 9(2):164-70

Tracer and maximal specific binding of tritiated spiperone or N-n-propylnorapomorphine to quantify dopamine receptors in rat brain regions in vivo. Van der Werf JF, et al. **Life Sci** 1986 Jul 14; 39(2):155-60

The effects of REM sleep deprivation on striatal dopamine receptor sites. Zwicker AP, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):809-12

Prenatal reserpine exposure in rats decreases caudate nucleus dopamine receptor binding in female offspring. Ali SF, et al. **Toxicol Lett** 1986 Jun;31(3):195-201

CARBAMAZEPINE

Determination of carbamazepine by HPLC electrochemical detection and application for estimation of imipramine desipramine, doxepin and nordoxepin. Messiha FS. **Alcohol** 1986 Mar-Apr;3(2):135-8

Lithium counteracts carbamazepine-induced leukopenia while increasing its therapeutic effect. Brewerton TD. **Biol Psychiatry** 1986 Jun;

21(7):677–85

Inhibitory effect of valproic acid on the disposition of carbamazepine and carbamazepine–10,11–epoxide in the rat. Chang SL, et al. **Drug Metab Dispos** 1986 May–Jun;14(3):281–6

Effect of carbamazepine on psychomotor performance in näive subjects. MacPhee GJ, et al. **Eur J Clin Pharmacol** 1986;30(1):37–42

Effects of acute and chronic carbamazepine administration on apomorphine–elicited stereotypy. Barros HM, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):345–9

Carbamazepine and ECT: a paradoxical combination [letter] Cantor C. **J Clin Psychiatry** 1986 May;47(5):276–7

Effect of carbamazepine on body weight in affectively ill patients. Joffe RT, et al. **J Clin Psychiatry** 1986 Jun;47(6):313–4

Use of carbamazepine in acute psychosis: a controlled study. Lenzi A, et al. **J Int Med Res** 1986;14(2):78–84

Severe carbamazepine intoxication after coadministration of erythromycin. Goulden KJ, et al. **J Pediatr** 1986 Jul;109(1):135–8

Inhibition of epoxidation of carbamazepine by valproic acid in the isolated perfused rat liver. Chang SL, et al. **J Pharmacokinet Biopharm** 1985 Oct;13(5):453–66

Interaction between carbamazepine and dextropropoxyphene. Yu YL, et al. **Postgrad Med J** 1986 Mar;62(725):231–3

Effects of carbamazepine on serum electrolytes in affectively ill patients. Joffe RT, et al. **Psychol Med** 1986 May;16(2):331–5

CATATONIA

Relief from catatonic immobility can be maintained [letter] McEvoy JP. **J Clin Psychopharmacol** 1986 Apr;6(2):126–7

CATECHOL ESTROGENS

Active nonaromatic intermediates in the conversion of steroidal estrogens into catechol estrogens. Le Quesne PW, et al. **Biochemistry** 1986 Apr 22;25(8):2065–72

Catecholestrogen production by porcine ovarian cells. Hammond JM, et al. **Endocrinology** 1986 Jun;118(6):2292–9

Inhibition of the preovulatory prolactin surge in the rat by catechol estrogens: functional and temporal specificity. Okatani Y, et al. **Endocrinology** 1986 Jul;119(1):261–7

Absence of reactive intermediates in the formation of catechol estrogens by rat liver microsomes. Jellinck PH, et al. **J Biol Chem** 1986 Jun 15; 261(17):7729–32

Different metabolism by mammalian and horseradish peroxidases in vitro of steroidal estrogens and their catechol metabolites. Metzler M, et al. **J Steroid Biochem** 1986 Feb;24(2):653–5

[Catechol estrogens and their physiologic relevance] Parvizi N. **DTW** 1986 Feb 7;93(2):94–8 (Eng. Abstr.) **(Ger)**

CATECHOLAMINES

Involvement of a serotonergic control in the regulation of plasma levels of immunoreactive beta–endorphin. Cancela LM, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):409–13

Effect of prolonged exercise on plasma catecholamines. Stejskal P. **Acta Univ Palacki Olomuc Fac Med** 1982;102:107–15

Peripheral venous catecholamines versus adrenal secretory rates after brain stem stimulation in cats. Bereiter DA, et al. **Am J Physiol** 1986 Jul;251(1 Pt 1):E14–20

Titrimetric determination of catecholamines and related compounds via bromine oxidation and substitution. Amin D. **Analyst** 1986 Feb; 111(2):255–7

Occurrence and functional significance of serotonin and catecholamine uptake by astrocytes. Kimelberg HK. **Biochem Pharmacol** 1986 Jul 15; 35(14):2273–81

Catecholamine content of the preovulatory follicles of the domestic hen. Bahr JM, et al. **Biol Reprod** 1986 Apr;34(3):502–6

Catecholamines in sow graafian follicles at proestrus and at diestrus. Fernández–Pardal J, et al. **Biol Reprod** 1986 Apr;34(3):439–45

Brain serotonin and catecholamine responses to repeated stress in rats. De Souza EB, et al. **Brain Res** 1986 Mar 5;367(1–2):77–86

Plasticity of catecholaminergic terminals in rat paraventricular hypothalamic nucleus after 6–hydroxydopamine lesion: an emphasis on bouton sizes and synaptic frequency. Hwang BH, et al. **Brain Res** 1986 Mar 26;369(1–2):267–74

Relationships between catecholaminergic neurons and cholecystokinin–containing neurons in the caudal part of the dorsomedial medulla oblongata of the rat: light and electron microscopic observations by the 'mirror technique'. Kubota Y, et al. **Brain Res** 1986 Apr 9;370(2):343–8

Innervation of substance P neurons by catecholaminergic terminals in the neostriatum. Kubota Y, et al. **Brain Res** 1986 Jun 4;375(1):163–7

Synthesis and release of catecholamines by the cat carotid body in vitro: effects of hypoxic stimulation. Rigual R, et al. **Brain Res** 1986 May 21;374(1):101–9

Serotonin–immunoreactive nerve fibers of the rat pituitary: effects of anticatecholamine and antiserotonin drugs on staining patterns. Saland LC, et al. **Brain Res** 1986 Mar 19;368(2):310–8

Immunohistochemical study of catecholaminergic cell bodies in the rat spinal cord. Mouchet P, et al. **Brain Res Bull** 1986 Mar; 16(3):341–53

Cysteamine effects on somatostatin, catecholamines, pineal NAT and melatonin in rats. Webb SM, et al. **Brain Res Bull** 1986 Mar; 16(3):315–20

A color reaction of 1,2–diphenols based on colored complex formation with phenylfluorone and iron(III) and its application to the assay of catecholamines in pharmaceutical preparations. Fujita Y, et al. **Chem Pharm Bull (Tokyo)** 1985 Dec;33(12):5385–92

The platelet phenolsulfotransferase is not indispensable for the sulfoconjugation of plasma catecholamines. Kuchel O, et al. **Endocr Res** 1985;11(3–4):225–32

Elevation in plasma catecholamines in response to insulin stress is under both neuronal and nonneuronal control. Khalil Z, et al. **Endocrinology** 1986 Jul;119(1):159–67

The effect of hypothalamic catecholamine synthesis inhibition by alpha–methyltyrosine on gonadotropin secretion during sexual maturation in the male Wistar rat. Raum WJ, et al. **Endocrinology** 1986 Jul;119(1):168–75

Mental and physical components of sawmill operatives' workload. Fibiger W, et al. **Ergonomics** 1986 Mar;29(3):363–75

The effect of bromocriptine on plasma catecholamine concentrations in normal volunteers. Steardo L, et al. **Eur J Clin Pharmacol** 1986; 29(6):713–5

Central and peripheral changes in catecholamine–synthesizing enzyme activities after systemic administration of the neurotoxin DSP–4. Féty R, et al. **Eur J Pharmacol** 1986 May 13;124(1–2):197–202

Effects of catecholamine and monophenolamine agonists on identifiable giant neurones, sensitive to these amines, of an African giant snail (Achatina fulica Férussac). Ku BS, et al. **Eur J Pharmacol** 1986 May 13;124(1–2):21–9

Differential time course of protection by monoamine oxidase inhibition and uptake inhibition against MPTP neurotoxicity on central catecholamine neurons in mice. Sundström E, et al. **Eur J Pharmacol** 1986 Mar 18;122(2):275–8

Effect of adrenergic stimulation on ornithine decarboxylase activity in the rat spleen. Stefanelli C, et al. **Gen Pharmacol** 1986;17(3):355–7

Urinary catecholamines and stress in male and female police cadets. Pollack AC, et al. **Hum Biol** 1986 Apr;58(2):209–20

Effect of graded distension of urinary bladder on arterial blood pressure and neurohumors in rabbits. Shukla M, et al. **Indian J Physiol Pharmacol** 1985 Jul–Sep;29(3):159–64

Simplified automated procedure for measurement of certain catecholamine drugs delivered from aerosol inhalation units. Lukovits FS, et al. **J Assoc Off Anal Chem** 1986 Mar–Apr;69(2):183–6

Control of stimulus–secretion coupling in adrenal medullary chromaffin cells by microfilament–specific macromolecules. Friedman JE, et al. **J Biol Chem** 1986 May 5;261(13):5745–50

Catecholamines induce an increase in nerve growth factor content in the medium of mouse L–M cells. Furukawa Y, et al. **J Biol Chem** 1986 May 5;261(13):6039–47

Analytical differences between the determination of plasma catecholamines by liquid chromatography with electrochemical detection and by radioenzymatic assay. Eisenhofer G. **J Chromatogr** 1986 Apr 25;377:328–33

Determination of free and total catecholamines and salsolinol in urine by ion–pair reversed–phase liquid chromatography with electrochemical detection after a one–step sample clean–up. Odink J, et al. **J Chromatogr** 1986 Apr 25;377:145–54

Determination of catecholamines in plasma by HPLC and amperometric detection. Comparison with a radioenzymatic method. Bauersfeld W, et al. **J Clin Chem Clin Biochem** 1986 Mar;24(3):185–8

Plasma catecholamines, dietary carbohydrate, and glucose intolerance: a comparison between young and old men. Chen M, et al. **J Clin Endocrinol Metab** 1986 Jun;62(6):1193–8

Central adrenergic activity in the mediobasal hypothalamus is temporally related to surge outputs of gonadotrophins in oestrogen–stimulated infant female rats. Clement EM, et al. **J Endocrinol** 1986 Apr; 109(1):45–51

Calcium–independent stimulation of glycogenolysis by arginine vasotocin and catecholamines in liver of the axolotl (Ambystoma mexicanum) in vitro. Janssens PA, et al. **J Endocrinol** 1986 Apr;109(1):75–84

Catecholamine–induced transport systems in trout erythrocyte. Na+/H+ countertransport or NaCl cotransport? Borgese F, et al. **J Gen Physiol** 1986 Apr;87(4):551–66

An improved method for tyrosine hydroxylase immunolabeling of catecholamine cells in whole mounted rat retina. Versaux–Botteri C, et al. **J Histochem Cytochem** 1986 Jun;34(6):743–7

Studies on rat brain catecholamine synthesis and beta–adrenoceptor number following administration of electroconvulsive shock, desipramine and clenbuterol. Nimgaonkar VL, et al. **J Neural Transm** 1986;65(3–4):245–59

Catecholamine–metabolizing enzymes of bovine brain microvessel endothelial cell monolayers. Baranczyk–Kuzma A, et al.

J Neurochem 1986 Jun;46(6):1956-60

A semiautomated analysis method for catecholamines, indoleamines, and some prominent metabolites in microdissected regions of the nervous system: an isocratic HPLC technique employing coulometric detection and minimal sample preparation. Kilpatrick IC, et al. **J Neurochem** 1986 Jun;46(6):1865-76

Expression and regulation of catecholaminergic traits in primary sensory neurons: relationship to target innervation in vivo. Katz DM, et al. **J Neurosci** 1986 Apr;6(4):983-9

Spectrophotometric determination of catecholamines. Salem FB. **J Pharm Belg** 1986 Jan-Feb;41(1):35-8

beta-Endorphin-induced stimulation of central sympathetic outflow: inhibitory modulation by central noradrenergic neurons. Appel NM, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):695-701

Age-dependent changes in the response of isolated beagle coronary arteries to transmural electrical stimulation and catecholamines. Toda N, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):319-26

Effects of propranolol on catecholamine synthesis and uptake in the central nervous system of the rat. Tuross N, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):739-45

High concentrations of catecholamines selectively diminish the sensitivity of CRF-stimulated ACTH release by cultured rat pituitary cells to the suppressive effects of dexamethasone. Lamberts SW, et al. **Life Sci** 1986 Jul 14;39(2):97-102

Histamine-induced fluid efflux in the canine forelimb as affected by carotid occlusion or hemorrhage. Dabney JM, et al. **Microcirc Endothelium Lymphatics** 1984 Jun;1(3):247-71

Rudolf Buchheim lecture. The metabolizing systems involved in the inactivation of catecholamines. Trendelenburg U. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar;332(3):201-7

Sensation seeking, paired associate learning and brain catecholamines. Kulcsár Z, et al. **Neuropsychobiology** 1986;15(1):43-8

Carotid sinus nerve C-fibers release catecholamines from the cat carotid body. Almaraz L, et al. **Neurosci Lett** 1986 Jun 18;67(2):153-8

Anatomical evidence for interactions between catecholamine- and adrenocorticotropin-containing neurons. Baker H, et al. **Neuroscience** 1986 Feb;17(2):469-84

Changes in nociception after 6-hydroxydopamine lesions of descending catecholaminergic pathways in mice. Fasmer OB, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1441-4

Lack of evidence for the involvement of catecholaminergic mechanisms in the behavioral anti-methamphetamine effect of L-histidine in the mouse. Itoh Y, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):571-4

Short-term feeding-related changes in mediodorsal hypothalamic catecholamine release. Kruissink N, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):575-9

Pharmacological evidence of catecholaminergic involvement in the behavioral effects of luteinizing hormone releasing hormone in rats. Mora S, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):433-8

Roles of catecholamine terminals and intrinsic neurons of the ventral tegmentum in self-stimulation investigated in neonatally dopamine-depleted rats. Takeichi T, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1101-9

Catecholamine metabolism: basic aspects and clinical significance. Kopin IJ. **Pharmacol Rev** 1985 Dec;37(4):333-64 (301 ref.)

Plasma catecholamines associated with hypothalamically-elicited defense behavior. Stoddard SL, et al. **Physiol Behav** 1986;36(5):867-73

Positive inotropic effects of an ACTH analogue (ACTH 1-17) on myocardial performance. Levi G, et al. **Ric Clin Lab** 1985 Oct-Dec; 15(4):349-56

Trimethyltin as a selective adrenal chemosympatholytic agent in vivo: effect precedes both clinical and histopathological evidence of toxicity. Ally AI, et al. **Toxicology** 1986 Aug;40(2):215-29

Response of the cardiovascular system to catecholamines in rats given small doses of lead. Skoczyńska A, et al. **Toxicology** 1986 Jun; 39(3):275-89

[Separation of catecholamines by micro high-performance liquid chromatography with electrochemical detection] Zou GW, et al. **Yao Hsueh Hsueh Pao** 1985 Nov;20(11):870-3 (Eng. Abstr.) **(Chi)**

[Role of gamma-aminobutyric acid in the process of catecholamine secretion from the adrenal medulla] Kitayama S. **Hiroshima Daigaku Shigaku Zasshi** 1985 Jun;17(1):21-34 **(Jpn)**

[The dynamic changes in catecholamine secretion from adrenal glands during hemorrhagic shock] Tani N. **Hiroshima Daigaku Shigaku Zasshi** 1985 Dec;17(2):289-303 **(Jpn)**

[The function of the sympathetic nervous system determined by humoral factors in the maintenance hemodialysis patients] Minami M, et al. **Hokkaido Igaku Zasshi** 1986 Mar;61(2):186-94 (Eng. Abstr.) **(Jpn)**

[Effect of intrathecal beta-endorphin and electrical tooth pulp stimulation on endocrine and cardiovascular functions] Miyata A. **Masui** 1986 Feb; 35(2):250-9 (Eng. Abstr.) **(Jpn)**

[Changes in cardiovascular, sympathoadrenal and metabolic responses during exercise corresponding to the lactate threshold in middle-aged and elderly women] Yoshitake Y. **Nippon Eiseigaku Zasshi** 1986 Feb; 40(6):867-75 (Eng. Abstr.) **(Jpn)**

[Urinary excretion of catecholamines, 17-ketosteroids and 17-hydroxycorticosteroids in children exposed to the toxic effects of cadmium and lead in selected areas of Katowice province] Orgacka H, et al. **Pediatr Pol** 1985 Nov-Dec;60(11-12):775-9 (Eng. Abstr.) **(Pol)**

[Effect of beta-endorphin on catecholamine levels in the rat hypothalamus and cerebral cortex] Slavnov VN, et al. **Biull Eksp Biol Med** 1986 May; 101(5):562-4 (Eng. Abstr.) **(Rus)**

[Combination of the method of catecholamine fluorescence with the technic of retrograde labeling of neurons] Maiskii VA, et al. **Fiziol Zh** 1986 May-Jun;32(3):371-4 (Eng. Abstr.) **(Rus)**

[Indicators of catecholamine excretion in air traffic controllers] Kuprianov VA, et al. **Gig Tr Prof Zabol** 1986 Feb;(2):53-6 **(Rus)**

[Participation of catecholamines in the regulation of an induced wave of gonadotropins in ovariectomized rats] Bukiia NG, et al. **Probl Endokrinol (Mosk)** 1986 Mar-Apr;32(2):47-51 (Eng. Abstr.) **(Rus)**

[Catecholamine content in the wall of the thoracic duct of the dog during postnatal development] Prozorovskaia MP, et al. **Zh Evol Biokhim Fiziol** 1986 Mar-Apr;22(2):203-5 (Eng. Abstr.) **(Rus)**

[Clinico-biochemical approach to the problem of psychogenic disorders and background] Pelipas VE, et al. **Zh Nevropatol Psikhiatr** 1986; 86(3):409-12 (Eng. Abstr.) **(Rus)**

CENTRAL NERVOUS SYSTEM AGENTS

[Effects of central acting drugs on the mirror staircase test] Houri D. **Nippon Yakurigaku Zasshi** 1986 Feb;87(2):135-42 (Eng. Abstr.) **(Jpn)**

CHILD BEHAVIOR DISORDERS

[New indications for fenfluramine (letter)] De Villard R, et al. **Presse Med** 1986 Apr 5;15(14):668 **(Fre)**

CHLORAMINES

The alteration of hamster serum elastase inhibitory capacities by chloramine T, in vitro and in vivo. Williams JC, et al. **Exp Lung Res** 1986;10(4):357-68

Effect of oxidizing agents on rabbit mammary prolactin receptors. Mahajan PB, et al. **Mol Cell Endocrinol** 1986 Jun;46(1):37-42

[Chloramine concentration in the room air of indoor pools] Jessen HJ. **Z Gesamte Hyg** 1986 Mar;32(3):180-1 (Eng. Abstr.) **(Ger)**

CHLORDIAZEPOXIDE

Differential effects of dorsal raphe lesions and intraraphe GABA and benzodiazepines on conflict behavior in rats. Green S, et al. **Behav Neural Biol** 1986 Jul;46(1):13-29

Peptide derivatives as prodrugs. Thomas WA. **Biochem Soc Trans** 1986 Apr;14(2):383-7

Differential interactions between chlordiazepoxide, pentobarbital and benzodiazepine antagonists Ro 15-1788 and CGS 8216 in a drug discrimination procedure. De Vry J, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):999-1005

Effects of chlordiazepoxide on cued radial maze performance in rats. Hodges H, et al. **Psychopharmacology (Berlin)** 1986;88(4):460-6

Behavioural and pharmacological dissociation of chlordiazepoxide effects on discrimination and punished responding. Hodges H, et al. **Psychopharmacology (Berlin)** 1986;89(2):155-61

P-CHLOROPHENYLALANINE

Involvement of a serotonergic control in the regulation of plasma levels of immunoreactive beta-endorphin. Cancela LM, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):409-13

P-chlorophenylalanine attenuates tonic immobility duration in chickens. Hughes RA. **Physiol Behav** 1986;36(3):427-30

Parachlorophenylalanine-induced serotonin depletion increases offensive but not defensive aggression in male rats. Vergnes M, et al. **Physiol Behav** 1986;36(4):653-8

CHLORPROMAZINE

Relationship between the displacement of phosphatidate phosphohydrolase from the membrane-associated compartment by chlorpromazine and the inhibition of the synthesis of triacylglycerol and phosphatidylcholine in rat hepatocytes. Martin A, et al. **Biochim Biophys Acta** 1986 May 21;876(3):581-91

Promazine. A major plasma metabolite of chlorpromazine in a population of chronic schizophrenics. Sgaragli G, et al. **Drug Metab Dispos** 1986 Mar-Apr;14(2):263-6

Effects of an i.v. lethal dose of 3,4-methylenedioxyamphetamine (MDA) in the dog and antagonism by chlorpromazine. Davis WM, et al. **Gen Pharmacol** 1986;17(2):179-83

Chlorpromazine inhibits the mitotic index, cell number, and formation of mouse blastocysts, and delays implantation of CBA mouse embryos.

Kola I, et al. **J Reprod Fertil** 1986 Mar;76(2):527-36

Effects of chlorpromazine-pretreated melanin on lysosomal acid phosphatase and N-acetyl-beta-D-glucosaminidase in bovine ciliary body and iris in vitro. Nakazawa M, et al. **Jpn J Ophthalmol** 1986; 30(1):36-42

Simultaneous determination of the pharmacokinetics and pharmacodynamics of chlorpromazine in the brain of mice. Gotoh Y, et al. **Jpn J Pharmacol** 1986 Feb;40(2):231-7

Prevention of flap necrosis by chlorpromazine. Bibi R, et al. **Plast Reconstr Surg** 1986 Jun;77(6):954-9

Structure of the high-affinity binding site for noncompetitive blockers of the acetylcholine receptor: serine-262 of the delta subunit is labeled by [3H]chlorpromazine. Giraudat J, et al. **Proc Natl Acad Sci USA** 1986 Apr;83(8):2719-23

Inhibition of the formation of 13,14-dihydroprostaglandin F2-alpha induced by chlorpromazine in rat ovary. Kogo H, et al. **Prostaglandins Leukotrienes Med** 1986 Apr;22(1):11-20

Effect of membrane-interacting amphiphiles on association of membrane glycoproteins with assembled cytoskeletal proteins in concanavalin A-activated rabbit platelets. Kometani M, et al. **Thromb Res** 1986 May 15;42(4):567-77

[EEG studies in rats to determine the threshold levels of chlorpromazine with respect to the state of vigilance] Bergschicker R, et al. **Biomed Biochim Acta** 1986;45(3):401-12 (Eng. Abstr.) **(Ger)**

[Neuronal types of rat substantia nigra and striatum and effects on them of chronic chlorpromazine administration. Quantitative light and electron microscopic morphometry] Yoshida H. **Fukuoka Igaku Zasshi** 1986 Feb;77(2):144-72 (Eng. Abstr.) **(Jpn)**

[Determining the serum level of chlorpromazine by high-performance liquid chromatography] Przyborowska M, et al. **Acta Pol Pharm** 1985; 42(5):467-72 (Eng. Abstr.) **(Pol)**

[Healing of bone tissue in rabbits after administration of chlorpromazine as a calmodulin inhibitor] Sikorski L. **Chir Narzadow Ruchu Ortop Pol** 1985;50(5):361-5 (Eng. Abstr.) **(Pol)**

CHOICE BEHAVIOR

Lack of preference for diazepam in anxious volunteers. de Wit H, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):533-41

Effect of beta-endorphin on sociosexual proclivity in a choice paradigm. Wiesner JB, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):507-11

CLOMIPRAMINE

Clomipramine: an antiobsessive drug. Ananth J. **Can J Psychiatry** 1986 Apr;31(3):253-8 (34 ref.)

Acute effects of desipramine and clomipramine on pituitary-adrenal axis in man. Holl WR, et al. **Horm Metab Res** 1986 Feb;18(2):134-7

A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. Blackburn IM, et al. **J Affective Disord** 1986 Jan-Feb;10(1):67-75

Effect of neonatal clomipramine treatment on adult alcohol drinking in the AA and ANA rat lines. Hilakivi L, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1451-5

Understanding the response lag to tricyclics. I. Application of pulse-loading regimens with intravenous clomipramine. Pollock BG, et al. **Psychopharmacol Bull** 1986;22(1):214-9

Comparison of the metabolism of the three antidepressants amitriptyline, imipramine, and chlorimipramine in vitro in rat liver microsomes. Krüger R, et al. **Psychopharmacology (Berlin)** 1986;88(4):505-13

[Action of clomipramine on gastric secretion in the rat] Taddei E, et al. **Boll Soc Ital Biol Sper** 1986 Feb 28;62(2):191-6 (Eng. Abstr.) **(Ita)**

[Effect of clomipramine and imipramine in vivo on genetic material in the mouse] Theodorescu R. **Rev Med Interna [Neurol Psihiatr]** 1985 Oct-Dec;30(4):309-14 **(Rum)**

CLOPAMIDE

High-performance liquid chromatographic determination of xipamide and clopamide in pharmaceuticals. Sane RT, et al. **J Chromatogr** 1986 Apr 18;356(3):468-72

COCAINE

Topical anesthesia for laceration repair: tetracaine versus TAC (tetracaine, adrenaline, and cocaine). White WB, et al. **Am J Emerg Med** 1986 Jul; 4(4):319-22

Cocaine, phencyclidine, and procaine inhibition of the acetylcholine receptor: characterization of the binding site by stopped-flow measurements of receptor-controlled ion flux in membrane vesicles. Karpen JW, et al. **Biochemistry** 1986 Apr 8;25(7):1777-85

Regional brain homovanillic acid following delta 9-tetrahydrocannabinol and cocaine. Bowers MB Jr, et al. **Brain Res** 1986 Feb 26; 366(1-2):405-7

Intravenous self-administration of fencamfamine and cocaine by beagle dogs under fixed-ratio and progressive-ratio schedules of reinforcement. Risner ME, et al. **Drug Alcohol Depend** 1986 May;17(1):93-102

Cocaine use and dental treatment. Chiodo GT, et al. **Gen Dent** 1986 May-Jun;34(3):218-9

Determination of benzoylecgonine in urine from drug abusers using ion pair high performance liquid chromatography. Svensson JO. **J Anal Toxicol** 1986 May-Jun;10(3):122-4

Crack [letter] Washton AM, et al. **JAMA** 1986 Aug 8;256(6):711

The looming cocaine problem in Australia [editorial] Pierce JP, et al. **Med J Aust** 1986 May 26;144(11):562-3

'Crack'. **Med Lett Drugs Ther** 1986 Jul 18;28(718):69-70

Madarosis from cocaine use [letter] Tames SM, et al. **N Engl J Med** 1986 May 15;314(20):1324

Effects of L-cocaine on local cerebral glucose utilization in the rat. London ED, et al. **Neurosci Lett** 1986 Jul 11;68(1):73-8

Cocaine induced-gingival necrosis. Gariulo AV Jr, et al. **Periodont Case Rep** 1985;7(2):44-5

The discriminative stimulus properties of cocaine and d-amphetamine: the effects of three routes of administration. de la Garza R, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):765-8

Neuropharmacological assessment of cocaine self-administration into the medial prefrontal cortex. Goeders NE, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1429-40

Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Woolverton WL. **Pharmacol Biochem Behav** 1986 Mar;24(3):531-5

Repeated testing attenuates conditioned place preference with cocaine. Bardo MT, et al. **Psychopharmacology (Berlin)** 1986;89(2):239-43

[Intestinal drug smuggling: the cocaine 'body-packer' syndrome] Deuel W, et al. **Schweiz Rundsch Med Prax** 1986 May 6;75(19):557-60 (Eng. Abstr.) **(Ger)**

COGNITION

A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. Blackburn IM, et al. **J Affective Disord** 1986 Jan-Feb;10(1):67-75

A comparison of the effects of trazodone and amitriptyline on skills performance by geriatric subjects. Burns M, et al. **J Clin Psychiatry** 1986 May;47(5):252-4

Cognitive processes in anxiety and depression: discussion paper. Mathews A. **J R Soc Med** 1986 Mar;79(3):158-61

Cognitive performance in geriatric subjects after acute treatment with antidepressants. Moskowitz H, et al. **Neuropsychobiology** 1986; 15 Suppl 1:38-43

Human cognitive function following binedaline (50 mg and 100 mg) and imipramine (75 mg): results with a new battery on tests. Jones DM, et al. **Psychopharmacology (Berlin)** 1986;89(2):198-202

[Cognitive therapy in the treatment of psychotic and postpsychotic states--an overview] Perris C. **Lakartidningen** 1986 Apr 16; 83(16):1488-91 (61 ref.) **(Swe)**

COMPULSIVE BEHAVIOR

Clomipramine: an antiobsessive drug. Ananth J. **Can J Psychiatry** 1986 Apr;31(3):253-8 (34 ref.)

CONDITIONING (PSYCHOLOGY)

Stereoselective behavioral effects of the isomers of pentobarbital and secobarbital in the pigeon. Wenger GR, et al. **J Pharmacol Exp Ther** 1986 May;237(2):445-9

Substitution of natural conditioned and unconditioned stimuli by artificial stimuli does not prevent acquisition of conditioned taste aversion in rats. Brožek G, et al. **Physiol Bohemoslov** 1985;34 Suppl:13-6

Repeated testing attenuates conditioned place preference with cocaine. Bardo MT, et al. **Psychopharmacology (Berlin)** 1986;89(2):239-43

CONDITIONING, CLASSICAL

Failure of hippocampectomy to facilitate classical conditioning at an optimal interstimulus interval is not due to a 'ceiling effect'. Port RL, et al. **Behav Neurosci** 1986 Apr;100(2):161-4

Congener characteristics influence aversion conditioning to alcoholic beverages in rats. Franchina JJ, et al. **Behav Res Ther** 1986; 24(3):299-306

Single unit activity of locus coeruleus neurons in the freely moving cat. II. Conditioning and pharmacologic studies. Rasmussen K, et al. **Brain Res** 1986 Apr 23;371(2):335-44

Conditioning of aversion to alcohol orosensory cues in 5- and 10-day rats: subsequent reduction in alcohol ingestion. Molina JC, et al. **Dev Psychobiol** 1986 May;19(3):175-83

Conditioned aversions and their memories in 5-day-old rats during suckling. Kehoe P, et al. **J Exp Psychol [Anim Behav]** 1986 Jan; 12(1):40-7

[Comparison of the effect of serotonin administered into the dorsal hippocampus on conditioned passive and active avoidance in rats] Gasanov GG, et al. **Biull Eksp Biol Med** 1986 May;101(5):517-9 (Eng.

Abstr.) **(Rus)**

CONDITIONING, OPERANT

Behavioral effects of CGS 8216 alone, and in combination with diazepam and pentobarbital in dogs. Risner ME, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1071-6

The effects of prenatal morphine on the responsiveness to morphine and amphetamine. Wagner GC, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):757-9

Interaction of buspirone and dopaminergic agents on punished behavior of pigeons. Witkin JM, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):751-6

[Neuronal activity of the monkey amygdala during operant feeding behavior and the effects of drugs] Nakano Y. **Fukuoka Igaku Zasshi** 1986 Jan;77(1):55-73 (Eng. Abstr.) **(Jpn)**

CONFLICT (PSYCHOLOGY)

Differential effects of dorsal raphe lesions and intraraphe GABA and benzodiazepines on conflict behavior in rats. Green S, et al. **Behav Neural Biol** 1986 Jul;46(1):13-29

Low doses of muscimol produce anticonflict actions in the lateral septum of the rat. Drugan RC, et al. **Neuropharmacology** 1986 Feb; 25(2):203-5

Comparison of the effects of the benzodiazepine midazolam and three serotonin antagonists on a consummatory conflict paradigm. Becker HC. **Pharmacol Biochem Behav** 1986 Apr;24(4):1057-64

CONSCIOUSNESS

Enigma of drug-induced altered states of consciousness among the !Kung Bushmen of the Kalahari Desert. Dobkin De Rios M. **J Ethnopharmacol** 1986 Mar;15(3):297-304

CONSUMMATORY BEHAVIOR

Comparison of the effects of the benzodiazepine midazolam and three serotonin antagonists on a consummatory conflict paradigm. Becker HC. **Pharmacol Biochem Behav** 1986 Apr;24(4):1057-64

CONVERSION DISORDER

Globus hystericus syndrome responsive to antidepressants. Brown SR, et al. **Am J Psychiatry** 1986 Jul;143(7):917-8

Conversion without hysteria: a case report and review of the literature. Shalev A, et al. **Br J Psychiatry** 1986 Feb;148:198-203 (46 ref.)

CORTICOSTERONE

In vitro study of antral gastrin biosynthesis in response to weaning and corticosterone acetate in rats. Okahata H, et al. **Acta Endocrinol (Copenh)** 1986 Apr;111(4):539-45

Corticosterone secretion by rats after adrenalectomy. Damasco MC, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):415-7

Seasonal changes in the plasma concentration of sexual steroids, corticosterone and thyroid hormone in the hen with special respect to the moulting period. Szelényi Z, et al. **Acta Vet Hung** 1985; 33(3-4):189-98

Stimulation of corticosterone secretion in vitro by brief ACTH exposure. Keith LD, et al. **Am J Physiol** 1986 Jun;250(6 Pt 1):E629-33

Hormones in perinatal rat and spiny mouse: relation to altricial and precocial timing of birth. Lamers WH, et al. **Am J Physiol** 1986 Jul; 251(1 Pt 1):E78-85

Does corticosterone affect gastric mucosal cell growth during development? Tseng CC, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):G633-8

Suppression of corticosterone synthesis alters the behavior of hippocampally lesioned rats. Ryan JP, et al. **Behav Neural Biol** 1985 Jul;44(1):47-59

Neuroendocrine parameters in the rat exposed to 60-Hz electric fields. Quinlan WJ, et al. **Bioelectromagnetics** 1985;6(4):381-9

Circadian corticosterone rhythm did not develop in rats seven weeks after destruction with 5,7-dihydroxytryptamine of the serotoninergic nerve terminals in the suprachiasmatic nucleus at the age of 16 days. Bánky Z, et al. **Brain Res** 1986 Mar 26;369(1-2):119-24

In vivo release of corticosterone in discrete brain areas of rats. A push-pull perfusion study. Dietl H. **Brain Res** 1986 Mar 26;369(1-2):373-6

Impact of circulating corticosterone on alpha 1- and alpha 2-noradrenergic receptors in discrete brain areas. Jhanwar-Uniyal M, et al. **Brain Res** 1986 Mar 19;368(2):404-8

Loss of 3H-corticosterone binding capacity in hippocampal slices maintained in vitro. Halpain S, et al. **Brain Res Bull** 1986 Feb; 16(2):167-70

Relationship between endogenous cyclic AMP production and steroid hormone secretion in chick adrenal cells. Rosenberg J, et al. **Comp Biochem Physiol [B]** 1986;84(1):71-5

Effects of corticosterone infusion on the lipogenic activity and ultrastructure of the liver of laying hens. Pilo B, et al. **Cytobios** 1985; 44(179S):273-85

Effect of adrenalectomy and corticosterone on [3H]imipramine binding in rat blood platelets and brain. Arora RC, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):415-9

Chronic corticosterone administration in rats: behavioral and biochemical evidence of increased central dopaminergic activity. Wolkowitz O, et al. **Eur J Pharmacol** 1986 Apr 2;122(3):329-38

Plasma ACTH and corticosterone responses to limbic kindling in the rat. Szafarczyk A, et al. **Exp Neurol** 1986 Jun;92(3):583-90

Further studies on the inhibitory effects of somatostatin on the growth and steroidogenic capacity of rat adrenal zona glomerulosa. Robba C, et al. **Exp Pathol** 1986;29(2):77-82

The influence of social cues on the reproductive endocrinology of male brown-headed cowbirds: field and laboratory studies. Dufty AM Jr, et al. **Horm Behav** 1986 Jun;20(2):222-34

Effects of stimulation on steroid output and perfusion medium flow rate in the isolated perfused rat adrenal gland in situ. Hinson JP, et al. **J Endocrinol** 1986 May;109(2):279-85

The actions of N-terminal fragments of corticotrophin on steroidogenesis in dispersed rat adrenal cells in vitro. Vinson GP, et al. **J Endocrinol** 1986 May;109(2):275-8

Influence of subcutaneous melatonin implantation on gonadal development and on plasma levels of luteinizing hormone, testosterone, estradiol, and corticosterone in the pigeon. John TM, et al. **J Pineal Res** 1986;3(2):169-79

Corticosteroid receptors in rat hippocampal sections: effect of adrenalectomy and corticosterone replacement. Sarrieau A, et al. **J Steroid Biochem** 1986 Mar;24(3):721-4

Bidirectional responsiveness of the pituitary-adrenal system in old and young male and female rats. Brett LP, et al. **Neurobiol Aging** 1986 May-Jun;7(3):153-9

Selective control by corticosterone of serotonin1 receptor capacity in raphe-hippocampal system. De Kloet ER, et al. **Neuroendocrinology** 1986;42(6):513-21

Aldosterone effects on salt appetite in adrenalectomized rats. McEwen BS, et al. **Neuroendocrinology** 1986;43(1):38-43

Effects of 6-hydroxydopamine-induced lesions of the paraventricular nucleus, and of prazosin, on the corticosterone response to restraint in rats. Gibson A, et al. **Neuropharmacology** 1986 Mar;25(3):257-60

Morphine-elicited feeding: diurnal rhythm, circulating corticosterone and macronutrient selection. Bhakthavatsalam P, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):911-7

Central norepinephrine and plasma corticosterone following acute and chronic stressors: influence of social isolation and handling. Irwin J, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1151-4

Regioselective inhibition of benzo(a)pyrene metabolism by corticosterone in comparison with metyrapone and alpha-naphthoflavone. Bogdanffy MS, et al. **Toxicol Lett** 1986 Apr;31(1):57-64

[Stimulation of pituitary-adrenocortical system by cepharanthine] Yoshikawa N, et al. **Nippon Yakurigaku Zasshi** 1986 Feb; 87(2):99-104 (Eng. Abstr.) **(Jpn)**

[Effect of corticosterone on mitochondrial respiration of slices of rat liver] Leshchenko MV. **Probl Endokrinol (Mosk)** 1986 Mar-Apr;32(2):67-9 (Eng. Abstr.) **(Rus)**

CORTICOTROPIN

Ovine corticotrophin-releasing factor in dogs: dose-response relationships and effects of dexamethasone. Kemppainen RJ, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):12-9

Stimulation of corticosterone secretion in vitro by brief ACTH exposure. Keith LD, et al. **Am J Physiol** 1986 Jun;250(6 Pt 1):E629-33

The periaqueductal gray: a prerequisite for ACTH-induced excessive grooming. Spruijt BM, et al. **Behav Brain Res** 1986 Apr;20(1):19-25

Neonatal treatment with monosodium glutamate does not alter grooming behavior induced by novelty or adrenocorticotropic hormone. Dunn AJ, et al. **Behav Neural Biol** 1985 Jul;44(1):80-9

Corticotropin-releasing factor (CRF) and vasopressin concentration in major brain regions after adrenalectomy and their involvement in adrenalectomy-induced ACTH elevation. Hashimoto K, et al. **Endocrinol Jpn** 1986 Feb;33(1):95-103

Adrenocorticotropin-induced changes in ovine pituitary gonadotropin secretion in vitro. Matteri RL, et al. **Endocrinology** 1986 May; 118(5):2091-6

Antagonism of beta-endorphin-induced prolactin release by alpha-melanocyte-stimulating hormone and corticotropin-like intermediate lobe peptide. Wardlaw SL, et al. **Endocrinology** 1986 Jul; 119(1):112-8

Regulation of beta-endorphin, corticotropin-like intermediate lobe peptide, and alpha-melanotropin-stimulating hormone in the hypothalamus by testosterone. Wardlaw SL. **Endocrinology** 1986 Jul; 119(1):19-24

Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. de Meirleir K, et al. **Eur J Appl Physiol** 1986;55(1):5-8

Plasma ACTH and corticosterone responses to limbic kindling in the rat.

Szafarczyk A, et al. **Exp Neurol** 1986 Jun;92(3):583-90

Dissimilar responsiveness of cultured corticotrophs and melanotrophs to tripeptide aldehydes. Fazekas I, et al. **Histochemistry** 1986; 84(4-6):418-22

Discordances in the temporal pattern of the ACTH/beta-endorphin releasing effects of synthetic CRFs and partially purified bovine CRF in a superfusion system. Yasuda Y, et al. **Horm Metab Res** 1986 May; 18(5):313-7

Effects of stimulation on steroid output and perfusion medium flow rate in the isolated perfused rat adrenal gland in situ. Hinson JP, et al. **J Endocrinol** 1986 May;109(2):279-85

The actions of N-terminal fragments of corticotrophin on steroidogenesis in dispersed rat adrenal cells in vitro. Vinson GP, et al. **J Endocrinol** 1986 May;109(2):275-8

Effect of repeated restraint stress, desmethylimipramine or adrenocorticotropin on the alpha and beta adrenergic components of the cyclic AMP response to norepinephrine in rat brain slices. Stone EA, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):702-7

Compared effects of ACTH, angiotensin II and POMC peptides on isolated human adrenal cells. Pham-Huu-Trung MT, et al. **J Steroid Biochem** 1986 Jan;24(1):345-8

Action of partially purified ACTH-potentiating substance from rat serum on isolated rat adrenal cells. Morita Y. **Jpn J Pharmacol** 1986 Feb; 40(2):205-14

High concentrations of catecholamines selectively diminish the sensitivity of CRF-stimulated ACTH release by cultured rat pituitary cells to the suppressive effects of dexamethasone. Lamberts SW, et al. **Life Sci** 1986 Jul 14;39(2):97-102

Effect of various blockers of arachidonic acid metabolism on release of beta-endorphin- and adrenocorticotropin-like immunoreactivity induced by phospholipase A2 from rat adenohypophysis in vitro. Knepel W, et al. **Neuroendocrinology** 1986;43(1):44-8

Anatomical evidence for interactions between catecholamine- and adrenocorticotropin-containing neurons. Baker H, et al. **Neuroscience** 1986 Feb;17(2):469-84

Effects of corticotropin-releasing factor, corticotropin and cortisol on gastrointestinal motility in dogs. Bueno L, et al. **Peptides** 1986 Jan-Feb; 7(1):73-7

Opioid and other peptides as inhibitors of leumorphin (dynorphin B-29) converting activity. Devi L, et al. **Peptides** 1986 Jan-Feb;7(1):87-90

Immunohistochemical localization of follicle-stimulating hormone, luteinizing hormone, growth hormone, adrenocorticotrophic hormone and prolactin in the human placenta. Al-Timimi A, et al. **Placenta** 1986 Mar-Apr;7(2):163-72

Role of cholecystokinin in corticotropin release: coexistence with vasopressin and corticotropin-releasing factor in cells of the rat hypothalamic paraventricular nucleus. Mezey E, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3510-2

Positive inotropic effects of an ACTH analogue (ACTH 1-17) on myocardial performance. Levi G, et al. **Ric Clin Lab** 1985 Oct-Dec; 15(4):349-56

The role of calcium ions in the mechanism of ACTH stimulation of cortisol synthesis. Davies E, et al. **Steroids** 1985 Jun;45(6):551-60

[Plasma levels of beta-endorphin and ACTH during critical increase in arterial pressure in man] Giovannini C, et al. **Boll Soc Ital Biol Sper** 1986 Jan 31;62(1):7-13 (Eng. Abstr.) **(Ita)**

[Detection of the pro-opiomelanocortin peptide fragments--beta-endorphin and ACTH--in the adrenals of rats and mice by immunohistochemistry] Arefolov VA, et al. **Biull Eksp Biol Med** 1986 Apr;101(4):445-7 (Eng. Abstr.) **(Rus)**

[Beta-endorphin and corticotropin in the blood of patients during the acute period of severe craniocerebral injury] Marzoian RA, et al. **Vopr Med Khim** 1986 May-Jun;32(3):95-8 (Eng. Abstr.) **(Rus)**

[Selective effect of antiepileptics on the cortex and medulla of the adrenal glands] Nović M, et al. **Srp Arh Celok Lek** 1985 Nov-Dec; 113(11-12):983-90 (Eng. Abstr.) **(Scc)**

CORTICOTROPIN RELEASING HORMONE

Ovine corticotrophin-releasing factor in dogs: dose-response relationships and effects of dexamethasone. Kemppainen RJ, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):12-9

Intragranular colocalization of CRF and Met-Enk-8 in nerve terminals in the rat median eminence. Hisano S, et al. **Brain Res** 1986 Apr 9; 370(2):321-6

Sympatho-adrenal medullary functions in response to intracerebroventricularly injected corticotropin-releasing factor in anesthetized rats. Kurosawa M, et al. **Brain Res** 1986 Mar 5; 367(1-2):250-7

Adrenocortical responses to corticotropin-releasing factor in the rat. Normand M, et al. **Can J Physiol Pharmacol** 1986 Mar;64(3):269-72

Ultrastructural characterization of neurosecretory fibres immunoreactive for vasotocin, isotocin, somatostatin, LHRH and CRF in the pituitary of a teleost fish, Poecilia latipinna. Batten TF. **Cell Tissue Res** 1986; 244(3):661-72

Ontogenetic development of corticotropin-releasing factor (CRF)-containing neural elements in the brain of the chicken during incubation and after hatching. Józsa R, et al. **Cell Tissue Res** 1986; 244(3):681-5

Corticotropin-releasing factor (CRF) and vasopressin concentration in major brain regions after adrenalectomy and their involvement in adrenalectomy-induced ACTH elevation. Hashimoto K, et al. **Endocrinol Jpn** 1986 Feb;33(1):95-103

Release of corticotropin-releasing factor from rat brain regions in vitro. Smith MA, et al. **Endocrinology** 1986 May;118(5):1997-2001

Discordances in the temporal pattern of the ACTH/beta-endorphin releasing effects of synthetic CRFs and partially purified bovine CRF in a superfusion system. Yasuda Y, et al. **Horm Metab Res** 1986 May; 18(5):313-7

Corticotropin-releasing factor receptors in the pituitary gland and central nervous system: methods and overview. De Souza EB, et al. **Methods Enzymol** 1986;124:560-90

Autoradiographic localization of brain receptors for peptide hormones: angiotensin II, corticotropin-releasing factor, and gonadotropin-releasing hormone. Millan M, et al. **Methods Enzymol** 1986;124:590-606

Receptor-mediated actions of corticotropin-releasing factor in pituitary gland and nervous system. Aguilera G, et al. **Neuroendocrinology** 1986; 43(1):79-88 (37 ref.)

Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. Ehlers CL, et al. **Neuroendocrinology** 1986;42(6):467-74

Predominant release of vasopressin vs. corticotropin-releasing factor from the isolated median eminence after adrenalectomy. Holmes MC, et al. **Neuroendocrinology** 1986;43(2):245-51

Effects of corticotropin-releasing factor, corticotropin and cortisol on gastrointestinal motility in dogs. Bueno L, et al. **Peptides** 1986 Jan-Feb; 7(1):73-7

Ultrastructural alterations of the paraventriculo-infundibular corticotropin releasing factor (CRF)-immunoreactive neuronal system in long term adrenalectomized rats. Liposits Z, et al. **Peptides** 1985 Nov-Dec;6(6):1021-36

Localization of urotensin I- and corticotropin-releasing factor-like immunoreactivity in the central nervous system of Catostomus commersoni. Yulis CR, et al. **Peptides** 1986 Jan-Feb;7(1):79-86

Role of cholecystokinin in corticotropin release: coexistence with vasopressin and corticotropin-releasing factor in cells of the rat hypothalamic paraventricular nucleus. Mezey E, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3510-2

Purification and characterization of peptides with corticotropin-releasing factor activity from porcine hypothalami. Patthy M, et al. **Proc Natl Acad Sci USA** 1986 May;83(9):2969-73

EEG stability following corticotropin releasing factor in rats. Ehlers CL. **Psychoneuroendocrinology** 1986;11(1):121-5

Comparison of a specific two-site immunoradiometric assay with radioimmunoassay for rat/human CRF-41. Linton EA, et al. **Regul Pept** 1986 Mar;14(1):69-84

Corticotropin-releasing factor receptors: autoradiographic identification. De Souza EB, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986; 64:179-98

[The development of immunoreactive corticotropin-releasing factor (IR-CRF) in the hypothalamus, pancreas and gastrointestinal tract of immature rats] Ohtsuka K, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Jan 20;62(1):34-44 (Eng. Abstr.) **(Jpn)**

[Study on the development of the radioimmunoassay of the corticotropin releasing factor (CRF)] Ui K, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 May;38(5):657-62 (Eng. Abstr.) **(Jpn)**

CRITICAL PERIOD (PSYCHOLOGY)

Neonatal 6-hydroxydopamine lesion of forebrain norepinephrine does not eliminate critical period for behavioral effects of gonadal hormone manipulation. Pappas BA, et al. **Brain Res** 1986 May;391(2):310-4

DANSYL COMPOUNDS

Fitting fluorescence emission spectra of probes bound to biological membranes. Rooney EK, et al. **J Biochem Biophys Methods** 1986 Mar; 12(3):175-89

DELUSIONS

Delusional depression: phenomenology and response to treatment. A prospective study. Lykouras E, et al. **Acta Psychiatr Scand** 1986 Mar; 73(3):324-9

Course and outcome of the delusional misidentification syndromes. Christodoulou GN. **Bibl Psychiatr** 1986;(164):143-8

Treating delusional depressives with amitriptyline. Spiker DG, et al. **J Clin Psychiatry** 1986 May;47(5):243-6

DEPRESSION

A simplified radioimmunoassay of plasma nortriptyline in depressed patients compared with high-pressure liquid chromatography and gas-liquid chromatography. Sayegh JF. **Neurochem Res** 1986 Feb; 11(2):193-206

Diclofensine and imipramine. A double-blind comparative trial in depressive out-patients. Capponi R, et al. **Neuropsychobiology** 1985; 14(4):173-80

[Comparative evaluation of the therapeutic efficacy of the antidepressants adepren, linamiphen and emovit] Guliamov MG. **Zh Nevropatol Psikhiatr** 1986;86(4):582-7 (Eng. Abstr.) **(Rus)**

DEPRESSIVE DISORDER

Dysregulation of plasma pro-opiomelanocortin-related peptides in neurotic depression. Genazzani AR, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):1-6

The management of resistant depression. Levine S. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):141-51

Serum dopamine-beta-hydroxylase activity in patients with major depressive disorders. Kjellman BF, et al. **Acta Psychiatr Scand** 1986 Mar;73(3):266-70

Delusional depression: phenomenology and response to treatment. A prospective study. Lykouras E, et al. **Acta Psychiatr Scand** 1986 Mar; 73(3):324-9

Comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressed outpatients. Biochemical aspects. Nyström C, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):133-8

Imipramine in adolescent major depression: plasma level and clinical response. Ryan ND, et al. **Acta Psychiatr Scand** 1986 Mar; 73(3):275-88

Depressive relapses and incomplete recovery from index episode. Faravelli C, et al. **Am J Psychiatry** 1986 Jun;143(7):888-91

Lithium potentiation of tricyclic antidepressants following lack of T3 potentiation. Garbutt JC, et al. **Am J Psychiatry** 1986 Aug; 143(8):1038-9

Current antidepressants. Hollister LE. **Annu Rev Pharmacol Toxicol** 1986; 26:23-37 (30 ref.)

Current management of depression. Kerr K, et al. **Aust Fam Physician** 1986 Apr;15(4):500-2

Depression in childhood. Birleson P. **Aust Paediatr J** 1986 Feb; 22(1):7-10

Efficacy of phenelzine in geriatric depression. Lazarus LW, et al. **Biol Psychiatry** 1986 Jun;21(7):699-701

Pirbuterol trial as antidepressant [letter] Nurnberger JI Jr, et al. **Biol Psychiatry** 1986 May;21(5-6):565-6

Synergistic action of alprazolam with tranylcypromine in drug-resistant atypical depression with panic attacks. Ries RK, et al. **Biol Psychiatry** 1986 May;21(5-6):522-6

Depression in general practice [letter] Blacker CV, et al. **Br J Psychiatry** 1986 Mar;148:333-5

Affective disorders and circadian rhythms. Hallonquist JD, et al. **Can J Psychiatry** 1986 Apr;31(3):259-72 (143 ref.)

Alprazolam and desipramine in moderately severe depression [letter] McCormick WO. **Can J Psychiatry** 1986 May;31(4):378

Who responds to prophylactic lithium? Abou-Saleh MT, et al. **J Affective Disord** 1986 Mar-Apr;10(2):115-25

A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. Blackburn IM, et al. **J Affective Disord** 1986 Jan-Feb;10(1):67-75

Unipolar depression in the elderly. Reoccurrence on discontinuation of tricyclic antidepressants. Cook BL, et al. **J Affective Disord** 1986 Mar-Apr;10(2):91-4

Folic acid enhances lithium prophylaxis. Coppen A, et al. **J Affective Disord** 1986 Jan-Feb;10(1):9-13

Impairment of work and leisure in depressed outpatients. A preliminary communication. De Lisio G, et al. **J Affective Disord** 1986 Mar-Apr; 10(2):79-84

Hypochondriacal fears and beliefs in DSM-III melancholia. Changes with amitriptyline. Kellner R, et al. **J Affective Disord** 1986 Jan-Feb; 10(1):21-6

Depression in general practice attenders. 'Caseness', natural history and predictors of outcome. Parker G, et al. **J Affective Disord** 1986 Jan-Feb; 10(1):27-35

Lymphocyte beta-adrenergic receptor density of patients with recurrent affective illness. Wood K, et al. **J Affective Disord** 1986 Jan-Feb; 10(1):3-8

Effective low dose tricyclic antidepressant treatment for depressed geriatric rehabilitation patients. A double-blind study. Lakshmanan M, et al. **J Am Geriatr Soc** 1986 Jun;34(6):421-6

Tricyclic-resistant depression [letter] Berkowitz HL. **J Clin Psychiatry** 1986 Jul;47(7):393

Antidepressant treatment for posttraumatic stress disorder (PTSD) [letter] Harris SE. **J Clin Psychiatry** 1986 May;47(5):275

Phenelzine for chronic depression: a study of continuation treatment. Harrison W, et al. **J Clin Psychiatry** 1986 Jul;47(7):346-9

Effect of carbamazepine on body weight in affectively ill patients. Joffe RT, et al. **J Clin Psychiatry** 1986 Jun;47(6):313-4

Early placebo response in anxious and depressed patients. Loebel AD, et al. **J Clin Psychiatry** 1986 May;47(5):230-3

Treating delusional depressives with amitriptyline. Spiker DG, et al. **J Clin Psychiatry** 1986 May;47(5):243-6

Medication effects on one-carbon metabolism in schizophrenia, mania, and major depression. Morere DA, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):155-61

Dissociation of depressive mood and vegetative symptoms during treatment with L-tryptophan [letter] Siddiqui AR, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):118-9

Rapid antidepressant effect of addition of lithium to tranylcypromine. Tariot PN, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):165-7

Dissociation between CSF and plasma B-endorphin in major depressive disorders: evidence for a different regulation. Facchinetti F, et al. **J Endocrinol Invest** 1986 Feb;9(1):11-4

Hostility and recovery from melancholia. Fava GA, et al. **J Nerv Ment Dis** 1986 Jul;174(7):414-7

Cognitive processes in anxiety and depression: discussion paper. Mathews A. **J R Soc Med** 1986 Mar;79(3):158-61

Symposium on trazodone. New clinical applications and safety considerations for a third generation antidepressant. IVth World Congress of Biological Psychiatry. Philadelphia, September 1985. **Neuropsychobiology** 1986;15 Suppl 1:1-52

Possible nonlinear pharmacokinetics of desipramine after once daily dosing. Amsterdam JD, et al. **Pharmacopsychiatry** 1986 Mar; 19(2):84-7

A double-blind comparative trial of zimelidine, amitriptyline, and placebo in patients with mixed anxiety and depression. Amsterdam JD, et al. **Pharmacopsychiatry** 1986 May;19(3):115-9

Double-blind comparison of diclofensine with nomifensine in outpatients with dysphoric mood. Funke HJ, et al. **Pharmacopsychiatry** 1986 May; 19(3):120-3

Age, therapeutic 'milieu' and clinical outcome in depressive patients treated with viloxazine: a study with plasma levels. Altamura AC, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1986;10(1):67-75

Chronic imipramine treatment and weight gain. Fernstrom MH, et al. **Psychiatry Res** 1986 Apr;17(4):269-73

Clinical studies on norepinephrine metabolism: how to interpret the numbers. Linnoila M, et al. **Psychiatry Res** 1986 Mar;17(3):229-39

Antidepressants and biochemical theories of depression. McNeal ET, et al. **Psychol Bull** 1986 May;99(3):361-74

Effects of carbamazepine on serum electrolytes in affectively ill patients. Joffe RT, et al. **Psychol Med** 1986 May;16(2):331-5

Use of a standardized documentation system (BLIPS/BDP) in the conduct of a multicenter international trial comparing fluvoxamine, imipramine, and placebo. Cassano GB, et al. **Psychopharmacol Bull** 1986; 22(1):52-8

A review of controlled studies of adinazolam mesylate in patients with major depressive disorder. Feighner JP. **Psychopharmacol Bull** 1986; 22(1):186-91

Problems with and promises of monoamine oxidase inhibitors. Klein DF, et al. **Psychopharmacol Bull** 1986;22(1):7-11

The relationship of antiobsessional and antidepressant effects of tricyclic antidepressants. Mavissakalian M, et al. **Psychopharmacol Bull** 1986; 22(1):161-6

Understanding the response lag to tricyclics. I. Application of pulse-loading regimens with intravenous clomipramine. Pollock BG, et al. **Psychopharmacol Bull** 1986;22(1):214-9

New perspectives on long-standing issues: the monoamine oxidase inhibitors. Robinson DS. **Psychopharmacol Bull** 1986;22(1):12-5

Discussion on the monoamine oxidase inhibitors. Schiele BC. **Psychopharmacol Bull** 1986;22(1):16-8

Open trial of buspirone in the treatment of major depressive disorder. Schweizer EE, et al. **Psychopharmacol Bull** 1986;22(1):183-5

Investigating opioid peptides in schizophrenia and depression. Berger PA, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986;64:309-33 (91 ref.)

[DST urinary MHPG.SO4 excretion and platelet MAO activity in depression] Zhou DF. **Chung Hua Shen Ching Ching Shen Ko Tsa Chih** 1985 Oct; 18(5):274-8 (Eng. Abstr.) **(Chi)**

[Erythrocyte membrane transport of L-tyrosine and L-tryptophan in 66 patients with depressive syndromes. Preliminary results] Pringuey D, et al. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):131-40 (Eng. Abstr.) **(Fre)**

[Circadian rhythms and depression] Souetre E, et al. **Ann Med Psychol (Paris)** 1985 Nov;143(9):845-70 (105 ref.) (Eng. Abstr.) **(Fre)**

[Rapid response of a disorder to the addition of lithium carbonate: panic resistant to tricyclic antidepressants] Cournoyer J. **Can J Psychiatry** 1986 May;31(4):335-8 (Eng. Abstr.) **(Fre)**

[Treatment of depressive disorders. Clinical evaluation of the relative effectiveness of flupenthixol in comparison with bromazepam] Paulmann F. **Fortschr Med** 1986 Mar 13;104(10):218-22 (Eng. Abstr.) **(Ger)**

[Steps in the recovery from severe depression. On the psychosomatic aspects of a convalescent process] Böker W. **Psychiatr Prax** 1986 Mar; 13(2):41-8 (Eng. Abstr.) **(Ger)**

[Serotonin transport by blood platelets of depressive patients] Modai I, et al. **Harefuah** 1986 Jan 15;110(2):64-7 (Eng. Abstr.) **(Heb)**

[Determination of dopamine-beta-hydroxylase (DBH) and monoamine oxidase (MAO) activities in platelets and plasma in schizophrenic, maniac-depressive and neurotic patients] Xavier Vieira R, et al. **Acta Med Port** 1986 Jan-Feb;7(1):45-8 (Eng. Abstr.) **(Por)**

[Critical study of the clinical actions of 5-HTP] Teixeira M. **Actas Luso Esp Neurol Psiquiatr Cienc Afines** 1986 Mar-Apr; 14(2):104-12 **(Por)**

[Comparative clinical study of imipramine and mianserin in depressions] Chiriţă V, et al. **Rev Med Chir Soc Med Nat Iasi** 1985 Oct-Dec; 89(4):651-6 (Eng. Abstr.) **(Rum)**

[Therapeutic effect of parlodel in resistant depressions and its relation to the effect of dopamine metabolism] Bel'tiukova TA, et al. **Vopr Med Khim** 1986 Mar-Apr;32(2):19-21 (Eng. Abstr.) **(Rus)**

[Comparative evaluation of the therapeutic efficacy of the antidepressants adepren, linamiphen and emovit] Guliamov MG. **Zh Nevropatol Psikhiatr** 1986;86(4):582-7 (Eng. Abstr.) **(Rus)**

[Prediction of the effect of antidepressants in patients with endogenous depression] Litvinova NM, et al. **Zh Nevropatol Psikhiatr** 1986; 86(4):577-82 (Eng. Abstr.) **(Rus)**

DESIPRAMINE

Characterization of desmethylimipramine 2-hydroxylation in human foetal and adult liver microsomes. Spina E, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Apr;58(4):277-81

Inhibitory effects of desmethylimipramine, metanephrine and normetanephrine on the neuronal and extraneuronal accumulation of catecholamines in fish spleen. Ungell AL. **Acta Physiol Scand** 1986 May; 127(1):27-31

Chronic exposure of human cells in culture to the tricyclic antidepressant desipramine reduces the number of beta-adrenoceptors. Honegger UE, et al. **Biochem Pharmacol** 1986 Jun 1;35(11):1899-902

Clorgyline and desipramine alter the sensitivity of [3H]noradrenaline release to calcium but not to clonidine. Campbell IC, et al. **Brain Res** 1986 May 7;372(2):253-9

Alprazolam and desipramine in moderately severe depression [letter] McCormick WO. **Can J Psychiatry** 1986 May;31(4):378

Quantitative homogeneous enzyme immunoassays for amitriptyline, nortriptyline, imipramine, and desipramine. Pankey S, et al. **Clin Chem** 1986 May;32(5):768-72

Differential effects of cimetidine and ranitidine on imipramine demethylation and desmethylimipramine hydroxylation by human liver microsomes. Spina E, et al. **Eur J Clin Pharmacol** 1986;30(2):239-42

The effects of desipramine, zimelidine, electroconvulsive treatment and lithium on rat brain biogenic amines: a comparison with peripheral changes. Karoum F, et al. **Eur J Pharmacol** 1986 Mar 4; 121(3):377-85

Acute effects of desipramine and clomipramine on pituitary-adrenal axis in man. Holl WR, et al. **Horm Metab Res** 1986 Feb;18(2):134-7

Symptom exacerbation in psychotically depressed adolescents due to high desipramine plasma concentrations. Conrad CD, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):161-4

Studies on rat brain catecholamine synthesis and beta-adrenoceptor number following administration of electroconvulsive shock, desipramine and clenbuterol. Nimgaonkar VL, et al. **J Neural Transm** 1986;65(3-4):245-59

Effect of chronic desipramine treatment on dihydroalprenolol, imipramine, and desipramine binding sites: a quantitative autoradiographic study in the rat brain. Biegon A. **J Neurochem** 1986 Jul;47(1):77-80

Effect of repeated restraint stress, desmethylimipramine or adrenocorticotropin on the alpha and beta adrenergic components of the cyclic AMP response to norepinephrine in rat brain slices. Stone EA, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):702-7

Possible nonlinear pharmacokinetics of desipramine after once daily dosing. Amsterdam JD, et al. **Pharmacopsychiatry** 1986 Mar; 19(2):84-7

DESOXYCORTICOSTERONE

Effect of corticosteroids on the thymus of the fish Oryzias latipes. Ghoneum MH, et al. **Dev Comp Immunol** 1986 Winter;10(1):35-44

Immunoreactive atrial natriuretic hormone levels increase in deoxycorticosterone acetate-treated pigs. Grekin RJ, et al. **Hypertension** 1986 Jun;8(6 Pt 2):II16-20

Neurotoxicity of triorthotolyl phosphate in chickens of different genotypes in the presence and absence of deoxycorticosterone. Ehrich M, et al. **Poult Sci** 1986 Feb;65(2):375-9

Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Majewska MD, et al. **Science** 1986 May 23; 232(4753):1004-7

[The receptor system for glucocorticoids in myocardial cells. New approaches to the studies of its regulation and function] Seleznev IuM. **Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR** 1986; 9(1):94-9 **(Rus)**

DEXTROAMPHETAMINE

Reinstatement of orienting behavior by d-amphetamine in rats with superior colliculus lesions. Midgley GC, et al. **Behav Neurosci** 1986 Apr; 100(2):246-55

Differential effects of dopamine agonists on acoustically and electrically elicited startle responses: comparison to effects of strychnine. Davis M, et al. **Brain Res** 1986 Apr 16;371(1):58-69

Release of endogenous dopamine and cholecystokinin from rat striatal slices: effects of amphetamine and dopamine antagonists. Hutchison JB, et al. **Brain Res** 1986 Apr 9;370(2):310-4

Glucose regulates [3H](+)-amphetamine binding and Na+K+ ATPase activity in the hypothalamus: a proposed mechanism for the glucostatic control of feeding and satiety. Hauger R, et al. **Brain Res Bull** 1986 Feb;16(2):281-8 (41 ref.)

The discriminative stimulus properties of cocaine and d-amphetamine: the effects of three routes of administration. de la Garza R, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):765-8

Amphetamine-induced anorexia: analysis with hypothalamic lesions and knife cuts. McCabe JT, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):1047-56

Evidence that thioridazine enhances amphetamine-induced stereotypy via anticholinergic activity. Robertson A, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1986;10(1):33-40

The discriminative stimulus and subjective effects of d-amphetamine, phenmetrazine and fenfluramine in humans. Chait LD, et al. **Psychopharmacology (Berlin)** 1986;89(3):301-6

DIAZEPAM

Formulation and stability of diazepam suspension compounded from tablets. Strom JG Jr, et al. **Am J Hosp Pharm** 1986 Jun; 43(6):1489-91

Lack of preference for diazepam in anxious volunteers. de Wit H, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):533-41

Effects of diazepam on pancreatic exocrine secretion in the dog. Yamagishi F, et al. **Arch Int Pharmacodyn Ther** 1986 Apr; 280(2):314-23

Peptide derivatives as prodrugs. Thomas WA. **Biochem Soc Trans** 1986 Apr;14(2):383-7

Serum protein binding of diazepam and propranolol in the feto-maternal unit from early to late pregnancy. Krauer B, et al. **Br J Obstet Gynaecol** 1986 Apr;93(4):322-8

Release of [3H]norepinephrine: alteration by early developmental exposure to diazepam. Kellogg CK, et al. **Brain Res** 1986 Feb 26; 366(1-2):137-44

Effects of diazepam on circadian phase advances and delays. Ralph MR, et al. **Brain Res** 1986 May 7;372(2):405-8

Single unit activity of locus coeruleus neurons in the freely moving cat. II. Conditioning and pharmacologic studies. Rasmussen K, et al. **Brain Res** 1986 Apr 23;371(2):335-44

Plasma concentration profile of diazepam after oral administration of the open-ring form of diazepam to man. Inotsume N, et al. **Chem Pharm Bull (Tokyo)** 1986 Feb;34(2):937-40

The behavior of 1,4-benzodiazepine drugs in acidic media. IV. Proton and carbon-13 nuclear magnetic resonance spectra of diazepam and fludiazepam in acidic aqueous solution. Kuwayama T, et al. **Chem Pharm Bull (Tokyo)** 1985 Dec;33(12):5503-10

Effects of the intraperitoneal administration of diazepam on rat serum lipoproteins separated by polyacrylamide gel electrophoresis. Cuparencu B, et al. **Clin Exp Pharmacol Physiol** 1985 Nov-Dec; 12(6):593-602

Acute tolerance to diazepam induced by benzodiazepines. Wong PT, et al. **Clin Exp Pharmacol Physiol** 1986 Jan;13(1):1-8

Acute tolerance to diazepam in mice: pharmacokinetic considerations. Yoong YL, et al. **Clin Exp Pharmacol Physiol** 1986 Feb;13(2):153-8

Comparison of two benzodiazepines with differing accumulation: behavioral changes during and after 3 weeks of dosing. Ghoneim MM, et al. **Clin Pharmacol Ther** 1986 May;39(5):491-500

Comparison of controlled-release diazepam capsules and placebo in patients in general practice. Montandon A, et al. **Curr Med Res Opin** 1986;10(1):10-6

Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. de Wit H, et al. **Drug Alcohol Depend** 1986 Feb;16(4):341-60

Repeated administration of diazepam and triazolam to subjects with histories of drug abuse. Roache JD, et al. **Drug Alcohol Depend** 1986 May;17(1):15-29

The action of cisapride on gastric emptying and the pharmacodynamics and pharmacokinetics of oral diazepam. Bateman DN. **Eur J Clin Pharmacol** 1986;30(2):205-8

Calcium alters the properties of [3H]diazepam binding sites in rat brain membranes. Wu PH, et al. **Int J Biochem** 1986;18(4):345-50

Interaction of diazepam with famotidine and cimetidine, two H2-receptor antagonists. Locniskar A, et al. **J Clin Pharmacol** 1986 Apr; 26(4):299-303

Effect of the anticonvulsant denzimol on the disposition of diazepam in the rat. Caccia S, et al. **J Pharm Pharmacol** 1986 Jun;38(6):469–72

Solubility of diazepam and prazepam in aqueous non-ionic surfactants. Moro ME, et al. **J Pharm Pharmacol** 1986 Apr;38(4):294–6

Does alprazolam, in contrast to diazepam, activate alpha 2-adrenoceptors involved in the regulation of rat growth hormone secretion? Eriksson E, et al. **Life Sci** 1986 Apr 21;38(16):1491–8

The role of benzodiazepine receptors in the discriminative stimulus properties of delta-9-tetrahydrocannabinol. Mokler DJ, et al. **Life Sci** 1986 Apr 28;38(17):1581–9

Potencies of diazepam metabolites in rats trained to discriminate diazepam. Young R, et al. **Life Sci** 1986 Jul 7;39(1):17–20

Brain histamine regulation following chronic diazepam treatment and stress. Mazurkiewicz-Kwilecki IM, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):513–7

Behavioral effects of CGS 8216 alone, and in combination with diazepam and pentobarbital in dogs. Risner ME, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1071–6

Differential antagonism of diazepam-induced loss of the righting response. Witkin JM, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):963–5

Correction. Study of an octadecaneuropeptide derived from diazepam binding inhibitor (DBI): biological activity and presence in rat brain. **Proc Natl Acad Sci USA** 1986 Apr;83(8):2776

Maternal diazepam exposure on brain ornithine decarboxylase and growth of offspring. Su MQ, et al. **Proc Natl Sci Counc Repub China [B]** 1986 Jan;10(1):70–4

[An in vitro study of the adsorption of diazepam on microcrystalline bismuth subnitrate] Liu CT, et al. **Yao Hsueh Hsueh Pao** 1986 Jan; 21(1):47–50 (Eng. Abstr.) **(Chi)**

[FSH, LH, estradiol and testosterone levels after Seda-Presomen in women following hysterectomy with bilateral adnexotomy] Stehlíková J, et al. **Acta Univ Palacki Olomuc Fac Med** 1981;101:139–45 **(Ger)**

[Comparison of the bioavailability of two diazepam preparations. Clinical comparison between a new commercial preparation and a standard preparation after oral and intramuscular administration] Resch F, et al. **Arzneimittelforschung** 1986 Apr;36(4):735–8 (Eng. Abstr.) **(Ger)**

DIBENZAZEPINES

In vitro metabolism of desmethyltrimipramine to yield hydroxylamino compound. Ozkirimli S, et al. **Acta Pharm Suec** 1986;23(1):57–9

A multicentre trial of lofepramine. Holden JM, et al. **Br J Clin Pract** 1986 Feb;40(2):59–67

Determination of metapramine, imipramine, trimipramine and their major metabolites in plasma by reversed-phase column liquid chromatography. Pok Phak R, et al. **J Chromatogr** 1986 Mar 7;375(2):339–47

Effect of chronic administration of the 6-aza analogue of mianserin (Org. 3770) and its enantiomers on behaviour and changes in noradrenaline metabolism of olfactory-bulbectomized rats in the 'open field' apparatus. O'Connor WT, et al. **Neuropharmacology** 1986 Mar;25(3):267–70

Comparison of circling induced by unilateral intrastriatal microinjections of haloperidol, clozapine and CCK-8 in rats. Weiss F, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):983–9

Fluperlapine vs haloperidol: a comparison of their neuroendocrinological profiles and the influence on serum lipids. Fleischhacker WW, et al. **Pharmacopsychiatry** 1986 May;19(3):111–4

The AMDP system in international clinical trials: a double-blind comparison of fluperlapine and haloperidol. Woggon B, et al. **Psychopharmacol Bull** 1986;22(1):47–51

Effects of repeated doses of fluvoxamine, mianserin and placebo on memory and measures of sedation. Curran HV, et al. **Psychopharmacology (Berlin)** 1986;89(3):360–3

Receptor binding of N-(methyl-11C) clozapine in the brain of rhesus monkey studied by positron emission tomography (PET). Hartvig P, et al. **Psychopharmacology (Berlin)** 1986;89(2):248–52

[The biochemical effects of a new antidepressive, metapramine (RP 19560) on activity of the dopaminergic and cholinergic systems of the rat striatum] Boireau A, et al. **J Pharmacol** 1986 Jan–Mar;17(1):75–84 (Eng. Abstr.) **(Fre)**

[Studies of the side effect profile of clozapine] Nitzsche M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1986 Mar;38(3):148–52 (Eng. Abstr.) **(Ger)**

[Comparative clinical study of imipramine and mianserin in depressions] Chiriţă V, et al. **Rev Med Chir Soc Med Nat Iasi** 1985 Oct–Dec; 89(4):651–6 (Eng. Abstr.) **(Rum)**

[Effect of haloperidol and clozapine on the bioelectric activity of the human cerebral cortex] Sviderskaia NE, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):428–31 (Eng. Abstr.) **(Rus)**

DIBENZOTHIEPINS

Urinary excretion of conjugates of dothiepin and northiaden (mono-N-demethyl-dothiepin) after an oral dose of dothiepin to humans. Kawahara K, et al. **Eur J Drug Metab Pharmacokinet** 1986 Jan–Mar;11(1):29–32

Contractions of isolated canine coronary arteries resistant to S2-serotonergic blockade. Cohen RA. **J Pharmacol Exp Ther** 1986 May; 237(2):548–52

[Pharmacokinetic study of isofloxythepin in animals] Poláková L, et al. **Cesk Farm** 1986 Apr;35(3):97–101 (Eng. Abstr.) **(Cze)**

DIBENZOXEPINS

Stabilization of AD-1590, a non-steroidal antiinflammatory agent, in suppository bases by beta-cyclodextrin complexation. Takahashi T, et al. **Chem Pharm Bull (Tokyo)** 1986 Apr;34(4):1770–4

DIETHYLAMINES

Subchronic inhalation of diethylamine vapor in Fischer-344 rats: organ system toxicity. Lynch DW, et al. **Fundam Appl Toxicol** 1986 Apr; 6(3):559–65

DIIODOTYROSINE

Internalization and heterochromatic localization of 3H-di-iodothyrosine (T2) in the unicellular organism Tetrahymena and rat thymocytes. Csaba G, et al. **Acta Morphol Hung** 1985;33(1–2):61–8

In vivo formation of diiodotyrosine by extrathyroidal thyroxine ether-link cleavage and effects of mononitrotyrosine on this pathway in the rat. Meinhold H, et al. **Endocrinology** 1986 Jun;118(6):2305–11

DISCRIMINATION (PSYCHOLOGY)

The role of benzodiazepine receptors in the discriminative stimulus properties of delta-9-tetrahydrocannabinol. Mokler DJ, et al. **Life Sci** 1986 Apr 28;38(17):1581–9

Potencies of diazepam metabolites in rats trained to discriminate diazepam. Young R, et al. **Life Sci** 1986 Jul 7;39(1):17–20

Discriminative stimulus properties of PCP mimetics. Browne RG. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:134–47

Interactions between delta 9-tetrahydrocannabinol and cannabidiol as evaluated by drug discrimination procedures in rats and pigeons. Hiltunen AJ, et al. **Neuropharmacology** 1986 Feb;25(2):133–42

The discriminative stimulus properties of cocaine and d-amphetamine: the effects of three routes of administration. de la Garza R, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):765–8

Discriminative properties of l-cathinone compared to dl- and d-cathinone. Schechter MD. **Pharmacol Biochem Behav** 1986 May; 24(5):1161–5

Behavioural and pharmacological dissociation of chlordiazepoxide effects on discrimination and punished responding. Hodges H, et al. **Psychopharmacology (Berlin)** 1986;89(2):155–61

DISCRIMINATION LEARNING

Discriminative stimulus effects of atypical anxiolytics in baboons and rats. Ator NA, et al. **J Pharmacol Exp Ther** 1986 May;237(2):393–403

Differential interactions between chlordiazepoxide, pentobarbital and benzodiazepine antagonists Ro 15-1788 and CGS 8216 in a drug discrimination procedure. De Vry J, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):999–1005

The discriminative stimulus and subjective effects of d-amphetamine, phenmetrazine and fenfluramine in humans. Chait LD, et al. **Psychopharmacology (Berlin)** 1986;89(3):301–6

The discriminative stimulus properties of zolpidem, a novel imidazopyridine hypnotic. Sanger DJ, et al. **Psychopharmacology (Berlin)** 1986;89(3):317–22

Taste/tactile cue discriminations in taste-aversion learning following depletion of noradrenaline. Archer T, et al. **Scand J Psychol** 1986; 27(1):39–51

DOPA

Domperidone treatment in man inhibits the fall in plasma renin activity induced by intravenous gamma-L-glutamyl-L-dopa. Worth DP, et al. **Br J Clin Pharmacol** 1986 May;21(5):497–502

High yield synthesis of 6-[18F]fluoro-L-dopa. Chirakal R, et al. **J Nucl Med** 1986 Mar;27(3):417–21

Occurrence and distribution of 5-S-cysteinyl derivatives of dopamine, dopa and dopac in the brains of eight mammalian species. Fornstedt B, et al. **Neuropharmacology** 1986 Apr;25(4):451–4

[Inhibition by melanin of lipid photo-oxidation] Sakina NL, et al. **Biokhimiia** 1986 May;51(5):864–8 (Eng. Abstr.) **(Rus)**

DOPAMINE

The sensitivity of prolactin secretion to dopamine changes during pregnancy in mice. Swartz SR, et al. **Acta Endocrinol (Copenh)** 1986 Apr;111(4):567–71

Histochemistry of puberty. A multidisciplinary study in the rat. Rietveld WJ, et al. **Acta Histochem [Suppl] (Jena)** 1986;32:63–8

Effect on brain monoamines in the rat of substituted and protected analogues of the oxytocin fragment, prolyl-leucyl-glycinamide following N-terminal substitution by D- and L-pipecolic acid. Szabó

BIBLIOGRAPHY

G, et al. **Acta Physiol Hung** 1986;67(1):155-61

Renal extraction of endogenous and radiolabelled catecholamines in the dog. Bradley T, et al. **Acta Physiol Scand** 1986 Apr;126(4):505-10

Catecholamines of endoneurial laryngeal paraganglia in the rat. Dahlqvist A, et al. **Acta Physiol Scand** 1986 Jun;127(2):257-61

Binding of catecholamines to phospholipids isolated from adrenal medullary granules. Lishajko F. **Acta Physiol Scand** 1986 Jun; 127(2):177-85

Striatal dopamine does not appear involved in the voluntary intake of ethanol by rats. Daoust M, et al. **Alcohol** 1986 Jan-Feb;3(1):15-7

Handling of dopamine and dopamine sulfate by isolated perfused rat kidney. Buu NT, et al. **Am J Physiol** 1986 Jun;250(6 Pt 2):F975-9

Dopamine inhibits maitotoxin-stimulated pituitary 45Ca2+ efflux and prolactin release. Login IS, et al. **Am J Physiol** 1986 Jun; 250(6 Pt 1):E731-5

Alternating current voltammetry of dopamine and ascorbic acid at carbon paste and stearic acid modified carbon paste electrodes. Gelbert MB, et al. **Anal Chem** 1986 May;58(6):1028-32

Effect of electrocatalytic and nucleophilic reactions on fast voltammetric measurements of dopamine at carbon fiber microelectrodes. Stamford JA. **Anal Chem** 1986 May;58(6):1033-6

Behavioral and neurochemical consequences associated with stressors. Anisman H, et al. **Ann NY Acad Sci** 1986;467:205-25 (67 ref.)

Effect of low-dose dopamine on the pharmacokinetics of tobramycin in dogs. Kirby MG, et al. **Antimicrob Agents Chemother** 1986 Jan; 29(1):168-70

Blocking effects of verapamil on pancreatic exocrine secretion induced by dopamine in the dog. Iwatsuki K, et al. **Arch Int Pharmacodyn Ther** 1986 Mar;280(1):145-52

Ibopamine. **Arzneimittelforschung** 1986 Feb;36(2A):285-407

Synthesis and chemical properties of ibopamine and of related esters of N-substituted dopamines--synthesis of ibopamine metabolites. Casagrande C, et al. **Arzneimittelforschung** 1986 Feb;36(2A):291-303

Activity of ibopamine on central nervous system in mice and rats. Ferrini R, et al. **Arzneimittelforschung** 1986 Feb;36(2A):327-30

Humoral and renal effects of ibopamine in normal subjects. Incerti PL, et al. **Arzneimittelforschung** 1986 Feb;36(2A):405-7

Ibopamine kinetics after a single oral dose in healthy volunteers. Lodola E, et al. **Arzneimittelforschung** 1986 Feb;36(2A):345-8

Effect of ibopamine on diuresis in conscious rats in normal and experimentally altered conditions. Miragoli G, et al. **Arzneimittelforschung** 1986 Feb;36(2A):318-22

Ibopamine, an orally active dopamine-like drug: metabolism and pharmacokinetics in rats. Pocchiari F, et al. **Arzneimittelforschung** 1986 Feb;36(2A):334-40

Ibopamine, an orally active dopamine-like drug: metabolism and pharmacokinetics in dogs. Pocchiari F, et al. **Arzneimittelforschung** 1986 Feb;36(2A):341-4

6-Hydroxydopamine and excitotoxin lesions of medial prefrontal cortex fail to affect schedule-induced drinking in the rat. Christie MJ, et al. **Behav Brain Res** 1986 Feb;19(2):183-6

Reinstatement of orienting behavior by d-amphetamine in rats with superior colliculus lesions. Midgley GC, et al. **Behav Neurosci** 1986 Apr; 100(2):246-55

The propensity for nonregulatory ingestive behavior is related to differences in dopamine systems: behavioral and biochemical evidence. Mittleman G, et al. **Behav Neurosci** 1986 Apr;100(2):213-20

Regional turnover of norepinephrine and dopamine in rat brain following acute exposure to air ions. Charry JM, et al. **Bioelectromagnetics** 1985; 6(4):415-25

Protective and restitutive effects of antihypoxic drugs on posthypoxic dopamine release inhibition. Wustmann C, et al. **Biomed Biochim Acta** 1986;45(4):549-56

Action of dopamine on the exocrine pancreatic secretion of the intact dog. Delcenserie R, et al. **Br J Pharmacol** 1986 May;88(1):189-95

Modulation of [3H]-dopamine released by different frequencies of stimulation from rabbit retina. Dubocovich ML, et al. **Br J Pharmacol** 1986 May;88(1):51-61

Unilateral peri-substantia nigra catecholaminergic lesion and amygdala kindling. Albala BJ, et al. **Brain Res** 1986 Apr 9;370(2):388-92

Effect of aging on in vitro dopamine biosynthesis in the median eminence of rat hypothalamic slices. Arita J, et al. **Brain Res** 1986 Mar 26; 369(1-2):391-4

Adenosine 3',5'-cyclic monophosphate stimulates dopamine biosynthesis in the median eminence of rat hypothalamic slices. Arita J, et al. **Brain Res** 1986 May 21;374(1):37-44

Dopaminergic amacrine cells in the retina of Japanese dace. Chino YM, et al. **Brain Res** 1986 May 7;372(2):323-37

Interactions between dopamine and amino acid-induced excitation and inhibition in the striatum. Chiodo LA, et al. **Brain Res** 1986 Jun 4; 375(1):198-203

Dopaminergic control of male sex behavior in rats: effects of an intracerebrally-infused agonist. Hull EM, et al. **Brain Res** 1986 Apr 2;370(1):73-81

Release of endogenous dopamine and cholecystokinin from rat striatal slices: effects of amphetamine and dopamine antagonists. Hutchison JB, et al. **Brain Res** 1986 Apr 9;370(2):310-4

Stimulation by gastrin-releasing peptide, neurotensin and DN1417, a novel TRH analog, of dopamine and norepinephrine release from perifused rat hypothalamic fragments in vitro. Kabayama Y, et al. **Brain Res** 1986 May 7;372(2):394-9

Denervation-like postsynaptic supersensitivity to dopamine agonists induced by microinjection of colchicine into the substantia nigra pars compacta. Kamata K, et al. **Brain Res** 1986 Mar 5;367(1-2):1-7

Ultrastructural evidence of dopaminergic input to enkephalinergic neurons in rat neostriatum. Kubota Y, et al. **Brain Res** 1986 Mar 5; 367(1-2):374-8

Permanent alteration of peptide feedback on dopamine neurons after injection of alpha-melanotropin antiserum at a critical period of postnatal development. Lichtensteiger W, et al. **Brain Res** 1986 Mar 19;368(2):205-10

One perfusion mixture for immunocytochemical detection of noradrenaline, dopamine, serotonin and acetylcholine in the same rat brain. McRae-Degueurce A, et al. **Brain Res** 1986 Jun 18; 376(1):217-9

Effect of postnatal light deprivation on the ontogenesis of dopamine neurons in rat retina. Melamed E, et al. **Brain Res** 1986 May; 391(2):280-4

Excitatory effect of iontophoretically applied dopamine on identified neurons of the rat subthalamic nucleus. Mintz I, et al. **Brain Res** 1986 Jun 4:375(1):172-5

Decrease in rat striatal dopamine synthesis and metabolism in vivo by metabolically stable adenosine receptor agonists. Myers S, et al. **Brain Res** 1986 Jun 4;375(1):193-7

Evidence for, and nature of, the tonic inhibitory influence of habenulointerpeduncular pathways upon cerebral dopaminergic transmission in the rat. Nishikawa T, et al. **Brain Res** 1986 May 14; 373(1-2):324-36

Effects of intraventricular 6-hydroxydopamine on the dopaminergic innervation of striatum: histochemical and neurochemical analysis. Onn SP, et al. **Brain Res** 1986 Jun 18;376(1):8-19

Single unit response of noradrenergic, serotonergic and dopaminergic neurons in freely moving cats to simple sensory stimuli. Rasmussen K, et al. **Brain Res** 1986 Mar 26;369(1-2):336-40

Circadian rhythm in the light response of rat retinal disk-shedding and autophagy. Remé C, et al. **Brain Res** 1986 Mar 26;369(1-2):356-60

Dopamine modulates neuronal activities related to motor performance in the monkey prefrontal cortex. Sawaguchi T, et al. **Brain Res** 1986 Apr 23;371(2):404-8

Regulation of mating behaviour in the female rat by gonadotropin-releasing hormone in the ventral tegmental area: effects of selective destruction of the A10 dopamine neurones. Sirinathsinghji DJ, et al. **Brain Res** 1986 May 21;374(1):167-73

An in vivo voltammetric comparison of the effects of three psychomotor stimulants on electrically evoked neostriatal dopamine release. Stamford JA, et al. **Brain Res** 1986 Feb 26;366(1-2):350-3

In vivo voltammetric characterization of low affinity striatal dopamine uptake: drug inhibition profile and relation to dopaminergic innervation density. Stamford JA, et al. **Brain Res** 1986 May 14;373(1-2):85-91

Dendritic morphology of dopaminergic cells revealed by intracellular injection of Lucifer yellow in fixed carp retina. Teranishi T, et al. **Brain Res** 1986 Apr 2;370(1):196-9

Dopamine stimulates rat cortical somatostatin release. Thal LJ, et al. **Brain Res** 1986 May 7;372(2):205-9

Bay K 8644 stimulation of calcium entry and endogenous dopamine release in rat striatal synaptosomes antagonized by nimodipine. Woodward JJ, et al. **Brain Res** 1986 Apr 9;370(2):397-400

Mesolimbic dopamine projection modulates amygdala-evoked EPSP in nucleus accumbens neurons: an in vivo study. Yim CY, et al. **Brain Res** 1986 Mar 26;369(1-2):347-52

Dissociation of the effects of castration and testosterone replacement on sexual behavior and neural metabolism of dopamine in the male rat. Baum MJ, et al. **Brain Res Bull** 1986 Feb;16(2):145-8

Variation in the ability of neuroleptics to block the inhibitory influence of dopaminergic neurons on the activity of cells in the rat prefrontal cortex. Thierry AM, et al. **Brain Res Bull** 1986 Feb;16(2):155-60

Circling from unilateral VTA morphine: direction is controlled by environmental stimuli. Wise RA, et al. **Brain Res Bull** 1986 Feb; 16(2):267-9

Combined effects of n-hexane and toluene on norepinephrine and dopamine levels in rat brain tissues after long-term exposures. Ikeda M, et al. **Bull Environ Contam Toxicol** 1986 Apr;36(4):510-7

An opioid mechanism modulates central and not peripheral dopaminergic control of ciliary activity in the marine mussel Mytilus edulis. Aiello E, et al. **Cell Mol Neurobiol** 1986 Mar;6(1):17-30

The dopaminergic innervation of the goldfish pituitary. An immunocytochemical study at the electron-microscope level using antibodies against dopamine. Kah O, et al. **Cell Tissue Res** 1986; 244(3):577-82

In vitro studies on the maturation of mesencephalic dopaminergic neurons. Barbin G, et al. **Dev Neurosci** 1985;7(5-6):296-307 (52 ref.)

Subpopulations of lactotropes detected with the reverse hemolytic plaque

assay show differential responsiveness to dopamine. Luque EH, et al. **Endocrinology** 1986 May;118(5):2120-4

Reversal by thiols of dopamine-, stalk-median eminence-, and zinc-induced inhibition of prolactin transformation in adenohypophyses of lactating rats. Martinez-Escalera G, et al. **Endocrinology** 1986 May; 118(5):1803-7

Effects of epinephrine, norepinephrine, and dopamine on gonadotropin-releasing hormone-induced secretion of luteinizing hormone in vitro. Swartz SR, et al. **Endocrinology** 1986 Jun; 118(6):2425-31

Dopaminergic mechanisms and motor function: characterization of D-1 and D-2 dopamine receptor interactions. Barone P, et al. **Eur J Pharmacol** 1986 Apr 9;123(1):109-14

GBR 12783, a potent and selective inhibitor of dopamine uptake: biochemical studies in vivo and ex vivo. Bonnet JJ, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):199-209

Evidence for a specific effect of BHT 920, an azepine derivative, on tyrosine hydroxylase in the dopaminergic system of the rat. Jennewein HM, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):363-9

Alteration of striatal dopaminergic functions implicated in methamphetamine-induced reverse tolerance in rats. Kaneno S, et al. **Eur J Pharmacol** 1986 Apr 16;123(2):287-94

Apomorphine enantiomers' effects on dopamine metabolism: receptor and non-receptor related actions. Saller CF, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):181-8

Effects of dopamine and amphetamine on mouse caudate neurons recorded in vitro. Trulson ME, et al. **Eur J Pharmacol** 1986 May 13; 124(1-2):161-5

In vivo evaluation by differential pulse voltammetry of the effect of thyrotropin-releasing hormone (TRH) on dopaminergic and serotoninergic synaptic activity in the striatum and nucleus accumbens of the rat. Crespi F, et al. **Exp Brain Res** 1986;62(2):329-34

Effects of somatostatin on dopamine sensitive adenylate cyclase activity in the caudate-putamen of the rat. Moser A, et al. **Exp Brain Res** 1986; 62(3):567-71

Determination of sulfated biogenic amines: emphasis on dopamine sulfate isomers. Elchisak MA. **Fed Proc** 1986 Jul;45(8):2241-6

Amine sulfate formation in the central nervous system. Tyce GM, et al. **Fed Proc** 1986 Jul;45(8):2247-53

The anti-oestrogen tamoxifen does not interfere with the dopaminergic control of prolactin and TSH release in normogonadotrophic oligozoospermic man. van Bergeijk L, et al. **Horm Metab Res** 1986 Apr;18(4):272-6

Dopamine selectively inhibits aldosterone responses to angiotensin II in humans. Carey RM, et al. **Hypertension** 1986 May;8(5):399-406

Neural regulation of adrenal chromaffin cell function in the mouse: fate and distribution of [3H]dopamine in denervated adrenal medulla. Hirano T. **J Auton Nerv Syst** 1986 Apr;15(4):285-95

Dopamine and L-dopa potentiation of pressor responses to norepinephrine in isolated perfused rat kidneys. Lam BK, et al. **J Cardiovasc Pharmacol** 1986 May-Jun;8(3):554-8

Dopamine inhibits the aldosterone response to upright posture. Malchoff CD, et al. **J Clin Endocrinol Metab** 1986 Jul;63(1):197-201

Dopamine selectively inhibits aldosterone responses to angiotensin II in man. Carey RM, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S267-9

Dopamine receptor blockade does not affect the natriuresis accompanying sodium chloride infusion in dogs. Bradley T, et al. **J Lab Clin Med** 1986 Jun;107(6):525-8

Histamine-induced prolactin release and activity of tuberoinfundibular dopaminergic neurons in male rats. Seltzer AM, et al. **J Neural Transm** 1986;65(2):115-23

Free and conjugated 3,4-dihydroxyphenylacetic acid and homovanillic acid in brain dopaminergic areas at basal state and after pipotiazine activation. Tavitian E, et al. **J Neural Transm** 1986;65(3-4):261-75

Effects of hypoxia on the activities of noradrenergic and dopaminergic neurons in the rat brain. Miwa S, et al. **J Neurochem** 1986 Jul; 47(1):63-9

An in vivo study of dopamine release and metabolism in rat brain regions using intracerebral dialysis. Sharp T, et al. **J Neurochem** 1986 Jul; 47(1):113-22

The effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on presynaptic dopamine uptake sites in the mouse striatum. Donnan GA, et al. **J Neurol Sci** 1986 Jun;74(1):111-9

DARPP-32, a dopamine- and adenosine 3':5'-monophosphate-regulated phosphoprotein: regional, tissue, and phylogenetic distribution. Hemmings HC Jr, et al. **J Neurosci** 1986 May;6(5):1469-81

In vivo comparison of the regulation of releasable dopamine in the caudate nucleus and the nucleus accumbens of the rat brain. Kuhr WG, et al. **J Neurosci** 1986 Apr;6(4):974-82

Chronic treatment with iprindole reduces immobility of rats in the behavioural 'despair' test by activating dopaminergic mechanisms in the brain. Berettera C, et al. **J Pharm Pharmacol** 1986 Apr; 38(4):313-5

Amineptine: its effect on the dopaminergic system of rats. Ponzio F, et al. **J Pharm Pharmacol** 1986 Apr;38(4):301-3

Desensitization of rat striatal dopamine-stimulated adenylate cyclase after acute amphetamine administration. Barnett JV, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):820-5

In vivo voltammetric study of dopamine release in the striatum following microinjection of apomorphine into the substantia nigra zona reticulata. Kamata K, et al. **Jpn J Pharmacol** 1986 Mar;40(3):472-7

Renal hemodynamics during separate and combined infusion of amino acids and dopamine. ter Wee PM, et al. **Kidney Int** 1986 Apr; 29(4):870-4

Dopamine inhibition of prolactin release but not synthesis in the male Syrian hamster: in vitro studies. Blask DE, et al. **Life Sci** 1986 May 26;38(21):1915-21

3H-xylamine binds to presynaptic rat striatal membranes. Cushing SD, et al. **Life Sci** 1986 May 12;38(19):1715-21

Effects of dopaminergic drugs on plasma levels of steroid hormones in conscious dogs. Goiny M, et al. **Life Sci** 1986 Jun 23; 38(25):2293-300

Prevention of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic toxicity in mice by MDL 72145, a selective inhibitor of MAO-B. Kindt MV, et al. **Life Sci** 1986 Apr 21;38(16):1459-62

Rat striatal dopamine and tetrahydrobiopterin content following an intrastriatal injection of manganese chloride. Lista A, et al. **Life Sci** 1986 Jun 9;38(23):2121-7

Selective dopamine D2 receptor reduction enhances a D1-mediated oral dyskinesia in rats. Rosengarten H, et al. **Life Sci** 1986 Jul 7; 39(1):29-35

Participation of angiotensin II in learning and memory. II. Interactions of angiotensin II with dopaminergic drugs. Yonkov DI, et al. **Methods Find Exp Clin Pharmacol** 1986 Apr;8(4):203-6

Effects of dopamine and vasopressin on histamine-induced increases in macromolecular permeability in the canine forelimb. Adamski SW, et al. **Microcirc Endothelium Lymphatics** 1985 Feb;2(1):27-39

Dopamine and somatostatin inhibit forskolin-stimulated prolactin and growth hormone secretion but not stimulated cyclic AMP levels in sheep anterior pituitary cell cultures. Ray KP, et al. **Mol Cell Endocrinol** 1986 May;45(2-3):175-82

Dopamine autoreceptor regulation of the kinetic state of striatal tyrosine hydroxylase. Strait KA, et al. **Mol Pharmacol** 1986 Jun;29(6):561-9

Involvement of dopaminergic, cholinergic, and glutamatergic mechanisms in the actions of phencyclidine-like drugs. Johnson KM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:52-66

Neurotensin effect on dopamine release and calcium transport in rat striatum: interactions with diphenylalkylamine calcium antagonists. Battaini F, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar; 332(3):267-70

Dopaminergic mediation of long-term behavioral effects of in utero drug exposure. Middaugh LD, et al. **Neurobehav Toxicol Teratol** 1985 Nov-Dec;7(6):685-9

The effect of raphé nuclei lesions on striatal tyramine concentration and dopamine turnover in the rat. Juorio AV, et al. **Neurochem Res** 1986 May;11(5):687-93

The increase of anterior pituitary dopamine in aging C57BL/6J female mice is caused by ovarian steroids, not intrinsic pituitary aging. Telford N, et al. **Neuroendocrinology** 1986;43(2):135-42

Antioxidants fail to inhibit depletion of striatal dopamine by MPTP [letter] Baldessarini RJ, et al. **Neurology** 1986 May;36(5):735

Dopamine D2 receptors and dopamine metabolism. Relationship between biochemical and behavioural effects of substituted benzamide drugs. Magnusson O, et al. **Neuropharmacology** 1986 Feb;25(2):187-97

Control of sensorimotor function by dopaminergic nigrostriatal neurons: influence on eating and drinking. White NM. **Neurosci Biobehav Rev** 1986 Spring;10(1):15-36 (189 ref.)

Preferential vulnerability of A8 dopamine neurons in the primate to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Deutch AY, et al. **Neurosci Lett** 1986 Jul 11;68(1):51-6

Light ON depresses and light OFF enhances the release of dopamine from the cat's retina. Hamasaki DI, et al. **Neurosci Lett** 1986 Jul 11; 68(1):112-6

Dopaminergic and noradrenergic sympathetic nerves of the dog have different DOPA decarboxylase activities. Harris T, et al. **Neurosci Lett** 1986 Apr 11;65(2):155-60

Striatal neuropeptide Y neurones are under the influence of the nigrostriatal dopaminergic pathway: immunohistochemical evidence. Kerkerian L, et al. **Neurosci Lett** 1986 May 6;66(1):106-12

Responsiveness to 'autoreceptor' doses of apomorphine inversely correlated with the firing rate of dopaminergic A9 neurons: action of baclofen. Mereu G, et al. **Neurosci Lett** 1986 Apr 11;65(2):161-6

Regional cerebral pharmacokinetics of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine as examined by positron emission tomography in a baboon is altered by tranylcypromine. Moerlein SM, et al. **Neurosci Lett** 1986 May 15;66(2):205-9

Strain differences in the density of dopaminergic cells of the retina in albino rats. Nguyen-Legros J, et al. **Neurosci Lett** 1986 May 6; 66(1):13-8

Distinct functions for dopamine and serotonin in locomotor behaviour: evidence using the 5-HT1 agonist RU 24969 in globus pallidus-lesioned rats. Oberlander C, et al. **Neurosci Lett** 1986 Jun 18;67(2):113-8

Catecholamine sensitivities of motor cortical neurons of the monkey. Sawaguchi T, et al. **Neurosci Lett** 1986 May 15;66(2):135-40

Reduced apomorphine sensitivity of dopamine metabolism in rat striatum after repeated administration of methamphetamine. Kashihara K, et al. **Neurosci Res** 1986 May;3(4):351-5

Effects of dopamine and its agonists and antagonists on the receptive field properties of ganglion cells in the rabbit retina. Jensen RJ, et al. **Neuroscience** 1986 Mar;17(3):837-55

Simultaneous monitoring of dopamine release in rat frontal cortex, nucleus accumbens and striatum: effect of drugs, circadian changes and correlations with motor activity. O'Neill RD, et al. **Neuroscience** 1985 Sep;16(1):49-55

Glutamate decarboxylase-immunoreactive boutons in synaptic contacts with hypothalamic dopaminergic cells: a light and electron microscopy study combining immunocytochemistry and radioautography. Tappaz ML, et al. **Neuroscience** 1985 Sep;16(1):111-22

Effect of DN-1417, a thyrotropin releasing hormone analog, on dopaminergic neurons in rat brain. Nakahara T, et al. **Peptides** 1985 Nov-Dec;6(6):1093-9

Behavioral and biochemical assessment of time-related changes in globus pallidus and striatal dopamine induced by intranigrally administered neurotensin. Napier TC, et al. **Peptides** 1985 Nov-Dec;6(6):1057-68

Involvement of extrapyramidal motor mechanisms in the suppression of locomotor activity by antipsychotic drugs: a comparison between the effects produced by pre- and post-synaptic inhibition of dopaminergic neurotransmission. Ahlenius S, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1409-15

Effects of dopaminergic agents on eye tracking before and after repeated methamphetamine. Ando K, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):693-9

Selective involvement of dopamine in the nucleus accumbens in the feeding response elicited by muscimol injection in the nucleus raphe dorsalis of sated rats. Bendotti C, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1189-93

Dopamine neurotransmission in the nucleus accumbens may be involved in oxytocin-enhanced grooming behavior of the rat. Drago F, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1185-8

Synergistic effects of dopamine agonists and centrally administered neurotensin on feeding. Hawkins MF, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1195-201

Effects of acute and chronic bupropion on locomotor activity and dopaminergic neurons. Nielsen JA, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):795-9

Grooming in the mouse is stimulated by the dopamine D1 agonist SKF 38393 and by low doses of the D1 antagonist SCH 23390, but is inhibited by dopamine D2 agonists, D2 antagonists and high doses of SCH 23390. Starr BS, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):837-9

The interaction of neurotensin with dopaminergic pathways in the central nervous system: basic neurobiology and implications for the pathogenesis and treatment of schizophrenia. Nemeroff CB. **Psychoneuroendocrinology** 1986;11(1):15-37

Lithium and bupropion antagonise the phasic changes in locomotor activity caused by dopamine infused into the rat nucleus accumbens. Barnes JC, et al. **Psychopharmacology (Berlin)** 1986;89(3):311-6

Mesolimbic dopamine and its control of locomotor activity in rats: differences in pharmacology and light/dark periodicity between the olfactory tubercle and the nucleus accumbens. Cools AR. **Psychopharmacology (Berlin)** 1986;88(4):451-9

Effect of in vitro inorganic lead on dopamine release from superfused rat striatal synaptosomes. Minnema DJ, et al. **Toxicol Appl Pharmacol** 1986 Jun 30;84(2):400-11

[Biochemical characterization and differentiation of dopaminergic supersensitivity in the rat] Funk KF, et al. **Biomed Biochim Acta** 1986; 45(3):393-9 (Eng. Abstr.) **(Ger)**

[Dopaminergic circuits and the blink reflex] Raffaele R, et al. **Boll Soc Ital Biol Sper** 1986 Feb 28;62(2):263-9 (Eng. Abstr.) **(Ita)**

[Evaluation of the dopaminergic neuroendocrine control of prolactin release during labor in humans] Nishii O, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Feb 20;62(2):108-16 (Eng. Abstr.) **(Jpn)**

[The effect of metoclopramide and dopamine on mineralocorticoid secretion--in vivo and in vitro studies] Ojima M, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Mar 20;62(3):197-207 (Eng. Abstr.) **(Jpn)**

[Role of the dopaminergic system in the development of caudate-induced spindle-type activity in the cat] Oleshko NN. **Fiziol Zh** 1986 May-Jun; 32(3):263-72 (Eng. Abstr.) **(Rus)**

[The effect of irradiation on dopamine level and metabolism in the rat brain] Legeza VI, et al. **Radiobiologiia** 1986 Mar-Apr;26(2):262-4 (Eng. Abstr.) **(Rus)**

[Therapeutic effect of parlodel in resistant depressions and its relation to the effect of dopamine metabolism] Bel'tiukova TA, et al. **Vopr Med Khim** 1986 Mar-Apr;32(2):19-21 (Eng. Abstr.) **(Rus)**

[Participation of the cortical dopaminergic mechanism in latent inhibition in cats] Il'iuchenok RIu, et al. **Zh Vyssh Nerv Deiat** 1986 Jan-Feb; 36(1):176-8 **(Rus)**

[Effects of dopamine on the conduction of the atrioventricular node] Valentin V, et al. **Rev Esp Cardiol** 1986 Mar-Apr;39(2):146-50 (Eng. Abstr.) **(Spa)**

[Role of the presynaptic receptors in the control of dopamine synthesis in the striate complex and nucleus accumbens] Palarea MD, et al. **Rev Esp Fisiol** 1986 Mar;42(1):71-5 (Eng. Abstr.) **(Spa**

DOPAMINE BETA-HYDROXYLASE

Serum dopamine-beta-hydroxylase activity in patients with major depressive disorders. Kjellman BF, et al. **Acta Psychiatr Scand** 1986 Mar;73(3):266-70

A comprehensive study of chronic schizophrenic patients. II: Biological, neuropsychological, and clinical correlates of CT abnormality. Pandurangi AK, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):161-71

Specific lysis of noradrenergic synaptosomes by an antiserum to dopamine-beta-hydroxylase. Docherty M, et al. **FEBS Lett** 1986 Jun 23;202(1):37-40

Electron microscopic analysis of tyrosine hydroxylase, dopamine-beta-hydroxylase and phenylethanolamine-N-methyltransferase immunoreactive innervation of the hypothalamic paraventricular nucleus in the rat. Liposits Z, et al. **Histochemistry** 1986;84(2):105-20

Adenosine 5'-diphosphate-dependent subunit dissociation of bovine dopamine beta-hydroxylase. Dhawan S, et al. **J Biol Chem** 1986 Jun 15;261(17):7680-4

Substituted 1-benzylimidazole-2-thiols as potent and orally active inhibitors of dopamine beta-hydroxylase. Kruse LI, et al. **J Med Chem** 1986 Jun;29(6):887-9

Peripheral and central short-term effects of fusaric acid, a DBH inhibitor, on tryptophan and serotonin metabolism in the rat. Chaouloff F, et al. **J Neural Transm** 1986;65(3-4):219-32

Inhibitory action of hydralazine on catecholamine-synthesizing enzymes prepared from bovine adrenal medulla. Morita K, et al. **Jpn J Pharmacol** 1986 Mar;40(3):445-53

Some catecholamine inhibitors do not cause accumulation of nuclear estrogen receptors in rat hypothalamus and anterior pituitary gland. Blaustein JD, et al. **Neuroendocrinology** 1986;43(2):143-9

Dopamine-beta-hydroxylase inhibitors modulate the concentration of functional estrogen receptors in female rat hypothalamus and pituitary gland. Blaustein JD, et al. **Neuroendocrinology** 1986;43(2):150-8

Sensation seeking, paired associate learning and brain catecholamines. Kulcsár Z, et al. **Neuropsychobiology** 1986;15(1):43-8

[The function of the sympathetic nervous system determined by humoral factors in the maintenance hemodialysis patients] Minami M, et al. **Hokkaido Igaku Zasshi** 1986 Mar;61(2):186-94 (Eng. Abstr.) **(Jpn)**

[Determination of dopamine-beta-hydroxylase (DBH) and monoamine oxidase (MAO) activities in platelets and plasma in schizophrenic, maniac-depressive and neurotic patients] Xavier Vieira R, et al. **Acta Med Port** 1986 Jan-Feb;7(1):45-8 (Eng. Abstr.) **(Por)**

DOXAPRAM

Doxapram: cardiopulmonary effects in the horse. Wernette KM, et al. **Am J Vet Res** 1986 Jun;47(6):1360-2

DOXEPIN

Pharmacokinetic evaluation of two doxepin products. Wecker MT, et al. **Clin Ther** 1986;8(3):342-7

A controlled comparison of clonidine and doxepin in the treatment of the opiate withdrawal syndrome. Täschner KL. **Pharmacopsychiatry** 1986 May;19(3):91-5

DRUG EVALUATION

The AMDP-system in clinical psychopharmacology. Bobon D, et al. **Pharmacopsychiatry** 1986 Mar;19(2):55-7

DRUG SCREENING

[Effects of central acting drugs on the mirror staircase test] Houri D. **Nippon Yakurigaku Zasshi** 1986 Feb;87(2):135-42 (Eng. Abstr.) **(Jpn)**

ELECTROCONVULSIVE THERAPY

Effect of electroconvulsive shock (ECS) treatment on the histaminergic system in rat brain: biochemical and behavioural studies. Zawilska J, et al. **Agents Actions** 1986 Apr;18(1-2):222-5

Biochemical and neuroendocrinological effects of electroconvulsive therapy. Discussion of Part II. Barkai AI. **Ann NY Acad Sci** 1986; 462:120-3

Interactions of drugs and electroshock treatment on cerebral monoaminergic systems. Barkai AI. **Ann NY Acad Sci** 1986; 462:147-62

Neuroendocrine responses as a probe into the mechanisms of action of electroconvulsive therapy. Cowen PJ. **Ann NY Acad Sci** 1986; 462:163-71 (32 ref.)

The biochemistry of electroconvulsive therapy. Discussion of Part III. Decina P. **Ann NY Acad Sci** 1986;462:172–3

Effect of electroconvulsive shock on serotonin activity. Essman WB. **Ann NY Acad Sci** 1986;462:99–104

Electroconvulsive therapy and lateralized affective systems. Flor-Henry P. **Ann NY Acad Sci** 1986;462:389–97 (43 ref.)

What have we learned ? Frankel FH. **Ann NY Acad Sci** 1986; 462:411–5

Changes in gamma-aminobutyric acid biochemistry and seizure threshold. Green AR. **Ann NY Acad Sci** 1986;462:105–19 (29 ref.)

Neurochemical mechanisms of mood stabilization. Focus on electroconvulsive therapy. Lerer B, et al. **Ann NY Acad Sci** 1986; 462:366–75 (74 ref.)

Electroconvulsive therapy in the treatment of manic episodes. Small JG, et al. **Ann NY Acad Sci** 1986;462:37–49

Carbamazepine and ECT: a paradoxical combination [letter] Cantor C. **J Clin Psychiatry** 1986 May;47(5):276–7

ELECTROENCEPHALOGRAPHY

A comprehensive study of chronic schizophrenic patients. II: Biological, neuropsychological, and clinical correlates of CT abnormality. Pandurangi AK, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):161–71

EEG asymmetry in schizophrenic patients before and during neuroleptic treatment. Merrin EL, et al. **Biol Psychiatry** 1986 May; 21(5–6):455–64

Evidence that serotonin mediates non-cholinergic neocortical low voltage fast activity, non-cholinergic hippocampal rhythmical slow activity and contributes to intelligent behavior. Vanderwolf CH, et al. **Brain Res** 1986 May 28;374(2):342–56

Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. Peloquin LJ, et al. **J Abnorm Psychol** 1986 Feb;95(1):88–98

Contribution to the search for vigilance-indicative EEG variables. Results of a controlled, double-blind study with pyritinol in elderly patients with symptoms of mental dysfunction. Herrmann WM, et al. **Pharmacopsychiatry** 1986 Mar;19(2):75–83

EEG stability following corticotropin releasing factor in rats. Ehlers CL. **Psychoneuroendocrinology** 1986;11(1):121–5

[Refinement of an EEG diurnal vigilance index. Application to drug trials] Goldenberg F. **Rev Electroencephalogr Neurophysiol Clin** 1986 Mar; 16(1):39–48 (Eng. Abstr.) **(Fre)**

[EEG studies in rats to determine the threshold levels of chlorpromazine with respect to the state of vigilance] Bergschicker R, et al. **Biomed Biochim Acta** 1986;45(3):401–12 (Eng. Abstr.) **(Ger)**

[Identification of neuroleptics by using the characteristics of the spatial organization of the EEG] Monakhov KK, et al. **Farmakol Toksikol** 1986 May–Jun;49(3):27–32 (Eng. Abstr.) **(Rus)**

[Effect of haloperidol and clozapine on the bioelectric activity of the human cerebral cortex] Sviderskaia NE, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):428–31 (Eng. Abstr.) **(Rus)**

ELECTROLYTES

Substance P-induced intestinal secretion of water and electrolytes. McFadden D, et al. **Gut** 1986 Mar;27(3):267–72

Effects of carbamazepine on serum electrolytes in affectively ill patients. Joffe RT, et al. **Psychol Med** 1986 May;16(2):331–5

ELECTROSHOCK

Changes in the behavioural response to a TRH analogue following chronic amitriptyline treatment and repeated electroconvulsive shock in the rat. Bennett GW, et al. **Br J Pharmacol** 1986 May;88(1):129–39

The effects of desipramine, zimelidine, electroconvulsive treatment and lithium on rat brain biogenic amines: a comparison with peripheral changes. Karoum F, et al. **Eur J Pharmacol** 1986 Mar 4; 121(3):377–85

Correlation of indices of stress with intensity of electrical shock for cows. Lefcourt AM, et al. **J Dairy Sci** 1986 Mar;69(3):833–42

Studies on rat brain catecholamine synthesis and beta-adrenoceptor number following administration of electroconvulsive shock, desipramine and clenbuterol. Nimgaonkar VL, et al. **J Neural Transm** 1986;65(3–4):245–59

Electroconvulsive shock and cyclic AMP signal transduction: effects distal to the receptor. Newman ME, et al. **J Neurochem** 1986 Jun; 46(6):1667–9

Disruption of conditioned taste aversion by ECS: the role of lithium chloride. Shaw N. **Physiol Behav** 1986;36(6):1193–5

EMOTIONS

Antiemotional and anticonvulsant activity of brotizolam and its effects on motor performance in animals. Böke-Kuhn K, et al. **Arzneimittelforschung** 1986 Mar;36(3A):528–31

Food, mood and health: the Medieval outlook. Mauron J. **Int J Vitam Nutr Res [Suppl]** 1986;29:9–26

Central muscarinic effects of physostigmine on mood, cardiovascular function, pituitary and adrenal neuroendocrine release. Janowsky DS, et al. **Psychopharmacology (Berlin)** 1986;89(2):150–4

Steroids may influence changes in mood [news] Barnes DM. **Science** 1986 Jun 13;232(4756):1344–5

[Subjective findings in emotionally stable and labile subjects following oral application of flupenthixol in small doses] Stieglitz RD, et al. **Arzneimittelforschung** 1986 May;36(5):850–4 (Eng. Abstr.) **(Ger)**

ENDORPHINS

Dysregulation of plasma pro-opiomelanocortin-related peptides in neurotic depression. Genazzani AR, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):1–6

Plasma beta-endorphin-like immunoreactivity during pregnancy, parturition, puerperium and in newborn. Zivný J, et al. **Acta Obstet Gynecol Scand** 1986;65(2):129–31

Involvement of a serotonergic control in the regulation of plasma levels of immunoreactive beta-endorphin. Cancela LM, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):409–13

Eating behavior and plasma beta-endorphin in bulimia. Waller DA, et al. **Am J Clin Nutr** 1986 Jul;44(1):20–3

Opioid peptide processing and receptor selectivity. Höllt V. **Annu Rev Pharmacol Toxicol** 1986;26:59–77 (127 ref.)

The periaqueductal gray: a prerequisite for ACTH-induced excessive grooming. Spruijt BM, et al. **Behav Brain Res** 1986 Apr;20(1):19–25

A putative met-enkephalin releaser, kyotorphin enhances intracellular Ca2+ in the synaptosomes. Ueda H, et al. **Biochem Biophys Res Commun** 1986 Jun 13;137(2):897–902

Degradation of beta-casomorphin in the rat brain in vivo. Stark H, et al. **Biomed Biochim Acta** 1986;45(4):557–63

gamma-Endorphin and schizophrenia: amino acid composition of gamma-endorphin and nucleotide sequence of gamma-endorphin cDNA from pituitary glands of schizophrenic patients. Bovenberg RA, et al. **Brain Res** 1986 Jun 18;376(1):29–37

Opioid-induced feeding: localization of sensitive brain sites. Gosnell BA, et al. **Brain Res** 1986 Mar 26;369(1–2):177–84

Central nervous system mediation of positive and negative reinforcement in neonatal albino rats. Kehoe P, et al. **Brain Res** 1986 Jun; 392(1–2):69–75

The course of the decrease of hypothalamic beta-endorphin induced by training, and the development of the effect of beta-endorphin on the retrieval of inhibitory avoidance in rats. Izquierdo I, et al. **Braz J Med Biol Res** 1985;18(3):391–5

Hormonal and metabolic responses to intracarotid and intrajugular infusion of beta-endorphin in normal dogs. el-Tayeb KM, et al. **Can J Physiol Pharmacol** 1986 Mar;64(3):306–10

An opioid mechanism modulates central and not peripheral dopaminergic control of ciliary activity in the marine mussel Mytilus edulis. Aiello E, et al. **Cell Mol Neurobiol** 1986 Mar;6(1):17–30

Cardiocirculatory effects of physiological doses of beta-endorphin. Tuggle DW, et al. **Circ Shock** 1986;18(3):215–25

Endorphins and amylase secretion [letter] Davison JS. **Dig Dis Sci** 1986 May;31(5):556–7

Acute hemorrhagic stress in conscious sheep elevates immunoreactive beta-endorphin in plasma but not in cerebrospinal fluid. Smith R, et al. **Endocrinology** 1986 Jun;118(6):2572–6

Antagonism of beta-endorphin-induced prolactin release by alpha-melanocyte-stimulating hormone and corticotropin-like intermediate lobe peptide. Wardlaw SL, et al. **Endocrinology** 1986 Jul; 119(1):112–8

Regulation of beta-endorphin, corticotropin-like intermediate lobe peptide, and alpha-melanotropin-stimulating hormone in the hypothalamus by testosterone. Wardlaw SL. **Endocrinology** 1986 Jul; 119(1):19–24

Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. de Meirleir K, et al. **Eur J Appl Physiol** 1986;55(1):5–8

Stress hormonal response to exercise after sleep loss. Martin BJ, et al. **Eur J Appl Physiol** 1986;55(2):210–4

Opioid peptides. Structure-activity relationships in [OGly4] dermorphin tetrapeptides. X. Salvadori S, et al. **Farmaco [Sci]** 1986 Feb; 41(2):103–10

Discordances in the temporal pattern of the ACTH/beta-endorphin releasing effects of synthetic CRFs and partially purified bovine CRF in a superfusion system. Yasuda Y, et al. **Horm Metab Res** 1986 May; 18(5):313–7

The interaction between gamma-type endorphins and HLA class I antigens. Claas FH, et al. **Hum Immunol** 1986 Apr;15(4):347–56

Influence of beta-endorphin, somatostatin, substance P and vasoactive intestinal peptide on the proliferative response of human peripheral blood T lymphocytes to mercuric chloride. Nordlind K, et al. **Int Arch Allergy Appl Immunol** 1986;80(3):326–8

beta-Endorphin-(1–27) inhibits the spinal beta-endorphin-induced release of Met-enkephalin. Tseng LF, et al. **Int J Pept Protein Res** 1986 Apr; 27(4):394–7

Relationships among concentrations of four opioid neuropeptides and luteinizing hormone-releasing hormone in neural tissues of beef cows following early weaning. Malven PV, et al. **J Anim Sci** 1986 Mar; 62(3):723-33

High-performance liquid chromatography of amino acids, peptides and proteins. LXVII. Evaluation of bandwidth relationships of peptides related to human beta-endorphin, separated by gradient-elution reversed-phase high-performance liquid chromatography. Hearn MT, et al. **J Chromatogr** 1986 Feb 21;352:35-66

Pro-opiomelanocortin messenger ribonucleic acid and posttranslational processing of beta endorphin in spleen macrophages. Lolait SJ, et al. **J Clin Invest** 1986 Jun;77(6):1776-9

Pregnancy-associated changes in ovarian immunoreactive beta-endorphin in rats. Autelitano DJ, et al. **J Endocrinol** 1986 Mar;108(3):343-50

Dissociation between CSF and plasma B-endorphin in major depressive disorders: evidence for a different regulation. Facchinetti F, et al. **J Endocrinol Invest** 1986 Feb;9(1):11-4

Conversion of leumorphin (dynorphin B-29) to dynorphin B and dynorphin B-14 by thiol protease activity. Devi L, et al. **J Neurochem** 1986 Jul;47(1):154-7

beta-Endorphin-induced stimulation of central sympathetic outflow: inhibitory modulation by central noradrenergic neurons. Appel NM, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):695-701

Structural modifications of pro-opiomelanocortin-derived peptides alter their behavioral effects markedly. Hirsch MD, et al. **J Pharmacol Exp Ther** 1986 May;237(2):378-85

Enzyme linked immunosorbent assay (ELISA) for beta-endorphin and its antibodies. Sarma JK, et al. **Life Sci** 1986 May 12;38(19):1723-32

Uptake and release of kyotorphin in rat brain synaptosomes. Ueda H, et al. **Life Sci** 1986 Jun 30;38(26):2405-11

Computationally directed biorational drug design of peptides. Momany FA, et al. **Methods Enzymol** 1986;124:3-18

Structure-activity studies of morphiceptin analogs: receptor binding and molecular determinants of mu-affinity and selectivity. Loew G, et al. **Mol Pharmacol** 1986 Jun;29(6):546-53

Plasma beta-endorphin and beta-lipotropin in patients with end-stage renal disease--effects of hemodialysis. Elias AN, et al. **Nephron** 1986; 43(3):173-6

Effect of various blockers of arachidonic acid metabolism on release of beta-endorphin- and adrenocorticotropin-like immunoreactivity induced by phospholipase A2 from rat adenohypophysis in vitro. Knepel W, et al. **Neuroendocrinology** 1986;43(1):44-8

Acetylation of melanocyte-stimulating hormone and beta-endorphin in the pars intermedia of the perinatal pituitary gland in the mouse. Leenders HJ, et al. **Neuroendocrinology** 1986;43(2):166-74

Suppression of receptive and proceptive behavior in ovariectomized, estrogen-progesterone-primed rats by intraventricular beta-endorphin: studies of behavioral specificity. Wiesner JB, et al. **Neuroendocrinology** 1986;43(1):57-62

The effects of aging on molecular forms of beta- and gamma-endorphins in rat hypothalamus. Wilkinson CW, et al. **Neuroendocrinology** 1986; 43(2):124-31

RIA/chromatographic evidence for novel opioid peptide(s) in Squilla mantis ganglia. Palmisano A, et al. **Neuropeptides** 1986 Apr; 7(3):281-9

Estradiol target sites immunoreactive for beta-endorphin in the arcuate nucleus of rat and mouse hypothalamus. Jirikowski GF, et al. **Neurosci Lett** 1986 Apr 11;65(2):121-6

alpha-N-acetylated beta-endorphin is differentially processed in the normal and hypothalamo-pituitary-disconnected (HPD) ewe. Smith AI, et al. **Neurosci Lett** 1986 Apr 11;65(2):229-33

Opioid and other peptides as inhibitors of leumorphin (dynorphin B-29) converting activity. Devi L, et al. **Peptides** 1986 Jan-Feb;7(1):87-90

Characterization of endorphins from the pituitary of the spiny dogfish Squalus acanthias. Lorenz RG, et al. **Peptides** 1986 Jan-Feb; 7(1):119-26

Does placebo response mediate runner's high? Hinton ER, et al. **Percept Mot Skills** 1986 Jun;62(3):789-90

Effect of beta-endorphin on sociosexual proclivity in a choice paradigm. Wiesner JB, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):507-11

The effect of altered 5-hydroxytryptamine levels on beta-endorphin content in rat brain. Soliman KF, et al. **Proc Soc Exp Biol Med** 1986 Jun;182(2):187-93

Diurnal rhythm of plasma beta endorphin, cortisol and growth hormone in schizophrenics as compared to control subjects. Gil-Ad I, et al. **Psychopharmacology (Berlin)** 1986;88(4):496-9

Selective potentiations in opioid analgesia following scopolamine pretreatment. Sperber ES, et al. **Psychopharmacology (Berlin)** 1986; 89(2):175-6

Release of immunoreactive met-enkephalin by intraventricular beta-endorphin in anesthetized rats. Tseng LF, et al. **Regul Pept** 1986 May;14(3):181-92

Des-enkephalin-gamma-endorphin: bioavailability in rats following the subcutaneous and intramuscular route of administration. Verhoef JC, et al. **Regul Pept** 1986 Apr;14(2):113-24

Investigating opioid peptides in schizophrenia and depression. Berger PA, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986;64:309-33 (91 ref.)

[Beta-endorphin and dynorphin are involved in the central depressor action of clonidine or norepinephrine in rats] Xie CW, et al. **Sheng Li Hsueh Pao** 1985 Apr;37(2):172-9 (Eng. Abstr.) **(Chi)**

[A new group of hormones, endogenous ligands for drug receptors] Schreiber V. **Cesk Fysiol** 1986;35(3):219-23 **(Cze)**

[Development of a radioimmunoassay for beta-casomorphin (1-5)] Furkert J, et al. **Radiobiol Radiother (Berl)** 1986;27(2):205-13 (Eng. Abstr.) **(Ger)**

[Plasma levels of beta-endorphin and ACTH during critical increase in arterial pressure in man] Giovannini C, et al. **Boll Soc Ital Biol Sper** 1986 Jan 31;62(1):7-13 (Eng. Abstr.) **(Ita)**

[Effect of intrathecal beta-endorphin and electrical tooth pulp stimulation on endocrine and cardiovascular functions] Miyata A. **Masui** 1986 Feb; 35(2):250-9 (Eng. Abstr.) **(Jpn)**

[Maternal beta-endorphin secretion during pregnancy--measurement of immunoreactive beta-endorphin in urine] Sumioki H, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 Apr;38(4):499-504 (Eng. Abstr.) **(Jpn)**

[Detection of the pro-opiomelanocortin peptide fragments--beta-endorphin and ACTH--in the adrenals of rats and mice by immunohistochemistry] Arefolov VA, et al. **Biull Eksp Biol Med** 1986 Apr;101(4):445-7 (Eng. Abstr.) **(Rus)**

[Immunohistochemical identification of endogenous sources of cardiac glycoside biosynthesis] Kvetnoi IM, et al. **Biull Eksp Biol Med** 1986 Apr;101(4):392-3 (Eng. Abstr.) **(Rus)**

[Effect of beta-endorphin on catecholamine levels in the rat hypothalamus and cerebral cortex] Slavnov VN, et al. **Biull Eksp Biol Med** 1986 May; 101(5):562-4 (Eng. Abstr.) **(Rus)**

[Beta-endorphin and corticotropin in the blood of patients during the acute period of severe craniocerebral injury] Marzoian RA, et al. **Vopr Med Khim** 1986 May-Jun;32(3):95-8 (Eng. Abstr.) **(Rus)**

[Changes in the chemosensitive properties of the central neurons of the snail Helix pomatia and of the mouse as affected by opioid peptides] Zakharov ND, et al. **Zh Evol Biokhim Fiziol** 1986 Mar-Apr; 22(2):166-9 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, LEUCINE

Simple synthesis of (leucine5)-enkephaline. Vičar J. **Acta Univ Palacki Olomuc Fac Med** 1982;103:139-46

Long-term effects of leucine-enkephalin on active avoidance responding in mice. Dana RC, et al. **Behav Neurosci** 1986 Apr;100(2):185-9

In vitro activity profiles of cyclic and linear enkephalin pseudopeptide analogs. Edwards JV, et al. **Biochem Biophys Res Commun** 1986 Apr 29;136(2):730-6

Cyclic AMP or forskolin rapidly attenuates the depressant effects of opioids on sensory-evoked dorsal-horn responses in mouse spinal cord-ganglion explants. Crain SM, et al. **Brain Res** 1986 Apr 2; 370(1):61-72

Opioid-induced feeding: localization of sensitive brain sites. Gosnell BA, et al. **Brain Res** 1986 Mar 26;369(1-2):177-84

Release of [Leu5]enkephalin immunoreactivity from the isolated perfused rat stomach. Nishimura E, et al. **Eur J Pharmacol** 1986 May 13; 124(1-2):43-9

Cystamine-enkephalin dimer. Syntheses and biological activities of enkephalin analogs containing cystamine and cysteamine. Kondo M, et al. **Int J Pept Protein Res** 1986 Feb;27(2):153-9

Enkephalin-like substance in aplysia nervous tissue and actions of leu-enkephalin on single neurons. Leung MK, et al. **Life Sci** 1986 Apr 21;38(16):1529-34

Production and characterization of a rat monoclonal antibody against leu5 enkephalin. Hérion P, et al. **Mol Immunol** 1986 Feb;23(2):209-15

Leu-enkephalin content in rat brain during prolonged treatment with imipramine or amitriptyline. Herman ZS, et al. **Neuropeptides** 1986 Feb-Mar;7(2):113-24

Maturation of opioid sensitivity of fetal mouse dorsal root ganglion neuron perikarya in organotypic cultures: regulation by spinal cord. Chalazonitis A, et al. **Neuroscience** 1986 Apr;17(4):1181-98

The glutamate decarboxylase-, leucine enkephalin-, methionine enkephalin- and substance P-immunoreactive neurons in the neostriatum of the rat and cat: evidence for partial population overlap. Penny GR, et al. **Neuroscience** 1986 Apr;17(4):1011-45

The crystal structures of [Met5]enkephalin and a third form of [Leu5]enkephalin: observations of a novel pleated beta-sheet. Griffin JF, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3272-6

Selective potentiations in opioid analgesia following scopolamine pretreatment. Sperber ES, et al. **Psychopharmacology (Berlin)** 1986; 89(2):175-6

Enkephalin contents reflect noradrenergic large dense cored vesicle populations in vasa deferentia. Douglas BH 2d, et al. **Regul Pept** 1986 May;14(3):193-210

[Enkephalin metabolism in human serum--the measurement of Leu-enkephalin-like substance in human serum] Machi T, et al. **Masui** 1985 Dec;34(12):1588-93 (Eng. Abstr.) **(Jpn)**

[Effect of enkephalins on various mechanisms regulating glycogen concentration in the liver] Zoloev GK. **Probl Endokrinol (Mosk)** 1986 Mar-Apr;32(2):58-60 (Eng. Abstr.) **(Rus)**

ENKEPHALIN, METHIONINE

A putative met-enkephalin releaser, kyotorphin enhances intracellular Ca2+ in the synaptosomes. Ueda H, et al. **Biochem Biophys Res Commun** 1986 Jun 13;137(2):897-902

Intragranular colocalization of CRF and Met-Enk-8 in nerve terminals in the rat median eminence. Hisano S, et al. **Brain Res** 1986 Apr 9; 370(2):321-6

Influence of nitrous oxide upon regional brain levels of methionine-enkephalin-like immunoreactivity in rats. Quock RM, et al. **Brain Res Bull** 1986 Mar;16(3):321-3

Quality control of azure B preparations by liquid chromatography and standardization with azure B tetrafluoroborate. Nelis HJ, et al. **Clin Chim Acta** 1986 May 15;156(3):247-57

Disturbance of a met-enkephalin-like hormone in the hepatopancreas of crabs contaminated by metals. Amiard-Triquet C, et al. **Ecotoxicol Environ Safety** 1986 Apr;11(2):198-209

beta-Endorphin-(1-27) inhibits the spinal beta-endorphin-induced release of Met-enkephalin. Tseng LF, et al. **Int J Pept Protein Res** 1986 Apr; 27(4):394-7

Immunohistochemical distribution of substance P, serotonin, and methionine enkephalin in sexually dimorphic nuclei of the rat lumbar spinal cord. Micevych PE, et al. **J Comp Neurol** 1986 Jun 8; 248(2):235-44

Effects of hypoxia on neuropeptide levels in the rabbit superior cervical ganglion. Hanson G, et al. **J Neurobiol** 1986 Jan;17(1):51-4

Effects of kelatorphan and other peptidase inhibitors on the in vitro and in vivo release of methionine-enkephalin-like material from the rat spinal cord. Bourgoin S, et al. **J Pharmacol Exp Ther** 1986 Jul; 238(1):360-6

Evidence that long-term methionine-enkephalin administration stimulates rat adrenal zona fasciculata. Robba C, et al. **J Steroid Biochem** 1986 Apr;24(4):917-9

The inactivation of [Met5]-enkephalin by bestatin-sensitive aminopeptidase, captopril-sensitive peptidyl dipeptidase A and thiorphan-sensitive endopeptidase-24.11 in mouse vas deferens. Aoki K, et al. **Jpn J Pharmacol** 1986 Feb;40(2):297-302

Stabilization of methionine-enkephalin in human and rat blood. Aloyo VJ, et al. **Life Sci** 1986 Jul 7;39(1):21-8

Localization of Met-enkephalin-Arg6-Gly7-Leu8 immunoreactivity in rat duodenum. Wolter HJ. **Neuropeptides** 1986 Apr;7(3):201-6

Met-enkephalin selectively increases the spontaneous release of amino acid neurotransmitters from rat striatal slices. Arneric SP, et al. **Neurosci Lett** 1986 May 6;66(1):73-8

Distribution of Met-enkephalin immunoreactive fibres in the thalamus of the cat. Conrath M, et al. **Neurosci Lett** 1986 Apr 24; 65(3):299-303

The glutamate decarboxylase-, leucine enkephalin-, methionine enkephalin- and substance P-immunoreactive neurons in the neostriatum of the rat and cat: evidence for partial population overlap. Penny GR, et al. **Neuroscience** 1986 Apr;17(4):1011-45

Age-dependent influence of hypoxia on methionine-enkephalin concentration within rabbit brainstem nuclei. Gingras-Leatherman JL, et al. **Pediatr Res** 1986 Jul;20(7):655-7

Episodic secretion of met-enkephalin immunoreactive material in human plasma and CSF. Govoni S, et al. **Pharmacol Res Commun** 1986 Feb; 18(2):155-9

The crystal structures of [Met5]enkephalin and a third form of [Leu5]enkephalin: observations of a novel pleated beta-sheet. Griffin JF, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3272-6

Enkephalin contents reflect noradrenergic large dense cored vesicle populations in vasa deferentia. Douglas BH 2d, et al. **Regul Pept** 1986 May;14(3):193-210

Release of immunoreactive met-enkephalin by intraventricular beta-endorphin in anesthetized rats. Tseng LF, et al. **Regul Pept** 1986 May;14(3):181-92

ENKEPHALINS

Light and electron microscope demonstration of VIP- and enkephalin-immunoreactive nerves in the human male genitourinary tract. Vaalasti A, et al. **Anat Rec** 1986 May;215(1):21-7

In vitro activity profiles of cyclic and linear enkephalin pseudopeptide analogs. Edwards JV, et al. **Biochem Biophys Res Commun** 1986 Apr 29;136(2):730-6

Tyr1-substituted and fluorescent Pya1-enkephalins bind strongly and selectively to mu and delta opiate receptors. Mihara H, et al. **Biochem Biophys Res Commun** 1986 May 14;136(3):1170-6

Ultrastructural evidence of dopaminergic input to enkephalinergic neurons in rat neostriatum. Kubota Y, et al. **Brain Res** 1986 Mar 5; 367(1-2):374-8

Enkephalin-containing polypeptides in human cerebrospinal fluid. Nyberg F, et al. **Brain Res** 1986 Apr 23;371(2):278-86

Changes in the immunoreactivities of an opioid peptide leumorphin in the hypothalamus and anterior pituitary during the estrous cycle of the rat and their relation to sexual behavior. Suda M, et al. **Brain Res** 1986 May 28;374(2):236-43

Control mechanisms of peripheral enkephalin hydrolysis in mammalian plasma. Venturelli F, et al. **Comp Biochem Physiol [C]** 1986; 83(2):307-11

Proenkephalin A gene expression in bovine adrenal chromaffin cells is regulated by changes in electrical activity. Kley N, et al. **EMBO J** 1986 May;5(5):967-70

The proenkephalin gene is widely expressed within the male and female reproductive systems of the rat and hamster. Kilpatrick DL, et al. **Endocrinology** 1986 Jul;119(1):370-4

Conversion of leumorphin (dynorphin B-29) to dynorphin B and dynorphin B-14 by thiol protease activity. Devi L, et al. **J Neurochem** 1986 Jul;47(1):154-7

Enkephalin hydrolysis in homogenates of various absorptive mucosae of the albino rabbit: similarities in rates and involvement of aminopeptidases. Kashi SD, et al. **Life Sci** 1986 Jun 2; 38(22):2019-28

Enkephalin-like substance in aplysia nervous tissue and actions of leu-enkephalin on single neurons. Leung MK, et al. **Life Sci** 1986 Apr 21;38(16):1529-34

Use of vaccinia virus as a neuropeptide expression vector. Hruby DE, et al. **Methods Enzymol** 1986;124:295-309

Computationally directed biorational drug design of peptides. Momany FA, et al. **Methods Enzymol** 1986;124:3-18

Methods for estimating the contribution of proenkephalin A and proenkephalin B input to neuronal areas. Sundberg [illegible], et al. **Methods Enzymol** 1986;124:617-26

RIA/chromatographic evidence for novel opioid peptide(s) in Squilla mantis ganglia. Palmisano A, et al. **Neuropeptides** 1986 Apr; 7(3):281-9

Immunocytochemical localization of proenkephalin-derived peptides in the central nervous system of the rat. Merchenthaler I, et al. **Neuroscience** 1986 Feb;17(2):325-48

Opioid and other peptides as inhibitors of leumorphin (dynorphin B-29) converting activity. Devi L, et al. **Peptides** 1986 Jan-Feb;7(1):87-90

Opioid mydriasis: cross-tolerance between morphine and enkephalins. Ben-Am M, et al. **Pharmacology** 1986;32(5):278-82

Expression of proenkephalin messenger RNA by mouse spermatogenic cells. Kilpatrick DL, et al. **Proc Natl Acad Sci USA** 1986 Jul; 83(14):5015-8

Expression and cell type--specific processing of human preproenkephalin with a vaccinia recombinant. Thomas G, et al. **Science** 1986 Jun 27; 232(4758):1641-3

[Enkephalin-forming enzymes (review)] Grigor'iants OO, et al. **Vopr Med Khim** 1986 May-Jun;32(3):15-20 (52 ref.) **(Rus)**

ENURESIS

[Enuresis nocturna in school children in Bodö. A therapeutic trial with a vasopressin analog: desmopressin and imipramine] Holt J, et al. **Tidsskr Nor Laegeforen** 1986 Mar 20;106(8):651-4 (Eng. Abstr.)**(Nor)**

EPHEDRINE

New liquid membrane electrode for the determination of ephedrine, epinephrine, and norepinephrine. Hassan SS, et al. **Anal Chem** 1986 May; 58(6):1052-4

Pharmacological studies of two novel polycyclic derivatives of ephedrine. van der Schyf CJ, et al. **Arch Pharm (Weinheim)** 1986 May; 319(5):409-15

Production of nitrosamines from ephedrine, pseudoephedrine and extracts of Ephedra foliata under physiological conditions. Alwan SM, et al. **Cancer Lett** 1986 May;31(2):221-6

Chiral recognition model for the resolution of ephedrine and related alpha,beta-aminoalcohols as enantiomeric oxazolidine derivatives. Wainer IW, et al. **J Chromatogr** 1986 Mar 14;355(1):149-56

EPINEPHRINE

Renal extraction of endogenous and radiolabelled catecholamines in the dog. Bradley T, et al. **Acta Physiol Scand** 1986 Apr;126(4):505-10

Catecholamines of endoneurial laryngeal paraganglia in the rat. Dahlqvist A, et al. **Acta Physiol Scand** 1986 Jun;127(2):257-61

Binding of catecholamines to phospholipids isolated from adrenal medullary granules. Lishajko F. **Acta Physiol Scand** 1986 Jun; 127(2):177-85

Altered cardiovascular responsiveness to adrenaline in endurance-trained subjects. Svedenhag J, et al. **Acta Physiol Scand** 1986 Apr; 126(4):539-50

Temperature effects on catecholamine accumulation in neuronal and extraneuronal compartments in the cod spleen. Ungell AL. **Acta Physiol Scand** 1986 Apr;126(4):589-92

Inhibitory effects of desmethylimipramine, metanephrine and normetanephrine on the neuronal and extraneuronal accumulation of catecholamines in fish spleen. Ungell AL. **Acta Physiol Scand** 1986 May; 127(1):27-31

Topical anesthesia for laceration repair: tetracaine versus TAC (tetracaine, adrenaline, and cocaine). White WB, et al. **Am J Emerg Med** 1986 Jul; 4(4):319–22

Interaction between epinephrine and renal nerves in control of renin secretion rate. Kopp UC, et al. **Am J Physiol** 1986 Jun; 250(6 Pt 2):F999–1007

Metabolic effects of chronic infusions of epinephrine and norepinephrine in rats. Racotta R, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):E518–22

New liquid membrane electrode for the determination of ephedrine, epinephrine, and norepinephrine. Hassan SS, et al. **Anal Chem** 1986 May; 58(6):1052–4

Monitoring maternal heart rate during epidural injection of a test dose containing epinephrine [letter] Chestnut DH, et al. **Anesthesiology** 1986 Jun;64(6):839–40

On the acceleration of epinephrine absorption by lidocaine [letter] Sosis M, et al. **Anesthesiology** 1986 Jul;65(1):103–4

Induction of refractoriness of cyclic AMP responses to prostaglandin E1 and epinephrine by prior exposure of guinea pig macrophages to lipopolysaccharide. Hazeki K, et al. **Arch Biochem Biophys** 1986 May 1;246(2):772–82

Glucose modulation of memory storage processing. Gold PE. **Behav Neural Biol** 1986 May;45(3):342–9

Epinephrine modulates long-term retention of an aversively motivated discrimination. Introini-Collison IB, et al. **Behav Neural Biol** 1986 May; 45(3):358–65

Comparative responses of the central adrenaline- and noradrenaline-containing neurons after reserpine injections. Lambás-Señas L, et al. **Biochem Pharmacol** 1986 Jul 1; 35(13):2207–11

Homologous and heterologous desensitization of one of the pathways of the alpha 1-adrenergic action. Effects of epinephrine, vasopressin, angiotensin II and phorbol 12-myristate 13-acetate. Garcia-Sáinz JA, et al. **Biochim Biophys Acta** 1986 Jun 16;887(1):73–9

Phorbol esters, vasopressin and angiotensin II block alpha 1-adrenergic action in rat hepatocytes. Possible role of protein kinase C. Garcia-Sáinz JA, et al. **Biochim Biophys Acta** 1986 Jun 16;887(1):69–72

Oxygen tension changes in the outer vascular wall supplied by vasa vasorum following adenosine and epinephrine. Buerk DG, et al. **Blood Vessels** 1986;23(1):9–21

Extradural morphine: influence of adrenaline admixture. Nordberg G, et al. **Br J Anaesth** 1986 Jun;58(6):598–604

Effects of i.a. lignocaine on adrenaline-induced vasoconstriction. Pateromichelakis S, et al. **Br J Anaesth** 1986 Jun;58(6):649–52

Comparison of the effects of the ionophore salinomycin and adrenaline on the haemodynamics and work efficiency of the dog heart. Fahim M, et al. **Cardiovasc Res** 1986 Feb;20(2):145–52

Reduced imprecision of the radioenzymatic assay of plasma catecholamines by improving the stability of the internal standards. Hoffmann JJ, et al. **Clin Chim Acta** 1986 Apr 30;156(2):221–5

Effects of histamine receptor antagonism on adrenaline-induced changes in blood pressure in intact dogs. Johnson MD, et al. **Clin Exp Pharmacol Physiol** 1985 Nov–Dec;12(6):557–64

Comparison of the inhibitory effects of spermine, papaverine and adrenaline upon isolated segments of the rat small intestine. Martin JS, et al. **Clin Exp Pharmacol Physiol** 1986 Jan;13(1):87–90

Stimulus-induced release of endogenous catecholamines from human washed platelets. Smith CC, et al. **Clin Sci** 1986 May;70(5):495–500

Ventilatory effects of the stress hormones in normal man. Askanazi J, et al. **Crit Care Med** 1986 Jul;14(7):602–5

Responses to epinephrine in patients with anorexia nervosa. Nakagawa K, et al. **Endocrinol Jpn** 1985 Dec;32(6):845–9

Effects of epinephrine, norepinephrine, and dopamine on gonadotropin-releasing hormone-induced secretion of luteinizing hormone in vitro. Swartz SR, et al. **Endocrinology** 1986 Jun; 118(6):2425–31

Sex-related differences in free plasma catecholamines in individuals of similar performance ability during graded ergometric exercise. Lehmann M, et al. **Eur J Appl Physiol** 1986;55(1):54–8

Labelling of human platelet alpha 2-adrenoceptors with the full agonist [3H](-)adrenaline. Garcia-Sevilla JA, et al. **Eur J Pharmacol** 1986 May 13;124(1–2):31–41

Inactivation of basal glycogen synthase by glucagon and epinephrine in hepatocytes from fed rats. Bosch F, et al. **FEBS Lett** 1986 May 5; 200(1):47–50

A suppressive role of c-kinase for the stimulation of hepatic ketogenesis by glucagon and epinephrine. Kojima H, et al. **FEBS Lett** 1986 Jun 9;201(2):271–6

Effect of different beta-blocking drugs and adrenaline on the conversion of thyroxine to triiodothyronine in isolated rat hepatocytes. Aanderud S, et al. **Horm Metab Res** 1986 Feb;18(2):110–3

Relationship between sleep variables and urinary excretion of adrenaline in nocturnal sleep. Nishihara K, et al. **Ind Health** 1985;23(4):279–82

Butyltin compounds in vitro inhibition of human platelet epinephrine-induced aggregation and blockade of epinephrine binding to platelets. Yanagisawa H, et al. **Ind Health** 1985;23(4):255–68

Interaction of epinephrine and propranolol [letter] Spencer PS, et al. **J Am Acad Dermatol** 1986 Jun;14(6):1093–4

The effects of intrathecal administration of arginine-vasopressin and substance P on blood pressure and adrenal secretion of epinephrine in rats. Riphagen CL, et al. **J Auton Nerv Syst** 1986 Jun;16(2):91–9

Platelet ADP receptor and alpha 2-adrenoreceptor interaction. Evidence for an ADP requirement for epinephrine-induced platelet activation and an influence of epinephrine on ADP binding. Figures WR, et al. **J Biol Chem** 1986 May 5;261(13):5981–6

Catecholamines induce an increase in nerve growth factor content in the medium of mouse L-M cells. Furukawa Y, et al. **J Biol Chem** 1986 May 5;261(13):6039–47

Inhibitors of Na+/H+ exchange block epinephrine- and ADP-induced stimulation of human platelet phospholipase C by blockade of arachidonic acid release at a prior step. Sweatt JD, et al. **J Biol Chem** 1986 Jul 5;261(19):8660–6

Distribution of tyrosine hydroxylase and neuropeptide Y-like immunoreactive neurons in rabbit medulla oblongata, with attention to colocalization studies, presumptive adrenaline-synthesizing perikarya, and vagal preganglionic cells. Blessing WW, et al. **J Comp Neurol** 1986 Jun 8;248(2):285–300

Effect of chronic growth hormone treatment on responses to epinephrine and thyrotropin-releasing hormone in lactating cows. McCutcheon SN, et al. **J Dairy Sci** 1986 Jan;69(1):44–51

Mechanism of long-term potentiation of transmitter release induced by adrenaline in bullfrog sympathetic ganglia. Kumamoto E, et al. **J Gen Physiol** 1986 May;87(5):775–93

Effects of intravenous epinephrine on macaque platelets. Beatty CH, et al. **J Med Primatol** 1986;15(1):49–61

Low plasma concentrations of adrenaline and physiological tremor in man. Fellows IW, et al. **J Neurol Neurosurg Psychiatry** 1986 Apr; 49(4):396–9

Effects of epinephrine, isoproterenol and IPS-339 on sympathetic transmission to the dog heart: evidence against the facilitatory role of presynaptic beta adrenoceptors. Yorikane R, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):334–40

Administration of intratracheal epinephrine by cricothyroid needle puncture [letter] Ravenel SD. **JAMA** 1986 Jun 6;255(21):2898–9

Effect of epinephrine infusion and adrenergic blockade on glucose oxidation in conscious dogs. Wolfe RR, et al. **Metabolism** 1986 Jul; 35(7):673–8

Effects of epinephrine on electrical properties of Madin-Darby canine kidney cells. Paulmichl M, et al. **Pflugers Arch** 1986 Apr; 406(4):367–71

[Intra-chamber adrenaline infusion in the extracapsular surgery of the lens. Value and limitations of the method] Dupeyron G, et al. **Bull Soc Ophtalmol Fr** 1985 May;85(5):631–4 **(Fre)**

[The stability of commercial adrenaline solutions. 3. The stability of adrenaline solutions] Thoma K, et al. **Pharm Acta Helv** 1986; 61(3):66–8 (Eng. Abstr.) **(Ger)**

[Sexual dimorphism in the pressor response to l-adrenaline in rats] Tomori M, et al. **Nippon Yakurigaku Zasshi** 1986 Mar;87(3):323–9 (Eng. Abstr.) **(Jpn)**

[Effect of continuous, intermittent and impulse acoustic stimuli on plasma catecholamine levels in humans at rest and during physical exertion] Buczyński A, et al. **Pol Tyg Lek** 1986 Jan 27;41(4):110–3 (Eng. Abstr.) **(Pol)**

[Role of adrenergic receptors in the regulation of glycogen metabolism in the liver] Torlińska T, et al. **Postepy Hig Med Dosw** 1985 Sep–Oct; 39(5):561–77 (75 ref.) (Eng. Abstr.) **(Pol)**

[Changes in blood volume in the heart and lungs and its role in the regulation of left-ventricular blood output after administration of catecholamines] Osadchil LI, et al. **Fiziol Zh** 1986 Mar–Apr; 32(2):149–54 (Eng. Abstr.) **(Rus)**

[Activity of presynaptic alpha-adrenoreceptors during prolonged perfusion with adrenaline] Berdysheva LV, et al. **Fiziol Zh SSSR** 1986 May;72(5):590–4 (Eng. Abstr.) **(Rus)**

[Circadian curve of adrenaline excretion as an indicator of the functional status of the body] Kuindzhi NN, et al. **Gig Sanit** 1986 Mar; (3):60–3 **(Rus)**

[Effect of adrenaline, hydrocortisone and serum HDL lipoproteins on the activity of multiple forms of glucose-6-phosphate dehydrogenase in the rat liver] Panin LE, et al. **Vopr Med Khim** 1986 May–Jun; 32(3):61–5 (Eng. Abstr.) **(Rus)**

ESCAPE REACTION

5,7-Dihydroxytryptamine lesions of crayfish serotonin-containing neurons: effect on the lateral giant escape reaction. Glanzman DL, et al. **J Neurosci** 1986 Jun;6(6):1560–9

ESTRADIOL

The effect of oestriol and tamoxifen on oestradiol induced prolactin secretion in anaesthetised rats. Gilna P, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):71–8

Biochemical and radioautographic analysis of estrogen-inducible progestin receptors in female ferret brain and pituitary: correlations with effects of progesterone on sexual behavior and gonadotropin-releasing hormone-stimulated secretion of luteinizing hormone. Baum MJ, et al. **Brain Res** 1986 Mar 19;368(2):296-309

Analysis of temporal and dose-dependent effects of estrogen on monoamines in brain nuclei. Renner K, et al. **Brain Res** 1986 Feb 26; 366(1-2):64-71

Modulation of the estradiol-induced luteinizing hormone surge by progesterone or antiestrogens: effects on pituitary gonadotropin-releasing hormone receptors. Attardi B, et al. **Endocrinology** 1986 Jul;119(1):274-83

The effect of oestradiolum benzoicum and progesterone on the noradrenalin content in organs of the female reproductive system of sexually immature pigs. Lakomy M, et al. **Gegenbaurs Morphol Jahrb** 1986;132(1):129-43

Anterior pituitary concentrations of gonadotropins, GnRH-receptors and ovarian characteristics following early weaning in beef cows. Parfet JR, et al. **J Anim Sci** 1986 Mar;62(3):717-22

Pituitary self-priming actions of gonadotropin-releasing hormone. Kinetics of estradiol's potentiating effects on gonadotropin-releasing hormone-facilitated luteinizing hormone and follicle-stimulating hormone release in healthy postmenopausal women. Veldhuis JD, et al. **J Clin Invest** 1986 Jun;77(6):1849-56

Central adrenergic activity in the mediobasal hypothalamus is temporally related to surge outputs of gonadotrophins in oestrogen-stimulated infant female rats. Clement EM, et al. **J Endocrinol** 1986 Apr; 109(1):45-5

Influence of subcutaneous melatonin implantation on gonadal development and on plasma levels of luteinizing hormone, testosterone, estradiol, and corticosterone in the pigeon. John TM, et al. **J Pineal Res** 1986;3(2):169-79

Activation-inactivation of hormone binding sites of the oestradiol-17 beta receptor is a multiregulated process. Auricchio F, et al. **J Steroid Biochem** 1986 Jan;24(1):39-43

Effects of estradiol and progesterone on immunoreactive forms of hypothalamic luteinizing hormone-releasing hormone. Drouva SV, et al. **Neuroendocrinology** 1986;43(1):32-7

Activation of estradiol-positive feedback at puberty: estradiol sensitizes the LHRH-releasing system at two different biochemical steps. Ojeda SR, et al. **Neuroendocrinology** 1986;43(2):259-65

Estradiol target sites immunoreactive for beta-endorphin in the arcuate nucleus of rat and mouse hypothalamus. Jirikowski GF, et al. **Neurosci Lett** 1986 Apr 11;65(2):121-6

[Preliminary study in female rats of the immunoregulatory effect of estradiol, progesterone and pituitary prolactin on natural killer-like cell mediated cytotoxic activity] Mohammad M, et al. **Ann Endocrinol (Paris)** 1985;46(6):415-9 (Eng. Abstr.) **(Fre)**

EUPHORIA

Does placebo response mediate runner's high? Hinton ER, et al. **Percept Mot Skills** 1986 Jun;62(3):789-90

EXPLORATORY BEHAVIOR

The inhibition of the cage-leaving response—a model for studies of the serotonergic neurotransmission in the rat. Rényi L, et al. **J Neural Transm** 1986;65(3-4):193-210

Sensation seeking, paired associate learning and brain catecholamines. Kulcsár Z, et al. **Neuropsychobiology** 1986;15(1):43-8

EXTINCTION (PSYCHOLOGY)

Effects of pimozide on appetitive behavior and locomotor activity: dissimilarity of effects when compared to extinction. Spivak KJ, et al. **Physiol Behav** 1986;36(3):457-63

FEAR

How antipanic drugs might work [letter] Nesse RM, et al. **Am J Psychiatry** 1986 Jul;143(7):945

Synergistic action of alprazolam with tranylcypromine in drug-resistant atypical depression with panic attacks. Ries RK, et al. **Biol Psychiatry** 1986 May;21(5-6):522-6

Hypochondriacal fears and beliefs in DSM-III melancholia. Changes with amitriptyline. Kellner R, et al. **J Affective Disord** 1986 Jan-Feb; 10(1):21-6

Pharmacokinetics and clinical effects of alprazolam following single and multiple oral doses in patients with panic disorder. Ciraulo DA, et al. **J Clin Pharmacol** 1986 Apr;26(4):292-8

Alprazolam treatment for panic disorders. Alexander PE, et al. **J Clin Psychiatry** 1986 Jun;47(6):301-4

Pharmacotherapy of the panic disorders. Ballenger JC. **J Clin Psychiatry** 1986 Jun;47 Suppl:27-32 (55 ref.)

Nonsteroidal anti-inflammatory drugs and panic disorder [letter] Goldstein JA. **J Clin Psychiatry** 1986 May;47(5):277

Pharmacotherapeutic considerations in anxiety disorders. Hollister LE. **J Clin Psychiatry** 1986 Jun;47 Suppl:33-6 (21 ref.)

Current trends in clinical research on panic attacks, agoraphobia, and related anxiety disorders. Klerman GL. **J Clin Psychiatry** 1986 Jun; 47 Suppl:37-9 (10 ref.)

Treatment of panic disorder and agoraphobia with clonazepam. Spier SA, et al. **J Clin Psychiatry** 1986 May;47(5):238-42

Clonazepam in the treatment of panic disorder [letter] Judd FK, et al. **Med J Aust** 1986 Jul 7;145(1):59

The design and conduct of the Upjohn Cross-National Collaborative Panic Study. Klerman GL, et al. **Psychopharmacol Bull** 1986; 22(1):59-64

Taper withdrawal studies with alprazolam in patients with panic disorder and agoraphobia. Pecknold JC, et al. **Psychopharmacol Bull** 1986; 22(1):173-6

Benzodiazepines for treatment of panic attacks: a new look. Rickels K, et al. **Psychopharmacol Bull** 1986;22(1):93-9

A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. Rizley R, et al. **Psychopharmacol Bull** 1986;22(1):167-72

[Psychopharmacology of panic attacks] Dugas M, et al. **Ann Med Interne (Paris)** 1986;137(2):152-4 (Eng. Abstr.) **(Fre)**

[Rapid response of a disorder to the addition of lithium carbonate: panic resistant to tricyclic antidepressants] Cournoyer J. **Can J Psychiatry** 1986 May;31(4):335-8 (Eng. Abstr.) **(Fre)**

FENFLURAMINE

Inhibition of gastric emptying and feeding by fenfluramine. Robinson PH, et al. **Am J Physiol** 1986 May;250(5 Pt 2):R764-9

Effects of fenfluramine on eight outpatients with the syndrome of autism. Stubbs EG, et al. **Dev Med Child Neurol** 1986 Apr;28(2):229-35

Side effects of fenfluramine in autistic children. Piggott LR, et al. **J Am Acad Child Psychiatry** 1986 Mar;25(2):287-9

Amphetamine-induced anorexia: analysis with hypothalamic lesions and knife cuts. McCabe JT, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):1047-56

Short-term efficacy and safety of fenfluramine in hospitalized preschool-age autistic children: an open study. Campbell M, et al. **Psychopharmacol Bull** 1986;22(1):141-7

Fenfluramine treatment of childhood attention deficit disorder with hyperactivity: a preliminary report. Donnelly M, et al. **Psychopharmacol Bull** 1986;22(1):152-4

The effects of fenfluramine on suicidal behavior. Meyendorff E, et al. **Psychopharmacol Bull** 1986;22(1):155-9

Fenfluramine treatment of autism: UCLA collaborative study of 81 patients at nine medical centers. Ritvo ER, et al. **Psychopharmacol Bull** 1986;22(1):133-40

The discriminative stimulus and subjective effects of d-amphetamine, phenmetrazine and fenfluramine in humans. Chait LD, et al. **Psychopharmacology (Berlin)** 1986;89(3):301-6

Dissociation of the anorectic actions of 5-HTP and fenfluramine. Fletcher PJ, et al. **Psychopharmacology (Berlin)** 1986;89(2):216-20

[New indications for fenfluramine (letter)] De Villard R, et al. **Presse Med** 1986 Apr 5;15(14):668 **(Fre)**

FLUPHENAZINE

Longitudinal measurement of plasma homovanillic acid levels in schizophrenic patients. Correlation with psychosis and response to neuroleptic treatment. Pickar D, et al. **Arch Gen Psychiatry** 1986 Jul; 43(7):669-76

Relapse in chronic schizophrenics treated with fluphenazine decanoate is associated with low serum neuroleptic levels. Jayaram G, et al. **J Clin Psychiatry** 1986 May;47(5):247-8

Plasma fluphenazine levels in patients receiving two doses of fluphenazine decanoate. Marder SR, et al. **Psychopharmacol Bull** 1986;22(1):264-6

Fluphenazine plasma levels in patients receiving low and conventional doses of fluphenazine decanoate. Marder SR, et al. **Psychopharmacology (Berlin)** 1986;88(4):480-3

Flupenthixol decanoate and fluphenazine decanoate in chronic schizophrenia. Kong DS, et al. **Singapore Med J** 1985 Dec; 26(7):551-5

[Use of fluphenazine decanoate in psychiatric therapy. Multicenter study in 1095 patients preselected for long-acting neuroleptic treatment] Bogliolo C. **Minerva Psichiatr** 1986 Jan-Mar;27(1):1-18 **(Ita)**

[Children and travel to the South. Risk for drug intoxication (letter)] Haugen T, et al. **Tidsskr Nor Laegeforen** 1986 Apr 30;106(11):974 **(Nor)**

FLURAZEPAM

Peptide derivatives as prodrugs. Thomas WA. **Biochem Soc Trans** 1986 Apr;14(2):383-7

The inhibitory effect of endogenous convulsants quinolinic acid and kynurenine on the pentobarbital stimulation of [3H]flunitrazepam binding. Zarkovsky AM. **Pharmacol Biochem Behav** 1986 May; 24(5):1215-7

FOOD DEPRIVATION

6-Hydroxydopamine and excitotoxin lesions of medial prefrontal cortex fail to affect schedule-induced drinking in the rat. Christie MJ, et al. **Behav Brain Res** 1986 Feb;19(2):183-6

Food-restricted, prepubertal, female rats: rapid recovery of luteinizing hormone pulsing with excess food, and full recovery of pubertal development with gonadotropin-releasing hormone. Bronson FH. **Endocrinology** 1986 Jun;118(6):2483-7

FSH

Can neonatal treatment with a related hormone adapt the receptor for itself? Csaba G, et al. **Acta Physiol Hung** 1986;67(1):65-9

Selective reduction of elevated FSH levels in infertile men by pulsatile LHRH treatment. Hönigl W, et al. **Clin Endocrinol (Oxf)** 1986 Feb; 24(2):177-82

Episodic patterns of luteinizing hormone and follicle-stimulating hormone release: differential secretory dynamics and adrenergic control in ovariectomized rats. Condon TP, et al. **Endocrinology** 1986 Jun; 118(6):2525-33

Adrenocorticotropin-induced changes in ovine pituitary gonadotropin secretion in vitro. Matteri RL, et al. **Endocrinology** 1986 May; 118(5):2091-6

Luteinizing hormone and follicle-stimulating hormone responses to intranasal gonadotropin-releasing hormone. Rajfer J, et al. **Fertil Steril** 1986 Jun;45(6):794-9

Single dose responses to the gonadotropin-releasing hormone agonist analogue [(imBz 1)-D-His6,Pro9-NEt]GnRH. Doelle GC, et al. **Horm Metab Res** 1986 Mar;18(3):201-2

Anterior pituitary concentrations of gonadotropins, GnRH-receptors and ovarian characteristics following early weaning in beef cows. Parfet JR, et al. **J Anim Sci** 1986 Mar;62(3):717-22

Pulsatile or continuous infusion of luteinizing hormone-releasing hormone and hormonal concentrations in prepubertal beef heifers. Skaggs CL, et al. **J Anim Sci** 1986 Apr;62(4):1034-48

Effects of intermittent injections of LHRH on secretory patterns of LH and FSH and ovarian follicular growth during postpartum anovulation in suckled beef cows. Spicer LJ, et al. **J Anim Sci** 1986 May; 62(5):1317-23

Single subcutaneous doses of a luteinizing hormone-releasing hormone antagonist suppress serum gonadotropin and testosterone levels in normal men. Pavlou SN, et al. **J Clin Endocrinol Metab** 1986 Aug; 63(2):303-8

Pituitary self-priming actions of gonadotropin-releasing hormone. Kinetics of estradiol's potentiating effects on gonadotropin-releasing hormone-facilitated luteinizing hormone and follicle-stimulating hormone release in healthy postmenopausal women. Veldhuis JD, et al. **J Clin Invest** 1986 Jun;77(6):1849-56

Ontogeny of serum and pituitary gonadotrophins in male rats treated with low doses of 5 alpha-dihydrotestosterone. Karanth S, et al. **J Endocrinol** 1986 Mar;108(3):369-75

Varying the patterns and concentrations of gonadotrophin-releasing hormone stimulation does not alter the ratio of LH and FSH released from perifused sheep pituitary cells. McIntosh JE, et al. **J Endocrinol** 1986 May;109(2):155-61

Timing of multiple ovulations in the ewe after treatment with FSH or PMSG with and without GnRH. Walker SK, et al. **J Reprod Fertil** 1986 May;77(1):135-42

Steroid regulation of gonadotropins in genetically hypoprolactinemic females (IPL nude rats). Cohen H, et al. **J Steroid Biochem** 1986 Jan; 24(1):431-5

Immunohistochemical localization of follicle-stimulating hormone, luteinizing hormone, growth hormone, adrenocorticotrophic hormone and prolactin in the human placenta. Al-Timimi A, et al. **Placenta** 1986 Mar-Apr;7(2):163-72

Effect of atrial natriuretic peptide on gonadotropin release in superfused rat pituitary cells. Horvath J, et al. **Proc Natl Acad Sci USA** 1986 May; 83(10):3444-6

[Effect of tyrosine on serum concentrations of LH, FSH and testosterone in adult men] Ni J, et al. **Sheng Li Hsueh Pao** 1985 Jun;37(3):303-6 (Eng. Abstr.) **(Chi)**

[The effect of synthetic chicken LH-RH on the release of LH and FSH and ovulation in rats (a comparative study of synthetic mammalian LH-RH and chicken LH-RH)] Takahashi Y, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Feb 20;62(2):126-39 (Eng. Abstr.) **(Jpn)**

GABA

Lack of involvement of GABA in baroreceptor-mediated sympathoinhibition. McCall RB. **Am J Physiol** 1986 Jun; 250(6 Pt 2):R1065-73

Reversible depression of ventilation and cardiovascular function by ventriculocisternal perfusion with gamma-aminobutyric acid in dogs. Kneussl MP, et al. **Am Rev Respir Dis** 1986 Jun;133(6):1024-8

Changes in gamma-aminobutyric acid biochemistry and seizure threshold. Green AR. **Ann NY Acad Sci** 1986;462:105-19 (29 ref.)

Gamma aminobutyric acid mediates ventromedial hypothalamic mechanisms controlling the execution of lordotic responses in the female rat. Mascó D, et al. **Behav Brain Res** 1986 Feb;19(2):153-62

Differential effects of dorsal raphe lesions and intraraphe GABA and benzodiazepines on conflict behavior in rats. Green S, et al. **Behav Neural Biol** 1986 Jul;46(1):13-29

Anti-convulsant effects of manipulation of brain 4-aminobutyrate concentrations by selective enzyme inhibition. John RA, et al. **Biochem Soc Trans** 1986 Apr;14(2):408-10

A GABA-activated chloride-conductance not blocked by picrotoxin on spiny lobster neuromuscular preparations. Albert J, et al. **Br J Pharmacol** 1986 Apr;87(4):771-9

Loss of inhibition in the CA1 region of the kainic acid lesioned hippocampus is not associated with changes in postsynaptic responses to GABA. Ashwood TJ, et al. **Brain Res** 1986 Mar 5; 367(1-2):390-4

Effects of D-aspartate on excitatory amino acid-induced release of [3H]GABA from goldfish retina. Cha JH, et al. **Brain Res** 1986 Jun 18;376(1):140-8

Interactions between dopamine and amino acid-induced excitation and inhibition in the striatum. Chiodo LA, et al. **Brain Res** 1986 Jun 4; 375(1):198-203

gamma-Aminobutyric acid immunoreactivity in mouse barrel field: a light microscopical study. Chmielowska J, et al. **Brain Res** 1986 Mar 19; 368(2):371-4

Nipecotic acid, an uptake blocker, prevents fading of the gamma-aminobutyric acid effect. Dalkara T. **Brain Res** 1986 Feb 26; 366(1-2):314-9

Elicitation of intraspecific defensive behaviors in the rat by microinjection of picrotoxin, a gamma-aminobutyric acid antagonist, into the midbrain periaqueductal gray matter. Depaulis A, et al. **Brain Res** 1986 Mar 5; 367(1-2):87-95

GABA visualized by immunocytochemistry in the guinea pig cochlea in axons and endings of efferent neurons. Fex J, et al. **Brain Res** 1986 Feb 26;366(1-2):106-17

GABA and serotonin (5-HT) pattern in the supraependymal fibers of the rat epithalamus: combined radioautographic and immunocytochemical studies. Effect of 5-HT content on [3H]GABA accumulation. Harandi M, et al. **Brain Res** 1986 Apr 9;370(2):241-9

Inhibition of GABA uptake in the rat hippocampal slice. Korn SJ, et al. **Brain Res** 1986 Mar 19;368(2):247-55

Immunohistochemical demonstration of GABA containing neurons in the guinea pig ileum using purified GABA antiserum. Saito N, et al. **Brain Res** 1986 Jun 18;376(1):78-84

GABA imbalance in squirrel monkey after unilateral vestibular end-organ ablation. Thompson GC, et al. **Brain Res** 1986 Apr 2;370(1):182-5

GABA-like immunoreactivity in the squirrel monkey organ of Corti. Thompson GC, et al. **Brain Res** 1986 Apr 30;372(1):72-9

GABA in the PNS: demonstration in enteric neurons. Baetge G, et al. **Brain Res Bull** 1986 Mar;16(3):421-4

Optic nerve stimulation-induced increase of release of 3H-glutamate and 3H-aspartate but not 3H-GABA from the suprachiasmatic nucleus in slices of rat hypothalamus. Liou SY, et al. **Brain Res Bull** 1986 Apr; 16(4):527-31

Pharmacological evaluation of GABAergic and glutamatergic inputs to the nucleus basalis--cortical and the septal-hippocampal cholinergic projections. Wood PL. **Can J Physiol Pharmacol** 1986 Mar; 64(3):325-8

gamma-Aminobutyric acid (GABA) removal from the synaptic cleft: a postsynaptic event? Cupello A, et al. **Cell Mol Neurobiol** 1986 Mar; 6(1):1-16

The occurrence of gamma-aminobutyric acid (GABA)-containing cells in cultures of retinas from the human fetus. Osborne NN, et al. **Cell Mol Neurobiol** 1986 Mar;6(1):87-93

Light- and electron-microscopic visualization of gamma-aminobutyric acid and GABA-transaminase in the oviduct of rats. Predominant occurrence in epithelium. Erdö SL, et al. **Cell Tissue Res** 1986; 244(3):621-6

Immunocytochemistry of GABA in the antennal lobes of the sphinx moth Manduca sexta. Hoskins SG, et al. **Cell Tissue Res** 1986; 244(2):243-52

Cultured neurons as model systems for biochemical and pharmacological studies on receptors for neurotransmitter amino acids. Schousboe A, et al. **Dev Neurosci** 1985;7(5-6):252-62 (56 ref.)

Anisotropic inhibition in the receptive field surround of the frog retinal ganglion cells, evidenced by bicuculline and SR 95103, a new GABA antagonist. Bonaventure N, et al. **Eur J Pharmacol** 1986 Mar 4; 121(3):327-36

Effect of GABAergic drugs in the behavioral 'despair' test in rats. Borsini F, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):265-8

Spontaneous paroxysmal activity induced by zero magnesium and bicuculline: suppression by NMDA antagonists and GABA mimetics. Horne AL, et al. **Eur J Pharmacol** 1986 Mar 18;122(2):231-8

Pharmacological evidence that at least two different non-adrenergic non-cholinergic inhibitory systems are present in the rat small intestine.

Manzini S, et al. **Eur J Pharmacol** 1986 Apr 16;123(2):229–36

The effect of apomorphine and pergolide on the potassium–evoked overflow of GABA in rat striatum studied by microdialysis. Tossman U, et al. **Eur J Pharmacol** 1986 Apr 16;123(2):295–8

Experimental neuropathy induced by methyl mercury compounds: autoradiographic study of GABA uptake by dorsal root ganglia. Kumamoto T, et al. **Eur Neurol** 1986;25(4):269–77

GABA–like immunoreactivity in the vertebrate retina: a species comparison. Mosinger JL, et al. **Exp Eye Res** 1986 Jun;42(6):631–44

GABA–induced hypothermia in rats: involvement of serotonergic and cholinergic mechanisms. Serrano JS, et al. **Gen Pharmacol** 1986; 17(3):327–32

Insect optic lobe neurons identifiable with monoclonal antibodies to GABA. Meyer EP, et al. **Histochemistry** 1986;84(3):207–16

Control of rat gastric somatostatin release by gamma–aminobutyric acid (GABA). Koop H, et al. **Horm Metab Res** 1986 Feb;18(2):94–7

GABA immunoreactivity in the retina. Agardh E, et al. **Invest Ophthalmol Vis Sci** 1986 May;27(5):674–8

Distribution of gamma–aminobutyric acid–immunoreactive neurons in the septal region of the rat brain. Onteniente B, et al. **J Comp Neurol** 1986 Jun 15;248(3):422–30

Distribution of GABA–like immunoreactivity in the brain of the honeybee. Schäfer S, et al. **J Comp Neurol** 1986 Apr 15; 246(3):287–300

Presence of gamma–aminobutyric acid in embryonic palates of AJ and SWV mouse strains. Wee EL, et al. **J Craniofac Genet Dev Biol** 1986; 6(1):53–61

Inter– and intracellular relationship of substance P–containing neurons with serotonin and GABA in the dorsal raphe nucleus: combination of autoradiographic and immunocytochemical techniques. Mâgoul R, et al. **J Histochem Cytochem** 1986 Jun;34(6):735–42

4–Amino–2–(substituted methyl)–2–butenoic acids: substrates and potent inhibitors of gamma–aminobutyric acid aminotransferase. Silverman RB, et al. **J Med Chem** 1986 May;29(5):764–70

Studies on analogues of succinic semialdehyde as substrates for succinate semialdehyde dehydrogenase from rat brain. Manzocchi A, et al. **J Neurochem** 1986 Jun;46(6):1895–8

Spontaneous release of gamma–aminobutyric acid formed from putrescine and its enhanced Ca2+–dependent release by high K+ stimulation in the brains of freely moving rats. Noto T, et al. **J Neurochem** 1986 Jun; 46(6):1877–80

Effect of early iron deficiency in rat on the gamma–aminobutyric acid shunt in brain. Taneja V, et al. **J Neurochem** 1986 Jun;46(6):1670–4

Immunohistochemical demonstration of GABAergic neurons in the enteric nervous system. Jessen KR, et al. **J Neurosci** 1986 Jun; 6(6):1628–34

The rat ventromedial thalamic nucleus and motor control: role of N–methyl–D–aspartate–mediated excitation, GABAergic inhibition, and muscarinic transmission. Klockgether T, et al. **J Neurosci** 1986 Jun; 6(6):1702–11

In–vitro release of [14C]glutamate from dentate gyrus is modulated by GABA. Spencer P, et al. **J Pharm Pharmacol** 1986 May;38(5):393–5

Effects of insecticides on GABA–induced chloride influx into rat brain microsacs. Abalis IM, et al. **J Toxicol Environ Health** 1986; 18(1):13–23

Synthesis of radioactive (–)–carnitine from gamma–aminobutyrate. Pande SV. **Methods Enzymol** 1986;123:297–302

Reduction in number of immunostained GABAergic neurones in deprived–eye dominance columns of monkey area 17. Hendry SH, et al. **Nature** 1986 Apr 24–30;320(6064):750–3

GABA and GAD immunoreactivity of photoreceptor terminals in primate retina. Nishimura Y, et al. **Nature** 1986 Apr 24–30;320(6064):753–6

Neurochemistry. Is GABA the neurotransmitter for some photoreceptors? [news] Yazulla S. **Nature** 1986 Apr 24–30;320(6064):685–6

Acute and chronic effects of lithium chloride on GABA–ergic function in the rat corpus striatum and frontal cerebral cortex. Otero Losada ME, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Feb; 332(2):169–72

Asymmetric diffusion into the postsynaptic neuron: an extremely efficient mechanism for removing excess GABA from synaptic clefts on the Deiters' neurone plasma membrane. Hyden H, et al. **Neurochem Res** 1986 May;11(5):695–706

Changes in gamma–aminobutyric acid high affinity binding to cerebral cortex membranes after pinealectomy or melatonin administration to rats. Castroviejo DA, et al. **Neuroendocrinology** 1986;43(1):24–31

Evidence for estrogen–receptive GABAergic neurons in the preoptic/anterior hypothalamic area of the rat brain. Flügge G, et al. **Neuroendocrinology** 1986;43(1):1–5

Pipecolic acid enhancement of GABA response in single neurons of rat brain. Takahama K, et al. **Neuropharmacology** 1986 Mar;25(3):339–42

Pharmacological modulation of GABAergic transmission in cultured cerebellar neurons. Vicini S, et al. **Neuropharmacology** 1986 Feb; 25(2):207–11

GABA receptor binding in rat cerebral cortex and superior cervical ganglion in the absence of GABAergic synapses. Balcar VJ, et al. **Neurosci Lett** 1986 May 23;66(3):269–74

Ion channels activated by acetylcholine and gamma–aminobutyric acid in freshly dissociated sympathetic neurones of the rat. Cull–Candy SG, et al. **Neurosci Lett** 1986 May 23;66(3):275–80

Synapses between GABA–immunoreactive axonal and dendritic elements in monkey substantia nigra. Holstein GR, et al. **Neurosci Lett** 1986 May 23;66(3):316–22

gamma–Aminobutyric acid–dependent motility induced by avermectin B1a in the isolated intestine of the guinea pig. Kerr DI, et al. **Neurosci Lett** 1986 Mar 28;65(1):7–10

GABAergic neurons in the cerebral cortex of the brain of a lizard (Podarcis hispanica). Schwerdtfeger WK, et al. **Neurosci Lett** 1986 Jul 11;68(1):117–21

Calcium–independent release of gamma–aminobutyrate from nerve processes in the developing rabbit retina. Jönsson U, et al. **Neuroscience** 1986 Apr;17(4):1235–41

Gamma–aminobutyrate, gastrin releasing peptide, serotonin, somatostatin, and vasopressin: ultrastructural immunocytochemical localization in presynaptic axons in the suprachiasmatic nucleus. van den Pol AN. **Neuroscience** 1986 Mar;17(3):643–59

Lordosis behavior and GABAergic neurotransmission. Fernández–Guasti A, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):673–6

GABAergic control of masculine sexual behavior. Fernández–Guasti A, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1065–70

Effects of the potentiation of the GABAergic neurotransmission in the olfactory bulbs on mouse–killing behavior. Molina V, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):657–64

Activity of biotin–dependent and GABA metabolizing enzymes in chorionic villus samples: potential for 1st trimester prenatal diagnosis. Sweetman FR, et al. **Prenat Diagn** 1986 May–Jun;6(3):187–94

L–glutamic acid, a neurotrophic factor for maintenance of acetylcholinesterase and butyrylcholinesterase in the preganglionically denervated superior cervical ganglion of the cat. Koelle GB, et al. **Proc Natl Acad Sci USA** 1986 Apr;83(8):2751–4

Possible involvement of low and high affinity GABA receptors in the chloride influx into synaptosomes. Sánchez C, et al. **Rev Esp Fisiol** 1986 Mar;42(1):1–5

Brain glutamate decarboxylase cloned in lambda gt–11: fusion protein produces gamma–aminobutyric acid. Kaufman DL, et al. **Science** 1986 May 30;232(4754):1138–40

The role of chloride transport in postsynaptic inhibition of hippocampal neurons. Misgeld U, et al. **Science** 1986 Jun 13;232(4756):1413–5

[Role of gamma–aminobutyric acid in the process of catecholamine secretion from the adrenal medulla] Kitayama S. **Hiroshima Daigaku Shigaku Zasshi** 1985 Jun;17(1):21–34 **(Jpn)**

[Monoamine oxidase activity and gamma–aminobutyric acid levels in hyperoxia. The effect of clorgyline] Goroshinskaia IA, et al. **Vopr Med Khim** 1986 Mar–Apr;32(2):76–9 (Eng. Abstr.) **(Rus)**

GALVANIC SKIN RESPONSE

Skin conductance habituation and cerebrospinal fluid 5–hydroxyindoleacetic acid in suicidal patients. Edman G, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):586–92

Periaqueductal gray inhibition of viscerointercostal and galvanic skin reflexes. Sonoda H, et al. **Brain Res** 1986 Mar 26;369(1–2):91–102

GENERALIZATION (PSYCHOLOGY)

[Neuropharmacological analysis of the compensatory–recovery processes in deficiency of the generalization function in lobectomized cats] Mukhin EI. **Zh Vyssh Nerv Deiat** 1986 Jan–Feb;36(1):52–7 (Eng. Abstr.) **(Rus)**

GLUCURONIDASE

Identity of esterase–22 and egasyn, the protein which complexes with microsomal beta–glucuronidase. Medda S, et al. **Biochem Genet** 1986 Apr;24(3–4):229–43

Effect of the cholangiographic agent, ioglycamide, on the beta–glucuronidase activity in rat liver and bile: relevance with regard to bilirubin deconjugation. Mesa VA, et al. **Biochem Pharmacol** 1986 May 15;35(10):1755–7

Steroid content of beta–glucuronidase and sulfatase preparations. Graef V, et al. **Clin Chem** 1986 Jul;32(7):1416

Impaired biliary elimination of beta–glucuronidase–resistant 'glucuronides' of valproic acid after intravenous administration in the rat. Evidence for oxidative metabolism of the resistant isomers. Dickinson RG, et al. **Drug Metab Dispos** 1986 Mar–Apr;14(2):255–62

Age–dependent variations of intralysosomal enzyme release from human PMN leukocytes under various stimuli. Fülöp T Jr, et al. **Immunobiology** 1986 Apr;171(3):302–10

Acid phosphatase and beta–glucuronidase activities in mast cells, macrophages, plasma cells and lymphocytes in gingival fibromatosis. Tanaka A, et al. **J Osaka Dent Univ** 1985 Apr;19(1):33–41

Breast milk beta–glucuronidase and neonatal jaundice [letter] Gaffney PT, et al. **Lancet** 1986 May 17;1(8490):1161–2

GONADOTROPINS, PITUITARY

Serotonin stimulates gonadotrophin release by acting directly on the median eminence. Vitale ML, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):473–9

The effects of the cholecystokinin antagonist, proglumide, on gonadotropin release in the rat. Vijayan E, et al. **Brain Res Bull** 1986 Apr;16(4):533–6

Evidence for activation of the central nervous system–pituitary mechanism for gonadotropin secretion at the time of puberty in the male rat. Matsumoto AM, et al. **Endocrinology** 1986 Jul;119(1):362–9

The effect of hypothalamic catecholamine synthesis inhibition by alpha-methyltyrosine on gonadotropin secretion during sexual maturation in the male Wistar rat. Raum WJ, et al. **Endocrinology** 1986 Jul;119(1):168–75

Central adrenergic activity in the mediobasal hypothalamus is temporally related to surge outputs of gonadotrophins in oestrogen–stimulated infant female rats. Clement EM, et al. **J Endocrinol** 1986 Apr; 109(1):45–51

Regulation of ovarian function in the post partum cow: an endocrine model. Peters AR, et al. **Vet Rec** 1986 Mar 1;118(9):236–9

[FSH, LH, estradiol and testosterone levels after Seda–Presomen in women following hysterectomy with bilateral adnexotomy] Stehlíková J, et al. **Acta Univ Palacki Olomuc Fac Med** 1981;101:139–45 **(Ger)**

[Participation of catecholamines in the regulation of an induced wave of gonadotropins in ovariectomized rats] Bukiia NG, et al. **Probl Endokrinol (Mosk)** 1986 Mar–Apr;32(2):47–51 (Eng. Abstr.) **(Rus)**

GUANETHIDINE

Liquid chromatographic determination of guanethidine salts and hydrochlorothiazide using electrochemical detection and ion–pair techniques. Stewart JT, et al. **J Pharm Sci** 1986 Apr;75(4):413–5

HABITUATION (PSYCHOPHYSIOLOGY)

Skin conductance habituation and cerebrospinal fluid 5–hydroxyindoleacetic acid in suicidal patients. Edman G, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):586–92

HALOPERIDOL

Interactions of drugs and electroshock treatment on cerebral monoaminergic systems. Barkai AI. **Ann NY Acad Sci** 1986; 462:147–62

Progress in pharmacotherapy of borderline disorders. A double–blind study of amitriptyline, haloperidol, and placebo. Soloff PH, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):691–7

Bromocriptine in the treatment of neuroleptic–resistant schizophrenia. Gattaz WF, et al. **Biol Psychiatry** 1986 May;21(5–6):519–21

Effects of intermittent and continuous haloperidol administration on the dopaminergic system in the rat brain. Kashihara K, et al. **Biol Psychiatry** 1986 Jun;21(7):650–6

Lithium and haloperidol [letter] Nemes ZC, et al. **Biol Psychiatry** 1986 May;21(5–6):568–9

Dopamine antagonist haloperidol decreases substance P, substance K, and preprotachykinin mRNAs in rat striatonigral neurons. Bannon MJ, et al. **J Biol Chem** 1986 May 25;261(15):6640–2

Drug holidays and serum haloperidol levels in schizophrenic patients. McMillan DE, et al. **J Clin Psychiatry** 1986 Jul;47(7):373–4

Differential effects of apomorphine on spinal reflex activity following 6–hydroxydopamine or long–term haloperidol pretreatment. Jensen TS, et al. **J Neural Transm** 1986;65(2):125–34

Effects of apomorphine on morphine analgesia during the state of dopaminergic supersensitivity after chronic treatment with haloperidol. Kamata K, et al. **J Pharmacobiodyn** 1986 Jan;9(1):88–94

The effect of thioridazine on haloperidol induced behavioral hypersensitivity. Klawans HL, et al. **Life Sci** 1986 May 12; 38(19):1707–14

Haloperidol binding to monoclonal antibodies: conformational analysis and relationships to D–2 receptor binding. Sherman MA, et al. **Mol Pharmacol** 1986 Jun;29(6):589–98

Neuroleptic treatment induces region–specific changes in levels of neurokinin A and substance P in rat brain. Lindefors N, et al. **Neuropeptides** 1986 Apr;7(3):265–80

Comparison of circling induced by unilateral intrastriatal microinjections of haloperidol, clozapine and CCK–8 in rats. Weiss F, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):983–9

Fluperlapine vs haloperidol: a comparison of their neuroendocrinological profiles and the influence on serum lipids. Fleischhacker WW, et al. **Pharmacopsychiatry** 1986 May;19(3):111–4

Amitriptyline and haloperidol in unstable and schizotypal borderline disorders. Soloff PH, et al. **Psychopharmacol Bull** 1986;22(1):177–82

The AMDP system in international clinical trials: a double–blind comparison of fluperlapine and haloperidol. Woggon B, et al. **Psychopharmacol Bull** 1986;22(1):47–51

Effects of haloperidol and nomifensine on the visual aftereffects of tilt and movement. Harris JP, et al. **Psychopharmacology (Berlin)** 1986; 89(2):177–82

Haloperidol facilitates memory retrieval in the rat. Sara SJ. **Psychopharmacology (Berlin)** 1986;89(3):307–10

[Plasma monitoring of haloperidol. Correlation with clinical efficacy and plasma prolactin levels] Giraud–Serio J, et al. **Ann Med Psychol (Paris)** 1985 Nov;143(9):900–11 **(Fre)**

[Studies on the diuretic effect of haloperidol in adult rats] Shirakura Y. **Nippon Yakurigaku Zasshi** 1986 Feb;87(2):189–97 (Eng. Abstr.) **(Jpn)**

[Nonuniform effect of prolonged haloperidol administration on the GABA(A) and benzodiazepine receptors in different parts of the brain] Vasar EE, et al. **Biull Eksp Biol Med** 1986 Apr;101(4):433–6 (Eng. Abstr.) **(Rus)**

[Effect of haloperidol and clozapine on the bioelectric activity of the human cerebral cortex] Sviderskaia NE, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):428–31 (Eng. Abstr.) **(Rus)**

[Aberrations of cortical and subcortical integration during chronic administration of haloperidol to the dog] Kachalova LM, et al. **Zh Vyssh Nerv Deiat** 1986 Mar–Apr;36(2):375–84 (Eng. Abstr.) **(Rus)**

[Bethanechol as treatment for urinary retention induced by a combination of neuroleptics and anticholinergics] Seguí Montesinos J, et al. **Actas Luso Esp Neurol Psiquiatr Cienc Afines** 1985 Nov–Dec; 13(6):402–5 (Eng. Abstr.) **(Spa)**

[Increasing the neuronal population of the nucleus accumbens in the rat using haloperidol] Rueda J, et al. **Arch Neurobiol (Madr)** 1986 Mar–Apr; 49(2):90–4 (Eng. Abstr.) **(Spa)**

HANDLING (PSYCHOLOGY)

Central norepinephrine and plasma corticosterone following acute and chronic stressors: influence of social isolation and handling. Irwin J, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1151–4

HEXOBARBITAL

Pipecolic acid antagonizes barbiturate–enhanced GABA binding to bovine brain membranes. Feigenbaum P, et al. **Brain Res** 1986 Apr 30; 372(1):176–9

Stereospecific analysis of racemic hexobarbital in rat blood by enantioselective capillary gas chromatography. van der Graaff M, et al. **J Chromatogr** 1986 Mar 7;375(2):411–5

Intra–arterial administration of hexobarbital enantiomers to the rat: disposition and estimation of apparent extraction ratio. Van der Graaff M, et al. **Pharm Weekbl [Sci]** 1986 Apr 25;8(2):139–44

Effects of methylmercury on hypnotic action of hexobarbital, liver hydroxylase and cytochrome P–450 in mice. Su MQ, et al. **Toxicology** 1986 Jun;39(3):233–45

HISTAMINE

Biochemical and pharmacological characterization of histamine–mediated up–regulation of human platelet serotonin uptake. Evidence for a subclass of histamine H2 receptors (H2h) highly sensitive to H2 receptor antagonists. Gespach C, et al. **Agents Actions** 1986 Apr; 18(1–2):115–9

Effect of electroconvulsive shock (ECS) treatment on the histaminergic system in rat brain: biochemical and behavioural studies. Zawilska J, et al. **Agents Actions** 1986 Apr;18(1–2):222–5

H1 action of histamine on aldosterone and cortisol secretion by perfused dog adrenal. Aikawa T, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):E523–9

Histamine as a neuroregulator. Prell GD, et al. **Annu Rev Neurosci** 1986; 9:209–54 (260 ref.)

Histamine–induced constriction and dilatation of rabbit middle cerebral arteries in vitro: role of the endothelium. Sercombe R, et al. **Blood Vessels** 1986;23(3):137–53

Allometric growth of the rat peritoneal mast cell mass and of the granular constituents: heparin, histamine and 5–hydroxytryptamine. Aldenborg F, et al. **Growth** 1985 Winter;49(4):510–8

Response of isolated uterus of rat, hamster and guinea pig to different uterine stimulants. Mehrotra PK, et al. **Indian J Exp Biol** 1985 Oct; 23(10):572–3

Studies on vascular permeability increasing factors involved in 48–hour homologous PCA in the mouse ear. Inagaki N, et al. **Int Arch Allergy Appl Immunol** 1986;80(3):285–90

Histamine–induced prolactin release and activity of tuberoinfundibular dopaminergic neurons in male rats. Seltzer AM, et al. **J Neural Transm** 1986;65(2):115–23

Effects of dopamine and vasopressin on histamine–induced increases in macromolecular permeability in the canine forelimb. Adamski SW, et al. **Microcirc Endothelium Lymphatics** 1985 Feb;2(1):27–39

Histamine–induced fluid efflux in the canine forelimb as affected by carotid occlusion or hemorrhage. Dabney JM, et al. **Microcirc Endothelium Lymphatics** 1984 Jun;1(3):247–71

Comparison of effects of phencyclidine and methamphetamine on body temperature in mice: a possible role for histamine neurons in thermoregulation. Itoh Y, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar;332(3):293-6

Variations of brain histamine levels in germ-free and nephrectomized rats. Hegstrand LR, et al. **Neurochem Res** 1986 Feb;11(2):185-91

Brain histamine regulation following chronic diazepam treatment and stress. Mazurkiewicz-Kwilecki IM, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):513-7

[The role of endogenous amines in anaphylactic shock in rats] Oyama M. **Kanagawa Shigaku** 1985 Dec;20(3):307-19 (Eng. Abstr.) **(Jpn)**

[The role of serotonin, histamine and prostaglandins on potentiation of hypoxic pulmonary vasoconstriction by repeated intermittent hypoxic challenges in dogs] Nakanishi S, et al. **Nippon Kyobu Shikkan Gakkai Zasshi** 1986 Jan;24(1):42-8 (Eng. Abstr.) **(Jpn)**

[Basophil histamine and peripheral blood serotonin in metal and toxic gas poisoning] Fal W, et al. **Med Pr** 1985;36(6):377-81 (Eng. Abstr.) **(Pol)**

HOMOVANILLIC ACID

Longitudinal measurement of plasma homovanillic acid levels in schizophrenic patients. Correlation with psychosis and response to neuroleptic treatment. Pickar D, et al. **Arch Gen Psychiatry** 1986 Jul; 43(7):669-76

Developmental variations in CSF monoamine metabolites during childhood. Hedner J, et al. **Biol Neonate** 1986;49(4):190-7

Regional brain homovanillic acid following delta 9-tetrahydrocannabinol and cocaine. Bowers MB Jr, et al. **Brain Res** 1986 Feb 26; 366(1-2):405-7

Early neuroleptic response in psychotic men and women: correlation with plasma HVA and MHPG. Bowers MB Jr, et al. **Compr Psychiatry** 1986 May-Jun;27(3):181-5

Free and conjugated 3,4-dihydroxyphenylacetic acid and homovanillic acid in brain dopaminergic areas at basal state and after pipotiazine activation. Tavitian E, et al. **J Neural Transm** 1986;65(3-4):261-75

HOSTILITY

Hostility and recovery from melancholia. Fava GA, et al. **J Nerv Ment Dis** 1986 Jul;174(7):414-7

HUNGER

Hunger perceptions and satiety responses among normal-weight bulimics and normals to a high-calorie, carbohydrate-rich food. Chiodo J, et al. **Psychol Med** 1986 May;16(2):343-9

[Regulation of food intake by the central nervous system and the gastrointestinal tract (II)] Schusdziarra V. **Leber Magen Darm** 1986 Mar; 16(2):104, 107-10, 113 **(Ger)**

HYDANTOINS

Family studies of mephenytoin hydroxylation deficiency. Inaba T, et al. **Am J Hum Genet** 1986 May;38(5):768-72

Separation of amino acid phenylthiohydantoin derivatives by high-pressure liquid chromatography. Meuth JL, et al. **Anal Biochem** 1986 May 1;154(2):478-84

Polymorphic metabolism of mephenytoin in man: pharmacokinetic interaction with a co-regulated substrate, mephobarbital. Jacqz E, et al. **Clin Pharmacol Ther** 1986 Jun;39(6):646-53

5,5-Diaryl-2-thiohydantoins and 5,5-diaryl-N3-substituted-2-thiohydantoins as potential hypolipidemic agents. Tompkins JE. **J Med Chem** 1986 May;29(5):855-9

Genetic polymorphism of mephenytoin metabolism. Inaba T. **Prog Clin Biol Res** 1986;214:139-56 (40 ref.)

HYDRAZINES

Synthesis of cell-impermeable inhibitor of phospholipase A2. Yedgar S, et al. **FEBS Lett** 1986 May 5;200(1):165-8

2,2'-Phthaloyl-,2,2'-isophthaloyl-, and 2,2'-terephthaloylbis[1,1,1-trimethylhydrazinium] dihydroxide, bis(inner salts): synthesis, partition coefficients, toxicity and effect on ganglionic transmission. Cates LA, et al. **J Pharm Sci** 1986 Apr; 75(4):407-9

Antagonism of thromboxane actions in the isolated perfused rat heart. Stahl GL, et al. **Life Sci** 1986 Jun 2;38(22):2037-41

Relationship between oxidative metabolites of hydrazine and hydrazine-induced mutagenicity. Noda A, et al. **Toxicol Lett** 1986 May; 31(2):131-7

[Hydrazine in drinking water] Bodenschatz W. **Off Gesundheitswes** 1986 Apr;48(4):205-8 (Eng. Abstr.) **(Ger)**

[Synthesis and anticoccidial activity of 3-(substituted benzylidenehydrazino)-6-(4-chlorophenyl)-1,2,4-triazines] Shibamoto S, et al. **Yakugaku Zasshi** 1986 Mar;106(3):233-9 (Eng. Abstr.) **(Jpn)**

[Hydrazine sulfate as a stabilizer of cell membranes] Filov VA, et al. **Biull Eksp Biol Med** 1986 May;101(5):610-1 **(Rus)**

HYDRAZONES

Determination of copper in biological tissue by means of photochemically generated (Z)-2-thiophenaldehyde 2-pyridylhydrazone. García Sánchez F, et al. **Analyst** 1986 Apr;111(4):445-8

Spectrophotometric determination of palladium in catalysts and carbenicillin with 1-(2-pyridylmethylidene)-5-(salicylidene)-thiocarbohydr azone. Rosales D, et al. **Analyst** 1986 Apr;111(4):449-53

Synthesis of some new hydrazone derivatives as biologically active agents. Sen Gupta AK, et al. **Arzneimittelforschung** 1986 May;36(5):790-3

[Antiviral and antibacterial activities of substituted benzalacetone amidinohydrazones] Yoshii S, et al. **Yakugaku Zasshi** 1986 Feb; 106(2):158-63 (Eng. Abstr.) **(Jpn)**

HYDROXYBUTYRATES

The effect of the dissolved oxygen concentration and anabolic limitations on the behaviour of Rhizobium ORS571 in chemostat cultures. de Vries W, et al. **Antonie Van Leeuwenhoek** 1986;52(1):85-96

Perchloric acid interference in enzymatic-fluorimetric-continuous-flow assay methods for measuring glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate in blood. Stappenbeck R, et al. **Clin Chem** 1986 Jun;32(6):1023-6

Determination of human ketone body kinetics using stable-isotope labelled tracers. Beylot M, et al. **Diabetologia** 1986 Feb;29(2):90-6

Is there Ca2+(Sr2+)-3-hydroxybutyrate symport in rat-liver mitochondria? A reappraisal. Moody AJ, et al. **Eur J Biochem** 1986 Jun 2;157(2):243-9

[Effect of lithium oxybutyrate on the viability of preserved donor kidney] Sholokhov VM, et al. **Farmakol Toksikol** 1986 May-Jun;49(3):69-70 (Eng. Abstr.) **(Rus)**

[The effect of gamma-hydroxybutyric acid on the biosynthesis of macromolecules and metabolic paramagnetic centers in hepatocytes in acute radiation injury] Sharygin VL, et al. **Radiobiologiia** 1986 Mar-Apr; 26(2):189-94 (Eng. Abstr.) **(Rus)**

[Use of lithium oxybutyrate in the combined therapy of burn injury patients] Iurasov II, et al. **Voen Med Zh** 1986 Apr;(4):20-1 **(Rus)**

[Use of sodium hydroxybutyrate electrophoresis in the complex treatment of lumbar osteochondrosis] Matesha AM, et al. **Vopr Kurortol Fizioter Lech Fiz Kult** 1986 Jan-Feb;(1):60-1 **(Rus)**

HYDROXYDOPAMINES

Studies on cyproheptadine-amphetamine interaction after pretreatment with 6-hydroxydopamine. Chodera A, et al. **Acta Physiol Pol** 1984 Sep-Dec;35(5-6):426-31

Effect of 6-hydroxydopamine on polymerization of tubulin. Protection by superoxide dismutase, catalase, or anaerobic conditions. Davison AJ, et al. **Biochem Pharmacol** 1986 May 1;35(9):1411-7

Effects of bilateral lesion of the locus coeruleus and of neonatal administration of 6-hydroxydopamine on the concentration of individual proteins in rat brain. Heydorn WE, et al. **Brain Res** 1986 Mar 5; 367(1-2):31-8

Plasticity of catecholaminergic terminals in rat paraventricular hypothalamic nucleus after 6-hydroxydopamine lesion: an emphasis on bouton sizes and synaptic frequency. Hwang BH, et al. **Brain Res** 1986 Mar 26;369(1-2):267-74

Effects of intraventricular 6-hydroxydopamine on the dopaminergic innervation of striatum: histochemical and neurochemical analysis. Onn SP, et al. **Brain Res** 1986 Jun 18;376(1):8-19

Neonatal 6-hydroxydopamine lesion of forebrain norepinephrine does not eliminate critical period for behavioral effects of gonadal hormone manipulation. Pappas BA, et al. **Brain Res** 1986 May;391(2):310-4

The acute effects of 6-hydroxydopamine treatment on noradrenergic function in the rat hippocampus in vitro. Yasuda RP, et al. **Brain Res** 1986 Mar 5;367(1-2):121-7

Differential effects of apomorphine on spinal reflex activity following 6-hydroxydopamine or long-term haloperidol pretreatment. Jensen TS, et al. **J Neural Transm** 1986;65(2):125-34

Sinus node function after selective elimination of sympathetic influences on the sinus node area of the dog. Yano K, et al. **Jpn Heart J** 1986 Jan;27(1):71-81

Effects of 6-hydroxydopamine-induced lesions of the paraventricular nucleus, and of prazosin, on the corticosterone response to restraint in rats. Gibson A, et al. **Neuropharmacology** 1986 Mar;25(3):257-60

Destruction of meningeal cells over the newborn hamster cerebellum with 6-hydroxydopamine prevents foliation and lamination in the rostral cerebellum. von Knebel Doeberitz C, et al. **Neuroscience** 1986 Feb; 17(2):409-26

Effect of 6-hydroxydopamine on neuropeptides in the rat female genitourinary tract. Allen JM, et al. **Peptides** 1985 Nov-Dec; 6(6):1213-7

Changes in nociception after 6-hydroxydopamine lesions of descending catecholaminergic pathways in mice. Fasmer OB, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1441-4

Effect of 6-OHDA injected into the locus coeruleus on apomorphine-induced aggression. Pucilowski O, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):773-5

HYDROXYINDOLEACETIC ACID

Effects of pentagastrin and oxyphenonium on the levels of serotonin and 5-hydroxyindoleacetic acid in different parts of the digestive tract, blood and brain of rats. Pokora J, et al. **Acta Physiol Pol** 1984 Jul-Aug; 35(4):317-23

Skin conductance habituation and cerebrospinal fluid 5-hydroxyindoleacetic acid in suicidal patients. Edman G, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):586-92

Serotonin and 5-hydroxyindoleacetic acid in brains of suicide victims. Comparison in chronic schizophrenic patients with suicide as cause of death. Korpi ER, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):594-600

Developmental variations in CSF monoamine metabolites during childhood. Hedner J, et al. **Biol Neonate** 1986;49(4):190-7

Time-related response of central serotonergic function to lithium administration. Otero Losada ME, et al. **Gen Pharmacol** 1986; 17(3):333-7

Peripheral and central short-term effects of fusaric acid, a DBH inhibitor, on tryptophan and serotonin metabolism in the rat. Chaouloff F, et al. **J Neural Transm** 1986;65(3-4):219-32

Regional distribution of immunoreactive-thyrotrophin-releasing hormone and substance P, and indoleamines in human spinal cord. Bennett GW, et al. **J Neurochem** 1986 Jun;46(6):1718-24

HYDROXYTRYPTOPHAN

Correction and amplification: cortisol response to 5-HTP [letter] Meltzer HY, et al. **Arch Gen Psychiatry** 1986 Aug;43(8):815

[Critical study of the clinical actions of 5-HTP] Teixeira M. **Actas Luso Esp Neurol Psiquiatr Cienc Afines** 1986 Mar-Apr; 14(2):104-12 **(Por)**

HYPOCHONDRIASIS

Hypochondriacal fears and beliefs in DSM-III melancholia. Changes with amitriptyline. Kellner R, et al. **J Affective Disord** 1986 Jan-Feb; 10(1):21-6

IMIPRAMINE

Imipramine in adolescent major depression: plasma level and clinical response. Ryan ND, et al. **Acta Psychiatr Scand** 1986 Mar; 73(3):275-88

How antipanic drugs might work [letter] Nesse RM, et al. **Am J Psychiatry** 1986 Jul;143(7):945

Interactions of drugs and electroshock treatment on cerebral monoaminergic systems. Barkai AI. **Ann NY Acad Sci** 1986; 462:147-62

Clinically significant improvement in agoraphobia research. Mavissakalian M. **Behav Res Ther** 1986;24(3):369-70

Imipramine-flupenthixol decanoate interaction. Cook PE, et al. **Can J Psychiatry** 1986 Apr;31(3):235-7

Regional distribution and elimination kinetics of imipramine in rat brain after multiple dosages. Masada M, et al. **Chem Pharm Bull (Tokyo)** 1986 Feb;34(2):927-30

Quantitative homogeneous enzyme immunoassays for amitriptyline, nortriptyline, imipramine, and desipramine. Pankey S, et al. **Clin Chem** 1986 May;32(5):768-72

Targeting imipramine dose in children with depression. Sallee F, et al. **Clin Pharmacol Ther** 1986 Jul;40(1):8-13

Steady-state levels of imipramine and its metabolites: significance of dose-dependent kinetics. Brøsen K, et al. **Eur J Clin Pharmacol** 1986; 30(1):43-9

Differential effects of cimetidine and ranitidine on imipramine demethylation and desmethylimipramine hydroxylation by human liver microsomes. Spina E, et al. **Eur J Clin Pharmacol** 1986;30(2):239-42

Effect of adrenalectomy and corticosterone on [3H]imipramine binding in rat blood platelets and brain. Arora RC, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):415-9

[3H]imipramine displacement and 5HT uptake inhibition by tryptoline derivatives: in rat brain 5-methoxytryptoline is not the autacoid for [3H]imipramine recognition sites. Barbaccia ML, et al. **Eur J Pharmacol** 1986 Apr 9;123(1):45-52

Determination of metapramine, imipramine, trimipramine and their major metabolites in plasma by reversed-phase column liquid chromatography. Pok Phak R, et al. **J Chromatogr** 1986 Mar 7;375(2):339-47

Effects of tranylcypromine enantiomers on monoamine uptake and release and imipramine binding. Tuomisto J, et al. **J Neural Transm** 1986; 65(2):135-45

Effect of chronic desipramine treatment on dihydroalprenolol, imipramine, and desipramine binding sites: a quantitative autoradiographic study in the rat brain. Biegon A. **J Neurochem** 1986 Jul;47(1):77-80

Subdivision of mouse brain [3H]imipramine binding based on ion dependence and serotonin sensitivity. Severson JA, et al. **J Neurochem** 1986 Jun;46(6):1743-54

The effect of antidepressants on ethylmorphine and imipramine N-demethylation in rat liver microsomes. Daniel W, et al. **J Pharm Pharmacol** 1986 May;38(5):396-8

Leu-enkephalin content in rat brain during prolonged treatment with imipramine or amitriptyline. Herman ZS, et al. **Neuropeptides** 1986 Feb-Mar;7(2):113-24

Diclofensine and imipramine. A double-blind comparative trial in depressive out-patients. Capponi R, et al. **Neuropsychobiology** 1985; 14(4):173-80

Effect of serotonin on the dissociation of high-affinity binding of [3H]imipramine in mouse cerebral cortex. Kim SS, et al. **Neurosci Lett** 1986 Jun 18;67(2):123-8

Accidental poisoning. Maroncelli RD. **Nursing** 1986 Jul;16(7):25

Escalating imipramine dosage requirements. Hudson CJ, et al. **Psychiatr J Univ Ottawa** 1986 Mar;11(1):26-7

Imipramine binding in agoraphobia [letter] Ambrosini P. **Psychiatry Res** 1986 Jun;18(2):189-92

Chronic imipramine treatment and weight gain. Fernstrom MH, et al. **Psychiatry Res** 1986 Apr;17(4):269-73

Use of a standardized documentation system (BLIPS/BDP) in the conduct of a multicenter international trial comparing fluvoxamine, imipramine, and placebo. Cassano GB, et al. **Psychopharmacol Bull** 1986; 22(1):52-8

A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. Rizley R, et al. **Psychopharmacol Bull** 1986;22(1):167-72

Human cognitive function following binedaline (50 mg and 100 mg) and imipramine (75 mg): results with a new battery on tests. Jones DM, et al. **Psychopharmacology (Berlin)** 1986;89(2):198-202

Comparison of the metabolism of the three antidepressants amitriptyline, imipramine, and chlorimipramine in vitro in rat liver microsomes. Krüger R, et al. **Psychopharmacology (Berlin)** 1986;88(4):505-13

[Binding of tritiated imipramine to human platelets. 1 or several binding sites?] Scotto di Tella AM, et al. **Encephale** 1986 Jan-Feb;12(1):13-7 (Eng. Abstr.) **(Fre)**

[Tofranil] Peutillot JF, et al. **Soins Psychiatr** 1986 Mar;(65):I-II **(Fre)**

[Enuresis nocturna in school children in Bodö. A therapeutic trial with a vasopressin analog: desmopressin and imipramine] Holt J, et al. **Tidsskr Nor Laegeforen** 1986 Mar 20;106(8):651-4 (Eng. Abstr.)**(Nor)**

[Comparative clinical study of imipramine and mianserin in depressions] Chiriţă V, et al. **Rev Med Chir Soc Med Nat Iasi** 1985 Oct-Dec; 89(4):651-6 (Eng. Abstr.) **(Rum)**

[Effect of clomipramine and imipramine in vivo on genetic material in the mouse] Theodorescu R. **Rev Med Interna [Neurol Psihiatr]** 1985 Oct-Dec;30(4):309-14 **(Rum)**

[Prediction of the effect of antidepressants in patients with endogenous depression] Litvinova NM, et al. **Zh Nevropatol Psikhiatr** 1986; 86(4):577-82 (Eng. Abstr.) **(Rus)**

ISOCARBOXAZID

The effects of isocarboxazid on blood pressure and pulse. Davidson J, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):139-43

LACTATES

Lactate utilization by the neonatal rat brain in vitro. Competition with glucose and 3-hydroxybutyrate. Fernández E, et al. **Biochem J** 1986 Mar 1;234(2):489-92

Long-term effects of combined vitamin B6-magnesium administration in an autistic child. Martineau J, et al. **Biol Psychiatry** 1986 May; 21(5-6):511-8

Perchloric acid interference in enzymatic-fluorimetric-continuous-flow assay methods for measuring glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate in blood. Stappenbeck R, et al. **Clin Chem** 1986 Jun;32(6):1023-6

Synthesis and identification of 3-(4-hydroxy-1-naphthoxy)lactic acid as a metabolite of propranolol in the rat, in man, and in the rat liver 9000 g supernatant fraction. Talaat RE, et al. **Drug Metab Dispos** 1986 Mar-Apr;14(2):202-7

Hormone and metabolite response to weight-lifting training sessions. Guezennec Y, et al. **Int J Sports Med** 1986 Apr;7(2):100-5

[Changes in cardiovascular, sympathoadrenal and metabolic responses during exercise corresponding to the lactate threshold in middle-aged and elderly women] Yoshitake Y. **Nippon Eiseigaku Zasshi** 1986 Feb; 40(6):867-75 (Eng. Abstr.) **(Jpn)**

LEARNING

Attenuation of sensory preconditioning by noradrenaline depletion in the rat. Archer T, et al. **Behav Brain Res** 1986 Apr;20(1):47-56

Central nervous system mediation of positive and negative reinforcement in neonatal albino rats. Kehoe P, et al. **Brain Res** 1986 Jun; 392(1-2):69-75

Learning impairment following lesion of the basal nucleus of Meynert in the marmoset: modification by cholinergic drugs. Ridley RM, et al. **Brain Res** 1986 Jun 18;376(1):108-16

Sedative effects and impaired learning and recall after single oral doses of lorazepam. Shader RI, et al. **Clin Pharmacol Ther** 1986 May; 39(5):526-9

Benzodiazepine impairs and beta-carboline enhances performance in learning and memory tasks. Venault P, et al. **Nature** 1986 Jun 26-Jul 2;321(6073):864-6

Cholinergic suppression: a postsynaptic mechanism of long-term associative learning. Morielli AD, et al. **Proc Natl Acad Sci USA** 1986 Jun;83(12):4556-60

[Chief trends in research into the neurochemical mechanisms of learning and memory] Kruglikov RI. **Zh Vyssh Nerv Deiat** 1986 Mar-Apr; 36(2):226-31 (24 ref.) **(Rus)**

LEARNING DISORDERS

Disruption of conditioned taste aversion by ECS: the role of lithium chloride. Shaw N. **Physiol Behav** 1986;36(6):1193-5

LEVODOPA

The effects of domperidone on the absorption of levodopa in normal subjects. Bradbrook ID, et al. **Eur J Clin Pharmacol** 1986; 29(6):721-3

Dopamine and L-dopa potentiation of pressor responses to norepinephrine in isolated perfused rat kidneys. Lam BK, et al. **J Cardiovasc Pharmacol** 1986 May-Jun;8(3):554-8

A lymphotropic prodrug of L-dopa: synthesis, pharmacological properties, and pharmacokinetic behavior of 1,3-dihexadecanoyl-2-[(S)-2-amino-3-(3,4-dihydroxyphenyl)propanoyl] propane-1,2,3-triol. Garzon-Aburbeh A, et al. **J Med Chem** 1986 May;29(5):687-91

Differential effect of repeated treatment with L-dopa on dopamine-D1 or -D2 receptors. Parenti M, et al. **Neuropharmacology** 1986 Mar; 25(3):331-4

[L-dopa extracted from seeds of Mucuna sempervirens Hemsl as a promoter of fracture healing] Yang HY. **Chung Hsi I Chieh Ho Tsa Chih** 1985 Jul;5(7):398-401, 386 (Eng. Abstr.) **(Chi)**

[Stimulation of ovulation with analogs of luliberin, androstenol and their combination with L-DOPA] Lupanova GE. **Farmakol Toksikol** 1986 Mar-Apr;49(2):35-7 (Eng. Abstr.) **(Rus)**

LH

Can neonatal treatment with a related hormone adapt the receptor for itself? Csaba G, et al. **Acta Physiol Hung** 1986;67(1):65-9

Colocalization of luteinizing hormone and serotonin in secretory granules of mammalian gonadotrophs. Payette RF, et al. **Anat Rec** 1986 May; 215(1):51-8

Secretion of the beta-subunit of luteinizing hormone in dispersed rat anterior pituitary cells. Seki T, et al. **Asia Oceania J Obstet Gynaecol** 1986 Mar;12(1):113-8

Copper induces luteinizing hormone release and desensitization of pituitary gonadotropes. Schvartz I, et al. **Biochem Biophys Res Commun** 1986 Apr 14;136(1):417-25

Changes in the dynamics of luteinizing hormone-releasing hormone-stimulated secretion of luteinizing hormone during sexual maturation of female rats. Nash SJ, et al. **Biol Reprod** 1986 Apr; 34(3):549-57

Effect of luteinising hormone releasing hormone and its analogues on plasma luteinising hormone concentrations in incubating bantam hens. Sharp PJ, et al. **Br Poult Sci** 1986 Mar;27(1):129-35

Biochemical and radioautographic analysis of estrogen-inducible progestin receptors in female ferret brain and pituitary: correlations with effects of progesterone on sexual behavior and gonadotropin-releasing hormone-stimulated secretion of luteinizing hormone. Baum MJ, et al. **Brain Res** 1986 Mar 19;368(2):296-309

Modulation of the estradiol-induced luteinizing hormone surge by progesterone or antiestrogens: effects on pituitary gonadotropin-releasing hormone receptors. Attardi B, et al. **Endocrinology** 1986 Jul;119(1):274-83

Food-restricted, prepubertal, female rats: rapid recovery of luteinizing hormone pulsing with excess food, and full recovery of pubertal development with gonadotropin-releasing hormone. Bronson FH. **Endocrinology** 1986 Jun;118(6):2483-7

Episodic patterns of luteinizing hormone and follicle-stimulating hormone release: differential secretory dynamics and adrenergic control in ovariectomized rats. Condon TP, et al. **Endocrinology** 1986 Jun; 118(6):2525-33

Gonadotropin-releasing hormone-mediated desensitization of cultured rat anterior pituitary cells can be uncoupled from luteinizing hormone release. Jinnah HA, et al. **Endocrinology** 1986 Jun;118(6):2599-604

Synthesis and release of luteinizing hormone by rat anterior pituitary cells: effects of cytochalasins B and D. Liu TC, et al. **Endocrinology** 1986 Jul;119(1):236-43

Adrenocorticotropin-induced changes in ovine pituitary gonadotropin secretion in vitro. Matteri RL, et al. **Endocrinology** 1986 May; 118(5):2091-6

Receptor binding and gonadotropin-releasing activity of a novel chicken gonadotropin-releasing hormone ([His5, Trp7, Tyr8]GnRH) and a D-Arg6 analog. Millar RP, et al. **Endocrinology** 1986 Jul; 119(1):224-31

Effects of epinephrine, norepinephrine, and dopamine on gonadotropin-releasing hormone-induced secretion of luteinizing hormone in vitro. Swartz SR, et al. **Endocrinology** 1986 Jun; 118(6):2425-31

Modification of luteinizing hormone secretion by activators of Ca2+/phospholipid-dependent protein kinase. Turgeon JL, et al. **Endocrinology** 1986 May;118(5):2053-8

Biosynthesis, glycosylation, and secretion of rat luteinizing hormone alpha- and beta-subunits: differential effects of orchiectomy and gonadotropin-releasing hormone. Vogel DL, et al. **Endocrinology** 1986 Jul;119(1):202-13

Luteinizing hormone and follicle-stimulating hormone responses to intransal gonadotropin-releasing hormone. Rajfer J, et al. **Fertil Steril** 1986 Jun;45(6):794-9

Single dose responses to the gonadotropin-releasing hormone agonist analogue [(imBz 1)-D-His6,Pro9-NEt]GnRH. Doelle GC, et al. **Horm Metab Res** 1986 Mar;18(3):201-2

Effects of pulsatile injection of GnRH into 6- to 14-wk-old Holstein bulls. Miller CJ, et al. **J Anim Sci** 1986 May;62(5):1332-9

Anterior pituitary concentrations of gonadotropins, GnRH-receptors and ovarian characteristics following early weaning in beef cows. Parfet JR, et al. **J Anim Sci** 1986 Mar;62(3):717-22

Pulsatile or continuous infusion of luteinizing hormone-releasing hormone and hormonal concentrations in prepubertal beef heifers. Skaggs CL, et al. **J Anim Sci** 1986 Apr;62(4):1034-48

Effects of intermittent injections of LHRH on secretory patterns of LH and FSH and ovarian follicular growth during postpartum anovulation in suckled beef cows. Spicer LJ, et al. **J Anim Sci** 1986 May; 62(5):1317-23

Participation of voltage-dependent calcium channels in the action of gonadotropin-releasing hormone. Chang JP, et al. **J Biol Chem** 1986 Jul 15;261(20):9105-8

Single subcutaneous doses of a luteinizing hormone-releasing hormone antagonist suppress serum gonadotropin and testosterone levels in normal men. Pavlou SN, et al. **J Clin Endocrinol Metab** 1986 Aug; 63(2):303-8

Pituitary self-priming actions of gonadotropin-releasing hormone. Kinetics of estradiol's potentiating effects on gonadotropin-releasing hormone-facilitated luteinizing hormone and follicle-stimulating hormone release in healthy postmenopausal women. Veldhuis JD, et al. **J Clin Invest** 1986 Jun;77(6):1849-56

Ontogeny of serum and pituitary gonadotrophins in male rats treated with low doses of 5 alpha-dihydrotestosterone. Karanth S, et al. **J Endocrinol** 1986 Mar;108(3):369-75

Seasonal changes in concentrations of plasma hormones in the male ring dove (Streptopelia risoria). Lea RW, et al. **J Endocrinol** 1986 Mar; 108(3):385-91

Varying the patterns and concentrations of gonadotrophin-releasing hormone stimulation does not alter the ratio of LH and FSH released from perifused sheep pituitary cells. McIntosh JE, et al. **J Endocrinol** 1986 May;109(2):155-61

Effects of LH and an LH-releasing hormone agonist on different second messenger systems in the regulation of steroidogenesis in isolated rat Leydig cells. Themmen AP, et al. **J Endocrinol** 1986 Mar; 108(3):431-40

Influence of subcutaneous melatonin implantation on gonadal development and on plasma levels of luteinizing hormone, testosterone, estradiol, and corticosterone in the pigeon. John TM, et al. **J Pineal Res** 1986;3(2):169-79

Steroid regulation of gonadotropins in genetically hypoprolactinemic females (IPL nude rats). Cohen H, et al. **J Steroid Biochem** 1986 Jan; 24(1):431-5

Top concentrations of dynorphin-like immunoreactivity in fractions of rat anterior pituitary cells enriched in gonadotrophs. Knepel W, et al. **Life Sci** 1986 Jun 23;38(25):2363-7

Modulation and role of Ca2+ in LH and LHRH agonist action in rat Leydig cells. Cooke BA, et al. **Med Biol** 1986;63(5-6):259-63

The different mechanisms for suppression of pituitary and testicular function. Sandow J, et al. **Med Biol** 1986;63(5-6):192-200

Perifusion of anterior pituitary cells: release of gonadotropins and somatotropins. Badger TM. **Methods Enzymol** 1986;124:79-90

Immunohistochemical localization of follicle-stimulating hormone, luteinizing hormone, growth hormone, adrenocorticotrophic hormone and prolactin in the human placenta. Al-Timimi A, et al. **Placenta** 1986 Mar-Apr;7(2):163-72

Effect of atrial natriuretic peptide on gonadotropin release in superfused rat pituitary cells. Horvath J, et al. **Proc Natl Acad Sci USA** 1986 May; 83(10):3444-6

Gonadotropin-releasing hormone differentially regulates expression of the genes for luteinizing hormone alpha and beta subunits in male rats. Papavasiliou SS, et al. **Proc Natl Acad Sci USA** 1986 Jun; 83(11):4026-9

[Effect of tyrosine on serum concentrations of LH, FSH and testosterone in adult men] Ni J, et al. **Sheng Li Hsueh Pao** 1985 Jun;37(3):303-6 (Eng. Abstr.) **(Chi)**

[The effect of synthetic chicken LH-RH on the release of LH and FSH and ovulation in rats (a comparative study of synthetic mammalian LH-RH and chicken LH-RH)] Takahashi Y, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Feb 20;62(2):126-39 (Eng. Abstr.) **(Jpn)**

[Role of various types of serotonin reception in the hypothalamic modulation of the release of luteinizing hormone] Ignatkov VIa, et al. **Fiziol Zh SSSR** 1986 Mar;72(3):316-22 (Eng. Abstr.) **(Rus)**

LH-FSH RELEASING HORMONE

Serotonin stimulates gonadotrophin release by acting directly on the median eminence. Vitale ML, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):473-9

Pulsatile administration of gonadotropin releasing hormone (Gn-RH) to lactating sows using a portable automatic pump ('Zyklomat'). Rojanasthien S, et al. **Acta Vet Scand** 1985;26(4):442-8

Induction of ovulation in anestrous mares with pulsatile administration of gonadotropin-releasing hormone. Johnson AL. **Am J Vet Res** 1986 May;47(5):983-6

Demonstration of immunoreactive LHRH in the human ovaries by peroxidase immunocytochemistry. Huang HJ, et al. **Asia Oceania J Obstet Gynaecol** 1986 Mar;12(1):149-54

Autoradiographical localization of luteinizing hormone releasing hormone (LHRH) receptors on rat testicular intertubular cells fractionated on Percoll density gradients. Hedger MP, et al. **Aust J Biol Sci** 1985; 38(4):435-44

Increased potency of antagonists of the luteinizing hormone releasing hormone which have D-3-Pal in position 6. Folkers K, et al. **Biochem Biophys Res Commun** 1986 Jun 13;137(2):709-15

Changes in the dynamics of luteinizing hormone-releasing hormone-stimulated secretion of luteinizing hormone during sexual maturation of female rats. Nash SJ, et al. **Biol Reprod** 1986 Apr; 34(3):549-57

Effect of luteinising hormone releasing hormone and its analogues on plasma luteinising hormone concentrations in incubating bantam hens. Sharp PJ, et al. **Br Poult Sci** 1986 Mar;27(1):129-35

Attempts to immunoprecipitate the LHRH precursor synthesized in cell free systems. Cohen S, et al. **Brain Res Bull** 1986 Mar;16(3):309-14

Ultrastructural characterization of neurosecretory fibres immunoreactive for vasotocin, isotocin, somatostatin, LHRH and CRF in the pituitary of a teleost fish, Poecilia latipinna. Batten TF. **Cell Tissue Res** 1986; 244(3):661-72

A reinvestigation of the Gn-RH (gonadotrophin-releasing hormone) systems in the goldfish brain using antibodies to salmon Gn-RH. Kah O, et al. **Cell Tissue Res** 1986;244(2):327-37

Induction of ovarian activity by pulsatile infusion of LHRH in women with lactational amenorrhoea. Glasier A, et al. **Clin Endocrinol (Oxf)** 1986 Mar;24(3):243-52

Selective reduction of elevated FSH levels in infertile men by pulsatile LHRH treatment. Hönigl W, et al. **Clin Endocrinol (Oxf)** 1986 Feb; 24(2):177-82

Modulation of the estradiol-induced luteinizing hormone surge by progesterone or antiestrogens: effects on pituitary gonadotropin-releasing hormone receptors. Attardi B, et al. **Endocrinology** 1986 Jul;119(1):274-83

Food-restricted, prepubertal, female rats: rapid recovery of luteinizing hormone pulsing with excess food, and full recovery of pubertal development with gonadotropin-releasing hormone. Bronson FH. **Endocrinology** 1986 Jun;118(6):2483-7

Gonadotropin-releasing hormone (GnRH) rapidly stimulates the formation of inositol phosphates and diacyglycerol in rat granulosa cells: further evidence for the involvement of Ca2+ and protein kinase C in the action of GnRH. Davis JS, et al. **Endocrinology** 1986 Jun; 118(6):2561-71

Cytodifferentiation of granulosa cells induced by gonadotropin-releasing hormone promotes fibronectin secretion. Dorrington JH, et al. **Endocrinology** 1986 May;118(5):2065-71

Gonadotropin-releasing hormone-mediated desensitization of cultured rat anterior pituitary cells can be uncoupled from luteinizing hormone release. Jinnah HA, et al. **Endocrinology** 1986 Jun;118(6):2599-604

Receptor binding and gonadotropin-releasing activity of a novel chicken gonadotropin-releasing hormone ([His5, Trp7, Tyr8]GnRH) and a D-Arg6 analog. Millar RP, et al. **Endocrinology** 1986 Jul; 119(1):224-31

Functional characteristics of the luteinizing hormone-releasing hormone pulse generator in conscious unrestrained female rabbits: activation by norepinephrine. Ramirez VD, et al. **Endocrinology** 1986 Jun; 118(6):2331-9

Baseline and luteinizing hormone-releasing hormone-perturbed patterns of estrogen receptor distribution in anterior pituitary cell nuclei. Singh P, et al. **Endocrinology** 1986 Jun;118(6):2355-61

Effects of epinephrine, norepinephrine, and dopamine on gonadotropin-releasing hormone-induced secretion of luteinizing hormone in vitro. Swartz SR, et al. **Endocrinology** 1986 Jun; 118(6):2425-31

Biosynthesis, glycosylation, and secretion of rat luteinizing hormone alpha- and beta-subunits: differential effects of orchiectomy and gonadotropin-releasing hormone. Vogel DL, et al. **Endocrinology** 1986 Jul;119(1):202-13

Regulation of human prolactin secretion by gonadotropin-releasing hormone in vitro. Blackwell RE, et al. **Fertil Steril** 1986 Jul; 46(1):26-31

Intranasal peptide contraception by inhibition of ovulation with the gonadotropin-releasing hormone superagonist nafarelin: six months' clinical results. Gudmundsson JA, et al. **Fertil Steril** 1986 May; 45(5):617-23

GnRH ovulation induction [letter] Leyendecker G. **Fertil Steril** 1986 May; 45(5):737-8

Stimulation of multiple follicular growth for in vitro fertilization by administration of pulsatile luteinizing hormone-releasing hormone during the midfollicular phase. Shaw RW, et al. **Fertil Steril** 1986 Jul; 46(1):135-7

Single dose responses to the gonadotropin-releasing hormone agonist analogue [(imBz 1)-D-His6,Pro9-NEt]GnRH. Doelle GC, et al. **Horm Metab Res** 1986 Mar;18(3):201-2

Active immunization of female dogs against luteinizing hormone releasing hormone (LHRH) and its effects on ovarian steroids and estrus suppression. Singh V. **Indian J Exp Biol** 1985 Dec;23(12):667-72

Specificity and affinity characteristics of dog luteinizing hormone releasing hormone (LHRH) antibodies. Singh V. **Indian J Exp Biol** 1985 Dec;23(12):673-5

Lack of correlation between fertility and sperm numbers in male rats treated with histrelin, a potent LHRH agonist. Foldesy RG, et al. **J Androl** 1986 May-Jun;7(3):140-6

Relationships among concentrations of four opioid neuropeptides and luteinizing hormone-releasing hormone in neural tissues of beef cows following early weaning. Malven PV, et al. **J Anim Sci** 1986 Mar; 62(3):723-33

Effects of pulsatile injection of GnRH into 6- to 14-wk-old Holstein bulls. Miller CJ, et al. **J Anim Sci** 1986 May;62(5):1332-9

Anterior pituitary concentrations of gonadotropins, GnRH-receptors and ovarian characteristics following early weaning in beef cows. Parfet JR, et al. **J Anim Sci** 1986 Mar;62(3):717-22

Pulsatile or continuous infusion of luteinizing hormone-releasing hormone and hormonal concentrations in prepubertal beef heifers. Skaggs CL, et al. **J Anim Sci** 1986 Apr;62(4):1034-48

Effects of intermittent injections of LHRH on secretory patterns of LH and FSH and ovarian follicular growth during postpartum anovulation in suckled beef cows. Spicer LJ, et al. **J Anim Sci** 1986 May; 62(5):1317-23

Effects of intermittent injections of LHRH on specific binding of 125I-labeled gonadotropins to granulosa and theca, and concentrations of steroids in serum and ovarian follicles during postpartum anovulation in suckled beef cows. Spicer LJ, et al. **J Anim Sci** 1986 May; 62(5):1324-31

Participation of voltage-dependent calcium channels in the action of gonadotropin-releasing hormone. Chang JP, et al. **J Biol Chem** 1986 Jul 15;261(20):9105-8

Single subcutaneous doses of a luteinizing hormone-releasing hormone antagonist suppress serum gonadotropin and testosterone levels in normal men. Pavlou SN, et al. **J Clin Endocrinol Metab** 1986 Aug; 63(2):303-8

Pituitary self-priming actions of gonadotropin-releasing hormone. Kinetics of estradiol's potentiating effects on gonadotropin-releasing hormone-facilitated luteinizing hormone and follicle-stimulating hormone release in healthy postmenopausal women. Veldhuis JD, et al. **J Clin Invest** 1986 Jun;77(6):1849-56

Varying the patterns and concentrations of gonadotrophin-releasing hormone stimulation does not alter the ratio of LH and FSH released from perifused sheep pituitary cells. McIntosh JE, et al. **J Endocrinol** 1986 May;109(2):155-61

Testosterone metabolites do not participate in the control of hypothalamic LH-releasing hormone. Zanisi M, et al. **J Endocrinol** 1986 May; 109(2):291-6

Isolation and characterization of a new peptide from hypothalamus and pituitary using a monoclonal antibody to LHRH. Knapp RJ, et al. **J Neuroimmunol** 1986 Jun;11(4):335-51

Prolonged controlled-release of nafarelin, a luteinizing hormone-releasing hormone analogue, from biodegradable polymeric implants: influence of composition and molecular weight of polymer. Sanders LM, et al. **J Pharm Sci** 1986 Apr;75(4):356-60

Absence of LHRH effect on testosterone production by Leydig cells from fetal mouse testis. Pointis G, et al. **J Steroid Biochem** 1986 Jan; 24(1):307-10

Effects of chronic administration of LH releasing hormone on age-dependent activities of testicular 4-ene-5 alpha-reductase and 17 beta-ol-dehydrogenase in mice. Takeyama M, et al. **J Steroid Biochem** 1986 May;24(5):1095-6

The undescended testis: is there a role for LHRH? [editorial] **Lancet** 1986 May 17;1(8490):1133-4

Luteinising-hormone-releasing hormone and cryptorchidism [letter] Chilvers C, et al. **Lancet** 1986 Jul 12;2(8498):101

Prolonged pulsatile release of gonadotropin-releasing hormone from the guinea pig hypothalamus in vitro. McKibbin PE, et al. **Life Sci** 1986 Jun 9;38(23):2145-50

Modulation and role of Ca2+ in LH and LHRH agonist action in rat Leydig cells. Cooke BA, et al. **Med Biol** 1986;63(5-6):259-63

Peptidergic secretory granules isolated from the brain: a model system for study of intracellular aspects of the process of peptide secretion. Barnea A. **Methods Enzymol** 1986;124:254-65

Detection of a high-molecular-weight LHRH precursor by cell-free translation of mRNA from human, rat, and mouse hypothalamus. Curtis A, et al. **Methods Enzymol** 1986;124:318-35

Measurement of neuropeptide release: in vitro and in vivo procedures. Levine JE, et al. **Methods Enzymol** 1986;124:466-94

Autoradiographic localization of brain receptors for peptide hormones: angiotensin II, corticotropin-releasing factor, and gonadotropin-releasing hormone. Millan M, et al. **Methods Enzymol** 1986;124:590-606

Computer-controlled perifusion system for neuroendocrine tissues: development and applications. Negro-Vilar A, et al. **Methods Enzymol** 1986;124:67-79

Luciferin derivatization of ligands for development of nonisotopic binding assays. Schaeffer JM. **Methods Enzymol** 1986;124:29-35

LHRH promotes the synthesis and release of a 87,000 Da protein (GP-87) by enriched gonadotrophs. Chanat E, et al. **Mol Cell Endocrinol** 1986 Jul;46(2):109-19

Degradation of luteinizing hormone-releasing hormone (LHRH) and an LHRH agonist by the rat testis. Hedger MP, et al. **Mol Cell Endocrinol** 1986 Jun;46(1):59-70

Hormone-stimulated redistribution of gonadotrope protein kinase C in vivo: dependence on Ca2+ influx. McArdle CA, et al. **Mol Pharmacol** 1986 Jun;29(6):570-6

Effects of estradiol and progesterone on immunoreactive forms of hypothalamic luteinizing hormone-releasing hormone. Drouva SV, et al. **Neuroendocrinology** 1986;43(1):32-7

Gonadotropin-releasing hormone neuronal system of the white-footed mouse, Peromyscus leucopus. Glass JD. **Neuroendocrinology** 1986; 43(2):220-9

In vitro LHRH release from superfused hypothalamus as a function of the rat estrous cycle: effect of progesterone. Kim K, et al. **Neuroendocrinology** 1986;42(5):392-8

Hypothalamic and pituitary enzymatic degradation of luteinizing hormone-releasing hormone during the 4-day estrous cycle of the rat. Assessment by high-performance liquid chromatography. Lapp CA, et al. **Neuroendocrinology** 1986;43(2):230-8

Removal of the vomeronasal organ impairs lordosis in female hamsters: effect is reversed by luteinising hormone-releasing hormone. Mackay-Sim A, et al. **Neuroendocrinology** 1986;42(6):489-93

Patch clamp recordings of single ion channel activation by gonadotrophin-releasing hormone in ovine pituitary gonadotrophs. Mason WT, et al. **Neuroendocrinology** 1986;43(2):205-19

Activation of estradiol-positive feedback at puberty: estradiol sensitizes the LHRH-releasing system at two different biochemical steps. Ojeda SR, et al. **Neuroendocrinology** 1986;43(2):259-65

Effects of cupric acetate on hypothalamic gonadotropin-releasing hormone release in intact and ovariectomized rabbits. Pau KY, et al. **Neuroendocrinology** 1986;43(2):197-204

Postnatal morphological changes in rat LHRH neurons correlated with sexual maturation. Wray S, et al. **Neuroendocrinology** 1986; 43(2):93-7

Use of cryoprotectant to maintain long-term peptide immunoreactivity and tissue morphology. Watson RE Jr, et al. **Peptides** 1986 Jan-Feb; 7(1):155-9

Pharmacological evidence of catecholaminergic involvement in the behavioral effects of luteinizing hormone releasing hormone in rats. Mora S, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):433-8

Activation of two different but complementary biochemical pathways stimulates release of hypothalamic luteinizing hormone-releasing hormone. Ojeda SR, et al. **Proc Natl Acad Sci USA** 1986 Jul; 83(13):4932-6

Gonadotropin-releasing hormone differentially regulates expression of the genes for luteinizing hormone alpha and beta subunits in male rats. Papavasiliou SS, et al. **Proc Natl Acad Sci USA** 1986 Jun; 83(11):4026-9

The neural control of luteinizing hormone release. Summerlee AJ. **Prog Neurobiol** 1986;26(2):147-78

Radioimmunoassay of [D-Trp6]-luteinizing hormone-releasing hormone: its application to animal pharmacokinetic studies after single injection and long-acting formulation administration. Ezan E, et al. **Regul Pept** 1986 Apr;14(2):155-67

[Luteinized unruptured follicle syndrome after induction of ovulation by pulsatile administration of gonadorelin (letter)] Pfister P, et al. **Presse Med** 1986 May 10;15(19):887-8 **(Fre)**

[Phase I study with LH-RH agonist, ICI 118630] Usami M, et al. **Hinyokika Kiyo** 1986 Mar;32(3):493-501 (Eng. Abstr.) **(Jpn)**

[The effect of synthetic chicken LH-RH on the release of LH and FSH and ovulation in rats (a comparative study of synthetic mammalian LH-RH and chicken LH-RH)] Takahashi Y, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Feb 20;62(2):126-39 (Eng. Abstr.) **(Jpn)**

[Stimulation of ovulation with analogs of luliberin, androstenol and their combination with L-DOPA] Lupanova GE. **Farmakol Toksikol** 1986 Mar-Apr;49(2):35-7 (Eng. Abstr.) **(Rus)**

LIPOTROPIN

Dysregulation of plasma pro-opiomelanocortin-related peptides in neurotic depression. Genazzani AR, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):1-6

Plasma beta-endorphin and beta-lipotropin in patients with end-stage renal disease--effects of hemodialysis. Elias AN, et al. **Nephron** 1986; 43(3):173-6

LITHIUM

Effect of renal nerve activity on tubular sodium and water reabsorption in dog kidneys as determined by the lithium clearance method. Abildgaard U, et al. **Acta Physiol Scand** 1986 Feb;126(2):251-7

Renal function and lithium: a longitudinal study. DePaulo JR Jr, et al. **Am J Psychiatry** 1986 Jul;143(7):892-5

Lithium potentiation of tricyclic antidepressants following lack of T3 potentiation. Garbutt JC, et al. **Am J Psychiatry** 1986 Aug; 143(8):1038-9

Safety of the combination of lithium and neuroleptic drugs. Goldney RD, et al. **Am J Psychiatry** 1986 Jul;143(7):882-4

Identifying lithium-responsive bipolar depressed patients using nuclear magnetic resonance. Rosenthal J, et al. **Am J Psychiatry** 1986 Jun; 143(6):779-80

Interactions of drugs and electroshock treatment on cerebral monoaminergic systems. Barkai AI. **Ann NY Acad Sci** 1986; 462:147-62

Lithium-induced reduction in intracellular inositol supply in cholinergically stimulated parotid gland. Downes CP, et al. **Biochem J** 1986 Feb 15;234(1):199-204

Mechanism of inhibition by lithium of sodium transport in the toad bladder. Herrera FC, et al. **Biol Cell** 1985;55(3):257-63

Lithium counteracts carbamazepine-induced leukopenia while increasing its therapeutic effect. Brewerton TD. **Biol Psychiatry** 1986 Jun; 21(7):677-85

Lithium mechanisms in bipolar illness and altered intracellular calcium functions. Meltzer HL. **Biol Psychiatry** 1986 May;21(5-6):492-510

Lithium and haloperidol [letter] Nemes ZC, et al. **Biol Psychiatry** 1986 May;21(5-6):568-9

Regular 48-hour cycling of sleep duration and mood in a 35-year-old woman: use of lithium in time isolation. Welsh DK, et al. **Biol Psychiatry** 1986 May;21(5-6):527-37

Lithium and piroxicam [letter] Shelley RK. **Br J Psychiatry** 1986 Mar; 148:343

The uptake of lithium ions by synthetic carbonated hydroxyapatite. Mayer I, et al. **Calcif Tissue Int** 1986 May;38(5):293-5

The complexation of 'crowned' 4-(2,4-dinitrophenylazo)phenol with alkali and alkaline earth metal ions, and its application to the determination of Li(I) in a pharmaceutical preparation. Nakashima K, et al. **Chem Pharm Bull (Tokyo)** 1986 Jan;34(1):168-73

Erythrocyte cation transport activities as a function of cell age. Hentschel WM, et al. **Clin Chim Acta** 1986 May 30;157(1):33-43

The renal lithium clearance and its correlations with other biological variables: observations in a large group of physically healthy persons. Schou M, et al. **Clin Nephrol** 1986 Apr;25(4):207-11

Lithium chloride as an enhancing agent for metaphase preparations from rodent lymphocytes. Dowling PK, et al. **Cytogenet Cell Genet** 1986; 42(1-2):33-5

Nephrotoxicity of cyclosporin A. A lithium clearance and micropuncture study in rats. Dieperink H, et al. **Eur J Clin Invest** 1986 Feb; 16(1):69-77

myo-Inositol reverses Li+-induced inhibition of phosphoinositide turnover and ornithine decarboxylase induction during early lymphocyte activation. Mustelin T, et al. **Eur J Immunol** 1986 Jul; 16(7):859-61

The effects of desipramine, zimelidine, electroconvulsive treatment and lithium on rat brain biogenic amines: a comparison with peripheral changes. Karoum F, et al. **Eur J Pharmacol** 1986 Mar 4; 121(3):377-85

Lithium and hematopoietic toxicity. I. Recovery in vivo of murine hematopoietic stem cells (CFU-S and CFU-Mix) after single-dose administration of cyclophosphamide. Gallicchio VS. **Exp Hematol** 1986 Jun;14(5):395-400

Evidence for an intestinal lithium excretion in rats. Kersten L, et al.

Exp Pathol 1986;29(1):55-63
Influence of the incubation of cells with zinc and lithium ions on GVH reactivity of cells and on their ability to form haemopoietic colonies. Hrubá A, et al. **Folia Biol (Praha)** 1986;32(2):81-90
Time-related response of central serotonergic function to lithium administration. Otero Losada ME, et al. **Gen Pharmacol** 1986; 17(3):333-7
Thermoluminescence response of LiF to alpha radiation. Barber DE, et al. **Health Phys** 1986 Jun;50(6):805-8
Uses of lithium in patients without major affective illness. van der Kolk BA. **Hosp Community Psychiatry** 1986 Jul;37(7):675, 684
In vitro study of local solubility of uric acid stones with lithium carbonate. Jávor A, et al. **Int Urol Nephrol** 1985;17(4):315-8
Who responds to prophylactic lithium? Abou-Saleh MT, et al. **J Affective Disord** 1986 Mar-Apr;10(2):115-25
Folic acid enhances lithium prophylaxis. Coppen A, et al. **J Affective Disord** 1986 Jan-Feb;10(1):9-13
Lithium-resistant adolescent mania. Hsu LK. **J Am Acad Child Psychiatry** 1986 Mar;25(2):280-3
Inhibition by lithium of the hydroosmotic action of vasopressin in the isolated perfused cortical collecting tubule of the rabbit. Cogan E, et al. **J Clin Invest** 1986 May;77(5):1507-14
Lithium interaction with sulindac and naproxen. Ragheb M, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):150-4
Rapid antidepressant effect of addition of lithium to tranylcypromine. Tariot PN, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):165-7
Use of carbamazepine in acute psychosis: a controlled study. Lenzi A, et al. **J Int Med Res** 1986;14(2):78-84
The in situ perfused spinal cord of the rat. Applicability of drugs and chemicals, sodium-lithium exchange, and calcium reduction to functional intact central nervous system tissue. Deutschmann W, et al. **J Pharmacol Methods** 1986 Apr;15(2):143-55
Effects of bipolar affective disorder and lithium administration on the cholinergic system in human blood. Jope RS, et al. **J Psychiatr Res** 1986;20(1):9-18
Spontaneous toxicokinetics of lithium during a therapeutic overdose with renal failure. Bismuth C, et al. **J Toxicol Clin Toxicol** 1986; 24(3):261-8
Pharmacokinetics of lithium in the dog. Rosenthal RC, et al. **J Vet Pharmacol Ther** 1986 Mar;9(1):81-7
Angiotensin converting enzyme inhibitors and lithium treatment [letter] Douste-Blazy P, et al. **Lancet** 1986 Jun 21;1(8495):1448
Symptomatic reactive hypoglycemia during glucose tolerance test in lithium-treated patients. Shah JH, et al. **Metabolism** 1986 Jul; 35(7):634-9
Acute and chronic effects of lithium chloride on GABA-ergic function in the rat corpus striatum and frontal cerebral cortex. Otero Losada ME, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Feb; 332(2):169-72
Effects of lithium on visual perception in manic-depressive patients without acute symptomatology. Kropf D, et al. **Neuropsychobiology** 1986;15(1):34-42
Lithium treatment and blood pressure. Vestergaard P, et al. **Pharmacopsychiatry** 1986 Mar;19(2):73-4
Erythrocyte lithium transport during lithium treatment in patients with affective disorders. Zaremba D, et al. **Pharmacopsychiatry** 1986 Mar; 19(2):63-7
Cholecystokinin octapeptide and lithium produce different effects on feeding and taste aversion learning. Ervin GN, et al. **Physiol Behav** 1986;36(3):507-12
Lithium treatment of mania: clinical characteristics, specificity of symptom change, and outcome. Swann AC, et al. **Psychiatry Res** 1986 Jun; 18(2):127-41
[Schizophrenic excitement and the role of lithium in its therapy (apropos of 2 recent cases)] Skurnik N, et al. **Ann Med Psychol (Paris)** 1985 Dec;143(10):960-2 **(Fre)**
[Rapid response of a disorder to the addition of lithium carbonate: panic resistant to tricyclic antidepressants] Cournoyer J. **Can J Psychiatry** 1986 May;31(4):335-8 (Eng. Abstr.) **(Fre)**
[Determination of micro-quantities of serum lithium by atomic absorption spectrophotometry. Significance and applications] Moynier I, et al. **Pathol Biol (Paris)** 1986 Jan;34(1):51-6 (Eng. Abstr.) **(Fre)**
[Effect of lithium on the immune system] Skotnicki AB, et al. **Przegl Lek** 1985;42(12):805-10 **(Pol)**
[Effect of lithium oxybutyrate on the viability of preserved donor kidney] Sholokhov VM, et al. **Farmakol Toksikol** 1986 May-Jun;49(3):69-70 (Eng. Abstr.) **(Rus)**
[Use of lithium oxybutyrate in the combined therapy of burn injury patients] Iurasov II, et al. **Voen Med Zh** 1986 Apr;(4):20-1 **(Rus)**
[Granulocytosis induced by lithium. Possible clinical applications] Alvarez E, et al. **Med Clin (Barc)** 1986 Feb 15;86(6):233-5 (Eng. Abstr.) **(Spa)**

LORAZEPAM

Lorazepam dependence and chronic psychosis [letter] Carr AC. **Br J Psychiatry** 1986 Mar;148:344
Sedative effects and impaired learning and recall after single oral doses of lorazepam. Shader RI, et al. **Clin Pharmacol Ther** 1986 May; 39(5):526-9
Alprazolam and lorazepam single and multiple-dose effects on psychomotor skills and sleep. Subhan Z, et al. **Eur J Clin Pharmacol** 1986;29(6):709-12
Determination of lormetazepam in plasma by gas chromatography and electron-capture detection. Zecca L, et al. **J Chromatogr** 1986 Apr 25; 377:368-72
Lorazepam-associated drug dependence [letter] Ross M. **J R Coll Gen Pract** 1986 Feb;36(283):86
A late-appearing benzodiazepine-induced hypoactivity that is not reversed by a receptor antagonist. Lister RG, et al. **Psychopharmacology (Berlin)** 1986;88(4):520-4

MANIC DISORDER

Open multicentre trial of zuclopenthixol in mania and schizophrenia based on the AMDP scales. Bobon D, et al. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):152-76
Rapid reduction of mania by means of reserpine therapy [letter] Telner JI, et al. **Am J Psychiatry** 1986 Aug;143(8):1058
Lithium-resistant adolescent mania. Hsu LK. **J Am Acad Child Psychiatry** 1986 Mar;25(2):280-3
Elevated blood neutrophil concentration in mania [letter] Wolf JM. **J Clin Psychiatry** 1986 Jun;47(6):331
Medication effects on one-carbon metabolism in schizophrenia, mania, and major depression. Morere DA, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):155-61
Lithium treatment of mania: clinical characteristics, specificity of symptom change, and outcome. Swann AC, et al. **Psychiatry Res** 1986 Jun; 18(2):127-41
[Studies of the side effect profile of clozapine] Nitzsche M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1986 Mar;38(3):148-52 (Eng. Abstr.) **(Ger)**

MEMORY

Glucose modulation of memory storage processing. Gold PE. **Behav Neural Biol** 1986 May;45(3):342-9
The use of avoidance training in studies of modulation of memory storage. Gold PE. **Behav Neural Biol** 1986 Jul;46(1):87-98
Epinephrine modulates long-term retention of an aversively motivated discrimination. Introini-Collison IB, et al. **Behav Neural Biol** 1986 May; 45(3):358-65
The course of the decrease of hypothalamic beta-endorphin induced by training, and the development of the effect of beta-endorphin on the retrieval of inhibitory avoidance in rats. Izquierdo I, et al. **Braz J Med Biol Res** 1985;18(3):391-5
Sedative effects and impaired learning and recall after single oral doses of lorazepam. Shader RI, et al. **Clin Pharmacol Ther** 1986 May; 39(5):526-9
Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. Peloquin LJ, et al. **J Abnorm Psychol** 1986 Feb;95(1):88-98
Conditioned aversions and their memories in 5-day-old rats during suckling. Kehoe P, et al. **J Exp Psychol [Anim Behav]** 1986 Jan; 12(1):40-7
Participation of angiotensin II in learning and memory. II. Interactions of angiotensin II with dopaminergic drugs. Yonkov DI, et al. **Methods Find Exp Clin Pharmacol** 1986 Apr;8(4):203-6
Benzodiazepine impairs and beta-carboline enhances performance in learning and memory tasks. Venault P, et al. **Nature** 1986 Jun 26-Jul 2;321(6073):864-6
Effects of repeated doses of fluvoxamine, mianserin and placebo on memory and measures of sedation. Curran HV, et al. **Psychopharmacology (Berlin)** 1986;89(3):360-3
Effects of chlordiazepoxide on cued radial maze performance in rats. Hodges H, et al. **Psychopharmacology (Berlin)** 1986;88(4):460-6
Haloperidol facilitates memory retrieval in the rat. Sara SJ. **Psychopharmacology (Berlin)** 1986;89(3):307-10
[Chief trends in research into the neurochemical mechanisms of learning and memory] Kruglikov RI. **Zh Vyssh Nerv Deiat** 1986 Mar-Apr; 36(2):226-31 (24 ref.) **(Rus)**

MENTAL DISORDERS

27th Annual Psychopharmacology Meeting. Jeseník Spa, January 1985. Abstracts. **Act Nerv Super (Praha)** 1986 Mar;28(1):27-49
The closing of the organic versus functional dichotomy [letter] Fox HA. **Am J Psychiatry** 1986 Aug;143(8):1059-60
Placebo problems in psychotherapy research. Social-psychological alternatives to chemotherapy concepts. Wilkins W. **Am Psychol** 1986 May;41(5):551-6
Skin conductance habituation and cerebrospinal fluid 5-hydroxyindoleacetic acid in suicidal patients. Edman G, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):586-92

Hospital doctors' management of psychological problems. Mayou R, et al. **Br J Psychiatry** 1986 Feb;148:194–7

Neuroleptic blood levels and clinical response. Rockland LH. **Can J Psychiatry** 1986 May;31(4):299–303

Ethnicity and psychopharmacology. Lin KM, et al. **Cult Med Psychiatry** 1986 Jun;10(2):151–65

Institutional therapy for adolescents. Uribe VM, et al. **Curr Psychiatr Ther** 1986;23:45–9

Biologic therapy in a rehabilitation system for mental patients. Vovin RY. **Curr Psychiatr Ther** 1986;23:269–74

New psychoactive drugs. Murray JB. **Genet Soc Gen Psychol Monogr** 1985 Nov;111(4):429–53

Patients' competency to give informed consent to medication. Beck JC, et al. **Hosp Community Psychiatry** 1986 Apr;37(4):400–2

In again, out again: preliminary evaluation of a state hospital's worst recidivists. Geller JL. **Hosp Community Psychiatry** 1986 Apr;37(4):386–90

Psychotropic prescribing patterns of nonpsychiatric residents in a general hospital in 1973 and 1982. Haggerty JJ Jr, et al. **Hosp Community Psychiatry** 1986 Apr;37(4):357–61

Uses of lithium in patients without major affective illness. van der Kolk BA. **Hosp Community Psychiatry** 1986 Jul;37(7):675, 684

A consumer survey of an adolescent unit. Pyne N, et al. **J Adolesc** 1986 Mar;9(1):63–72

Treatment of uncooperative psychiatric patients in the community [letter] Spencer S. **Lancet** 1986 May 10;1(8489):1095

The limits of liability for psychiatric malpractice. Taub S. **Leg Med** 1985;:258–70

Diagnostic and therapeutic problems in the psychopharmacological treatment of the elderly patient. Ravizza L. **Neuropsychobiology** 1986;15 Suppl 1:15–8

The use of psychotropic drugs in elderly patients with chronic mental illness. Howell T, et al. **New Dir Ment Health Serv** 1986 Mar;(29):47–58

The AMDP-system in clinical psychopharmacology. Bobon D, et al. **Pharmacopsychiatry** 1986 Mar;19(2):55–7

Annual NCDEU meeting (1985): New Clinical Drug Evaulation Unit. Abridged proceedings. **Psychopharmacol Bull** 1986;22(1):1–337

Use of placebo in clinical trials. Rickels K. **Psychopharmacol Bull** 1986;22(1):19–24

[Use of fluphenazine decanoate in psychiatric therapy. Multicenter study in 1095 patients preselected for long-acting neuroleptic treatment] Bogliolo C. **Minerva Psichiatr** 1986 Jan–Mar;27(1):1–18 **(Ita)**

[Basic principles of the rehabilitation process of the mental patient] Grecu G. **Rev Med Interna [Neurol Psihiatr]** 1985 Oct–Dec;30(4):241–53 **(Rum)**

[Clinical aspects and significance of measuring concentrations of neuroleptics and antidepressants in the blood] Cheshkova E, et al. **Zh Nevropatol Psikhiatr** 1986;86(4):573–6 (Eng. Abstr.) **(Rus)**

[Clinico-pharmacokinetic aspects of the optimization of psychopharmacotherapy] Gor'kov VA, et al. **Zh Nevropatol Psikhiatr** 1986;86(4):567–73 (Eng. Abstr.) **(Rus)**

[Clinico-biochemical approach to the problem of psychogenic disorders and background] Pelipas VE, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):409–12 (Eng. Abstr.) **(Rus)**

[Experimental modeling of the cellular mechanisms of various psychopathological syndromes] Rabinovich MIa. **Zh Vyssh Nerv Deiat** 1986 Mar–Apr;36(2):242–51 (22 ref.) **(Rus)**

MENTAL PROCESSES

Mental and physical components of sawmill operatives' workload. Fibiger W, et al. **Ergonomics** 1986 Mar;29(3):363–75

[Physical work capacity under different levels of measured stress in relation to type-A personality in intellectual workers] Mincheva L, et al. **Probl Khig** 1985;10:20–32 (Eng. Abstr.) **(Bul)**

MESORIDAZINE

Mesoridazine and thioridazine: clinical effects and blood levels in refractory schizophrenics. Vital-Herne J, et al. **J Clin Psychiatry** 1986 Jul;47(7):375–9

METHOTRIMEPRAZINE

Immobilon [letter] **Vet Rec** 1986 Apr 19;118(16):466

METHYLPHENIDATE

Vicissitudes of follow-up studies: differential effects of parent training and stimulant medication with hyperactives. Firestone P, et al. **Am J Orthopsychiatry** 1986 Apr;56(2):184–94

Determination of methylphenidate and its main metabolite in plasma by gas chromatography-chemical ionization mass spectrometry. Nakajima K, et al. **Chem Pharm Bull (Tokyo)** 1986 Apr;34(4):1701–8

A neuropathic substrate for stimulant drug effects in hyperactive children. Evans RW, et al. **Clin Neuropharmacol** 1986;9(3):264–81

Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. Peloquin LJ, et al. **J Abnorm Psychol** 1986 Feb;95(1):88–98

A thin layer chromatographic method for high volume screening of urine for methylphenidate abuse. Manno BR, et al. **J Anal Toxicol** 1986 May–Jun;10(3):116–9

Comparing classroom and clinic measures of attention deficit disorder: differential, idiosyncratic, and dose-response effects of methylphenidate. Rapport MD, et al. **J Consult Clin Psychol** 1986 Jun;54(3):334–41

Methylphenidate and cognitive therapy in children with attention deficit disorder: a double-blind trial. Brown RT, et al. **J Dev Behav Pediatr** 1986 Jun;7(3):163–74

The therapeutic effect of clonidine in attention deficit disorder with hyperactivity: a comparison with placebo and methylphenidate. Hunt RD, et al. **Psychopharmacol Bull** 1986;22(1):229–36

Methylphenidate: rate-dependent effects on hyperactivity. Rapport MD, et al. **Psychopharmacol Bull** 1986;22(1):223–8

[Effect of tsentedrin on the work capacity of operator specialists] Bakharev VD, et al. **Voen Med Zh** 1986 Mar;(3):44–5 **(Rus)**

METHYSERGIDE

Antimigraine drug interactions with 5-hydroxytryptamine1A receptors. Hiner BC, et al. **Ann Neurol** 1986 May;19(5):511–3

Methylergometrine, an active metabolite of methysergide. Müller-Schweinitzer E, et al. **Cephalalgia** 1986 Mar;6(1):35–41

Pharmacokinetics of methysergide and its metabolite methylergometrine in man. Bredberg U, et al. **Eur J Clin Pharmacol** 1986;30(1):75–7

Regional serotonin receptor studies: chronic methysergide treatment induces a selective and dose-dependent decrease in serotonin-2 receptors in mouse cerebral cortex. May PC, et al. **Life Sci** 1986 May 12;38(19):1741–7

MOTIVATION

Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. de Wit H, et al. **Drug Alcohol Depend** 1986 Feb;16(4):341–60

MOTOR ACTIVITY

Pituitary-adrenal correlates of schedule-induced polydipsia and wheel running in rats. Tazi A, et al. **Behav Brain Res** 1986 Mar;19(3):249–56

Within-session data [letter] Lynch MR, et al. **Biol Psychiatry** 1986 May;21(5–6):573–4

Inhibition of amphetamine-induced locomotor activity by injection of carbachol into the anterior hypothalamic/preoptic area: pharmacological and electrophysiological studies in the rat. Brudzynski SM, et al. **Brain Res** 1986 Jun 18;376(1):47–56

Denervation-like postsynaptic supersensitivity to dopamine agonists induced by microinjection of colchicine into the substantia nigra pars compacta. Kamata K, et al. **Brain Res** 1986 Mar 5;367(1–2):1–7

Effects of diazepam on circadian phase advances and delays. Ralph MR, et al. **Brain Res** 1986 May 7;372(2):405–8

Dopamine modulates neuronal activities related to motor performance in the monkey prefrontal cortex. Sawaguchi T, et al. **Brain Res** 1986 Apr 23;371(2):404–8

Involvement of neuronal cell bodies of the mesencephalic locomotor region in the initiation of locomotor activity of freely behaving rats. Brudzynski SM, et al. **Brain Res Bull** 1986 Mar;16(3):377–81

Circling from unilateral VTA morphine: direction is controlled by environmental stimuli. Wise RA, et al. **Brain Res Bull** 1986 Feb;16(2):267–9

Dissociation of the toxic and behavioral effects of lithium on rats. Teixeira NA, et al. **Braz J Med Biol Res** 1985;18(3):349–54

Dopaminergic mechanisms and motor function: characterization of D-1 and D-2 dopamine receptor interactions. Barone P, et al. **Eur J Pharmacol** 1986 Apr 9;123(1):109–14

Chronic corticosterone administration in rats: behavioral and biochemical evidence of increased central dopaminergic activity. Wolkowitz O, et al. **Eur J Pharmacol** 1986 Apr 2;122(3):329–38

Sensorimotor changes following lesion of mid-dorsal caudate nucleus in rats. Mulgaonker VK, et al. **Indian J Physiol Pharmacol** 1985 Jul–Sep;29(3):153–8

Chronic treatment with iprindole reduces immobility of rats in the behavioural 'despair' test by activating dopaminergic mechanisms in the brain. Berettera C, et al. **J Pharm Pharmacol** 1986 Apr;38(4):313–5

Dose related sequence of effects induced by the DA agonist 2-(N,N-dipropyl)-amino-5,6-dihydroxytetralin. Doaré L, et al. **J Pharmacol** 1986 Jan–Mar;17(1):60–4

Effect of glucose on amphetamine-induced motor behavior. White NM, et al. **Life Sci** 1986 Jun 16;38(24):2255–62

Involvement of dopaminergic, cholinergic, and glutamatergic mechanisms in the actions of phencyclidine-like drugs. Johnson KM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:52–66

Psychopharmacology of phencyclidine. Marwah J, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:127-33

Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. Ehlers CL, et al. **Neuroendocrinology** 1986;42(6):467-74

Infusion of adrenergic receptor agonists and antagonists into the locus coeruleus and ventricular system of the brain. Effects on swim-motivated and spontaneous motor activity. Weiss JM, et al. **Neuropharmacology** 1986 Apr;25(4):367-84

Distinct functions for dopamine and serotonin in locomotor behaviour: evidence using the 5-HT1 agonist RU 24969 in globus pallidus-lesioned rats. Oberlander C, et al. **Neurosci Lett** 1986 Jun 18;67(2):113-8

Simultaneous monitoring of dopamine release in rat frontal cortex, nucleus accumbens and striatum: effect of drugs, circadian changes and correlations with motor activity. O'Neill RD, et al. **Neuroscience** 1985 Sep;16(1):49-55

Effect of DN-1417, a thyrotropin releasing hormone analog, on dopaminergic neurons in rat brain. Nakahara T, et al. **Peptides** 1985 Nov-Dec;6(6):1093-9

Behavioral and biochemical assessment of time-related changes in globus pallidus and striatal dopamine induced by intranigrally administered neurotensin. Napier TC, et al. **Peptides** 1985 Nov-Dec;6(6):1057-68

Involvement of extrapyramidal motor mechanisms in the suppression of locomotor activity by antipsychotic drugs: a comparison between the effects produced by pre- and post-synaptic inhibition of dopaminergic neurotransmission. Ahlenius S, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1409-15

Lack of evidence for the involvement of catecholaminergic mechanisms in the behavioral anti-methamphetamine effect of L-histidine in the mouse. Itoh Y, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):571-4

Effects of serotonergic agonists and antagonists on the locomotor activity of neonatal rats. Lucot JB, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):537-41

Dissociation of locomotor depression and ChE activity after DFP, soman and sarin. Lynch MR, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):941-7

Pharmacological evidence of catecholaminergic involvement in the behavioral effects of luteinizing hormone releasing hormone in rats. Mora S, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):433-8

Effects of acute and chronic bupropion on locomotor activity and dopaminergic neurons. Nielsen JA, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):795-9

Biochemical and behavioral correlates of chronic stress: effects of tricyclic antidepressants. Soblosky JS, et al. **Pharmacol Biochem Behav** 1986 May; 24(5):1361-8

Antagonistic behavioral effects of calcitonin and amphetamine in the rat. Twery MJ, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1203-7

Effects of acute and long-term treatments with thyrotropin-releasing hormone on locomotor activity and jumping behavior in mice. Ushijima I, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1423-8

Comparison of motor depressant effects of caerulein and N-propylnorapomorphine in mice. Vasar E, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):469-78

Comparison of circling induced by unilateral intrastriatal microinjections of haloperidol, clozapine and CCK-8 in rats. Weiss F, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):983-9

Wheel-running activity after kainic acid injection into lateral hypothalamus of rats. Blake DJ, et al. **Physiol Behav** 1986; 36(6):1009-16

Effects of pimozide on appetitive behavior and locomotor activity: dissimilarity of effects when compared to extinction. Spivak KJ, et al. **Physiol Behav** 1986;36(3):457-63

Effects of Suanzaorentang on behavior changes and central monoamines. Hsieh MT, et al. **Proc Natl Sci Counc Repub China [B]** 1986 Jan; 10(1):43-8

Lithium and bupropion antagonise the phasic changes in locomotor activity caused by dopamine infused into the rat nucleus accumbens. Barnes JC, et al. **Psychopharmacology (Berlin)** 1986;89(3):311-6

Mesolimbic dopamine and its control of locomotor activity in rats: differences in pharmacology and light/dark periodicity between the olfactory tubercle and the nucleus accumbens. Cools AR. **Psychopharmacology (Berlin)** 1986;88(4):451-9

A late-appearing benzodiazepine-induced hypoactivity that is not reversed by a receptor antagonist. Lister RG, et al. **Psychopharmacology (Berlin)** 1986;88(4):520-4

Behavioural and pharmacological characterization of the mouth movements induced by muscarinic agonists in the rat. Salamone JD, et al. **Psychopharmacology (Berlin)** 1986;88(4):467-71

Involvement of different dopamine receptors in rat diphasic motility response to apomorphine. Vaccheri A, et al. **Psychopharmacology (Berlin)** 1986;89(3):265-8

N,N'-diallylbarbital potentiation of drug-induced sleep and motor incoordination. Tateoka Y, et al. **Res Commun Chem Pathol Pharmacol** 1986 Apr;52(1):17-28

[The central inhibitory action of hexoprenaline] Zhang SS. **Yao Hsueh Hsueh Pao** 1985 Sep;20(9):699-701 (Eng. Abstr.) (Chi)

[Synthesis and pharmacological studies of derivatives of 5- and 7-(O-hydroxyphenyl)-2,3-dihydro-1,4-diazepins] Kostka K, et al. **Acta Pol Pharm** 1985;42(5):442-7 (Eng. Abstr.) (Pol)

MSH

Permanent alteration of peptide feedback on dopamine neurons after injection of alpha-melanotropin antiserum at a critical period of postnatal development. Lichtensteiger W, et al. **Brain Res** 1986 Mar 19;368(2):205-10

Antagonism of beta-endorphin-induced prolactin release by alpha-melanocyte-stimulating hormone and corticotropin-like intermediate lobe peptide. Wardlaw SL, et al. **Endocrinology** 1986 Jul; 119(1):112-8

Regulation of beta-endorphin, corticotropin-like intermediate lobe peptide, and alpha-melanotropin-stimulating hormone in the hypothalamus by testosterone. Wardlaw SL. **Endocrinology** 1986 Jul; 119(1):19-24

Dissimilar responsiveness of cultured corticotrophs and melanotrophs to tripeptide aldehydes. Fazekas I, et al. **Histochemistry** 1986; 84(4-6):418-22

Melanocyte-stimulating hormone, tyrosinase activity and the regulation of eumelanogenesis and phaeomelanogenesis in the hair follicular melanocytes of the mouse. Burchill SA, et al. **J Endocrinol** 1986 Apr; 109(1):15-21

Structural modifications of pro-opiomelanocortin-derived peptides alter their behavioral effects markedly. Hirsch MD, et al. **J Pharmacol Exp Ther** 1986 May;237(2):378-85

Acetylation of melanocyte-stimulating hormone and beta-endorphin in the pars intermedia of the perinatal pituitary gland in the mouse. Leenders HJ, et al. **Neuroendocrinology** 1986;43(2):166-74

Coexpression of human growth hormone-releasing factor 1-37-like and alpha-melanotropin-like immunoreactivities in neurones of the rat lateral dorsal hypothalamus. Fellmann D, et al. **Neurosci Lett** 1986 Jul 11;68(1):122-6

GABAA and GABAB receptors on porcine pars intermedia cells in primary culture: functional role in modulating peptide release. Demeneix BA, et al. **Neuroscience** 1986 Apr;17(4):1275-85

NEUROPSYCHOLOGICAL TESTS

A comprehensive study of chronic schizophrenic patients. II. Biological, neuropsychological, and clinical correlates of CT abnormality. Pandurangi AK, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):161-71

NEUROREGULATORS

Feulgen lecture: phenotypic plasticity in the nervous system (summary). Black IB. **Acta Histochem [Suppl] (Jena)** 1986;32:9-10

Different neurotransmitter metabolite concentrations in CSF samples from inpatient and outpatient normal volunteers. Guthrie SK, et al. **Acta Psychiatr Scand** 1986 Mar;73(3):315-21

Neuroendocrine aspects of bulimia. Friedman EJ. **Adolesc Psychiatry** 1986;13:422-7

Interactions of drugs and electroshock treatment on cerebral monoaminergic systems. Barkai AI. **Ann NY Acad Sci** 1986; 462:147-62

Neurotransmitter receptor mapping by autoradiography and other methods. Kuhar MJ, et al. **Annu Rev Neurosci** 1986;9:27-59

Histamine as a neuroregulator. Prell GD, et al. **Annu Rev Neurosci** 1986; 9:209-54 (260 ref.)

Neurotransmitters in temperature control. Lipton JM, et al. **Annu Rev Physiol** 1986;48:613-23 (66 ref.)

Proceedings of a workshop on the non-adrenergic non-cholinergic nervous system in the gastrointestinal and respiratory tracts. Ghent, September 19-20, 1985. **Arch Int Pharmacodyn Ther** 1986 Apr; 280(2 Suppl):1-252

The action of thallium acetate on phasic transmitter release in the mouse neuromuscular junction. Wiegand H, et al. **Arch Toxicol** 1986 Apr; 58(4):265-70

Chemical lesions of the nucleus accumbens septi in rats: effects on muricide and apomorphine-induced aggression. Pucilowski O, et al. **Behav Brain Res** 1986 Feb;19(2):171-8

Behavior and brain neurotransmitters: correlations in different strains of mice. Krehbiel D, et al. **Behav Neural Biol** 1986 Jul;46(1):30-45

N-methyl D-aspartate acts as an antagonist of the photoreceptor transmitter in the carp retina. Ariel M, et al. **Brain Res** 1986 Apr 30; 372(1):143-8

Polyamines contribute to calcium-stimulated release of aspartate from brain particulate fractions. Bondy SC, et al. **Brain Res** 1986 Apr 16; 371(1):96-100

On the transmitter at the A-to-B cell in Aplysia californica. Gaillard WD, et al. **Brain Res** 1986 May 14;373(1-2):311-5

Spectra of neurotransmitter receptors and ionic responses on cerebral A and B neurons in Aplysia californica. Gaillard WD, et al. **Brain Res** 1986 May 14;373(1-2):303-10

Selective uptake of neuroactive amino acids by both oligodendrocytes and astrocytes in primary dissociated culture: a possible role for oligodendrocytes in neurotransmitter metabolism. Reynolds R, et al. **Brain Res** 1986 Apr 23;371(2):253–66

Histophotometric evaluation of glutamate dehydrogenase activity of the rat hippocampal formation during postnatal development, with special reference to the glutamate transmitter metabolism. Schünzel G, et al. **Cell Mol Neurobiol** 1986 Mar;6(1):31–42

Influence of dopaminergic, adrenergic and cholinergic blockade and TRH administration on GH responses to GRF 1–29. Jordan V, et al. **Clin Endocrinol (Oxf)** 1986 Mar;24(3):291–8

No effect of atrial natriuretic factor on cardiac rate, force and transmitter release. Hiwatari M, et al. **Clin Exp Pharmacol Physiol** 1986 Feb; 13(2):163–8

Non–adrenergic neurotransmitters in relation to sympathetic nervous control of the lower urinary tract. Burnstock G. **Clin Sci** 1986; 70 Suppl 14:15s–20s (61 ref.)

A microiontophoretic study on the nature of the putative synaptic neurotransmitter involved in the pedunculopontine–substantia nigra pars compacta excitatory pathway of the rat. Scarnati E, et al. **Exp Brain Res** 1986;62(3):470–8

Neuromodulators and transmitters in respiratory control. Moss IR, et al. **Fed Proc** 1986 Jun;45(7):2133–47

Sulfate conjugation of neurotransmitters and drugs. Introduction. Weinshilboum RM. **Fed Proc** 1986 Jul;45(8):2220–2

Nutrition. Neurotransmitter function and behavior. **Int J Vitam Nutr Res [Suppl]** 1986;29:1–109

Neurotransmitter precursor therapies in affective disorders. von Lerber–Good WF. **Int J Vitam Nutr Res [Suppl]** 1986;29:69–82 (39 ref.)

Intramural neurons of the guinea–pig urinary bladder: histochemical localization of putative neurotransmitters in cultures and newborn animals. Crowe R, et al. **J Auton Nerv Syst** 1986 Apr;15(4):319–39

Targeted immobilization of neurotransmitters and neuropeptides on agarose and on Acrylex polymers. Penke B, et al. **J Chromatogr** 1986 Apr 11;376:307–14

Neurotransmitter specificity of cells and fibers in the medial preoptic nucleus: an immunohistochemical study in the rat. Simerly RB, et al. **J Comp Neurol** 1986 Apr 15;246(3):343–63

Mechanism of long–term potentiation of transmitter release induced by adrenaline in bullfrog sympathetic ganglia. Kumamoto E, et al. **J Gen Physiol** 1986 May;87(5):775–93

Stimulation–produced spinal inhibition from the midbrain in the rat is mediated by an excitatory amino acid neurotransmitter in the medial medulla. Aimone LD, et al. **J Neurosci** 1986 Jun;6(6):1803–13

Expression and regulation of catecholaminergic traits in primary sensory neurons: relationship to target innervation in vivo. Katz DM, et al. **J Neurosci** 1986 Apr;6(4):983–9

Yohimbine affects the evoked overflow of neurotransmitters from rat brain slices by more than one mechanism. Hagan RM, et al. **J Pharm Pharmacol** 1986 Mar;38(3):195–200

Differential pharmacology and function of two 5–HT1 receptors modulating transmitter release in rat cerebellum. Raiteri M, et al. **J Pharmacol Exp Ther** 1986 May;237(2):644–8

Factors influencing an increase in spontaneous transmitter release by hypoxia at the mouse neuromuscular junction. Nishimura M. **J Physiol (Lond)** 1986 Mar;372:303–13

Factors affecting in vivo electrochemistry: electrode–tissue interaction and the ascorbate amplification effect. Echizen H, et al. **Life Sci** 1986 Jul 7;39(1):77–89

Neurochemical changes in brains of mice infected with Pichinde virus. Barrett AD, et al. **Med Microbiol Immunol (Berl)** 1986; 175(2–3):213–5

Tetrahydrobiopterin administration to rhesus macaques. Its appearance in CSF and effect on neurotransmitter synthesis. Miller L, et al. **Neurochem Res** 1986 Feb;11(2):291–8

Single–unit activity of hypothalamic arcuate neurons in brain tissue slices. Effects of anterior pituitary hormones, cholecystokinin–octapeptide, and neurotransmitters. Pan JT, et al. **Neuroendocrinology** 1986; 43(2):189–96

Met–enkephalin selectively increases the spontaneous release of amino acid neurotransmitters from rat striatal slices. Arnerić SP, et al. **Neurosci Lett** 1986 May 6;66(1):73–8

Transmitter secretion varies between visualized release sites at amphibian neuromuscular junctions. Bennett M, et al. **Neurosci Lett** 1986 Apr 24; 65(3):311–5

Chemical modulation of ephaptic activation of CA3 hippocampal pyramids. Dalkara T, et al. **Neuroscience** 1986 Feb;17(2):361–70

Neurons dissociated from rat myenteric plexus retain differentiated properties when grown in cell culture. I. Morphological properties and immunocytochemical localization of transmitter candidates. Nishi R, et al. **Neuroscience** 1985 Sep;16(1):187–99

Cytochemical study of developing neurotransmitter properties of dissociated sympathetic neurons grown in co–culture with dissociated pineal cells. Phillips CE, et al. **Neuroscience** 1986 Apr;17(4):1139–46

Neurons dissociated from rat myenteric plexus retain differentiated properties when grown in cell culture. II. Electrophysiological properties and responses to neurotransmitter candidates. Willard AL, et al. **Neuroscience** 1985 Sep;16(1):201–11

Somatostatin and CCK–8 modulate release of striatal amino acids: role of dopamine receptors. Arnerić SP, et al. **Peptides** 1986 Jan–Feb; 7(1):97–103

Identification and immunocytochemical localization of proctolin in pericardial organs of the shore crab, Carcinus maenas. Stangier J, et al. **Peptides** 1986 Jan–Feb;7(1):67–72

Facilitation, augmentation and potentiation of transmitter release at frog neuromuscular junctions poisoned with botulinum toxin. Lupa MT, et al. **Pflugers Arch** 1986 Jun;406(6):636–40

Human peripheral monocytes express putative receptors for neuroexcitatory amino acids. Malone JD, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3307–10

Relationship between transmitter release and presynaptic calcium influx when calcium enters through discrete channels. Zucker RS, et al. **Proc Natl Acad Sci USA** 1986 May;83(9):3032–6

Neurochemical and neuroendocrine dysregulation in affective disorders. Golden RN, et al. **Psychiatr Clin North Am** 1986 Jun;9(2):313–27

Antidepressants and biochemical theories of depression. McNeal ET, et al. **Psychol Bull** 1986 May;99(3):361–74

Neurotransmitters and differentiation antigens in subsets of sensory neurons projecting to the spinal dorsal horn. Jessell TM, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986;64:111–33 (111 ref.)

Nerve activity alters neurotransmitter synthesis [news] Marx JL. **Science** 1986 Jun 20;232(4757):1500–1

[Influence of praziquantel on monoamine transmitters in the rat brain] Liu GQ, et al. **Yao Hsueh Hsueh Pao** 1985 Nov;20(11):807–10 (Eng. Abstr.) **(Chi)**

[Effect of intrathecal morphine on plasma levels of neurohumoral substances] Kotani N. **Masui** 1986 Feb;35(2):208–16 (Eng. Abstr.) **(Jpn)**

[Effects of inhibitors of some mediators on the paw–edema induced by acetyl glyceryl ether phosphorylcholine in rats] Tajima M, et al. **Nippon Yakurigaku Zasshi** 1986 Apr;87(4):487–95 (Eng. Abstr.) **(Jpn)**

[Regulatory peptides. A functional continuum] Ashmarin IP, et al. **Biokhimiia** 1986 Apr;51(4):531–45 (149 ref.) (Eng. Abstr.) **(Rus)**

[Pharmacological pathways regulating neuromediator processes in the central nervous system during aging] Burchinskiĭ SG, et al. **Farmakol Toksikol** 1986 May–Jun;49(3):120–6 (91 ref.) **(Rus)**

[Specific neurohumoral activity of the cerebrospinal fluid of patients with manic–depressive psychosis] Vartanian GA, et al. **Fiziol Cheloveka** 1986 Jan–Feb;12(1):167–70 **(Rus)**

[Neurohumoral regulation of the processes of bile formation and bile excretion] Ivanichenkova RA. **Klin Med (Mosk)** 1986 Apr; 64(4):24–32 (59 ref.) **(Rus)**

NEUROTENSIN

Substance P and neurotensin: their roles in the regulation of anterior pituitary function. Aronin N, et al. **Annu Rev Physiol** 1986; 48:537–49 (57 ref.)

The amino acid sequence of kinetensin, a novel peptide isolated from pepsin–treated human plasma: homology with human serum albumin, neurotensin and angiotensin. Mogard MH, et al. **Biochem Biophys Res Commun** 1986 May 14;136(3):983–8

Stimulation by gastrin–releasing peptide, neurotensin and DN1417, a novel TRH analog, of dopamine and norepinephrine release from perifused rat hypothalamic fragments in vitro. Kabayama Y, et al. **Brain Res** 1986 May 7;372(2):394–9

Colocalization of immunoreactive substance P and neurotensin in amacrine cells of the goldfish retina. Li HB, et al. **Brain Res** 1986 Feb 26;366(1–2):307–13

Adaptation to cold antagonizes neurotensin–induced hypothermia in mice. Merritt WD, et al. **Brain Res** 1986 Mar 26;369(1–2):136–42

Neurotensin actions in the retina: mechanisms and variability. Zalutsky RA, et al. **Brain Res** 1986 Apr 23;371(2):360–3

[Ser7]neurotensin: isolation from guinea pig intestine. Shaw C, et al. **FEBS Lett** 1986 Jul 7;202(2):187–92

Neurotensin stimulates histamine release in in vivo skin 'blisters' in rats: an effect inhibited by cromolyn or somatostatin. Cochrane DE, et al. **Int Arch Allergy Appl Immunol** 1986;80(3):225–30

Neurotensin in the rat parabrachial region: ultrastructural localization and extrinsic sources of immunoreactivity. Milner TA, et al. **J Comp Neurol** 1986 May 15;247(3):326–43

Neurotensin effect on dopamine release and calcium transport in rat striatum: interactions with diphenylalkylamine calcium antagonists. Battaini F, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar; 332(3):267–70

Neurotensin–like immunoreactivities in human plasma: feeding responses and metabolism. Holst Pedersen J, et al. **Peptides** 1986 Jan–Feb; 7(1):15–20

Covalent labeling of neurotensin receptors in rat gastric fundus plasma membranes. Mazella J, et al. **Peptides** 1985 Nov–Dec;6(6):1137–41

Behavioral and biochemical assessment of time–related changes in globus pallidus and striatal dopamine induced by intranigrally administered neurotensin. Napier TC, et al. **Peptides** 1985 Nov–Dec;6(6):1057–68

Synergistic effects of dopamine agonists and centrally administered neurotensin on feeding. Hawkins MF, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1195-201

Molecular forms of somatostatin, substance P and neurotensin in fresh human cerebral cortex. Bateman DE, et al. **Regul Pept** 1986 May; 14(3):211-6

Catabolism of substance P and neurotensin in the rat stomach wall is susceptible to inhibitors of angiotensin converting enzyme. Orloff MS, et al. **Regul Pept** 1986 Mar;14(1):21-31

Computer analysis of intestinal motility: effects of cholecystokinin and neurotensin on jejunal contraction patterns. Schemann M, et al. **Z Gastroenterol** 1986 May;24(5):262-8

[Role of alpha-adrenoreceptors of the hypothalamus and amygdala in the response of the secretory glands of the stomach to neurotensin and somatostatin] Barashkova GM, et al. **Fiziol Zh SSSR** 1986 Apr; 72(4):498-502 (Eng. Abstr.) **(Rus)**

NEUROTIC DISORDERS

[Determination of dopamine-beta-hydroxylase (DBH) and monoamine oxidase (MAO) activities in platelets and plasma in schizophrenic, maniac-depressive and neurotic patients] Xavier Vieira R, et al. **Acta Med Port** 1986 Jan-Feb;7(1):45-8 (Eng. Abstr.) **(Por)**

[Antistress and antineurotic action of psychotropic preparations in experiments on monkeys] Startsev VG, et al **Vestn Akad Med Nauk SSSR** 1986;(3):30-3 (Eng. Abstr.) **(Rus)**

NITRAZEPAM

The carry-over effects of triazolam compared with nitrazepam and placebo in acute emergency driving situations and in monotonous simulated driving. Laurell H, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Mar;58(3):182-6

Development of tolerance to benzodiazepines. II. Baclofen effect on the activity of rats during tolerance to the sedative action of nitrazepam and oxazepam. Chodera A, et al. **Acta Physiol Pol** 1984 Jul-Aug; 35(4):301-9

Peptide derivatives as prodrugs. Thomas WA. **Biochem Soc Trans** 1986 Apr;14(2):383-7

Influence of some dopaminoceptor agents on nitrazepam-induced sleep in the domestic fowl (Gallus domesticus) and rats. Wambebe C. **Jpn J Pharmacol** 1986 Mar;40(3):357-65

NOMIFENSINE

Merital withdrawn by manufacturer [letter] Hendra N. **Am J Nurs** 1986 May;86(5):533

Protein binding of nomifensine and its three main metabolites. Lindberg RL. **Biochem Pharmacol** 1986 Jun 15;35(12):2044-6

Nomifensine--a farewell and future concerns [editorial] Shader RI, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):A21

Double-blind comparison of diclofensine with nomifensine in outpatients with dysphoric mood. Funke HJ, et al. **Pharmacopsychiatry** 1986 May; 19(3):120-3

Effects of haloperidol and nomifensine on the visual aftereffects of tilt and movement. Harris JP, et al. **Psychopharmacology (Berlin)** 1986; 89(2):177-82

[Hemolytic anemia with kidney failure after nomifensine (letter)] Oberhofer R, et al. **Dtsch Med Wochenschr** 1986 Jun 13; 111(24):960-2 **(Ger)**

[Comparative evaluation of the therapeutic efficacy of the antidepressants adepren, linamiphen and emovit] Guliamov MG. **Zh Nevropatol Psikhiatr** 1986;86(4):582-7 (Eng. Abstr.) **(Rus)**

NOREPINEPHRINE

Effect on brain monoamines in the rat of substituted and protected analogues of the oxytocin fragment, prolyl-leucyl-glycinamide following N-terminal substitution by D- and L-pipecolic acid. Szabó G, et al. **Acta Physiol Hung** 1986;67(1):155-61

Benzodiazepines decrease norepinephrine release from rat pineal nerves by acting on peripheral type binding sites. Lowenstein PR, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):441-9

Renal extraction of endogenous and radiolabelled catecholamines in the dog. Bradley T, et al. **Acta Physiol Scand** 1986 Apr;126(4):505-10

Catecholamines of endoneurial laryngeal paraganglia in the rat. Dahlqvist A, et al. **Acta Physiol Scand** 1986 Jun;127(2):257-61

Possible involvement of the Ni-protein in the prejunctional inhibitory effect of a stable adenosine analogue (R-PIA) on noradrenaline release in the rat hippocampus. Fredholm BB, et al. **Acta Physiol Scand** 1986 Feb;126(2):307-9

Temperature effects on catecholamine accumulation in neuronal and extraneuronal compartments in the cod spleen. Ungell AL. **Acta Physiol Scand** 1986 Apr;126(4):589-92

Inhibitory effects of desmethylimipramine, metanephrine and normetanephrine on the neuronal and extraneuronal accumulation of catecholamines in fish spleen. Ungell AL. **Acta Physiol Scand** 1986 May; 127(1):27-31

Comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressed outpatients. Biochemical aspects. Nyström C, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):133-8

Synergistic action of angiotensin II on norepinephrine-induced prostaglandin release from rat glomeruli. Matsumura Y, et al. **Am J Physiol** 1986 May;250(5 Pt 2):F811-6

Metabolic effects of chronic infusions of epinephrine and norepinephrine in rats. Racotta R, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):E518-22

Plasma cortisol and norepinephrine concentrations in castrated male pigs maintained in pairs in outdoor pens and in a confinement finishing house: assessment of stress. Benson GJ, et al. **Am J Vet Res** 1986 May; 47(5):1071-4

New liquid membrane electrode for the determination of ephedrine, epinephrine, and norepinephrine. Hassan SS, et al. **Anal Chem** 1986 May; 58(6):1052-4

Behavioral and neurochemical consequences associated with stressors. Anisman H, et al. **Ann NY Acad Sci** 1986;467:205-25 (67 ref.)

Neurochemical mechanisms of mood stabilization. Focus on electroconvulsive therapy. Lerer B, et al. **Ann NY Acad Sci** 1986; 462:366-75 (74 ref.)

Comparative alpha- and beta-adrenoceptor activity of 2- and 6-ring-chlorinated noradrenaline analogues. Squier GJ, et al. **Arzneimittelforschung** 1986 Mar;36(3):457-60

Attenuation of sensory preconditioning by noradrenaline depletion in the rat. Archer T, et al. **Behav Brain Res** 1986 Apr;20(1):47-56

Depletion of brain norepinephrine with DSP-4 does not alter acquisition or performance of a radial-arm maze task. Chrobak JJ, et al. **Behav Neural Biol** 1985 Jul;44(1):144-50

Lipolysis in rat adipocytes during recovery from lactation. Response to noradrenaline and adenosine. Vernon RG, et al. **Biochem J** 1986 Feb 15;234(1):229-31

Comparative responses of the central adrenaline- and noradrenaline-containing neurons after reserpine injections. Lambás-Señas L, et al. **Biochem Pharmacol** 1986 Jul 1; 35(13):2207-11

Effects of short-chain alcohols and norepinephrine on brain (Na+,K+)ATPase activity. Nhamburo PT, et al. **Biochem Pharmacol** 1986 Jun 15;35(12):1987-92

Effect of catecholamines on the hepatic rate-limiting enzymes of cholesterol metabolism in normally fed and cholesterol-fed rabbits. Deverey R, et al. **Biochim Biophys Acta** 1986 Jul 11;887(2):173-81

Regional turnover of norepinephrine and dopamine in rat brain following acute exposure to air ions. Charry JM, et al. **Bioelectromagnetics** 1985; 6(4):415-25

Adrenergic modulation of the delayed rectifier potassium channel in calf cardiac Purkinje fibers. Bennett P, et al. **Biophys J** 1986 Apr; 49(4):839-48

Noradrenergic innervation of gerbil large cerebral arteries. Alafaci C, et al. **Blood Vessels** 1986;23(3):154-9

Unilateral peri-substantia nigra catecholaminergic lesion and amygdala kindling. Albala BJ, et al. **Brain Res** 1986 Apr 9;370(2):388-92

Clorgyline and desipramine alter the sensitivity of [3H]noradrenaline release to calcium but not to clonidine. Campbell IC, et al. **Brain Res** 1986 May 7;372(2):253-9

Intracellular recordings from pineal cells in tissue culture: membrane properties and response to norepinephrine. Freschi JE, et al. **Brain Res** 1986 Mar 19;368(2):366-70

Changes in the noradrenergic innervation of the area dentata after axotomy of coeruleohippocampal projections or unilateral lesion of the locus coeruleus. Haring JH, et al. **Brain Res** 1986 Mar 19; 368(2):233-8

Effects of bilateral lesion of the locus coeruleus and of neonatal administration of 6-hydroxydopamine on the concentration of individual proteins in rat brain. Heydorn WE, et al. **Brain Res** 1986 Mar 5; 367(1-2):31-8

Characterization of hypothalamic noradrenaline receptors in the supraoptic nucleus and periventricular region of the paraventricular nucleus of mice in vitro. Inenaga K, et al. **Brain Res** 1986 Mar 26; 369(1-2):37-47

Impact of circulating corticosterone on alpha 1- and alpha 2-noradrenergic receptors in discrete brain areas. Jhanwar-Uniyal M, et al. **Brain Res** 1986 Mar 19;368(2):404-8

Pharmacological characterization of the receptor mediating the adrenergic inhibition of responses to substance P in the cingulate cortex. Jones RS, et al. **Brain Res** 1986 Mar 5;367(1-2):151-61

Stimulation by gastrin-releasing peptide, neurotensin and DN1417, a novel TRH analog, of dopamine and norepinephrine release from perifused rat hypothalamic fragments in vitro. Kabayama Y, et al. **Brain Res** 1986 May 7;372(2):394-9

Release of [3H]norepinephrine: alteration by early developmental exposure to diazepam. Kellogg CK, et al. **Brain Res** 1986 Feb 26; 366(1-2):137-44

Noradrenaline-stimulated inositol phospholipid breakdown in rat dorsal lateral geniculate nucleus neurones. Kemp JA, et al. **Brain Res** 1986

Apr 23;371(2):314-8

One perfusion mixture for immunocytochemical detection of noradrenaline, dopamine, serotonin and acetylcholine in the same rat brain. McRae-Degueurce A, et al. **Brain Res** 1986 Jun 18; 376(1):217-9

Neonatal 6-hydroxydopamine lesion of forebrain norepinephrine does not eliminate critical period for behavioral effects of gonadal hormone manipulation. Pappas BA, et al. **Brain Res** 1986 May;391(2):310-4

Peripheral sympathectomy and adrenal medullectomy do not alter cerebrospinal fluid norepinephrine. Peskind ER, et al. **Brain Res** 1986 Mar 5;367(1-2):258-64

Single unit response of noradrenergic, serotonergic and dopaminergic neurons in freely moving cats to simple sensory stimuli. Rasmussen K, et al. **Brain Res** 1986 Mar 26;369(1-2):336-40

The acute effects of 6-hydroxydopamine treatment on noradrenergic function in the rat hippocampus in vitro. Yasuda RP, et al. **Brain Res** 1986 Mar 5;367(1-2):121-7

Combined effects of n-hexane and toluene on norepinephrine and dopamine levels in rat brain tissues after long-term exposures. Ikeda M, et al. **Bull Environ Contam Toxicol** 1986 Apr;36(4):510-7

Haemodynamic reactions to succinylcholine--an alternative hypothesis [letter] Baraka A. **Can Anaesth Soc J** 1986 Mar;33(2):252-4

Distribution of subgroups of noradrenaline neurons in the coeliac ganglion of the guinea-pig. Macrae IM, et al. **Cell Tissue Res** 1986; 244(1):173-80

Decreased basal cardiac interstitial norepinephrine release after neuronal uptake inhibition in dogs. Cousineau D, et al. **Circ Res** 1986 Jun; 58(6):859-66

Reduced imprecision of the radioenzymatic assay of plasma catecholamines by improving the stability of the internal standards. Hoffmann JJ, et al. **Clin Chim Acta** 1986 Apr 30;156(2):221-5

The effect of aging on alpha-adrenoceptors and their responses in rabbits. Hamilton CA, et al. **Clin Exp Pharmacol Physiol** 1985 Nov-Dec; 12(6):535-47

Effect of pregnancy in the rabbit on the pressor response to angiotensin and noradrenaline. Joels N, et al. **Clin Exp Pharmacol Physiol** 1985 Nov-Dec;12(6):577-86

Effect of noradrenaline, vasopressin and angiotensin II on renal prostaglandins in man. Loup R, et al. **Clin Sci** 1986 Apr;70(4):371-7

Stimulus-induced release of endogenous catecholamines from human washed platelets. Smith CC, et al. **Clin Sci** 1986 May;70(5):495-500

The effect of insulin and catecholamines on the activities of 3-hydroxy-3-methyl glutaryl coenzyme A reductase and acyl-coenzyme A: cholesterol-o-acyltransferase in isolated rat hepatocytes. Devery R, et al. **Diabetologia** 1986 Feb;29(2):122-4

Functional characteristics of the luteinizing hormone-releasing hormone pulse generator in conscious unrestrained female rabbits: activation by norepinephrine. Ramirez VD, et al. **Endocrinology** 1986 Jun; 118(6):2331-9

Effects of epinephrine, norepinephrine, and dopamine on gonadotropin-releasing hormone-induced secretion of luteinizing hormone in vitro. Swartz SR, et al. **Endocrinology** 1986 Jun; 118(6):2425-31

Sex-related differences in free plasma catecholamines in individuals of similar performance ability during graded ergometric exercise. Lehmann M, et al. **Eur J Appl Physiol** 1986;55(1):54-8

The effect of selective noradrenergic lesions upon the stimulation by noradrenaline of inositol phospholipid breakdown in rat hippocampal miniprisms. Fowler CJ, et al. **Eur J Pharmacol** 1986 Apr 29; 123(3):401-7

Morphine increases locus coeruleus noradrenergic neuronal activity in vitro. Trulson ME, et al. **Eur J Pharmacol** 1986 May 13; 124(1-2):189-92

Intracavernous injection of noradrenaline to interrupt erections during surgical interventions. de Meyer JM, et al. **Eur Urol** 1986; 12(3):169-70

'Neuropeptide tyrosine' (NPY) is co-stored with noradrenaline in vascular but not in parenchymal sympathetic nerves of brown adipose tissue. Cannon B, et al. **Exp Cell Res** 1986 Jun;164(2):546-50

Specific lysis of noradrenergic synaptosomes by an antiserum to dopamine-beta-hydroxylase. Docherty M, et al. **FEBS Lett** 1986 Jun 23;202(1):37-40

Thyrotropin and norepinephrine stimulate the metabolism of phosphoinositides in FRTL-5 thyroid cells. Philp NJ, et al. **FEBS Lett** 1986 Jul 7;202(2):193-6

Amine sulfate formation in the central nervous system. Tyce GM, et al. **Fed Proc** 1986 Jul;45(8):2247-53

The effect of oestradiolum benzoicum and progesterone on the noradrenalin content in organs of the female reproductive system of sexually immature pigs. Lakomy M, et al. **Gegenbaurs Morphol Jahrb** 1986;132(1):129-43

Thyroid status and noradrenaline-induced regulatory thermogenesis in heat acclimated rats. Arieli A, et al. **Horm Metab Res** 1986 Feb; 18(2):103-6

Origin of the increased plasma concentration of noradrenaline after feeding. Sharman DF, et al. **Horm Metab Res** 1986 Feb;18(2):145

Diurnal variations of brain noradrenaline metabolism of the methylmercury chloride-administered rat with reference to an altered circadian rhythm of paradoxical sleep. Arito H, et al. **Ind Health** 1985; 23(4):245-53

Perivascular noradrenergic and peptide-containing nerves show different patterns of changes during development and ageing in the guinea-pig. Dhall U, et al. **J Auton Nerv Syst** 1986 Jun;16(2):109-26

Characterization of hormone and protein release from alpha-toxin-permeabilized chromaffin cells in primary culture. Bader MF, et al. **J Biol Chem** 1986 May 5;261(13):5777-83

Catecholamines induce an increase in nerve growth factor content in the medium of mouse L-M cells. Furukawa Y, et al. **J Biol Chem** 1986 May 5;261(13):6039-47

Noradrenaline release in the human pulmonary artery is modulated by presynaptic alpha 2-adrenoceptors. Hentrich F, et al. **J Cardiovasc Pharmacol** 1986 May-Jun;8(3):539-44

Dopamine and L-dopa potentiation of pressor responses to norepinephrine in isolated perfused rat kidneys. Lam BK, et al. **J Cardiovasc Pharmacol** 1986 May-Jun;8(3):554-8

Angiotensin facilitation of 3H-norepinephrine release in central tissue of spontaneously hypertensive rats but not in Wistar-Kyoto rats: effects of sodium depletion. Meldrum MJ, et al. **J Cardiovasc Pharmacol** 1986 May-Jun;8(3):582-7

Alterations in plasma noradrenaline in response to reflex modulation of sympathetic vasoconstrictor tone to skeletal muscles. Grassi G, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S131-3

Alteration of presynaptic alpha 2-mediated inhibition of norepinephrine release in perfused mesenteric arteries of young and adult spontaneously hypertensive rats. Tsuda K, et al. **J Hypertension [Suppl]** 1984 Dec; 2(3):S95-7

Vascular responsiveness of simian digital artery to various vasoactive substances. Ito T, et al. **J Invest Dermatol** 1986 Jun;86(6):678-82

Measurement of endogenous noradrenaline release in the rat cerebral cortex in vivo by transcortical dialysis: effects of drugs affecting noradrenergic transmission. L'Heureux R, et al. **J Neurochem** 1986 Jun; 46(6):1794-801

Effects of hypoxia on the activities of noradrenergic and dopaminergic neurons in the rat brain. Miwa S, et al. **J Neurochem** 1986 Jul; 47(1):63-9

Role of adenylate cyclase in presynaptic alpha 2-adrenoceptor- and mu-opioid receptor-mediated inhibition of [3H]noradrenaline release from rat brain cortex slices. Schoffelmeer AN, et al. **J Neurochem** 1986 Jun;46(6):1711-7

Effect of dietary saturated fatty acids on hormone-sensitive lipolysis in rat adipocytes. Awad AB, et al. **J Nutr** 1986 Jun;116(6):1088-94

Stimulation by noradrenaline of inositol phospholipid breakdown in the rat hippocampus: effect of the ambient potassium concentration. Fowler CJ, et al. **J Pharm Pharmacol** 1986 Mar;38(3):201-8

Alpha 1-adrenoceptor function in the rat hippocampus as assessed by noradrenaline-stimulated inositol phospholipid breakdown after destruction of noradrenergic neurons by neonatal 6-hydroxydopamine treatment. Fowler CJ, et al. **J Pharm Pharmacol** 1986 May; 38(5):385-8

beta-Endorphin-induced stimulation of central sympathetic outflow: inhibitory modulation by central noradrenergic neurons. Appel NM, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):695-701

Modification of serotonergic and noradrenergic neurotransmissions by repeated administration of monoamine oxidase inhibitors: electrophysiological studies in the rat central nervous system. Blier P, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):987-94

Effect of repeated restraint stress, desmethylimipramine or adrenocorticotropin on the alpha and beta adrenergic components of the cyclic AMP response to norepinephrine in rat brain slices. Stone EA, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):702-7

Presence of a noradrenaline uptake system on a ligated cat sympathetic nerve. Ceña V, et al. **J Physiol (Lond)** 1986 Mar;372:351-62

Cyclic adenosine 3',5'-monophosphate mediates beta-receptor actions of noradrenaline in rat hippocampal pyramidal cells. Madison DV, et al. **J Physiol (Lond)** 1986 Mar;372:245-59

Actions of noradrenaline recorded intracellularly in rat hippocampal CA1 pyramidal neurones, in vitro. Madison DV, et al. **J Physiol (Lond)** 1986 Mar;372:221-44

An improved radioenzymatic assay for plasma norepinephrine using purified phenylethanolamine N-methyltransferase. Henry DP, et al. **Life Sci** 1986 Apr 21;38(16):1473-83

Sodium-dependence of the saturability of carrier-mediated noradrenaline efflux from noradrenergic neurones in the rat vas deferens. Bönisch H, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Feb; 332(2):131-4

Vasoconstriction induced by noradrenaline and angiotensin II is antagonized by eicosapentaenoic acid independent of formation of trienoic eicosanoids. Juan H, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar;332(3):288-92

Clonidine reverses baclofen-induced increases in noradrenaline turnover in rat brain. Sawynok J, et al. **Neurochem Res** 1986 May; 11(5):723-31

Morphine inhibits electrically stimulated noradrenaline release from slices of rat medial preoptic area. Diez-Guerra FJ, et al. **Neuroendocrinology** 1986;43(1):89–91

Lesion of noradrenergic neurones with DSP4 does not modify benzodiazepine receptor binding in cortex and hippocampus of rat. Marcel D, et al. **Neuropharmacology** 1986 Mar;25(3):283–6

Effect of chronic administration of the 6-aza analogue of mianserin (Org. 3770) and its enantiomers on behaviour and changes in noradrenaline metabolism of olfactory-bulbectomized rats in the 'open field' apparatus. O'Connor WT, et al. **Neuropharmacology** 1986 Mar;25(3):267–70

Effect of plasma from patients containing bupropion and its metabolites on the uptake of norepinephrine. Perumal AS, et al. **Neuropharmacology** 1986 Feb;25(2):199–202

Dopaminergic and noradrenergic sympathetic nerves of the dog have different DOPA decarboxylase activities. Harris T, et al. **Neurosci Lett** 1986 Apr 11;65(2):155–60

Inhibitory influence of monoamines and brainstem monoaminergic regions on the medullary swallowing reflex. Kessler JP, et al. **Neurosci Lett** 1986 Mar 28;65(1):41–6

Dissociated cells of foetal rat pallium growa in culture medium supplemented with noradrenaline: effects on the expression of neuron-specific enolase and cell adhesion molecule L1. König N, et al. **Neurosci Lett** 1986 May 6;66(1):67–72

Glutamate-induced activation of rat locus coeruleus increases CA1 pyramidal cell excitability. Olpe HR, et al. **Neurosci Lett** 1986 Mar 28;65(1):11–6

Catecholamine sensitivities of motor cortical neurons of the monkey. Sawaguchi T, et al. **Neurosci Lett** 1986 May 15;66(2):135–40

Monoamine innervation of the oculomotor nucleus in the rat. A radioautographic study. Soghomonian JJ, et al. **Neuroscience** 1986 Apr; 17(4):1147–57

Norepinephrine infusions into the medial preoptic area inhibit lordosis behavior. Caldwell JD, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):1015–23

Central norepinephrine and plasma corticosterone following acute and chronic stressors: influence of social isolation and handling. Irwin J, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1151–4

Hemodynamics and vascular sensitivity to circulating norepinephrine in normal skin and delayed and acute random skin flaps in the pig. Pang CY, et al. **Plast Reconstr Surg** 1986 Jul;78(1):75–84

Blood--brain barrier sodium/potassium pump: modulation by central noradrenergic innervation. Harik SI. **Proc Natl Acad Sci USA** 1986 Jun; 83(11):4067–70

Norepinephrine alters PGE2/PGE1 output ratio in isolated uterus from ovariectomized rats. Chaud MA, et al. **Prostaglandins Leukotrienes Med** 1986 May;22(2):201–10

Clinical studies on norepinephrine metabolism: how to interpret the numbers. Linnoila M, et al. **Psychiatry Res** 1986 Mar;17(3):229–39

The interaction of neurotensin with dopaminergic pathways in the central nervous system: basic neurobiology and implications for the pathogenesis and treatment of schizophrenia. Nemeroff CB. **Psychoneuroendocrinology** 1986;11(1):15–37

Norepinephrine alterations under stress conditions following the regular practice of meditation. Morrell EM, et al. **Psychosom Med** 1986 Mar–Apr;48(3–4):270–7

Enkephalin contents reflect noradrenergic large dense cored vesicle populations in vasa deferentia. Douglas BH 2d, et al. **Regul Pept** 1986 May;14(3):193–210

Noradrenaline as a possible mediator of angiotensin II induced fluid transport in rat ileum in vitro. Souviron A, et al. **Rev Esp Fisiol** 1986 Mar;42(1):51–5

Taste/tactile cue discriminations in taste-aversion learning following depletion of noradrenaline. Archer T, et al. **Scand J Psychol** 1986; 27(1):39–51

[Beta-endorphin and dynorphin are involved in the central depressor action of clonidine or norepinephrine in rats] Xie CW, et al. **Sheng Li Hsueh Pao** 1985 Apr;37(2):172–9 (Eng. Abstr.) **(Chi)**

[Effects of OKY 046 on responses to norepinephrine in rat mesenteric arterioles] Kato T, et al. **Masui** 1986 Mar;35(3):393–8 (Eng. Abstr.) **(Jpn)**

[Effect of continuous, intermittent and impulse acoustic stimuli on plasma catecholamine levels in humans at rest and during physical exertion] Buczyński A, et al. **Pol Tyg Lek** 1986 Jan 27;41(4):110–3 (Eng. Abstr.) **(Pol)**

[Role of adrenergic receptors in the regulation of glycogen metabolism in the liver] Torlińska T, et al. **Postepy Hig Med Dosw** 1985 Sep–Oct; 39(5):561–77 (75 ref.) (Eng. Abstr.) **(Pol)**

[Effect of phentolamine and noradrenaline on cardiac output and the viability of animals recovering after clinical death] Evtushenko AIa, et al. **Anesteziol Reanimatol** 1986 Mar–Apr;(2):31–4 (Eng. Abstr.) **(Rus)**

[Noradrenaline suppression of the spinal efferent component of the pressor reflexes] Karagulova GO, et al. **Biull Eksp Biol Med** 1986 Apr; 101(4):387–9 (Eng. Abstr.) **(Rus)**

[Cholinesterase and noradrenaline activity in response to exposure of acupuncture points to a laser] Lupyr' VM, et al. **Fiziol Zh** 1986 May–Jun;32(3):297–303 (Eng. Abstr.) **(Rus)**

[Changes in blood volume in the heart and lungs and its role in the regulation of left-ventricular blood output after administration of catecholamines] Osadchil LI, et al. **Fiziol Zh** 1986 Mar–Apr; 32(2):149–54 (Eng. Abstr.) **(Rus)**

[Development of various responses to noradrenaline administration in the control and cold-adapted rat] Kozyreva TV, et al. **Fiziol Zh SSSR** 1986 Mar;72(3):377–81 **(Rus)**

[Binding of noradrenaline with chromatin proteins from cell nuclei of the rat brain] Bozhko GKh, et al. **Ukr Biokhim Zh** 1986 Mar–Apr; 58(2):50–4 (Eng. Abstr.) **(Rus)**

NORMETANEPHRINE

Inhibitory effects of desmethylimipramine, metanephrine and normetanephrine on the neuronal and extraneuronal accumulation of catecholamines in fish spleen. Ungell AL. **Acta Physiol Scand** 1986 May; 127(1):27–31

NORTRIPTYLINE

Quantitative homogeneous enzyme immunoassays for amitriptyline, nortriptyline, imipramine, and desipramine. Pankey S, et al. **Clin Chem** 1986 May;32(5):768–72

A simplified radioimmunoassay of plasma nortriptyline in depressed patients compared with high-pressure liquid chromatography and gas-liquid chromatography. Sayegh JF. **Neurochem Res** 1986 Feb; 11(2):193–206

OBSESSIVE-COMPULSIVE DISORDER

Antiandrogenic treatment of obsessive-compulsive neurosis. Casas M, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):221–2

Clomipramine: an antiobsessive drug. Ananth J. **Can J Psychiatry** 1986 Apr;31(3):253–8 (34 ref.)

Obsessive compulsive disorder [letter] Hardy JL. **Can J Psychiatry** 1986 Apr;31(3):290

An open clinical trial of fluoxetine in the treatment of obsessive-compulsive disorder. Fontaine R, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):98–101

An inverse relationship between mania and obsessive-compulsive disorder: a case report [letter] Keck PE Jr, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):123–4

Efficacy of trazodone as an anti-obsessional agent. Prasad A. **Neuropsychobiology** 1986;15 Suppl 1:19–21

The relationship of antiobsessional and antidepressant effects of tricyclic antidepressants. Mavissakalian M, et al. **Psychopharmacol Bull** 1986; 22(1):161–6

ORGANIC MENTAL DISORDERS

Propranolol treatment of assaultive patients with organic brain disease. A double-blind crossover, placebo-controlled study. Greendyke RM, et al. **J Nerv Ment Dis** 1986 May;174(5):290–4

Contribution to the search for vigilance-indicative EEG variables. Results of a controlled, double-blind study with pyritinol in elderly patients with symptoms of mental dysfunction. Herrmann WM, et al. **Pharmacopsychiatry** 1986 Mar;19(2):75–83

Neurochemical and neuroendocrine dysregulation in affective disorders. Golden RN, et al. **Psychiatr Clin North Am** 1986 Jun;9(2):313–27

[Current problems of organic brain syndrome in children] Măgureanu S, et al. **Rev Med Interna [Neurol Psihiatr]** 1986 Jan–Mar;31(1):53–8 (11 ref.) (Eng. Abstr.) **(Rum)**

ORGANIC MENTAL DISORDERS, PSYCHOTIC

A comprehensive study of chronic schizophrenic patients. II: Biological, neuropsychological, and clinical correlates of CT abnormality. Pandurangi AK, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):161–71

OXAZEPAM

Development of tolerance to benzodiazepines. II. Baclofen effect on the activity of rats during tolerance to the sedative action of nitrazepam and oxazepam. Chodera A, et al. **Acta Physiol Pol** 1984 Jul–Aug; 35(4):301–9

Comparison of two benzodiazepines with differing accumulation: behavioral changes during and after 3 weeks of dosing. Ghoneim MM, et al. **Clin Pharmacol Ther** 1986 May;39(5):491–500

Single dose oxazepam has no effect on acetaminophen clearance or metabolism. Sonne J, et al. **Eur J Clin Pharmacol** 1986;30(1):127–9

PAIRED-ASSOCIATE LEARNING

Sensation seeking, paired associate learning and brain catecholamines. Kulcsár Z, et al. **Neuropsychobiology** 1986;15(1):43–8

PARANOID DISORDERS

Paranoid disorder: the Soviet viewpoint. Swanson DW, et al. **Am J Psychiatry** 1986 Jul;143(7):825-30 (40 ref.)

PARASYMPATHOMIMETICS

Mechanisms of release of atrial natriuretic factor. II. Effect of chronic administration of alpha- and beta-adrenergic and cholinergic agonists on plasma and atrial ANF in the rat. Garcia R, et al. **Biochem Biophys Res Commun** 1986 Apr 29;136(2):510-20

Learning impairment following lesion of the basal nucleus of Meynert in the marmoset: modification by cholinergic drugs. Ridley RM, et al. **Brain Res** 1986 Jun 18;376(1):108-16

Rotifer neuropharmacology--I. Cholinergic drug effects on oviposition of Philodina acuticornis (Rotifera, Aschelminthes). Nogrady T, et al. **Comp Biochem Physiol [C]** 1986;83(2):335-8

Cholinergic stimulation of human pancreatic secretion. Valenzuela JE, et al. **Dig Dis Sci** 1986 Jun;31(6):615-9

Mechanism of cholinergic stimulation of aldosterone secretion in bovine adrenal glomerulosa cells. Kojima I, et al. **Endocrinology** 1986 Jul; 119(1):284-91

Muscarinic stimulation of prostacyclin synthesis by the rat penis. Jeremy JY, et al. **Eur J Pharmacol** 1986 Apr 9;123(1):67-71

QSAR in a series of muscarinic agents. Note VI. Five-membered cyclic ligands. Pratesi P, et al. **Farmaco [Sci]** 1986 May;41(5):336-45

Changes in the interaction between CNS cholinergic and dopaminergic neurons induced by L-alpha-glycerylphosphorylcholine, a cholinomimetic drug. Trabucchi M, et al. **Farmaco [Sci]** 1986 Apr; 41(4):325-34

Effects of slaframine on ruminant digestive function: resting salivary flow and composition in cattle. Froetschel MA, et al. **J Anim Sci** 1986 May; 62(5):1404-11

Cholinergic modulation of an acetylcholine receptor-like antigen on the surface of chick ciliary ganglion neurons in cell culture. Smith MA, et al. **J Neurosci** 1986 Apr;6(4):946-53

Nicotinic and muscarinic agonists, phorbol esters, and agents which raise cyclic AMP levels phosphorylate distinct groups of proteins in the superior cervical ganglion. Cahill AL, et al. **Neurochem Res** 1986 Mar; 11(3):327-38

Drugs as research tools in psychology: cholinergic drugs and aggression. Bell R, et al. **Neuropsychobiology** 1985;14(4):181-92 (84 ref.)

Cholinergic agonists suppress play fighting in juvenile rats. Wilson LI, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1157-9

Behavioural and pharmacological characterization of the mouth movements induced by muscarinic agonists in the rat. Salamone JD, et al. **Psychopharmacology (Berlin)** 1986;88(4):467-71

PARGYLINE

Role of propiolaldehyde and other metabolites in the pargyline inhibition of rat liver aldehyde dehydrogenase. DeMaster EG, et al. **Biochem Pharmacol** 1986 May 1;35(9):1481-9

Peroxidative N-oxidation and N-dealkylation reactions of pargyline. Weli AM, et al. **Xenobiotica** 1986 Mar;16(3):281-8

PEMOLINE

Measurement of whole blood serotonin as a guide in prescribing psychostimulant medication for children with attentional deficits. Saul RC, et al. **Clin Neuropharmacol** 1986;9(2):189-95

PENTOBARBITAL

Pipecolic acid antagonizes barbiturate-enhanced GABA binding to bovine brain membranes. Feigenbaum P, et al. **Brain Res** 1986 Apr 30; 372(1):176-9

Correlation between pentobarbital suppressed cerebellar cyclic GMP and performance of a swimming task. McCaslin PP, et al. **Brain Res** 1986 May 28;374(2):367-70

Blood pentobarbital concentrations during thiopental therapy. Watson WA, et al. **Drug Intell Clin Pharm** 1986 Apr;20(4):283-7

Oral pentobarbital intoxication in a bitch. Fucci V, et al. **J Am Vet Med Assoc** 1986 Jan 15;188(2):191-2

Stereoselective behavioral effects of the isomers of pentobarbital and secobarbital in the pigeon. Wenger GR, et al. **J Pharmacol Exp Ther** 1986 May;237(2):445-9

Variation in pentobarbitone sleeping time in mice. 1. Strain and sex differences. Lovell DP. **Lab Anim** 1986 Apr;20(2):85-90

Variation in pentobarbitone sleeping time in mice. 2. Variables affecting test results. Lovell DP. **Lab Anim** 1986 Apr;20(2):91-6

Inhibition of capillary transport reserve by sodium pentobarbital anesthesia in isometrically contracting dog heart. Durán WN, et al. **Microcirc Endothelium Lymphatics** 1984 Aug;1(4):453-63

Differential interactions between chlordiazepoxide, pentobarbital and benzodiazepine antagonists Ro 15-1788 and CGS 8216 in a drug discrimination procedure. De Vry J, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):999-1005

Behavioral effects of CGS 8216 alone, and in combination with diazepam and pentobarbital in dogs. Risner ME, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1071-6

Effect of sodium pentobarbital on behavioral thermoregulation in rats and mice. Strek KS, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):1147-50

The inhibitory effect of endogenous convulsants quinolinic acid and kynurenine on the pentobarbital stimulation of [3H]flunitrazepam binding. Zarkovsky AM. **Pharmacol Biochem Behav** 1986 May; 24(5):1215-7

Monitoring of pentobarbital plasma levels in critical care patients suffering from increased intracranial pressure. Heinemeyer G, et al. **Ther Drug Monit** 1986;8(2):145-50

[Duration of the narcotic action of nembutal under hyperbarism] Sledkov AIu, et al. **Farmakol Toksikol** 1986 May-Jun;49(3):32-5 (Eng. Abstr.) **(Rus)**

PEPTIDES

Peptide sequence analysis using exopeptidases with molecular analysis of the truncated polypeptides by mass spectrometry. Caprioli RM, et al. **Anal Biochem** 1986 May 1;154(2):596-603

Modulation by basic polypeptides of ATP-induced activation of tyrosine hydroxylase prepared from bovine adrenal medulla. Morita K, et al. **Arch Biochem Biophys** 1986 May 15;247(1):84-90

Regulatory peptides of the gastrointestinal and respiratory tracts. Polak JM, et al. **Arch Int Pharmacodyn Ther** 1986 Apr;280(2 Suppl):16-49 (82 ref.)

Elevation of plasma CCK concentration after intestinal administration of a pancreatic enzyme secretion-stimulating peptide purified from rat bile-pancreatic juice: analysis with N-terminal region specific radioimmunoassay. Iwai K, et al. **Biochem Biophys Res Commun** 1986 Apr 29;136(2):701-6

Stimulation by gastrin-releasing peptide, neurotensin and DN1417, a novel TRH analog, of dopamine and norepinephrine release from perifused rat hypothalamic fragments in vitro. Kabayama Y, et al. **Brain Res** 1986 May 7;372(2):394-9

Enkephalin-containing polypeptides in human cerebrospinal fluid. Nyberg F, et al. **Brain Res** 1986 Apr 23;371(2):278-86

Immunohistochemical localization of urotensin I and other neuropeptides in the caudal neurosecretory system of three species of teleosts and two species of elasmobranchs. Yamada C, et al. **Cell Tissue Res** 1986; 244(3):687-90

Separation of tryptophan pyrrolooxygenase into three molecular forms. A study of their substrate specificities using tryptophyl-containing peptides and proteins. Camoretti-Mercado B, et al. **Eur J Biochem** 1986 Apr 15;156(2):317-25

Scyliorhinin I and II: two novel tachykinins from dogfish gut. Conlon JM, et al. **FEBS Lett** 1986 May 5;200(1):111-6

Structure of asparagine-linked sugar chains in the major polypeptide of hepatitis B surface antigen. Hanaoka K, et al. **J Biochem (Tokyo)** 1986 Apr;99(4):1273-6

High-performance liquid chromatography of amino acids, peptides and proteins. LXVII. Evaluation of bandwidth relationships of peptides related to human beta-endorphin, separated by gradient-elution reversed-phase high-performance liquid chromatography. Hearn MT, et al. **J Chromatogr** 1986 Feb 21;352:35-66

High-performance liquid chromatography of tyrosine-containing peptides by pre-column derivatization involving formylation followed by fluorescence reaction with 1,2-diamino-4,5-dimethoxybenzene. Ishida J, et al. **J Chromatogr** 1986 Mar 28;356(1):171-7

Immunohistochemical study on the distribution of neuron-specific enolase-and peptide-containing nerves in the reticulorumen and the reticular groove of cattle. Kitamura N, et al. **J Comp Neurol** 1986 Jun 8;248(2):223-34

Neuropeptide-like immunoreactive cells in the retina of the larval tiger salamander: attention to the symmetry of dendritic projections. Yang CY, et al. **J Comp Neurol** 1986 Jun 1;248(1):105-18

Ultrastructural localization of serotonin and polypeptide YY (PYY) in endocrine cells of the human rectum. Lukinius AI, et al. **J Histochem Cytochem** 1986 Jun;34(6):719-26

Somatostatin immunoreactive neurons in rat visual cortex: a light and electron microscopic study. Meinecke DL, et al. **J Neurocytol** 1986 Feb;15(1):121-36

Peptidergic secretory granules isolated from the brain: a model system for study of intracellular aspects of the process of peptide secretion. Barnea A. **Methods Enzymol** 1986;124:254-65

Computationally directed biorational drug design of peptides. Momany FA, et al. **Methods Enzymol** 1986;124:3-18

A tissue culture model for the study of peptide synthesis and secretion from microdissected hypothalamic explants. Morris M, et al. **Methods Enzymol** 1986;124:359-71

Striatal neurons expressing somatostatin-like immunoreactivity: evidence for a peptidergic interneuronal system in the cat. Chesselet MF, et al. **Neuroscience** 1986 Mar;17(3):547-71

Somatostatin-immunoreactive amacrine cells of chicken retina: retinal mosaic, ultrastructural features, and light-driven variations in peptide metabolism. Ishimoto I, et al. **Neuroscience** 1986 Apr;17(4):1217-33

Use of cryoprotectant to maintain long-term peptide immunoreactivity and tissue morphology. Watson RE Jr, et al. **Peptides** 1986 Jan-Feb; 7(1):155-9

Localization of urotensin I- and corticotropin-releasing factor-like immunoreactivity in the central nervous system of Catostomus commersoni. Yulis CR, et al. **Peptides** 1986 Jan-Feb;7(1):79-86

Correction. Study of an octadecaneuropeptide derived from diazepam binding inhibitor (DBI): biological activity and presence in rat brain. **Proc Natl Acad Sci USA** 1986 Apr;83(8):2776

[Regulation of acinar cell receptors of the pancreas by peptides] Mössner J, et al. **Klin Wochenschr** 1986 Jun 2;64(11):489-98 (Eng. Abstr.) **(Ger)**

PERCEPTION

Single unit response of noradrenergic, serotonergic and dopaminergic neurons in freely moving cats to simple sensory stimuli. Rasmussen K, et al. **Brain Res** 1986 Mar 26;369(1-2):336-40

PERPHENAZINE

Prolactin and blood pressure responses to perphenazine in human subjects: comparison of the oral and intramuscular routes. Musey VC, et al. **Am J Med Sci** 1986 Jun;291(6):380-5

PERSONALITY DISORDERS

Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. Goldberg SC, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):680-6

Pharmacotherapy for patients with borderline personality disorder. Gunderson JG. **Arch Gen Psychiatry** 1986 Jul;43(7):698-700

Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. Soloff PH, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):691-7

A case of social phobia with avoidant personality disorder treated with MAOI. Deltito JA, et al. **Compr Psychiatry** 1986 May-Jun; 27(3):255-8

Etiology and treatment of borderline personality disorder in adolescents. Egan J. **Hosp Community Psychiatry** 1986 Jun;37(6):613-8

PERSONALITY INVENTORY

The effect of state anxiety on personality measurement. Reich J, et al. **Am J Psychiatry** 1986 Jun;143(6):760-3

PHENCYCLIDINE

The convulsant and anticonvulsant effects of phencyclidine (PCP) and PCP analogues in the rat. Leccese AP, et al. **Behav Brain Res** 1986 Feb;19(2):163-9

Cocaine, phencyclidine, and procaine inhibition of the acetylcholine receptor: characterization of the binding site by stopped-flow measurements of receptor-controlled ion flux in membrane vesicles. Karpen JW, et al. **Biochemistry** 1986 Apr 8;25(7):1777-85

Measurement of the amino acid metabolite of phencyclidine by selected ion monitoring. Syracuse CD, et al. **Biomed Environ Mass Spectrom** 1986 Mar;13(3):113-5

A comparison of the binding of sigma opioids and phencyclidine, and the interaction with antipsychotic drugs in rat brain membranes. Downes CP, et al. **Br J Pharmacol** 1986 May;88(1):231-7

Effects of sigma agonist compounds on local cerebral glucose utilization: relationship to psychotomimetic properties. Kozlowski MR. **Brain Res** 1986 Jun 18;376(1):190-3

Biotransformation of phencyclidine. Holsztynska EJ, et al. **Drug Metab Rev** 1985-86;16(3):285-320 (104 ref.)

Radioligand binding to central phencyclidine recognition sites is dependent on excitatory amino acid receptor agonists. Loo P, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):467-8

High correlation between the localization of [3H]TCP binding and NMDA receptors. Maragos WF, et al. **Eur J Pharmacol** 1986 Apr 9; 123(1):173-4

Quantitation of phencyclidine, its metabolites, and derivatives by gas chromatography with nitrogen-phosphorus detection: application for in vivo and in vitro biotransformation studies. Holsztynska EJ, et al. **J Anal Toxicol** 1986 May-Jun;10(3):107-15

Management of acute PCP intoxication with verapamil. Price WA, et al. **J Toxicol Clin Toxicol** 1986;24(1):85-7

Is Metaphit a phencyclidine antagonist? Studies with ketamine, phencyclidine and N-methylaspartate. Davies SN, et al. **Life Sci** 1986 Jun 30;38(26):2441-5

Phencyclidine: an update. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:1-260

Clinical implications of behavioral pharmacology research on phencyclidine. Balster RL. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:148-62

Phencyclidine (PCP) selectively blocks certain presynaptic potassium channels. Blaustein MP, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:37-51

Discriminative stimulus properties of PCP mimetics. Browne RG. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:134-47

Isolation and identification of an endogenous ligand for the phencyclidine receptor. DiMaggio DA, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:24-36

Characterization of phencyclidine and sigma receptor-binding sites in brain. Gundlach AL, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:1-13

Involvement of dopaminergic, cholinergic, and glutamatergic mechanisms in the actions of phencyclidine-like drugs. Johnson KM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:52-66

Psychopharmacology of phencyclidine. Marwah J, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:127-33

Modulation of phencyclidine (PCP) pharmacokinetics with PCP-specific Fab fragments. Owens SM, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:112-26

Further evidence of phencyclidine/sigma opioid receptor commonality. Sircar R, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:14-23

Comparison of effects of phencyclidine and methamphetamine on body temperature in mice: a possible role for histamine neurons in thermoregulation. Itoh Y, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar;332(3):293-6

Chronic iminodipropionitrile (IDPN) causes no changes in the rat brain phencyclidine (PCP) receptor. Rothman RB, et al. **Neuropeptides** 1986 Apr;7(3):259-63

Effects of phencyclidine on ventral tegmental A10 dopamine neurons in the rat. French ED. **Neuropharmacology** 1986 Mar;25(3):241-8

Phencyclidine selectively blocks a spinal action of N-methyl-D-aspartate in mice. Aanonsen LM, et al. **Neurosci Lett** 1986 Jun 18;67(2):191-7

Actions of phencyclidine on rat locus coeruleus neurones in vitro. Lacey MG, et al. **Neuroscience** 1986 Feb;17(2):485-94

Enhancement of brain calcium antagonist binding by phencyclidine and related compounds. Bolger GT, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):417-23

Phencyclidine-induced wet-dog shakes observed in rats after withdrawal from reserpine treatment. Nabeshima T, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1275-9

Interactions of phencyclidine with hippocampal circuitry: evidence for neuronal heterogeneity. Wang Y, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1403-7

Voltage- and time-dependent effects of phencyclidines on the endplate current arise from open and closed channel blockade. Aguayo LG, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3523-7

Antagonism of phencyclidine action by metaphit in rat cerebellar Purkinje neurons: an electrophysiological study. Wang Y, et al. **Proc Natl Acad Sci USA** 1986 Apr;83(8):2724-7

PHENCYCLIDINE ABUSE

Phencyclidine: an update. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:1-260

PHENELZINE

Efficacy of phenelzine in geriatric depression. Lazarus LW, et al. **Biol Psychiatry** 1986 Jun;21(7):699-701

A case of social phobia with avoidant personality disorder treated with MAOI. Deltito JA, et al. **Compr Psychiatry** 1986 May-Jun; 27(3):255-8

Phenelzine for chronic depression: a study of continuation treatment. Harrison W, et al. **J Clin Psychiatry** 1986 Jul;47(7):346-9

Phenelzine in social phobia. Liebowitz MR, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):93-8

Inhibition of aromatic L-amino acid decarboxylase and tyrosine aminotransferase by the monoamine oxidase inhibitor phenelzine. Dyck LE, et al. **J Neurochem** 1986 Jun;46(6):1899-903

PHENETHYLAMINES

An in vivo voltammetric comparison of the effects of three psychomotor stimulants on electrically evoked neostriatal dopamine release. Stamford JA, et al. **Brain Res** 1986 Feb 26;366(1-2):350-3

Tolerance and pilot pharmacokinetics of amiflamine after increasing single oral doses in healthy subjects. Alván G, et al. **Clin Pharmacol Ther** 1986 Jul;40(1):81-5

Development of a standardized analysis strategy for basic drugs using ion-pair extraction and high-performance liquid chromatography. VIII. Method construction for the determination of mebeverine in tablets and biological fluids. Hoogewijs G, et al. **J Chromatogr** 1986 Apr 25; 377:391-8

The concentration in brain of octopamine and tyramine after portal-systemic bypass in rats: neuroamine concentrations determined simultaneously by methane chemical ionization gas chromatography mass spectrometry. Meredith CG, et al. **Life Sci** 1986 May 5; 38(18):1701-5

beta-phenylethylamine effect on brain and blood catechol-O-methyltransferase activity. Hannan CJ Jr. **Pharmacol Biochem Behav** 1986 Apr;24(4):1141-6

[The central inhibitory action of hexoprenaline] Zhang SS. **Yao Hsueh Hsueh Pao** 1985 Sep;20(9):699-701 (Eng. Abstr.) **(Chi)**

[Effective vasodilation. The calmodulin key molecule] Busse R. **Fortschr Med** 1986;104 Suppl 3:12-3 **(Ger)**

PHENMETRAZINE

An in vivo voltammetric comparison of the effects of three psychomotor stimulants on electrically evoked neostriatal dopamine release. Stamford JA, et al. **Brain Res** 1986 Feb 26;366(1-2):350-3

The discriminative stimulus and subjective effects of d-amphetamine, phenmetrazine and fenfluramine in humans. Chait LD, et al. **Psychopharmacology (Berlin)** 1986;89(3):301-6

PHENOBARBITAL

Effects of phenobarbitone and short-term exposure to heat on microsomal cytochrome P-450 and associated monooxygenases in rat liver. Pachecka J, et al. **Acta Physiol Pol** 1984 Sep-Dec;35(5-6):546-50

Physiologic changes induced by endotracheal instillation and suctioning in critically ill preterm infants with and without sedation. Ninan A, et al. **Am J Perinatol** 1986 Apr;3(2):94-7

Subcellular fractionation of liver organelles from phenobarbital-treated rats by counter-current partition and sucrose gradient centrifugation. Morris WB, et al. **Biochem Pharmacol** 1986 Jul 1;35(13):2187-91

Sexually dimorphic response of rat hepatic monooxygenases to low-dose phenobarbital. Shapiro BH. **Biochem Pharmacol** 1986 May 15; 35(10):1766-8

Regulation of cytochrome P-450p by phenobarbital and phenobarbital-like inducers in adult rat hepatocytes in primary monolayer culture and in vivo. Schuetz EG, et al. **Biochemistry** 1986 Mar 11;25(5):1124-33

Interaction between cyclosporin A and phenobarbitone [letter] Carstensen H, et al. **Br J Clin Pharmacol** 1986 May;21(5):550-1

cDNA clones for liver cytochrome P-450s from individual aroclor-treated rats: constitutive expression of a new P-450 gene related to phenobarbital-inducible forms. Affolter M, et al. **DNA** 1986 Jun; 5(3):209-18

Comparative kinetics of phenobarbital after administration of the acid and the propylhexedrine salt (barbexaclone). Perucca E, et al. **Eur J Clin Pharmacol** 1986;29(6):729-30

NADPH-dependent and -independent loss of cytochrome P-450 in control and phenobarbital-induced rat hepatic microsomes incubated with carbon tetrachloride. Moody DE, et al. **Exp Mol Pathol** 1986 Jun; 44(3):318-28

ADP-ribosylation of nuclear proteins is increased by phenobarbital. Identification of the ADP-ribosylated histone fractions in rat liver nuclei. Bràz J, et al. **FEBS Lett** 1986 Apr 21;199(2):164-8

Valproic acid teratogenicity in mice after various administration and phenobarbital-pretreatment regimens: the parent drug and not one of the metabolites assayed is implicated as teratogen. Nau H. **Fundam Appl Toxicol** 1986 May;6(4):662-8

Effects of phenobarbital, 3-methylcholanthrene and polychlorinated biphenyls on sex-specific forms of cytochrome P-450 in liver microsomes of rats. Kamataki T, et al. **J Biochem (Tokyo)** 1986 Mar; 99(3):841-5

The cDNA and protein sequence of a phenobarbital-induced chicken cytochrome P-450. Hobbs AA, et al. **J Biol Chem** 1986 Jul 15; 261(20):9444-9

Rat liver UDP-glucuronosyltransferase. Sequence and expression of a cDNA encoding a phenobarbital-inducible form. Mackenzie PI. **J Biol Chem** 1986 May 5;261(13):6119-25

Isolation and characterization of genomic clones for two chicken phenobarbital-inducible cytochrome P-450 genes. Mattschoss LA, et al. **J Biol Chem** 1986 Jul 15;261(20):9438-43

Increased bile acid level in preterm infants treated with phenobarbital [letter] Schimmel MS, et al. **J Pediatr Gastroenterol Nutr** 1986 May-Jun; 5(3):508

Transport of phenobarbitone into the intestinal lumen and the biliary tract following i.v. administration to rats. Arimori K, et al. **J Pharm Pharmacol** 1986 May;38(5):391-3

Inhibition of high-affinity choline uptake in the rat hippocampus by in vivo injection of phenobarbital in the medial septum. Richter JA, et al. **J Pharmacol Exp Ther** 1986 May;237(2):563-8

Lipid composition of liver microsomes from rats treated with acetone. Hayes EP, et al. **Toxicol Lett** 1986 May;31(2):139-45

[The polymorphism of drugs in powders and tablets. 2. X-ray diffraction studies of polymorphic modifications of phenobarbital] Traue J, et al. **Pharmazie** 1986 Apr;41(4):291-2 **(Ger)**

[Cytochrome P-450 isoforms in the liver of rats treated with phenobarbital, 3-methylcholanthrene and Aroclor 1254 studied by monoclonal antibodies] Koliada AIu. **Biull Eksp Biol Med** 1986 Apr; 101(4):422-5 (Eng. Abstr.) **(Rus)**

[Selective effect of antiepileptics on the cortex and medulla of the adrenal glands] Nović M, et al. **Srp Arh Celok Lek** 1985 Nov-Dec; 113(11-12):983-90 (Eng. Abstr.) **(Sec)**

PHENOTHIAZINE TRANQUILIZERS

Automated flow injection spectrophotometric determination of some phenothiazines using iron perchlorate: applications in drug assays, content uniformity and dissolution studies. Koupparis MA, et al. **Analyst** 1986 Mar;111(3):313-8

Photo-decomposition and metabolism of the phenothiazine drug perazine. Schley J. **Arzneimittelforschung** 1986 Apr;36(4):635-7

Effects of phenothiazines on phosphate incorporation and chloride uptake in isolated intestinal epithelial cells. Wahawisan R, et al. **Gen Pharmacol** 1986;17(3):275-80

Colorimetric determination of certain phenothiazine drugs by using morpholine and iodine-potassium iodide reagents. Youssef AF, et al. **J Assoc Off Anal Chem** 1986 May-Jun;69(3):513-8

A comparative trial of depot pipothiazine. Steinert J, et al. **J Int Med Res** 1986;14(2):72-7

Free and conjugated 3,4-dihydroxyphenylacetic acid and homovanillic acid in brain dopaminergic areas at basal state and after pipotiazine activation. Tavitian E, et al. **J Neural Transm** 1986;65(3-4):261-75

Biotransformation of amitriptyline in man: interaction with phenothiazines. Vandel S, et al. **Neuropsychobiology** 1986;15(1):15-9

[Pharmacokinetics of pipothiazine palmitate, after intramuscular administration in schizophrenic patients] Blanc M, et al. **Therapie** 1986 Jan-Feb;41(1):27-30 (Eng. Abstr.) **(Fre)**

PHENOTHIAZINES

Interaction between calmodulin and five different spin-labelled chlorophenothiazines. Olivier JL, et al. **Biochem J** 1986 Feb 1; 233(3):853-7

Quality control of azure B preparations by liquid chromatography and standardization with azure B tetrafluoroborate. Nelis HJ, et al. **Clin Chim Acta** 1986 May 15;156(3):247-57

Use of ethopropazine and BW 284C51 as selective inhibitors for cholinesterases from various species. Mikalsen A, et al. **Comp Biochem Physiol [C]** 1986;83(2):447-9

Increased acidophilia of eosinophil granules after EDTA treatment. Gomez-Perretta C, et al. **Histochem J** 1986 Jan;18(1):1-4

Differential modulation of autonomic activity by ethmozin and ethacizin (analog of ethmozin) on the canine sinus node and atrioventricular junction. Urthaler F, et al. **J Am Coll Cardiol** 1986 Jul; 8(1 Suppl A):86A-94A

Chromatographic assay of 10-[3-(3-hydroxypyrrolidinyl)propyl]-2-trifluoromethyl phenothiazine using electrochemical detection. Shibanoki S, et al. **J Chromatogr** 1986 Apr 25;377:436-40

A theoretical study of the binding of phenothiazine derivatives to residues 82-93 of calmodulin. Gresh N, et al. **Mol Pharmacol** 1986 Apr; 29(4):355-62

[Effect of ethacizin (diethylamine analog of ethmozine) on the efferent activity of the sympathetic and parasympathetic nerves of the heart] Khageman GR, et al. **Kardiologiia** 1986 Apr;26(4):54-60 (Eng. Abstr.) **(Rus)**

PHENOXYBENZAMINE

Effect of an alpha-blocking agent (phenoxybenzamine) in the management of premature ejaculation. Beretta G, et al. **Acta Eur Fertil** 1986 Jan-Feb; 17(1):43-5

The effect of alpha-adrenergic stimulation and blockade on perfusion of myocutaneous flaps. Moore GK, et al. **Otolaryngol Head Neck Surg** 1986 Apr;94(4):489-96

PHENYLALANINE

Quantification of the importance of individual steps in the control of aromatic amino acid metabolism. Salter M, et al. **Biochem J** 1986 Mar 15;234(3):635-47

Molecular basis for the anti-sickling activity of aromatic amino acids and related compounds: a proton nuclear magnetic resonance investigation. Russu IM, et al. **Biochemistry** 1986 Feb 25;25(4):808-15

In vivo studies on the formation of m-tyrosine and o-tyrosine from L-phenylalanine in rats. Ishimitsu S, et al. **Chem Pharm Bull (Tokyo)** 1986 Feb;34(2):768-74

Tryptophan requirement of growing swine as determined by the oxidation of an indicator amino acid. Lin FD, et al. **J Anim Sci** 1986 Mar; 62(3):660-4

Mutagenesis by normal metabolites in Escherichia coli: phenylalanine mutagenesis is dependent on error-prone DNA repair. Sargentini NJ, et al. **Mutat Res** 1986 Jul;161(2):113-8

PHENYLPROPANOLAMINE

Metabolism of cathinone to (-)-norephedrine and (-)-norpseudoephedrine. Brenneisen R, et al. **J Pharm Pharmacol** 1986 Apr;38(4):298-300

Behavioral and neurochemical evaluation of phenylpropanolamine. Woolverton WL, et al. **J Pharmacol Exp Ther** 1986 Jun; 237(3):926-30

Weight loss induced by chronic phenylpropanolamine: anorexia and brown adipose tissue thermogenesis. Wellman PJ, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):605-11

PHENYTOIN

In vitro evaluation of nasogastric administration methods for phenytoin. Cacek AT, et al. **Am J Hosp Pharm** 1986 Mar;43(3):689-92

Recovery of phenytoin from an enteral nutrient formula. Hooks MA, et al. **Am J Hosp Pharm** 1986 Mar;43(3):685-8

Effect of phenytoin on rat bone resorption in vitro. Somerman MJ, et al. **Arch Oral Biol** 1986;31(4):267-8

Comparison of four single-point phenytoin dosage prediction techniques using computer-simulated pharmacokinetic values. Toscano JP, et al. **Clin Pharm** 1986 May;5(5):396-402

Characterization of collagens in phenytoin-enlarged human gingiva. Narayanan AS, et al. **Coll Relat Res** 1985 Dec;5(6):513-8

Single dose comparison of the relative bioavailability of phenytoin suspension and extended capsules. Fitzsimmons WE, et al. **Epilepsia** 1986 Jul-Aug;27(4):464-8

Postrotatory nystagmus during phenytoin treatment. Mameli O, et al. **Epilepsia** 1986 Jul-Aug;27(4):385-90

Competition between valproate & phenytoin for plasma protein binding. Jaffery NF, et al. **Indian J Med Res** 1986 Apr;83:426-8

5,5-Diaryl-2-thiohydantoins and 5,5-diaryl-N3-substituted-2-thiohydantoins as potential hypolipidemic agents. Tompkins JE. **J Med Chem** 1986 May;29(5):855-9

The laser gingivectomy. The use of the CO2 laser for the removal of phenytoin hyperplasia. Pick RM, et al. **J Periodontol** 1985 Aug; 56(8):492-6

Persistent defects in the hepatic monooxygenase system of adult rats exposed, perinatally, to maternally administered phenytoin. Shapiro BH, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):68-75

Adjunctive therapy of phenytoin overdose--a case report using plasmaphoresis. Larsen LS, et al. **J Toxicol Clin Toxicol** 1986; 24(1):37-49

Interaction of oral phenytoin with enteral feedings. Saklad JJ, et al. **JPEN J Parenter Enteral Nutr** 1986 May-Jun;10(3):322-3

Activity-dependent depression of nerve action potential by phenytoin. David G, et al. **Neurosci Lett** 1986 May 15;66(2):163-8

Check concentrations of medications ordered for children. Cohen MR. **Nursing** 1986 May;16(5):8

A unilateral gingival overgrowth (hyperplasia) in a Dilantin treated patient. Khatiblou FA. **Periodont Case Rep** 1985;7(2):46-7

Interaction of furosemide and phenytoin in the rat. Williamson HE. **Proc Soc Exp Biol Med** 1986 Jul;182(3):322-4

Ethnic differences in phenytoin kinetics. Hvidberg EF. **Prog Clin Biol Res** 1986;214:279-87

Review of alterations in oral phenytoin bioavailability associated with formulation, antacids, and food. Cacek AT. **Ther Drug Monit** 1986; 8(2):166-71

Protection by phenytoin and calcium channel blocking agents against the toxicity of diisopropylfluorophosphate. Dretchen KL, et al. **Toxicol Appl Pharmacol** 1986 May;83(3):584-9

[Gingival hyperplasia due to Dihydan. A semi-quantitative and ultrastrctural study] Boudat MA, et al. **J Parodontol** 1985 Oct; 4(4):301-10 (Eng. Abstr.) **(Fre)**

[Diphenylhydantoin in the prevention and therapy of AIDS? (letter)] Lehr HA, et al. **Dtsch Med Wochenschr** 1986 Jun 20;111(25):1001-2 **(Ger)**

[Inhibitory effect of phenytoin on nerve hyperexcitability induced by low calcium in frogs] Takagi T, et al. **Kanagawa Shigaku** 1985 Dec; 20(3):394-401 (Eng. Abstr.) **(Jpn)**

[Gingival hyperplasia induced by diphenylhydantoin. Effect of diphenylhydantoin on DNA, RNA, and protein synthesis in cultured bovine gingival explants] Nagata T, et al. **Nippon Shishubyo Gakkai Kaishi** 1986 Mar;28(1):161-7 (Eng. Abstr.) **(Jpn)**

[Application of drug monitoring with saliva--the influence of phenytoin upon the salivary inorganic constituents] Watanabe S, et al. **Rinsho Byori** 1986 Mar;34(3):254-61 **(Jpn)**

PHOBIC DISORDERS

Clinically significant improvement in agoraphobia research. Mavissakalian M. **Behav Res Ther** 1986;24(3):369-70

A case of social phobia with avoidant personality disorder treated with MAOI. Deltito JA, et al. **Compr Psychiatry** 1986 May-Jun; 27(3):255-8

Pharmacokinetics and clinical effects of alprazolam following single and multiple oral doses in patients with panic disorder. Ciraulo DA, et al. **J Clin Pharmacol** 1986 Apr;26(4):292-8

Treatment of panic disorder and agoraphobia with clonazepam. Spier SA, et al. **J Clin Psychiatry** 1986 May;47(5):238-42

Phenelzine in social phobia. Liebowitz MR, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):93-8

Imipramine binding in agoraphobia [letter] Ambrosini P. **Psychiatry Res** 1986 Jun;18(2):189-92

Taper withdrawal studies with alprazolam in patients with panic disorder and agoraphobia. Pecknold JC, et al. **Psychopharmacol Bull** 1986; 22(1):173-6

A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. Rizley R, et al. **Psychopharmacol Bull** 1986;22(1):167-72

PHYSOSTIGMINE

Inhibition of acetylcholinesterase from electric eel by (-)-and (+)-physostigmine and related compounds. Brossi A, et al. **FEBS Lett** 1986 Jun 9;201(2):190-2

Distribution and pharmacokinetics of physostigmine in rat after intramuscular administration. Somani SM, et al. **Fundam Appl Toxicol** 1986 Feb;6(2):327-34

In vitro inhibition of brain acetylcholinesterase by phosphamidon & physostigmine sulphate in adult chick. Chattopadhyay R, et al. **Indian J Med Res** 1986 Apr;83:435-40

In-vitro study of physostigmine salicylate and pilocarpine hydrochloride release from different gel formulations. Habib FS, et al. **Pharmazie** 1986 Feb;41(2):124-5

Central muscarinic effects of physostigmine on mood, cardiovascular function, pituitary and adrenal neuroendocrine release. Janowsky DS, et al. **Psychopharmacology (Berlin)** 1986;89(2):150-4

The effect of hemicholinium-3 and physostigmine on choline in rat brain. Slone HT, et al. **Res Commun Chem Pathol Pharmacol** 1986 Apr; 52(1):133-6

PILOCARPINE

Corneal changes during pilocarpine gel therapy [letter] Hook SR. **Am J Ophthalmol** 1986 May 15;101(5):623

Stirring device for direct microtitration of pilocarpine hydrochloride in individual single-dose containers. Johansson PA. **Anal Chem** 1986 Jun; 58(7):1587-9

Pilocarpine for the treatment of xerostomia associated with salivary gland dysfunction. Fox PC, et al. **Oral Surg Oral Med Oral Pathol** 1986 Mar; 61(3):243-8

In-vitro study of physostigmine salicylate and pilocarpine hydrochloride release from different gel formulations. Habib FS, et al. **Pharmazie** 1986 Feb;41(2):124-5

[Rapid semiquantitative evaluation by thin-layer chromatography of pilo- and isopilocarpic acids in eyedrops with a pilocarpine base] Durif C, et al. **Pharm Acta Helv** 1986;61(5-6):135-8 **(Fre)**

PITUITARY HORMONE RELEASING HORMONES

The effects of orchidectomy and replacement therapy on the ultrastructure and gonadotropin-releasing hormone content of the median eminence of the rat. Beckman WC Jr. **Am J Anat** 1986 May;176(1):33-52

Relationship of gonadotropin-releasing hormone, danazol, and prostaglandin blockade to ovarian enlargement and ascites formation of the ovarian hyperstimulation syndrome in the rabbit. Pride SM, et al. **Am J Obstet Gynecol** 1986 May;154(5):1155-60

Mechanism of action of gonadotropin releasing hormone. Conn PM, et al. **Annu Rev Physiol** 1986;48:495-513 (81 ref.)

Regulation of mating behaviour in the female rat by gonadotropin-releasing hormone in the ventral tegmental area: effects of selective destruction of the A10 dopamine neurones. Sirinathsinghji DJ, et al. **Brain Res** 1986 May 21;374(1):167-73

The interaction of growth hormone releasing hormone with other hypothalamic hormones on the release of anterior pituitary hormones. Looij BJ Jr, et al. **Clin Endocrinol (Oxf)** 1986 Feb;24(2):149-56

The effect of physiological changes in ovarian steroids on the prolactin response to gonadotrophin releasing factor. Tan YM, et al. **Clin Endocrinol (Oxf)** 1986 Jan;24(1):71-8

Luteinizing hormone and follicle-stimulating hormone responses to intransal gonadotropin-releasing hormone. Rajfer J, et al. **Fertil Steril** 1986 Jun;45(6):794-9

Gonadotropin-releasing hormone and prostaglandin F2 alpha for postpartum dairy cows: estrous, ovulation, and fertility traits. Benmrad M, et al. **J Dairy Sci** 1986 Mar;69(3):800-11

Timing of multiple ovulations in the ewe after treatment with FSH or PMSG with and without GnRH. Walker SK, et al. **J Reprod Fertil** 1986 May;77(1):135-42

Medical treatment for undescended testis [letter] de Muinck Keizer-Schrama S. **Lancet** 1986 Jul 26;2(8500):220-1

Physiological role of putative testicular gonadotrophin releasing hormone

(GnRH). Clayton RN, et al. **Med Biol** 1986;63(5-6):201-9

Gonadotropin releasing hormone (GnRH) agonists in male contraception. Swerdloff RS, et al. **Med Biol** 1986;63(5-6):218-24

Regulation of primate testicular function by GnRH analogues. Weinbauer GF, et al. **Med Biol** 1986;63(5-6):210-7

Hormonal treatment of cryptorchidism [letter] Hadziselimovic F. **N Engl J Med** 1986 Jul 31;315(5):322

Clinical studies in black women with isolated gonadotrophin-releasing hormone deficiency. Norman RJ, et al. **S Afr Med J** 1986 Apr 26; 69(9):546-8

PITUITARY HORMONES

Neuroendocrine parameters in the rat exposed to 60-Hz electric fields. Quinlan WJ, et al. **Bioelectromagnetics** 1985;6(4):381-9

PITUITARY HORMONES, ANTERIOR

The interaction of growth hormone releasing hormone with other hypothalamic hormones on the release of anterior pituitary hormones. Looij BJ Jr, et al. **Clin Endocrinol (Oxf)** 1986 Feb;24(2):149-56

Single-unit activity of hypothalamic arcuate neurons in brain tissue slices. Effects of anterior pituitary hormones, cholecystokinin-octapeptide, and neurotransmitters. Pan JT, et al. **Neuroendocrinology** 1986; 43(2):189-96

Effects of neuropeptide Y (NPY) on the release of anterior pituitary hormones in the rat. Kerkerian L, et al. **Peptides** 1985 Nov-Dec; 6(6):1201-4

PRAZEPAM

Solubility of diazepam and prazepam in aqueous non-ionic surfactants. Moro ME, et al. **J Pharm Pharmacol** 1986 Apr;38(4):294-6

PROGESTERONE

Hormonal effects on the activities of glycosidases in the endometrium of rabbit uterus. Munakata H, et al. **Biochem Med Metab Biol** 1986 Apr;35(2):179-83

Biochemical and radioautographic analysis of estrogen-inducible progestin receptors in female ferret brain and pituitary: correlations with effects of progesterone on sexual behavior and gonadotropin-releasing hormone-stimulated secretion of luteinizing hormone. Baum MJ, et al. **Brain Res** 1986 Mar 19;368(2):296-309

The effect of physiological changes in ovarian steroids on the prolactin response to gonadotrophin releasing factor. Tan YM, et al. **Clin Endocrinol (Oxf)** 1986 Jan;24(1):71-8

Modulation of the estradiol-induced luteinizing hormone surge by progesterone or antiestrogens: effects on pituitary gonadotropin-releasing hormone receptors. Attardi B, et al. **Endocrinology** 1986 Jul;119(1):274-83

The effect of oestradiolum benzoicum and progesterone on the noradrenalin content in organs of the female reproductive system of sexually immature pigs. Lakomy M, et al. **Gegenbaurs Morphol Jahrb** 1986;132(1):129-43

Anterior pituitary concentrations of gonadotropins, GnRH-receptors and ovarian characteristics following early weaning in beef cows. Parfet JR, et al. **J Anim Sci** 1986 Mar;62(3):717-22

Activation of protein kinase C potentiates cyclic AMP production and stimulates steroidogenesis in differentiated ovarian granulosa cells. Shinohara O, et al. **J Steroid Biochem** 1986 Jan;24(1):161-8

Effects of dopaminergic drugs on plasma levels of steroid hormones in conscious dogs. Goiny M, et al. **Life Sci** 1986 Jun 23; 38(25):2293-300

Anxiolytic effects of progesterone are sexually dimorphic. Rodriguez-Sierra JF, et al. **Life Sci** 1986 May 19;38(20):1841-5

Effects of estradiol and progesterone on immunoreactive forms of hypothalamic luteinizing hormone-releasing hormone. Drouva SV, et al. **Neuroendocrinology** 1986;43(1):32-7

In vitro LHRH release from superfused hypothalamus as a function of the rat estrous cycle: effect of progesterone. Kim K, et al. **Neuroendocrinology** 1986;42(5):392-8

Suppression of receptive and proceptive behavior in ovariectomized, estrogen-progesterone-primed rats by intraventricular beta-endorphin: studies of behavioral specificity. Wiesner JB, et al. **Neuroendocrinology** 1986;43(1):57-62

Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Majewska MD, et al. **Science** 1986 May 23; 232(4753):1004-7

[Preliminary study in female rats of the immunoregulatory effect of estradiol, progesterone and pituitary prolactin on natural killer-like cell mediated cytotoxic activity] Mohammad M, et al. **Ann Endocrinol (Paris)** 1985;46(6):415-9 (Eng. Abstr.) **(Fre)**

PROLACTIN

The effect of oestriol and tamoxifen on oestradiol induced prolactin secretion in anaesthetised rats. Gilna P, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):71-8

Human foetal prolactin but not thyrotropin secretion is decreased by bromocriptine. Roti E, et al. **Acta Endocrinol (Copenh)** 1986 May; 112(1):35-42

The sensitivity of prolactin secretion to dopamine changes during pregnancy in mice. Swartz SR, et al. **Acta Endocrinol (Copenh)** 1986 Apr;111(4):567-71

The phorbol ester TPA induces hormone release and electrical activity in clonal rat pituitary cells. Ostberg BC, et al. **Acta Physiol Scand** 1986 Apr;126(4):517-24

Therapeutic effect of bromocriptine in anovulatory women with normal prolactin levels. Waroński W, et al. **Acta Univ Palacki Olomuc Fac Med** 1981;101:125-32

Prolactin and blood pressure responses to perphenazine in human subjects: comparison of the oral and intramuscular routes. Musey VC, et al. **Am J Med Sci** 1986 Jun;291(6):380-5

Dopamine inhibits maitotoxin-stimulated pituitary 45Ca2+ efflux and prolactin release. Login IS, et al. **Am J Physiol** 1986 Jun; 250(6 Pt 1):E731-5

Effect of clonidine, quipazine, and LY 53857 on the prolactin-suppressant action of bromocriptine in rats. Lipham LB, et al. **Am J Vet Res** 1986 May;47(5):1089-91

The pituitary gland in primate mammary development: evidence that prolactin is not essential. Kleinberg DL, et al. **Ann NY Acad Sci** 1986; 464:37-43

Intracerebroventricular injection of anti-prolactin serum suppresses excessive grooming of pituitary homografted rats. Drago F, et al. **Behav Neural Biol** 1986 Jul;46(1):99-105

Benzodiazepine- and barbiturate-interactions with GABAA receptor responses on lactotrophs. Anderson RA, et al. **Brain Res** 1986 Apr 23; 371(2):287-92

Activation of GABA receptors in the hypothalamus stimulates secretion of growth hormone and prolactin. Willoughby JO, et al. **Brain Res** 1986 May 21;374(1):119-25

The effect of physiological changes in ovarian steroids on the prolactin response to gonadotrophin releasing factor. Tan YM, et al. **Clin Endocrinol (Oxf)** 1986 Jan;24(1):71-8

Plasma concentration of prolactin during four-day osmotic pump infusion of thyrotropin-releasing hormone and vasoactive intestinal polypeptide in rats. Niimi M, et al. **Endocrinol Jpn** 1985 Dec;32(6):929-32

Subpopulations of lactotropes detected with the reverse hemolytic plaque assay show differential responsiveness to dopamine. Luque EH, et al. **Endocrinology** 1986 May;118(5):2120-4

Reversal by thiols of dopamine-, stalk-median eminence-, and zinc-induced inhibition of prolactin transformation in adenohypophyses of lactating rats. Martinez-Escalera G, et al. **Endocrinology** 1986 May; 118(5):1803-7

Inhibition of the preovulatory prolactin surge in the rat by catechol estrogens: functional and temporal specificity. Okatani Y, et al. **Endocrinology** 1986 Jul;119(1):261-7

Antagonism of beta-endorphin-induced prolactin release by alpha-melanocyte-stimulating hormone and corticotropin-like intermediate lobe peptide. Wardlaw SL, et al. **Endocrinology** 1986 Jul; 119(1):112-8

Biphasic effect of GABAA receptor agonists on prolactin secretion: evidence for two types of GABAA receptor complex on lactotrophes. Anderson R, et al. **Eur J Pharmacol** 1986 May 13;124(1-2):1-9

Regulation of human prolactin secretion by gonadotropin-releasing hormone in vitro. Blackwell RE, et al. **Fertil Steril** 1986 Jul; 46(1):26-31

Immunoperoxidase localization of prolactin in endometrium during normal menstrual, luteal phase defect, and corrected luteal phase defect cycles. Kauma S, et al. **Fertil Steril** 1986 Jul;46(1):37-41

The anti-oestrogen tamoxifen does not interfere with the dopaminergic control of prolactin and TSH release in normogonadotrophic oligozoospermic man. van Bergeijk L, et al. **Horm Metab Res** 1986 Apr;18(4):272-6

Serum concentrations of prolactin, thyroxine and triiodothyronine relative to season and the estrous cycle in the mare. Johnson AL. **J Anim Sci** 1986 Apr;62(4):1012-20

Plasma levels of arginine vasotocin, prolactin, aldosterone and corticosterone during prolonged dehydration in the domestic fowl: effect of dietary NaCl. Arnason SS, et al. **J Comp Physiol [B]** 1986; 156(3):383-97

Prolactin release, oestrogens and proliferation of prolactin-secreting cells in the anterior pituitary gland of adult male rats. Pérez RL, et al. **J Endocrinol** 1986 Mar;108(3):399-403

Prolactin lowering effect of dihydroergokryptine in rat and in man. Poli M, et al. **J Endocrinol Invest** 1986 Feb;9(1):31-6

Histamine-induced prolactin release and activity of tuberoinfundibular dopaminergic neurons in male rats. Seltzer AM, et al. **J Neural Transm** 1986;65(2):115-23

Steroid regulation of gonadotropins in genetically hypoprolactinemic females (IPL nude rats). Cohen H, et al. **J Steroid Biochem** 1986 Jan; 24(1):431-5

Age-related differences in the pituitary prolactin response to thyrotropin-releasing hormone. Arnetz BB, et al. **Life Sci** 1986 Jul 14; 39(2):135-9

Dopamine inhibition of prolactin release but not synthesis in the male Syrian hamster: in vitro studies. Blask DE, et al. **Life Sci** 1986 May 26;38(21):1915-21

Dopamine and somatostatin inhibit forskolin-stimulated prolactin and growth hormone secretion but not stimulated cyclic AMP levels in sheep anterior pituitary cell cultures. Ray KP, et al. **Mol Cell Endocrinol** 1986 May;45(2-3):175-82

Immunohistochemical localization of follicle-stimulating hormone, luteinizing hormone, growth hormone, adrenocorticotrophic hormone and prolactin in the human placenta. Al-Timimi A, et al. **Placenta** 1986 Mar-Apr;7(2):163-72

Effect of mammalian growth hormone and prolactin on the growth of hypophysectomized chickens. King DB, et al. **Proc Soc Exp Biol Med** 1986 Jun;182(2):201-7

[Changes in plasma prolactin and magnesium in male rats treated with thioproperazine and/or bromocriptine] Marois G, et al. **Ann Endocrinol (Paris)** 1985;46(6):399-405 (Eng. Abstr.) **(Fre)**

[Preliminary study in female rats of the immunoregulatory effect of estradiol, progesterone and pituitary prolactin on natural killer-like cell mediated cytotoxic activity] Mohammad M, et al. **Ann Endocrinol (Paris)** 1985;46(6):415-9 (Eng. Abstr.) **(Fre)**

[Plasma monitoring of haloperidol. Correlation with clinical efficacy and plasma prolactin levels] Giraud-Serio J, et al. **Ann Med Psychol (Paris)** 1985 Nov;143(9):900-11 **(Fre)**

[Evaluation of the dopaminergic neuroendocrine control of prolactin release during labor in humans] Nishii O, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Feb 20;62(2):108-16 (Eng. Abstr.) **(Jpn)**

[The effect of prolactin on the production of surfactant in rat fetal lung] Sch E. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 Mar;38(3):337-45 (Eng. Abstr.) **(Jpn)**

[Nocturnal prolactin (PRL) levels and PRL release by metoclopramide in normoprolactinemic anovulation, and effects of bromocriptine in induction of ovulation] Suginami H, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 Apr;38(4):603-4 **(Jpn)**

[Serum prolactin levels during sleep and in metoclopramide stimulation in normoprolactinemic anovulation and ovulation induction with bromocriptine] Suginami H, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 May;38(5):728-34 (Eng. Abstr.) **(Jpn)**

PROMAZINE

Promazine. A major plasma metabolite of chlorpromazine in a population of chronic schizophrenics. Sgaragli G, et al. **Drug Metab Dispos** 1986 Mar-Apr;14(2):263-6

Analysis of promazine in pharmaceutical preparations by high-performance liquid chromatography. Tebbett IR. **J Chromatogr** 1986 Mar 28;356(1):227-9

PROMETHAZINE

Oral paediatric premedication. Paul AK, et al. **J Indian Med Assoc** 1984 Jul;82(7):233-5

Effect on bone ash weights of long-term treatment of mice with oral promethazine HCl. Tyan ML. **Mech Ageing Dev** 1986 May; 34(3):305-12

PROPANEDIOLS

Regulatory changes in the fucose system associated with the evolution of a catabolic pathway for propanediol in Escherichia coli. Hacking AJ, et al. **J Bacteriol** 1977 May;130(2):832-8

Pulpal response to an experimental adhesion promoter. Plant CG, et al. **J Oral Pathol** 1986 Apr;15(4):196-200

[Application of fatty alcohols to pharmaceutical dosage form. III. Percutaneous absorption of indomethacin from fatty alcohol and propylene glycol (FAPG) bases consisting of a mixture of fatty alcohol and propylene glycol] Kaiho F, et al. **Yakugaku Zasshi** 1986 Jan; 106(1):47-53 (Eng. Abstr.) **(Jpn)**

[Effect of 1,2-propandiol and glycerin on erythrocyte survival in hypothermia] Vorotilin AM, et al. **Gematol Transfuziol** 1986 May; 31(5):49-51 **(Rus)**

PROPRANOLOL

Effect of alpha and beta adrenoreceptor antagonists on glucagon-induced inhibition of gastric acid secretion in cats. Dzierżkowska J, et al. **Acta Physiol Pol** 1984 Sep-Dec;35(5-6):475-84

Stability of propranolol hydrochloride suspension compounded from tablets. Henry DW, et al. **Am J Hosp Pharm** 1986 Jun;43(6):1492-5

Antimigraine drug interactions with 5-hydroxytryptamine1A receptors. Hiner BC, et al. **Ann Neurol** 1986 May;19(5):511-3

Association and partitioning of propranolol in model and biological membranes. Rogers JA, et al. **Biochem Pharmacol** 1986 Jul 1; 35(13):2259-61

Phorbol esters, vasopressin and angiotensin II block alpha 1-adrenergic action in rat hepatocytes. Possible role of protein kinase C. García-Sáinz JA, et al. **Biochim Biophys Acta** 1986 Jun 16;887(1):69-72

Relationship between plasma propranolol concentration and dose in young, healthy volunteers. Dey M, et al. **Biopharm Drug Dispos** 1986 Mar-Apr;7(2):103-11

The pharmacokinetics of exaprolol and propranolol in rats with interrupted enterohepatic circulation. Motheová O, et al. **Biopharm Drug Dispos** 1986 Mar-Apr;7(2):151-62

Serum protein binding of diazepam and propranolol in the feto-maternal unit from early to late pregnancy. Krauer B, et al. **Br J Obstet Gynaecol** 1986 Apr;93(4):322-8

Concomitant food intake can increase the bioavailability of propranolol by transient inhibition of its presystemic primary conjugation. Liedholm H, et al. **Clin Pharmacol Ther** 1986 Jul;40(1):29-36

Enprostil, in contrast to cimetidine, does not inhibit propranolol metabolism. Reilly CS, et al. **Clin Pharmacol Ther** 1986 Jul; 40(1):37-41

Synthesis and identification of 3-(4-hydroxy-1-naphthoxy)lactic acid as a metabolite of propranolol in the rat, in man, and in the rat liver 9000 g supernatant fraction. Talaat RE, et al. **Drug Metab Dispos** 1986 Mar-Apr;14(2):202-7

Cardiorespiratory response to exercise before and after acute beta-adrenoreceptor blockade in nonsmokers and chronic smokers. Penny WJ, et al. **Int J Cardiol** 1986 Jun;11(3):293-304

Pharmacokinetic and pharmacodynamic interactions between nifedipine and propranolol or betaxolol. Vinceneux P, et al. **Int J Clin Pharmacol Ther Toxicol** 1986 Mar;24(3):153-8

Interaction of epinephrine and propranolol [letter] Spencer PS, et al. **J Am Acad Dermatol** 1986 Jun;14(6):1093-4

Effects of beta-adrenergic stimulation on 1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine-mediated vasoconstriction and glycogenolysis in the perfused rat liver. Fisher RA, et al. **J Biol Chem** 1986 Jul 5;261(19):8817-23

Propranolol binding to human serum proteins studied by high-performance liquid chromatography. Bree F, et al. **J Chromatogr** 1986 Mar 7;375(2):416-22

Acute hypotensive effects of oral and intravenous propranolol: early alterations in peripheral resistance. Fagan TC, et al. **J Clin Hypertens** 1986 Mar;2(1):21-9

The serotonin syndrome: case responsive to propranolol [letter] Guzé BH, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):119-20

Propranolol treatment of assaultive patients with organic brain disease. A double-blind crossover, placebo-controlled study. Greendyke RM, et al. **J Nerv Ment Dis** 1986 May;174(5):290-4

Effects of propranolol on catecholamine synthesis and uptake in the central nervous system of the rat. Tuross N, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):739-45

On the assessment of the beta-adrenoceptor blocking activity of propranolol using the rat isolated right ventricle. Doggrell SA, et al. **J Pharmacol Methods** 1986 Apr;15(2):119-31

Increased dependency of cardiac pacemaker activity on extracellular Ca after adrenergic blockade in the frog heart. Fukuda Y. **Jpn J Physiol** 1986;36(1):209-13

Branded or generic propranolol? [letter] Garcia-Buñuel L. **Lancet** 1986 Jun 21;1(8495):1443

Differences in side-effect incidence in patients on proprietary and generic propranolol [letter] Sanderson JH, et al. **Lancet** 1986 Apr 26; 1(8487):967-8

Daily propranolol administration reduces pineal concretion formation in the Mongolian gerbil. Vaughan MK, et al. **Proc Soc Exp Biol Med** 1986 Jul;182(3):372-4

[Propranolol poisoning] Bouwels LH. **Ned Tijdschr Geneeskd** 1986 Mar 29;130(13):596-9 (Eng. Abstr.) **(Dut)**

[Effect of forskolin, isoprenaline and propranolol on spontaneous contractions of the isolated atrium of guinea pigs] Varagic VM, et al. **C R Soc Biol (Paris)** 1985;179(6):777-81 (Eng. Abstr.) **(Fre)**

[The influence of central monoaminergic systems on the anticonvulsive action of propranolol] Lasek R, et al. **Pharmazie** 1986 Feb; 41(2):128-30 (Eng. Abstr.) **(Ger)**

PROSTAGLANDINS

Are prostaglandins involved in somatostatin mediated inhibition of gastric secretion in the cat? Albinus M, et al. **Agents Actions** 1986 Apr; 18(1-2):205-9

NaCl transport stimulates prostaglandin release in cultured renal epithelial (MDCK) cells. Kurtz A, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):C676-81

Synergistic action of angiotensin II on norepinephrine-induced prostaglandin release from rat glomeruli. Matsumura Y, et al. **Am J Physiol** 1986 May;250(5 Pt 2):F811-6

Prostaglandin interaction with histamine release and parietal cell activity in isolated gastric glands. Nylander O, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):G607-16

Effect of noradrenaline, vasopressin and angiotensin II on renal prostaglandins in man. Loup R, et al. **Clin Sci** 1986 Apr;70(4):371-7

Effects of prostaglandin synthesis inhibition on sympathetic-and parasympathetic-mediated coronary hemodynamic responses. Trimarco B, et al. **J Pharmacol Exp Ther** 1986 May;237(2):589-99

Regulation of renal cellular cAMP levels by prostaglandins and alpha 2-adrenoceptors: microdissection studies. Umemura S, et al. **Kidney Int** 1986 Mar;29(3):703-7

Prostaglandin synthesis by enterocyte microsomes of rabbit small intestine. Balaa MA, et al. **Prostaglandins** 1986 Apr;31(4):609-24

Prostacyclin and thromboxane formation in human umbilical arteries following stimulation with vasoactive autacoids. Bjøro K. **Prostaglandins** 1986 Apr;31(4):699-714

Indomethacin inhibits thrombin-, but not thyroxin-stimulated resorption of fetal rat limb bones. Hoffmann O, et al. **Prostaglandins** 1986 Apr; 31(4):601-8

[The role of serotonin, histamine and prostaglandins on potentiation of hypoxic pulmonary vasoconstriction by repeated intermittent hypoxic challenges in dogs] Nakanishi S, et al. **Nippon Kyobu Shikkan Gakkai Zasshi** 1986 Jan;24(1):42-8 (Eng. Abstr.) **(Jpn)**

PSYCHIATRIC STATUS RATING SCALES

The AMDP-system in clinical psychopharmacology. Bobon D, et al. **Pharmacopsychiatry** 1986 Mar;19(2):55-7

Predictors of outcome in schizophrenia: the process-reactive dimension. Harrow M, et al. **Schizophr Bull** 1986;12(2):195-207

PSYCHIATRY

Regulation of psychiatric practice [editorial] Baldessarini RJ, et al. **Am J Psychiatry** 1986 Jun;143(6):750-1

The policies and practices of American psychiatry are oppressive. Frank LR. **Hosp Community Psychiatry** 1986 May;37(5):497-501

American psychiatry's fundamental policy is to foster the patient's good. Ruben HL. **Hosp Community Psychiatry** 1986 May;37(5):501-4

PSYCHOLOGICAL TESTS

Clinically significant improvement in agoraphobia research. Mavissakalian M. **Behav Res Ther** 1986;24(3):369-70

Comparing classroom and clinic measures of attention deficit disorder: differential, idiosyncratic, and dose-response effects of methylphenidate. Rapport MD, et al. **J Consult Clin Psychol** 1986 Jun;54(3):334-41

PSYCHOLOGY

Increasing the societal contribution of organized psychology. DeLeon PH. **Am Psychol** 1986 Apr;41(4):466-74

PSYCHOMOTOR AGITATION

[Schizophrenic excitement and the role of lithium in its therapy (apropos of 2 recent cases)] Skurnik N, et al. **Ann Med Psychol (Paris)** 1985 Dec;143(10):960-2 **(Fre)**

PSYCHOMOTOR PERFORMANCE

Antiemotional and anticonvulsant activity of brotizolam and its effects on motor performance in animals. Böke-Kuhn K, et al. **Arzneimittelforschung** 1986 Mar;36(3A):528-31

Comparison of two benzodiazepines with differing accumulation: behavioral changes during and after 3 weeks of dosing. Ghoneim MM, et al. **Clin Pharmacol Ther** 1986 May;39(5):491-500

Repeated administration of diazepam and triazolam to subjects with histories of drug abuse. Roache JD, et al. **Drug Alcohol Depend** 1986 May;17(1):15-29

Residual effects of zopiclone and benzodiazepine hypnotics on psychomotor performance related to car driving. Harrison C, et al. **Drugs Exp Clin Res** 1985;11(12):823-9

Effect of carbamazepine on psychomotor performance in näive subjects. MacPhee GJ, et al. **Eur J Clin Pharmacol** 1986;30(1):37-42

Alprazolam and lorazepam single and multiple-dose effects on psychomotor skills and sleep. Subhan Z, et al. **Eur J Clin Pharmacol** 1986;29(6):709-12

Effect of sulpiride on vigilance in healthy subjects. Bartfai A, et al. **Int J Psychophysiol** 1986 May;4(1):1-5

A comparison of the effects of trazodone and amitriptyline on skills performance by geriatric subjects. Burns M, et al. **J Clin Psychiatry** 1986 May;47(5):252-4

Effects of drugs, age and illumination on response speed of squirrel monkeys. Steiner NO, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):503-6

PSYCHOPHARMACOLOGY

An inhalational behavioral chamber. Pradhan SN, et al. **J Pharmacol Methods** 1986 Jun;15(3):189-99

The AMDP-system in clinical psychopharmacology. Bobon D, et al. **Pharmacopsychiatry** 1986 Mar;19(2):55-7

Why a statistical package on a micro? Hill M. **Psychopharmacol Bull** 1986; 22(1):65-72

A brain function diagnostic and study unit for psychotropic drug development and psychopharmacology research. Itil TM, et al. **Psychopharmacol Bull** 1986;22(1):297-300

Scientific and ethical considerations in the use of placebo controls in clinical trials in psychopharmacology. Klerman GL. **Psychopharmacol Bull** 1986;22(1):25-9

Stereoselective analysis of racemic psychotropic compounds by HPLC on chiral stationary phase. Smith DF, et al. **Psychopharmacology (Berlin)** 1986;89(3):392-3

[Refinement of an EEG diurnal vigilance index. Application to drug trials] Goldenberg F. **Rev Electroencephalogr Neurophysiol Clin** 1986 Mar; 16(1):39-48 (Eng. Abstr.) **(Fre)**

[Proceedings of 15th annual meeting of the Japanese Society of Neuropsychopharmacology. Abstracts] **Yakubutsu Seishin Kodo** 1986 Mar;6(1):1-225 **(Jpn)**

PSYCHOPHYSIOLOGIC DISORDERS

[Steps in the recovery from severe depression. On the psychosomatic aspects of a convalescent process] Böker W. **Psychiatr Prax** 1986 Mar; 13(2):41-8 (Eng. Abstr.) **(Ger)**

[Psychogenic urinary retention--pathogenesis, pathophysiology, diagnosis and treatment] Yamanishi T, et al. **Nippon Hinyokika Gakkai Zasshi** 1985 Oct;76(10):1567-72 (Eng. Abstr.) **(Jpn)**

PSYCHOSES, SUBSTANCE-INDUCED

Lorazepam dependence and chronic psychosis [letter] Carr AC. **Br J Psychiatry** 1986 Mar;148:344

Management of acute PCP intoxication with verapamil. Price WA, et al. **J Toxicol Clin Toxicol** 1986;24(1):85-7

Prolonged psychosis with first-rank symptoms following metrizamide myelography. Davis RJ, et al. **Psychosomatics** 1986 May;27(5):373-5

PSYCHOSEXUAL DISORDERS

Family environment: implications for sexual dysfunction and methaqualone dependence. TenHouten S. **J Psychoactive Drugs** 1986 Jan-Mar;18(1):73-5

PSYCHOTHERAPY

The closing of the organic versus functional dichotomy [letter] Fox HA. **Am J Psychiatry** 1986 Aug;143(8):1059-60

Placebo problems in psychotherapy research. Social-psychological alternatives to chemotherapy concepts. Wilkins W. **Am Psychol** 1986 May;41(5):551-6

Psychopharmacology and psychotherapy in the treatment of anxiety. Freedman AM. **Curr Psychiatr Ther** 1986;23:101-18 (47 ref.)

Methylphenidate and cognitive therapy in children with attention deficit disorder: a double-blind trial. Brown RT, et al. **J Dev Behav Pediatr** 1986 Jun;7(3):163-74

[Cognitive therapy in the treatment of psychotic and postpsychotic states--an overview] Perris C. **Lakartidningen** 1986 Apr 16; 83(16):1488-91 (61 ref.) **(Swe)**

PSYCHOTIC DISORDERS

Lithium and haloperidol [letter] Nemes ZC, et al. **Biol Psychiatry** 1986 May;21(5-6):568-9

Limbic system dysfunction as a factor in some schizophreniform psychoses: case report and overview. MacCrimmon DJ, et al. **Can J Psychiatry** 1986 May;31(4):344-6

Two cases of 'pure' or 'primary' erotomania successfully treated with pimozide [letter] Stein MB. **Can J Psychiatry** 1986 Apr;31(3):289-90

Early neuroleptic response in psychotic men and women: correlation with plasma HVA and MHPG. Bowers MB Jr, et al. **Compr Psychiatry** 1986 May-Jun;27(3):181-5

Marfan's syndrome and neuropsychiatric symptoms: case report and literature review. Leone JC, et al. **Compr Psychiatry** 1986 May-Jun; 27(3):247-50

Low dose therapy: the future of neuroleptic psychopharmacology. A symposium held during the annual meeting of the American Psychiatric Association. May 1986, Washington, D.C. **J Clin Psychiatry** 1986 May; 47 Suppl:1-36

Depot neuroleptics: a comparative review of standard, intermediate, and low-dose regimens. Kane JM, et al. **J Clin Psychiatry** 1986 May; 47 Suppl:30-3 (18 ref.)

The future of neuroleptic psychopharmacology. Ortiz A, et al. **J Clin Psychiatry** 1986 May;47 Suppl:3-11 (122 ref.)

Low-dose treatment strategies. Van Putten T, et al. **J Clin Psychiatry** 1986 May;47 Suppl:12-6 (21 ref.)

Neuroleptics and reserpine in refractory psychoses. Berlant JL. **J Clin Psychopharmacol** 1986 Jun;6(3):180-4

The prescription of discretionary antipsychotic medication by state mental hospital psychiatrists. Benson PR. **J Health Soc Behav** 1986 Mar; 27(1):28–43

Use of carbamazepine in acute psychosis: a controlled study. Lenzi A, et al. **J Int Med Res** 1986;14(2):78–84

Increased blink rate in adolescent patients with psychosis. Karson CN, et al. **Psychiatry Res** 1986 Mar;17(3):195–8

Drug effects on serine metabolism in psychiatric patients. Waziri R, et al. **Psychiatry Res** 1986 Jun;18(2):119–26

The use of benzodiazepines for psychotic disorders: a literature review and preliminary clinical findings. Arana GW, et al. **Psychopharmacol Bull** 1986;22(1):77–87

[Determination of plasma concentrations in the drug treatment of psychoses] Knudsen P, et al. **Ugeskr Laeger** 1986 Mar 31; 148(14):849–52 **(Dan)**

[Plasma monitoring of haloperidol. Correlation with clinical efficacy and plasma prolactin levels] Giraud-Serio J, et al. **Ann Med Psychol (Paris)** 1985 Nov;143(9):900–11 **(Fre)**

[Cognitive therapy in the treatment of psychotic and postpsychotic states--an overview] Perris C. **Lakartidningen** 1986 Apr 16; 83(16):1488–91 (61 ref.) **(Swe)**

QUINIDINE

Renal handling and effects of [3H]digoxin and interactions with quinidine in the avian kidney. Milton A, et al. **Acta Physiol Scand** 1986 May; 127(1):9–16

Inhibition of ATP levels by quinidine in a human colonic epithelial cell line. Dharmsathaphorn K, et al. **Am J Physiol** 1986 Jun; 250(6 Pt 1):G806–13

Single potassium channels blocked by lidocaine and quinidine in isolated turtle colon epithelial cells. Richards NW, et al. **Am J Physiol** 1986 Jul;251(1 Pt 1):C85–9

Quinidine purpura: evidence that glycoprotein V is a target platelet antigen. Stricker RB, et al. **Blood** 1986 May;67(5):1377–81

Single-dose quinidine treatment inhibits metoprolol oxidation in extensive metabolizers. Leemann T, et al. **Eur J Clin Pharmacol** 1986; 29(6):739–41

Prediction of serum concentration time course of quinidine in human using a physiologically based pharmacokinetic model developed from the rat. Harashima H, et al. **J Pharmacobiodyn** 1986 Feb;9(2):132–8

Effects of quinidine and quinine on the excitability of pyramidal neurons in guinea-pig hippocampal slices. Yoshida S, et al. **Pflugers Arch** 1986 May;406(5):544–6

[TLC separation and fluorodensitometric determination of quinidine in human serum] He LY. **Yao Hsueh Hsueh Pao** 1985 Sep;20(9):702–5 (Eng. Abstr.) **(Chi)**

REACTION TIME

[Dynamics of the latent periods of the avoidance response and its correlation with adaptive behavior in the rat] Arushanian EB, et al. **Zh Vyssh Nerv Deiat** 1986 Mar–Apr;36(2):343–50 (Eng. Abstr.) **(Rus)**

[Participation of the cortical dopaminergic mechanism in latent inhibition in cats] Il'iuchenok RIu, et al. **Zh Vyssh Nerv Deiat** 1986 Jan–Feb; 36(1):176–8 **(Rus)**

RECEPTORS, ADRENERGIC

beta-Endorphin-induced stimulation of central sympathetic outflow: inhibitory modulation by central noradrenergic neurons. Appel NM, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):695–701

Central adrenergic control of vasopressin release. Brooks DP, et al. **Neuroendocrinology** 1986;42(5):416–20

RECEPTORS, ADRENERGIC, ALPHA

Comparative alpha- and beta-adrenoceptor activity of 2- and 6-ring-chlorinated noradrenaline analogues. Squier GJ, et al. **Arzneimittelforschung** 1986 Mar;36(3):457–60

Phorbol esters, vasopressin and angiotensin II block alpha 1-adrenergic action in rat hepatocytes. Possible role of protein kinase C. García-Sáinz JA, et al. **Biochim Biophys Acta** 1986 Jun 16;887(1):69–72

Homologous and heterologous desensitization of one of the pathways of the alpha 1-adrenergic action. Effects of epinephrine, vasopressin, angiotensin II and phorbol 12-myristate 13-acetate. García-Sáinz JA, et al. **Biochim Biophys Acta** 1986 Jun 16;887(1):73–9

Impact of circulating corticosterone on alpha 1- and alpha 2-noradrenergic receptors in discrete brain areas. Jhanwar-Uniyal M, et al. **Brain Res** 1986 Mar 19;368(2):404–8

Alpha adrenergic system in medial preoptic area involved in sleep-wakefulness in rats. Mohan Kumar V, et al. **Brain Res Bull** 1986 Apr;16(4):463–8

The effect of aging on alpha-adrenoceptors and their responses in rabbits. Hamilton CA, et al. **Clin Exp Pharmacol Physiol** 1985 Nov–Dec; 12(6):535–47

Labelling of human platelet alpha 2-adrenoceptors with the full agonist [3H](-)adrenaline. Garcia-Sevilla JA, et al. **Eur J Pharmacol** 1986 May 13;124(1-2):31–41

Receptor-mediated inositol phospholipid hydrolysis in astrocytes. Pearce B, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):231–43

Noradrenaline release in the human pulmonary artery is modulated by presynaptic alpha 2-adrenoceptors. Hentrich F, et al. **J Cardiovasc Pharmacol** 1986 May–Jun;8(3):539–44

Alteration of presynaptic alpha 2-mediated inhibition of norepinephrine release in perfused mesenteric arteries of young and adult spontaneously hypertensive rats. Tsuda K, et al. **J Hypertension [Suppl]** 1984 Dec; 2(3):S95–7

Role of adenylate cyclase in presynaptic alpha 2-adrenoceptor- and mu-opioid receptor-mediated inhibition of [3H]noradrenaline release from rat brain cortex slices. Schoffelmeer AN, et al. **J Neurochem** 1986 Jun;46(6):1711–7

Alpha 1-adrenoceptor function in the rat hippocampus as assessed by noradrenaline-stimulated inositol phospholipid breakdown after destruction of noradrenergic neurons by neonatal 6-hydroxydopamine treatment. Fowler CJ, et al. **J Pharm Pharmacol** 1986 May; 38(5):385–8

Effect of repeated restraint stress, desmethylimipramine or adrenocorticotropin on the alpha and beta adrenergic components of the cyclic AMP response to norepinephrine in rat brain slices. Stone EA, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):702–7

Regulation of renal cellular cAMP levels by prostaglandins and alpha 2-adrenoceptors: microdissection studies. Umemura S, et al. **Kidney Int** 1986 Mar;29(3):703–7

Does alprazolam, in contrast to diazepam, activate alpha 2-adrenoceptors involved in the regulation of rat growth hormone secretion? Eriksson E, et al. **Life Sci** 1986 Apr 21;38(16):1491–8

Long-term amitriptyline treatment alters the affinity state of alpha 2 adrenoceptors in rabbit hindbrain. Hamilton CA, et al. **Life Sci** 1986 Jun 30;38(26):2429–36

The effect of alpha-adrenergic stimulation and blockade on perfusion of myocutaneous flaps. Moore GK, et al. **Otolaryngol Head Neck Surg** 1986 Apr;94(4):489–96

[Role of adrenergic receptors in the regulation of glycogen metabolism in the liver] Torlińska T, et al. **Postepy Hig Med Dosw** 1985 Sep–Oct; 39(5):561–77 (75 ref.) (Eng. Abstr.) **(Pol)**

[Role of alpha-adrenoreceptors of the hypothalamus and amygdala in the response of the secretory glands of the stomach to neurotensin and somatostatin] Barashkova GM, et al. **Fiziol Zh SSSR** 1986 Apr; 72(4):498–502 (Eng. Abstr.) **(Rus)**

[Activity of presynaptic alpha-adrenoreceptors during prolonged perfusion with adrenaline] Berdysheva LV, et al. **Fiziol Zh SSSR** 1986 May;72(5):590–4 (Eng. Abstr.) **(Rus)**

RECEPTORS, ADRENERGIC, BETA

Comparative alpha- and beta-adrenoceptor activity of 2- and 6-ring-chlorinated noradrenaline analogues. Squier GJ, et al. **Arzneimittelforschung** 1986 Mar;36(3):457–60

Chronic exposure of human cells in culture to the tricyclic antidepressant desipramine reduces the number of beta-adrenoceptors. Honegger UE, et al. **Biochem Pharmacol** 1986 Jun 1;35(11):1899–902

Pharmacological characterization of the receptor mediating the adrenergic inhibition of responses to substance P in the cingulate cortex. Jones RS, et al. **Brain Res** 1986 Mar 5;367(1-2):151–61

Differential effects of antidepressant drugs on [3H]dihydroalprenolol and [3H]imipramine ligand recognition sites in olfactory bulbectomized and sham-lesioned rats. Jesberger JA, et al. **Gen Pharmacol** 1986; 17(3):293–307

Lymphocyte beta-adrenergic receptor density of patients with recurrent affective illness. Wood K, et al. **J Affective Disord** 1986 Jan–Feb; 10(1):3–8

Platelet ADP receptor and alpha 2-adrenoreceptor interaction. Evidence for an ADP requirement for epinephrine-induced platelet activation and an influence of epinephrine on ADP binding. Figures WR, et al. **J Biol Chem** 1986 May 5;261(13):5981–6

Effects of beta-adrenergic stimulation on 1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine-mediated vasoconstriction and glycogenolysis in the perfused rat liver. Fisher RA, et al. **J Biol Chem** 1986 Jul 5;261(19):8817–23

Studies on rat brain catecholamine synthesis and beta-adrenoceptor number following administration of electroconvulsive shock, desipramine and clenbuterol. Nimgaonkar VL, et al. **J Neural Transm** 1985;65(3–4):245–59

Responses mediated via beta-1 adrenoceptors but not beta-2 adrenoceptors exhibit supersensitivity after chronic reserpine pretreatment. Grassby PF, et al. **J Pharmacol Exp Ther** 1986 Jun; 237(3):950–8

Effect of repeated restraint stress, desmethylimipramine or adrenocorticotropin on the alpha and beta adrenergic components of the cyclic AMP response to norepinephrine in rat brain slices. Stone EA, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):702–7

Effects of epinephrine, isoproterenol and IPS-339 on sympathetic transmission to the dog heart: evidence against the facilitatory role of presynaptic beta adrenoceptors. Yorikane R, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):334–40

RECEPTORS, CHOLINERGIC

Contrasting cholinergic dependence of pancreatic and gallbladder responses to cholecystokinin. Strah KM, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):G665–9

Evidence that the acetylcholine binding site is not formed by the sequence alpha 127–143 of the acetylcholine receptor. Criado M, et al. **Biochemistry** 1986 May 20;25(10):2839–46

Cocaine, phencyclidine, and procaine inhibition of the acetylcholine receptor: characterization of the binding site by stopped–flow measurements of receptor–controlled ion flux in membrane vesicles. Karpen JW, et al. **Biochemistry** 1986 Apr 8;25(7):1777–85

Acetylcholine receptor: characterization of the voltage–dependent regulatory (inhibitory) site for acetylcholine in membrane vesicles from Torpedo californica electroplax. Takeyasu K, et al. **Biochemistry** 1986 Apr 8;25(7):1770–6

Haemodynamic reactions to succinylcholine––an alternative hypothesis [letter] Baraka A. **Can Anaesth Soc J** 1986 Mar;33(2):252–4

Cholinergic modulation of an acetylcholine receptor–like antigen on the surface of chick ciliary ganglion neurons in cell culture. Smith MA, et al. **J Neurosci** 1986 Apr;6(4):946–53

Channel properties of an insect neuronal acetylcholine receptor protein reconstituted in planar lipid bilayers. Hanke W, et al. **Nature** 1986 May 8–14;321(6066):171–4

Influence of estrogen levels on anticholinergic activity of tricyclic antidepressives. Kok EC, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1986;10(1):49–55

RECEPTORS, DOPAMINE

Human foetal prolactin but not thyrotropin secretion is decreased by bromocriptine. Roti E, et al. **Acta Endocrinol (Copenh)** 1986 May; 112(1):35–42

The diuretic effect of atrial natriuretic peptide (ANP) is dependent on dopaminergic activation. Pettersson A, et al. **Acta Physiol Scand** 1986 Apr;126(4):619–21

3H–spiperone binding in platelet membranes: a possible biological marker for schizophrenia. Sethi BB, et al. **Acta Psychiatr Scand** 1986 Feb; 73(2):186–90

A dopamine–dependent restitutive system for the maintenance of mental normalcy. Friedhoff AJ. **Ann NY Acad Sci** 1986;463:47–52

Affinity chromatography of the anterior pituitary D2–dopamine receptor. Senogles SE, et al. **Biochemistry** 1986 Feb 25;25(4):749–53

Effects of intermittent and continuous haloperidol administration on the dopaminergic system in the rat brain. Kashihara K, et al. **Biol Psychiatry** 1986 Jun;21(7):650–6

Somatostatin and cholecystokinin octapeptide differentially modulate the release of [3H]acetylcholine from caudate nucleus but not cerebral cortex: role of dopamine receptor activation. Arnerić SP, et al. **Brain Res** 1986 May 21;374(1):153–61

Dopamine receptor–mediated inhibition of serotonin N–acetyltransferase activity in retina. Iuvone PM, et al. **Brain Res** 1986 Mar 26; 369(1–2):168–76

Pharmacological effects of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) on striatal dopamine receptor system. Lau YS, et al. **Brain Res** 1986 Mar 26; 369(1–2):311–5

Typical and atypical antipsychotic occupancy of D2 and S2 receptors: an autoradiographic analysis in rat brain. Altar CA, et al. **Brain Res Bull** 1986 Apr;16(4):517–25

Dopamine receptor stimulation induces a potassium dependent hyperpolarizing response in growth hormone producing neuroendocrine cells of the gastropod mollusc Lymnaea stagnalis. de Vlieger TA, et al. **Comp Biochem Physiol [C]** 1986;83(2):429–33

Dopaminergic mechanisms and motor function: characterization of D–1 and D–2 dopamine receptor interactions. Barone P, et al. **Eur J Pharmacol** 1986 Apr 9;123(1):109–14

Neurophysiological evidence that D–1 dopamine receptor blockade attenuates postsynaptic but not autoreceptor–mediated effects of dopamine agonists. Carlson JH, et al. **Eur J Pharmacol** 1986 Apr 16; 123(2):237–51 (59 ref.)

Neuropharmacological profile of a new series of dopamine agonists: N–n–propyl–hexahydronaphthoxazines. Hazelhoff B, et al. **Eur J Pharmacol** 1986 May 13;124(1–2):93–106

Apomorphine enantiomers' effects on dopamine metabolism: receptor and non–receptor related actions. Saller CF, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):181–8

Dopamine receptors in pancreatic acinar cells from dog. Vayssette J, et al. **Eur J Pharmacol** 1986 Apr 2;122(3):321–8

Chronic corticosterone administration in rats: behavioral and biochemical evidence of increased central dopaminergic activity. Wolkowitz O, et al. **Eur J Pharmacol** 1986 Apr 2;122(3):329–38

Evidence for dopaminomimetic effect of intrastriatally injected cholecystokinin octapeptide in mice. Worms P, et al. **Eur J Pharmacol** 1986 Mar 4;121(3):395–401

Changes in the interaction between CNS cholinergic and dopaminergic neurons induced by L–alpha–glycerylphosphorylcholine, a cholinomimetic drug. Trabucchi M, et al. **Farmaco [Sci]** 1986 Apr; 41(4):325–34

Dopamine D1 receptors characterized with [3H]SCH 23390. Solubilization of a guanine nucleotide–sensitive form of the receptor. Niznik HB, et al. **J Biol Chem** 1986 Jun 25;261(18):8397–406

Purification of bovine striatal dopamine D–2 receptor by affinity chromatography. Ramwani J, et al. **J Biol Chem** 1986 Jul 5; 261(19):8894–8

Dopamine receptor blockade does not affect the natriuresis accompanying sodium chloride infusion in dogs. Bradley T, et al. **J Lab Clin Med** 1986 Jun;107(6):525–8

Dopamine receptor agonists: 3–allyl–6–chloro–2,3,4,5–tetrahydro–1–(4–hydroxyphenyl)–1H–3–benzazepine–7,8–diol and a series of related 3–benzazepines. Ross ST, et al. **J Med Chem** 1986 May;29(5):733–40

Pharmacological activity of amantadine: effect of N–alkyl substitution. Dunn JP, et al. **J Pharm Pharmacol** 1986 May;38(5):353–6

Effects of apomorphine on morphine analgesia during the state of dopaminergic supersensitivity after chronic treatment with haloperidol. Kamata K, et al. **J Pharmacobiodyn** 1986 Jan;9(1):88–94

Dose related sequence of effects induced by the DA agonist 2–(N,N–dipropyl)–amino–5,6–dihydroxytetralin. Doaré L, et al. **J Pharmacol** 1986 Jan–Mar;17(1):60–4

Influence of some dopaminoceptor agents on nitrazepam–induced sleep in the domestic fowl (Gallus domesticus) and rats. Wambebe C. **Jpn J Pharmacol** 1986 Mar;40(3):357–65

Specific binding of 3H–SCH 23390 to dopamine D1 receptors in vivo. Andersen PH, et al. **Life Sci** 1986 Apr 21;38(16):1507–14

Regulation of agonist and antagonist binding to striatal D–1 dopamine receptors: studies using the selective D–1 antagonist [3H]SK&F R–83566. Flaim KE, et al. **Life Sci** 1986 Jun 9;38(23):2087–96

Pharmacologic evidence for direct dopaminergic regulation of striatal acetylcholine release. Gorell JM, et al. **Life Sci** 1986 Jun 16; 38(24):2239–46

Functional antagonism of D–1 and D–2 dopaminergic mechanisms affecting striatal acetylcholine release. Gorell JM, et al. **Life Sci** 1986 Jun 16;38(24):2247–54

Excitation by dopamine D–2 receptor agonists, bromocriptine and LY 171555, in caudate nucleus neurons activated by nigral stimulation. Ohno Y, et al. **Life Sci** 1986 May 19;38(20):1867–73

Selective dopamine D2 receptor reduction enhances a D1–mediated oral dyskinesia in rats. Rosengarten H, et al. **Life Sci** 1986 Jul 7; 39(1):29–35

Tracer and maximal specific binding of tritiated spiperone or N–n–propylnorapomorphine to quantify dopamine receptors in rat brain regions in vivo. Van der Werf JF, et al. **Life Sci** 1986 Jul 14; 39(2):155–60

Haloperidol binding to monoclonal antibodies: conformational analysis and relationships to D–2 receptor binding. Sherman MA, et al. **Mol Pharmacol** 1986 Jun;29(6):589–98

Dopamine autoreceptor regulation of the kinetic state of striatal tyrosine hydroxylase. Strait KA, et al. **Mol Pharmacol** 1986 Jun;29(6):561–9

Effects of phencyclidine on ventral tegmental A10 dopamine neurons in the rat. French ED. **Neuropharmacology** 1986 Mar;25(3):241–8

Dopamine D2 receptors and dopamine metabolism. Relationship between biochemical and behavioural effects of substituted benzamide drugs. Magnusson O, et al. **Neuropharmacology** 1986 Feb;25(2):187–97

Differential effect of repeated treatment with L–dopa on dopamine–D1 or –D2 receptors. Parenti M, et al. **Neuropharmacology** 1986 Mar; 25(3):331–4

Effects of dopamine and its agonists and antagonists on the receptive field properties of ganglion cells in the rabbit retina. Jensen RJ, et al. **Neuroscience** 1986 Mar;17(3):837–55

Electrophysiological study of the effects of D1 and D2 dopamine antagonists on the interaction of converging inputs from the sensory–motor cortex and substantia nigra neurons in the rat. Vives F, et al. **Neuroscience** 1986 Feb;17(2):349–59

Somatostatin and CCK–8 modulate release of striatal amino acids: role of dopamine receptors. Arnerić SP, et al. **Peptides** 1986 Jan–Feb; 7(1):97–103

Reduction of the rewarding effect of brain stimulation by a blockade of dopamine D1 receptor with SCH 23390. Nakajima S, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):919–23

Grooming in the mouse is stimulated by the dopamine D1 agonist SKF 38393 and by low doses of the D1 antagonist SCH 23390, but is inhibited by dopamine D2 agonists, D2 antagonists and high doses of SCH 23390. Starr BS, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):837–9

Interaction of buspirone and dopaminergic agents on punished behavior of pigeons. Witkin JM, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):751–6

Effects of a D1 and a D2 dopamine antagonist on the self–administration of cocaine and piribedil by rhesus monkeys. Woolverton WL. **Pharmacol Biochem Behav** 1986 Mar;24(3):531–5

The effects of REM sleep deprivation on striatal dopamine receptor sites.

Zwicker AP, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):809–12

The effects of a 5-HT1 receptor ligand isapirone (TVX Q 7821) on 5-HT synthesis and the behavioural effects of 5-HT agonists in mice and rats. Goodwin GM, et al. **Psychopharmacology (Berlin)** 1986;89(3):382–7

Involvement of different dopamine receptors in rat diphasic motility response to apomorphine. Vaccheri A, et al. **Psychopharmacology (Berlin)** 1986;89(3):265–8

Behavioral and biochemical studies of dopamine receptor sensitivity in differentially housed mice. Wilmot CA, et al. **Psychopharmacology (Berlin)** 1986;89(3):364–9

Prenatal reserpine exposure in rats decreases caudate nucleus dopamine receptor binding in female offspring. Ali SF, et al. **Toxicol Lett** 1986 Jun;31(3):195–201

[The biochemical effects of a new antidepressive, metapramine (RP 19560) on activity of the dopaminergic and cholinergic systems of the rat striatum] Boireau A, et al. **J Pharmacol** 1986 Jan–Mar;17(1):75–84 (Eng. Abstr.) **(Fre)**

[Participation of the cortical dopaminergic mechanism in latent inhibition in cats] Il'iuchenok RIu, et al. **Zh Vyssh Nerv Deiat** 1986 Jan–Feb; 36(1):176–8 **(Rus)**

[Role of the presynaptic receptors in the control of dopamine synthesis in the striate complex and nucleus accumbens] Palarea MD, et al. **Rev Esp Fisiol** 1986 Mar;42(1):71–5 (Eng. Abstr.) **(Spa)**

RECEPTORS, DRUG

The role of phosphoinositides in signal transduction. Sekar MC, et al. **J Membr Biol** 1986;89(3):193–210 (328 ref.)

Binding of psychoactive drugs to rat brain amine receptors, measured ex vivo, and their effects on the metabolism of biogenic amines. Burki HR. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar;332(3):258–66

[A new group of hormones, endogenous ligands for drug receptors] Schreiber V. **Cesk Fysiol** 1986;35(3):219–23 **(Cze)**

RECEPTORS, ENDOGENOUS SUBSTANCES

Can neonatal treatment with a related hormone adapt the receptor for itself? Csaba G, et al. **Acta Physiol Hung** 1986;67(1):65–9

Autoradiographical localization of luteinizing hormone releasing hormone (LHRH) receptors on rat testicular intertubular cells fractionated on Percoll density gradients. Hedger MP, et al. **Aust J Biol Sci** 1985; 38(4):435–44

Occurrence of two cholecystokinin binding sites in guinea-pig brain cortex. Durieux C, et al. **Biochem Biophys Res Commun** 1986 Jun 30; 137(3):1167–73

Evidence for opiate action at the brain receptors for thyrotropin-releasing hormone. Bhargava HN, et al. **Brain Res** 1986 Mar 19;368(2):262–7

A comparison of 2-amino-4-phosphonobutyric acid (AP4) receptors and [3H]AP4 binding sites in the rat brain. Bridges RJ, et al. **Brain Res** 1986 Jun 4;375(1):204–9

Modifications in the cortical regional distribution of choline acetyltransferase, somatostatin and somatostatin binding sites in the normal rat and following lesion of the nucleus basalis. Epelbaum J, et al. **Brain Res** 1986 Apr 23;371(2):376–9

Decrease in rat striatal dopamine synthesis and metabolism in vivo by metabolically stable adenosine receptor agonists. Myers S, et al. **Brain Res** 1986 Jun 4;375(1):193–7

Modulation of the estradiol-induced luteinizing hormone surge by progesterone or antiestrogens: effects on pituitary gonadotropin-releasing hormone receptors. Attardi B, et al. **Endocrinology** 1986 Jul;119(1):274–83

Desensitization to growth hormone-releasing factor (GRF) is associated with down-regulation of GRF-binding sites. Bilezikjian LM, et al. **Endocrinology** 1986 May;118(5):2045–52

Receptor binding and gonadotropin-releasing activity of a novel chicken gonadotropin-releasing hormone ([His5, Trp7, Tyr8]GnRH) and a D-Arg6 analog. Millar RP, et al. **Endocrinology** 1986 Jul; 119(1):224–31

Characterization of the hepatic prolactin receptors induced by chronic iron deficiency and neuroleptics. Barkey RJ, et al. **Eur J Pharmacol** 1986 Mar 18;122(2):259–67

Radioligand binding to central phencyclidine recognition sites is dependent on excitatory amino acid receptor agonists. Loo P, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):467–8

Anterior pituitary concentrations of gonadotropins, GnRH-receptors and ovarian characteristics following early weaning in beef cows. Parfet JR, et al. **J Anim Sci** 1986 Mar;62(3):717–22

Platelet ADP receptor and alpha 2-adrenoreceptor interaction. Evidence for an ADP requirement for epinephrine-induced platelet activation and an influence of epinephrine on ADP binding. Figures WR, et al. **J Biol Chem** 1986 May 5;261(13):5981–6

Benzodiazepine interactions with central thyroid-releasing hormone binding sites: characterization and physiological significance. Rinehart RK, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):178–85

Physiological role of putative testicular gonadotrophin releasing hormone (GnRH). Clayton RN, et al. **Med Biol** 1986;63(5–6):201–9

The different mechanisms for suppression of pituitary and testicular function. Sandow J, et al. **Med Biol** 1986;63(5–6):192–200

Corticotropin-releasing factor receptors in the pituitary gland and central nervous system: methods and overview. De Souza EB, et al. **Methods Enzymol** 1986;124:560–90

Autoradiographic localization of brain receptors for peptide hormones: angiotensin II, corticotropin-releasing factor, and gonadotropin-releasing hormone. Millan M, et al. **Methods Enzymol** 1986;124:590–606

Localization of somatostatin receptors. Pelletier G, et al. **Methods Enzymol** 1986;124:607–17

Effect of oxidizing agents on rabbit mammary prolactin receptors. Mahajan PB, et al. **Mol Cell Endocrinol** 1986 Jun;46(1):37–42

Receptor-mediated actions of corticotropin-releasing factor in pituitary gland and nervous system. Aguilera G, et al. **Neuroendocrinology** 1986; 43(1):79–88 (37 ref.)

Down-regulation of growth hormone releasing factor receptors following continuous infusion of growth hormone releasing factor in vivo. Wehrenberg WB, et al. **Neuroendocrinology** 1986;43(2):266–8

Influence of excitatory amino acid receptor antagonists and of baclofen on synaptic transmission in the optic nerve to the suprachiasmatic nucleus in slices of rat hypothalamus. Shibata S, et al. **Neuropharmacology** 1986 Apr;25(4):403–9

Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist. Chang RS, et al. **Proc Natl Acad Sci USA** 1986 Jul;83(13):4923–6

Human peripheral monocytes express putative receptors for neuroexcitatory amino acids. Malone JD, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3307–10

Evidence for somatostatin binding sites in rabbit kidney. Roca B, et al. **Regul Pept** 1986 Feb;13(3–4):273–81

Corticotropin-releasing factor receptors: autoradiographic identification. De Souza EB, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986; 64:179–98

[Regulation of acinar cell receptors of the pancreas by peptides] Mössner J, et al. **Klin Wochenschr** 1986 Jun 2;64(11):489–98 (Eng. Abstr.) **(Ger)**

[Effect of thyroid hormones on the nuclear-cytoplasmic transport of RNA] Adylova AT, et al. **Probl Endokrinol (Mosk)** 1986 Mar–Apr; 32(2):74–6 (Eng. Abstr.) **(Rus)**

RECEPTORS, ENDORPHIN

Opioid peptide processing and receptor selectivity. Höllt V. **Annu Rev Pharmacol Toxicol** 1986;26:59–77 (127 ref.)

Tyr1-substituted and fluorescent Pya1-enkephalins bind strongly and selectively to mu and delta opiate receptors. Mihara H, et al. **Biochem Biophys Res Commun** 1986 May 14;136(3):1170–6

A comparison of the binding of sigma opioids and phencyclidine, and the interaction with antipsychotic drugs in rat brain membranes. Downes CP, et al. **Br J Pharmacol** 1986 May;88(1):231–7

Evidence for opiate action at the brain receptors for thyrotropin-releasing hormone. Bhargava HN, et al. **Brain Res** 1986 Mar 19;368(2):262–7

Increased delta, but not mu, opiate receptor binding in the medulla oblongata of Long-Evans rats following 5-day water deprivation. Hwang BH, et al. **Brain Res** 1986 Apr 23;371(2):345–9

The interaction between gamma-type endorphins and HLA class I antigens. Claas FH, et al. **Hum Immunol** 1986 Apr;15(4):347–56

Role of adenylate cyclase in presynaptic alpha 2-adrenoceptor- and mu-opioid receptor-mediated inhibition of [3H]noradrenaline release from rat brain cortex slices. Schoffelmeer AN, et al. **J Neurochem** 1986 Jun;46(6):1711–7

Evidence that the potential antipsychotic agent rimcazole (BW 234U) is a specific, competitive antagonist of sigma sites in brain. Ferris RM, et al. **Life Sci** 1986 Jun 23;38(25):2329–37

Structure-activity studies of morphiceptin analogs: receptor binding and molecular determinants of mu-affinity and selectivity. Loew G, et al. **Mol Pharmacol** 1986 Jun;29(6):546–53

Characterization of phencyclidine and sigma receptor-binding sites in brain. Gundlach AL, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:1–13

Further evidence of phencyclidine/sigma opioid receptor commonality. Sircar R, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:14–23

Dynorphin 1–8 binds to opiate kappa receptors in the neurohypophysis. Gerstberger R, et al. **Neuroendocrinology** 1986;42(5):376–82

[Direct interaction of tricyclic antidepressants with opiate binding sites in the bovine adrenal medulla] Carydakis C, et al. **C R Acad Sci [III]** 1986;302(11):419–22 (Eng. Abstr.) **(Fre)**

RECEPTORS, GABA-BENZODIAZEPINE

'Endogenous ligands' of benzodiazepine receptors, their structural analogs. Development of new psychotropic drugs. Akhundov RA, et al. **Acta Physiol Pharmacol Bulg** 1985;11(4):3–11 (33 ref.)

Benzodiazepine sensitivity in normal human subjects. Hommer DW, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):542–51

Benzodiazepine- and barbiturate-interactions with GABAA receptor responses on lactotrophs. Anderson RA, et al. **Brain Res** 1986 Apr 23; 371(2):287–92

Pipecolic acid antagonizes barbiturate-enhanced GABA binding to bovine brain membranes. Feigenbaum P, et al. **Brain Res** 1986 Apr 30; 372(1):176–9

Localization of GABAA and GABAB receptor subtypes on serotonergic neurons. Mennini T, et al. **Brain Res** 1986 Apr 23;371(2):372–5

Benzodiazepine receptor involvement in the control of receptive field size and responsiveness in primary somatosensory cortex. Oka JI, et al. **Brain Res** 1986 Jun 18;376(1):194–8

Activation of GABA receptors in the hypothalamus stimulates secretion of growth hormone and prolactin. Willoughby JO, et al. **Brain Res** 1986 May 21;374(1):119–25

Cultured neurons as model systems for biochemical and pharmacological studies on receptors for neurotransmitter amino acids. Schousboe A, et al. **Dev Neurosci** 1985;7(5–6):252–62 (56 ref.)

Biphasic effect of GABAA receptor agonists on prolactin secretion: evidence for two types of GABAA receptor complex on lactotrophes. Anderson R, et al. **Eur J Pharmacol** 1986 May 13;124(1–2):1–9

Decreased peripheral benzodiazepine binding sites in platelets of neuroleptic-treated schizophrenics. Gavish M, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):275–9

Calcium alters the properties of [3H]diazepam binding sites in rat brain membranes. Wu PH, et al. **Int J Biochem** 1986;18(4):345–50

Alterations in biodistribution of [3H]Ro 15–1788 in mice by acute stress: possible changes in in vivo binding availability of brain benzodiazepine receptor. Inoue O, et al. **Int J Nucl Med Biol** 1985;12(5):369–74

Diurnal variations of benzodiazepine binding in rat cerebral cortex: disruption by pinealectomy. Acuña-Castroviejo D, et al. **J Pineal Res** 1986;3(2):101–9

Effects of insecticides on GABA-induced chloride influx into rat brain microsacs. Abalis IM, et al. **J Toxicol Environ Health** 1986; 18(1):13–23

The role of benzodiazepine receptors in the discriminative stimulus properties of delta-9-tetrahydrocannabinol. Mokler DJ, et al. **Life Sci** 1986 Apr 28;38(17):1581–9

AHN 086: an irreversible ligand of 'peripheral' benzodiazepine receptors. Lueddens HW, et al. **Mol Pharmacol** 1986 Jun;29(6):540–5

Lesion of noradrenergic neurones with DSP4 does not modify benzodiazepine receptor binding in cortex and hippocampus of rat. Marcel D, et al. **Neuropharmacology** 1986 Mar;25(3):283–6

The anxiolytic but not the sedative properties of tracazolate are reversed by the benzodiazepine receptor antagonist, Ro 15–1788. File SE, et al. **Neuropsychobiology** 1985;14(4):193–7

GABA receptor binding in rat cerebral cortex and superior cervical ganglion in the absence of GABAergic synapses. Balcar VJ, et al. **Neurosci Lett** 1986 May 23;66(3):269–74

GABAA and GABAB receptors on porcine pars intermedia cells in primary culture: functional role in modulating peptide release. Demeneix BA, et al. **Neuroscience** 1986 Apr;17(4):1275–85

Benzodiazepine receptors in the human spinal cord: a detailed anatomical and pharmacological study. Faull RL, et al. **Neuroscience** 1986 Mar; 17(3):791–802

Rat pup ultrasonic isolation calls: possible mediation by the benzodiazepine receptor complex. Insel TR, et al. **Pharmacol Biochem Behav** 1986 May; 24(5):1263–7

The inhibitory effect of endogenous convulsants quinolinic acid and kynurenine on the pentobarbital stimulation of [3H]flunitrazepam binding. Zarkovsky AM. **Pharmacol Biochem Behav** 1986 May; 24(5):1215–7

Receptor variation as a source of differential response to centrally acting agents: phylogenetic evidence. Hebebrand J, et al. **Prog Clin Biol Res** 1986;214:367–71

Possible involvement of low and high affinity GABA receptors in the chloride influx into synaptosomes. Sánchez C, et al. **Rev Esp Fisiol** 1986 Mar;42(1):1–5

Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Majewska MD, et al. **Science** 1986 May 23; 232(4753):1004–7

[Pharmacochemistry through the history of benzodiazepines and their binding sites (2)] Gaignault JC, et al. **Ann Pharm Fr** 1985; 43(5):427–38 (Eng. Abstr.) **(Fre)**

[Current prospects for the benzodiazepines] Gut JP, et al. **Therapie** 1986 Jan–Feb;41(1):31–5 (Eng. Abstr.) **(Fre)**

[Occupation of central benzodiazepine receptors and anxiety] Le Fur G, et al. **Therapie** 1986 Jan–Feb;41(1):43–7 (Eng. Abstr.) **(Fre)**

[Nonuniform effect of prolonged haloperidol administration on the GABA(A) and benzodiazepine receptors in different parts of the brain] Vasar EE, et al. **Biull Eksp Biol Med** 1986 Apr;101(4):433–6 (Eng. Abstr.) **(Rus)**

[The role of GABA-benzodiazepine receptor complex in affecting the anxiolytic effect of 3-hydroxypyridines—new non-benzodiazepine tranquilizers] Voronina TA, et al. **Biull Eksp Biol Med** 1986 May; 101(5):571–3 (Eng. Abstr.) **(Rus)**

RECEPTORS, SEROTONIN

Antimigraine drug interactions with 5-hydroxytryptamine1A receptors. Hiner BC, et al. **Ann Neurol** 1986 May;19(5):511–3

Typical and atypical antipsychotic occupancy of D2 and S2 receptors: an autoradiographic analysis in rat brain. Altar CA, et al. **Brain Res Bull** 1986 Apr;16(4):517–25

Neuroleptic drugs and 5HT1 receptor: different potencies of various neuroleptic drugs on 5HT1 receptors in discrete regions of the rat brain. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1985;39(4):551–7

Three distinct subtypes of serotonergic receptors mediate the triphasic blood pressure response to serotonin in rats. Kalkman HO, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S143–5

Effect of serotonin on murine macrophages: suppression of Ia expression by serotonin and its reversal by 5-HT2 serotonergic receptor antagonists. Sternberg EM, et al. **J Immunol** 1986 Jul 1; 137(1):276–82

Differential pharmacology and function of two 5-HT1 receptors modulating transmitter release in rat cerebellum. Raiteri M, et al. **J Pharmacol Exp Ther** 1986 May;237(2):644–8

Regional serotonin receptor studies: chronic methysergide treatment induces a selective and dose-dependent decrease in serotonin-2 receptors in mouse cerebral cortex. May PC, et al. **Life Sci** 1986 May 12;38(19):1741–7

Selective control by corticosterone of serotonin1 receptor capacity in raphe-hippocampal system. De Kloet ER, et al. **Neuroendocrinology** 1986;42(6):513–21

Dihydroergocristine-induced stimulation of the 5-HT autoreceptor in the hypothalamus of the rat. Moret C, et al. **Neuropharmacology** 1986 Feb; 25(2):169–74

A unique serotonin receptor in choroid plexus is linked to phosphatidylinositol turnover. Conn PJ, et al. **Proc Natl Acad Sci USA** 1986 Jun;83(11):4086–8

3,4-Methylenedioxymethamphetamine (MDMA): stereoselective interactions at brain 5-HT1 and 5-HT2 receptors. Lyon RA, et al. **Psychopharmacology (Berlin)** 1986;88(4):525–6

[Pharmacological analysis of the serotonin- and glutamatergic mechanisms in the suppressive effect of neuroleptics on the pedal self-stimulation of the ventral tectum of the midbrain] Talalaenko AN, et al. **Farmakol Toksikol** 1986 May-Jun;49(3):40–3 (Eng. Abstr.) **(Rus)**

[Role of various types of serotonin reception in the hypothalamic modulation of the release of luteinizing hormone] Ignatkov VIa, et al. **Fiziol Zh SSSR** 1986 Mar;72(3):316–22 (Eng. Abstr.) **(Rus)**

[Immunocytochemical and autoradiographic research on the growth of serotoninergic fibers to the cerebral ventricles in the perinatal period in rats] Ugriumov MV, et al. **Tsitologiia** 1986 Feb;28(2):160–4 (Eng. Abstr.) **(Rus)**

REFLEX

Stimuli that produce sensitization lead to elevation of cyclic AMP levels in tail sensory neurons of Aplysia. Ocorr KA, et al. **Brain Res** 1986 Apr 16;371(1):190–2

Periaqueductal gray inhibition of viscerointercostal and galvanic skin reflexes. Sonoda H, et al. **Brain Res** 1986 Mar 26;369(1–2):91–102

Antagonism of drug-induced yawning and penile erections in rats. Gower AJ, et al. **Eur J Pharmacol** 1986 Mar 18;122(2):239–44

Angiotensin I and II in the assessment of baroreceptor function in fetal and neonatal sheep. Scroop GC, et al. **J Dev Physiol** 1986 Apr; 8(2):123–37

Alterations in plasma noradrenaline in response to reflex modulation of sympathetic vasoconstrictor tone to skeletal muscles. Grassi G, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S131–3

Differential effects of apomorphine on spinal reflex activity following 6-hydroxydopamine or long-term haloperidol pretreatment. Jensen TS, et al. **J Neural Transm** 1986;65(2):125–34

Stimulation-produced spinal inhibition from the midbrain in the rat is mediated by an excitatory amino acid neurotransmitter in the medial medulla. Aimone LD, et al. **J Neurosci** 1986 Jun;6(6):1803–13

A useful tool for predicting the clinical effects of hypnotics in humans: averaged photopalpebral reflex. Mizuki Y, et al. **Methods Find Exp Clin Pharmacol** 1986 May;8(5):327–32

The role of the capsaicin-sensitive innervation of the rat urinary bladder in the activation of micturition reflex. Maggi CA, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Mar;332(3):276–83

Differential antagonism of diazepam-induced loss of the righting response. Witkin JM, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):963–5

[Noradrenaline suppression of the spinal efferent component of the pressor reflexes] Karagulova GO, et al. **Biull Eksp Biol Med** 1986 Apr; 101(4):387–9 (Eng. Abstr.) **(Rus)**

REINFORCEMENT (PSYCHOLOGY)

Central nervous system mediation of positive and negative reinforcement in neonatal albino rats. Kehoe P, et al. **Brain Res** 1986 Jun; 392(1–2):69–75

REINFORCEMENT SCHEDULE

6-Hydroxydopamine and excitotoxin lesions of medial prefrontal cortex fail to affect schedule-induced drinking in the rat. Christie MJ, et al. **Behav Brain Res** 1986 Feb;19(2):183-6

Pituitary-adrenal correlates of schedule-induced polydipsia and wheel running in rats. Tazi A, et al. **Behav Brain Res** 1986 Mar; 19(3):249-56

Intravenous self-administration of fencamfamine and cocaine by beagle dogs under fixed-ratio and progressive-ratio schedules of reinforcement. Risner ME, et al. **Drug Alcohol Depend** 1986 May;17(1):93-102

RESERPINE

Rapid reduction of mania by means of reserpine therapy [letter] Telner JI, et al. **Am J Psychiatry** 1986 Aug;143(8):1058

Binding of wheat-germ agglutinin to glycoconjugates in the salivary glands of reserpinized rats. Klein RM, et al. **Arch Oral Biol** 1986; 31(2):133-7

Reserpine inhibition of lipid peroxidation and protein phosphorylation in rat brain. Chakrabarti S, et al. **Biochem Pharmacol** 1986 May 1; 35(9):1611-3

Comparative responses of the central adrenaline- and noradrenaline-containing neurons after reserpine injections. Lambás-Señas L, et al. **Biochem Pharmacol** 1986 Jul 1; 35(13):2207-11

Time course of the changes of TH mRNA in rat brain and adrenal medulla after a single injection of reserpine. Biguet NF, et al. **EMBO J** 1986 Feb;5(2):287-91

LC/MS determination of bromazepam, clopenthixol, and reserpine in serum of a non-fatal case of intoxication. Tas AC, et al. **J Anal Toxicol** 1986 Mar-Apr;10(2):46-8

Neuroleptics and reserpine in refractory psychoses. Berlant JL. **J Clin Psychopharmacol** 1986 Jun;6(3):180-4

Is reserpine a human teratogen? Pauli RM, et al. **J Med Genet** 1986 Jun; 23(3):267-8

Responses mediated via beta-1 adrenoceptors but not beta-2 adrenoceptors exhibit supersensitivity after chronic reserpine pretreatment. Grassby PF, et al. **J Pharmacol Exp Ther** 1986 Jun; 237(3):950-8

Monoamines and their catabolites in the rabbit carotid body. Effects of reserpine, sympathectomy and carotid sinus nerve section. Leitner LM, et al. **Pflugers Arch** 1986 Jun;406(6):552-6

Phencyclidine-induced wet-dog shakes observed in rats after withdrawal from reserpine treatment. Nabeshima T, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1275-9

RUBIDIUM

Chromium(III)ATP inactivating (Na+ + K+)-ATPase supports Na+-Na+ and Rb+-Rb+ exchanges in everted red blood cells but not Na+,K+ transport. Pauls H, et al. **Eur J Biochem** 1986 Jun 16; 157(3):585-95

Glucose reduces both Rb+ influx and efflux in pancreatic islet cells. Lindström P, et al. **FEBS Lett** 1986 May 5;200(1):67-70

[Evaluation of the local, skin-resorptive and sensitizing action of rubidium compounds] Akinfieva TA, et al. **Gig Tr Prof Zabol** 1986 Mar; (3):50-3 **(Rus)**

SCHIZOPHRENIA

Open multicentre trial of zuclopenthixol in mania and schizophrenia based on the AMDP scales. Bobon D, et al. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):152-76

A comprehensive study of chronic schizophrenic patients. II: Biological, neuropsychological, and clinical correlates of CT abnormality. Pandurangi AK, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):161-71

3H-spiperone binding in platelet membranes: a possible biological marker for schizophrenia. Sethi BB, et al. **Acta Psychiatr Scand** 1986 Feb; 73(2):186-90

Correlates of lateral ventricular size in chronic schizophrenia, I: Behavioral and treatment response measures. Losonczy MF, et al. **Am J Psychiatry** 1986 Aug;143(8):976-81

A dopamine-dependent restitutive system for the maintenance of mental normalcy. Friedhoff AJ. **Ann NY Acad Sci** 1986;463:47-52

Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia. I. One-year effects of a controlled study on relapse and expressed emotion. Hogarty GE, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):633-42

Longitudinal measurement of plasma homovanillic acid levels in schizophrenic patients. Correlation with psychosis and response to neuroleptic treatment. Pickar D, et al. **Arch Gen Psychiatry** 1986 Jul; 43(7):669-76

A negative, double-blind, placebo-controlled, clinical trial of verapamil in chronic schizophrenia. Grebb JA, et al. **Biol Psychiatry** 1986 Jun; 21(7):691-4

EEG asymmetry in schizophrenic patients before and during neuroleptic treatment. Merrin EL, et al. **Biol Psychiatry** 1986 May; 21(5-6):455-64

Lithium and haloperidol [letter] Nemes ZC, et al. **Biol Psychiatry** 1986 May;21(5-6):568-9

A randomised controlled trial of prophylactic neuroleptic treatment. Crow TJ, et al. **Br J Psychiatry** 1986 Feb;148:120-7

Short-term outcome in trial entrants and trial eligible patients. MacMillan JF, et al. **Br J Psychiatry** 1986 Feb;148:128-33

Schizophrenia with good and poor outcome [letter] Nimgaonkar VL, et al. **Br J Psychiatry** 1986 Mar;148:343-4

gamma-Endorphin and schizophrenia: amino acid composition of gamma-endorphin and nucleotide sequence of gamma-endorphin cDNA from pituitary glands of schizophrenic patients. Bovenberg RA, et al. **Brain Res** 1986 Jun 18;376(1):29-37

Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic-depressive patients. Abdalla DS, et al. **Clin Chem** 1986 May;32(5):805-7

Promazine. A major plasma metabolite of chlorpromazine in a population of chronic schizophrenics. Sgaragli G, et al. **Drug Metab Dispos** 1986 Mar-Apr;14(2):263-6

Decreased peripheral benzodiazepine binding sites in platelets of neuroleptic-treated schizophrenics. Gavish M, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):275-9

The interaction between gamma-type endorphins and HLA class I antigens. Claas FH, et al. **Hum Immunol** 1986 Apr;15(4):347-56

Low dose therapy: the future of neuroleptic psychopharmacology. A symposium held during the annual meeting of the American Psychiatric Association. May 1986, Washington, D.C. **J Clin Psychiatry** 1986 May; 47 Suppl:1-36

Early, targeted pharmacotherapeutic intervention in schizophrenia. Carpenter W Jr. **J Clin Psychiatry** 1986 May;47 Suppl:23-9 (48 ref.)

Relapse in chronic schizophrenics treated with fluphenazine decanoate is associated with low serum neuroleptic levels. Jayaram G, et al. **J Clin Psychiatry** 1986 May;47(5):247-8

Drug holidays and serum haloperidol levels in schizophrenic patients. McMillan DE, et al. **J Clin Psychiatry** 1986 Jul;47(7):373-4

Mesoridazine and thioridazine: clinical effects and blood levels in refractory schizophrenics. Vital-Herne J, et al. **J Clin Psychiatry** 1986 Jul;47(7):375-9

Behavioral changes following generic thioridazine [letter] Weber SS, et al. **J Clin Psychiatry** 1986 May;47(5):277-8

High dose alprazolam in schizophrenia [letter] Kulik FA, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):191-2

Medication effects on one-carbon metabolism in schizophrenia, mania, and major depression. Morere DA, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):155-61

The prescription of discretionary antipsychotic medication by state mental hospital psychiatrists. Benson PR. **J Health Soc Behav** 1986 Mar; 27(1):28-43

A comparative trial of depot pipothiazine. Steinert J, et al. **J Int Med Res** 1986;14(2):72-7

Topographic differences between normals and schizophrenics: the N120 evoked potential component. Buchsbaum MS, et al. **Neuropsychobiology** 1986;15(1):1-6

Fluperlapine vs haloperidol: a comparison of their neuroendocrinological profiles and the influence on serum lipids. Fleischhacker WW, et al. **Pharmacopsychiatry** 1986 May;19(3):111-4

Relevance of polymorphic drug oxidation in the use of neuroleptics in schizophrenia. Tang SW. **Prog Clin Biol Res** 1986;214:303-11 (20 ref.)

The interaction of neurotensin with dopaminergic pathways in the central nervous system: basic neurobiology and implications for the pathogenesis and treatment of schizophrenia. Nemeroff CB. **Psychoneuroendocrinology** 1986;11(1):15-37

Research methodology and the pharmacotherapy of the chronic schizophrenias. Ban TA, et al. **Psychopharmacol Bull** 1986; 22(1):36-41

An early phase II clinical trial of remoxipride in schizophrenia with measurement of plasma neuroleptic activity. Chouinard G, et al. **Psychopharmacol Bull** 1986;22(1):267-71

Clinical evaluation of ceruletide in schizophrenia: a multi-institutional cooperative double-blind controlled study. Itoh H, et al. **Psychopharmacol Bull** 1986;22(1):123-8

Ceruletide for schizophrenia: a review. Mattes JA, et al. **Psychopharmacol Bull** 1986;22(1):119-22 (32 ref.)

Pharmacological treatments of schizophrenia. Simpson GM. **Psychopharmacol Bull** 1986;22(1):33-5, 42-3

Cholecystokinin: a neuropeptide in the treatment of schizophrenia. Tamminga CA, et al. **Psychopharmacol Bull** 1986;22(1):129-32

The AMDP system in international clinical trials: a double-blind comparison of fluperlapine and haloperidol. Woggon B, et al. **Psychopharmacol Bull** 1986;22(1):47-51

Diurnal rhythm of plasma beta endorphin, cortisol and growth hormone in schizophrenics as compared to control subjects. Gil-Ad I, et al. **Psychopharmacology (Berlin)** 1986;88(4):496-9

Fluphenazine plasma levels in patients receiving low and conventional doses of fluphenazine decanoate. Marder SR, et al.

Psychopharmacology (Berlin) 1986;88(4):480–3

Attitudes of patients with schizophrenia toward taking medication. Davidhizar RE, et al. **Res Nurs Health** 1986 Jun;9(2):139–46

Investigating opioid peptides in schizophrenia and depression. Berger PA, et al. **Res Publ Assoc Res Nerv Ment Dis** 1986;64:309–33 (91 ref.)

Predictors of outcome in schizophrenia: the process-reactive dimension. Harrow M, et al. **Schizophr Bull** 1986;12(2):195–207

Flupenthixol decanoate and fluphenazine decanoate in chronic schizophrenia. Kong DS, et al. **Singapore Med J** 1985 Dec; 26(7):551–5

Cues of disability and treatment continuation of chronic schizophrenics. Dworkin RJ, et al. **Soc Sci Med** 1986;22(5):521–6

[Current aspects of the after care of schizophrenic patients] Maillard M, et al. **Ann Med Psychol (Paris)** 1985 Dec;143(10):946–51 **(Fre)**

[Schizophrenic excitement and the role of lithium in its therapy (apropos of 2 recent cases)] Skurnik N, et al. **Ann Med Psychol (Paris)** 1985 Dec;143(10):960–2 **(Fre)**

[Pharmacokinetics of pipothiazine palmitate, after intramuscular administration in schizophrenic patients] Blanc M, et al. **Therapie** 1986 Jan–Feb;41(1):27–30 (Eng. Abstr.) **(Fre)**

[Studies of the side effect profile of clozapine] Nitzsche M, et al. **Psychiatr Neurol Med Psychol (Leipz)** 1986 Mar;38(3):148–52 (Eng. Abstr.) **(Ger)**

[Dose and serum drug level and its clinical effects during the long-term treatment of chronic schizophrenia with flupenthixol depot] Lipska B, et al. **Psychiatr Pol** 1986 Jan–Feb;20(1):1–7 (Eng. Abstr.) **(Pol)**

[Determination of dopamine-beta-hydroxylase (DBH) and monoamine oxidase (MAO) activities in platelets and plasma in schizophrenic, maniac-depressive and neurotic patients] Xavier Vieira R, et al. **Acta Med Port** 1986 Jan–Feb;7(1):45–8 (Eng. Abstr.) **(Por)**

[Changes in the wave composition of evoked potentials during treatment of endogenous depression] Loginov VV, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):431–5 (Eng. Abstr.) **(Rus)**

[Typology of therapy-resistant states in schizophrenia] Neduba AA. **Zh Nevropatol Psikhiatr** 1986;86(3):424–8 (Eng. Abstr.) **(Rus)**

[Review and critical analysis of technics of psychosocial intervention in the family of schizophrenics] Adam A, et al. **Actas Luso Esp Neurol Psiquiatr Cienc Afines** 1986 Mar–Apr; 14(2):75–84 (49 ref.) (Eng. Abstr.) **(Spa)**

SCHIZOPHRENIA, CATATONIC

Catatonic schizophrenia: an international comparative study. Chandrasena R. **Can J Psychiatry** 1986 Apr;31(3):249–52

SCHIZOPHRENIA, PARANOID

Beta-adrenergic blockers for the control of aggressive behaviors in patients with chronic schizophrenia. Sorgi PJ, et al. **Am J Psychiatry** 1986 Jun;143(6):775–6

Bromocriptine in the treatment of neuroleptic-resistant schizophrenia. Gattaz WF, et al. **Biol Psychiatry** 1986 May;21(5–6):519–21

Imipramine-flupenthixol decanoate interaction. Cook PE, et al. **Can J Psychiatry** 1986 Apr;31(3):235–7

SCHIZOTYPAL PERSONALITY DISORDER

Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. Goldberg SC, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):680–6

Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. Soloff PH, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):691–7

Amitriptyline and haloperidol in unstable and schizotypal borderline disorders. Soloff PH, et al. **Psychopharmacol Bull** 1986;22(1):177–82

SELF STIMULATION

Reduction of the rewarding effect of brain stimulation by a blockade of dopamine D1 receptor with SCH 23390. Nakajima S, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):919–23

Roles of catecholamine terminals and intrinsic neurons of the ventral tegmentum in self-stimulation investigated in neonatally dopamine-depleted rats. Takeichi T, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1101–9

[Pharmacological analysis of the serotonin- and glutamatergic mechanisms in the suppressive effect of neuroleptics on the pedal self-stimulation of the ventral tectum of the midbrain] Talalaenko AN, et al. **Farmakol Toksikol** 1986 May–Jun;49(3):40–3 (Eng. Abstr.) **(Rus)**

SENSORY DEPRIVATION

Modification of ultrastructural and neurochemical parameters in synaptosomes of the retino-deprived goldfish optic tectum. Contestabile A, et al. **Exp Brain Res** 1986;62(3):560–6

SEROTONIN

Effect on brain monoamines in the rat of substituted and protected analogues of the oxytocin fragment, prolyl-leucyl-glycinamide following N-terminal substitution by D- and L-pipecolic acid. Szabó G, et al. **Acta Physiol Hung** 1986;67(1):155–61

Involvement of a serotonergic control in the regulation of plasma levels of immunoreactive beta-endorphin. Cancela LM, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):409–13

Serotonin stimulates gonadotrophin release by acting directly on the median eminence. Vitale ML, et al. **Acta Physiol Pharmacol Latinoam** 1985;35(4):473–9

Effects of pentagastrin and oxyphenonium on the levels of serotonin and 5-hydroxyindoleacetic acid in different parts of the digestive tract, blood and brain of rats. Pokora J, et al. **Acta Physiol Pol** 1984 Jul–Aug; 35(4):317–23

Regional and selective changes in blood flow of the feline small intestine induced by endoluminal serotonin. Grönstad KO, et al. **Acta Physiol Scand** 1986 Jun;127(2):207–13

Comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressed outpatients. Biochemical aspects. Nyström C, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):133–8

Biochemical and pharmacological characterization of histamine-mediated up-regulation of human platelet serotonin uptake. Evidence for a subclass of histamine H2 receptors (H2h) highly sensitive to H2 receptor antagonists. Gespach C, et al. **Agents Actions** 1986 Apr; 18(1–2):115–9

Separate purinoceptors mediate enhancement by adenosine of concanavalin A-induced mediator release and the cyclic AMP response in rat mast cells. Hughes PJ, et al. **Agents Actions** 1986 Apr; 18(1–2):81–4

Effects of aspartame ingestion on the carbohydrate-induced rise in tryptophan hydroxylation rate in rat brain. Fernstrom JD, et al. **Am J Clin Nutr** 1986 Aug;44(2):195–205

Changes in platelet beta-thromboglobulin, fibrinogen, albumin, 5-hydroxytryptamine, ATP, and ADP during and after surgery with extracorporeal circulation in man. Mezzano D, et al. **Am J Hematol** 1986 Jun;22(2):133–42

Serotonin uptake by bovine pulmonary artery endothelial cells in culture. II. Stimulation by hypoxia. Lee SL, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):C766–70

Serotonin uptake by bovine pulmonary artery endothelial cells in culture. I. Characterization. Lee SL, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):C761–5

Colocalization of luteinizing hormone and serotonin in secretory granules of mammalian gonadotrophs. Payette RF, et al. **Anat Rec** 1986 May; 215(1):51–8

Effect of electroconvulsive shock on serotonin activity. Essman WB. **Ann NY Acad Sci** 1986;462:99–104

Neurochemical mechanisms of mood stabilization. Focus on electroconvulsive therapy. Lerer B, et al. **Ann NY Acad Sci** 1986; 462:366–75 (74 ref.)

Serotonin and 5-hydroxyindoleacetic acid in brains of suicide victims. Comparison in chronic schizophrenic patients with suicide as cause of death. Korpi ER, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):594–600

Ontogenesis of 5-hydroxytryptamine-like immunoreactive cells and their relationship with bombesin in chicken proventriculus. D'Este L, et al. **Basic Appl Histochem** 1986;30(1):109–17

Occurrence and functional significance of serotonin and catecholamine uptake by astrocytes. Kimelberg HK. **Biochem Pharmacol** 1986 Jul 15; 35(14):2273–81

The effect of selective 5-hydroxytryptamine uptake inhibitors on 5-methoxy-N,N-dimethyltryptamine-induced ejaculation in the rat. Rényi L. **Br J Pharmacol** 1986 Apr;87(4):639–48

Ontogenesis of unit activity in the raphe dorsalis of the behaving kitten: its relationship with the states of vigilance. Adrien J, et al. **Brain Res** 1986 Feb 26;366(1–2):10–21

Immunocytochemical localization of serotonin in the rat dentate gyrus following raphe transplants. Anderson KJ, et al. **Brain Res** 1986 Mar 26;369(1–2):21–8

Circadian corticosterone rhythm did not develop in rats seven weeks after destruction with 5,7-dihydroxytryptamine of the serotoninergic nerve terminals in the suprachiasmatic nucleus at the age of 16 days. Bánky Z, et al. **Brain Res** 1986 Mar 26;369(1–2):119–24

The effects of serotonin on the morpho-functional development of rat cerebral neocortex in tissue culture. Chubakov AR, et al. **Brain Res** 1986 Mar 26;369(1–2):285–97

Brain serotonin and catecholamine responses to repeated stress in rats. De Souza EB, et al. **Brain Res** 1986 Mar 5;367(1–2):77–86

GABA and serotonin (5-HT) pattern in the supraependymal fibers of the rat epithalamus: combined radioautographic and immunocytochemical studies. Effect of 5-HT content on [3H]GABA accumulation. Harandi M, et al. **Brain Res** 1986 Apr 9;370(2):241–9

Serotonin innervation of physiologically identified lamina I projection neurons. Hylden JL, et al. **Brain Res** 1986 Apr 9;370(2):401–4

One perfusion mixture for immunocytochemical detection of

noradrenaline, dopamine, serotonin and acetylcholine in the same rat brain. McRae-Degueurce A, et al. **Brain Res** 1986 Jun 18; 376(1):217-9

Localization of GABAA and GABAB receptor subtypes on serotonergic neurons. Mennini T, et al **Brain Res** 1986 Apr 23;371(2):372-5

Immunohistochemical demonstration of serotonin neurons in autonomic regions of the rat spinal cord. Newton BW, et al. **Brain Res** 1986 Jun 18;376(1):155-63

Neuroanatomical site of the inhibitory influence of anxiolytic drugs on central serotonergic transmission. Nishikawa T, et al. **Brain Res** 1986 Apr 16;371(1):123-32

Spinal cord serotonin release and raised blood pressure after brainstem kainic acid injection. Pilowsky PM, et al. **Brain Res** 1986 Feb 26; 366(1-2):354-7

Single unit response of noradrenergic, serotonergic and dopaminergic neurons in freely moving cats to simple sensory stimuli. Rasmussen K, et al. **Brain Res** 1986 Mar 26;369(1-2):336-40

Serotonin-immunoreactive nerve fibers of the rat pituitary: effects of anticatecholamine and antiserotonin drugs on staining patterns. Saland LC, et al. **Brain Res** 1986 Mar 19;368(2):310-8

Evidence that serotonin mediates non-cholinergic neocortical low voltage fast activity, non-cholinergic hippocampal rhythmical slow activity and contributes to intelligent behavior. Vanderwolf CH, et al. **Brain Res** 1986 May 28;374(2):342-56

5-Hydroxytryptamine (serotonin) causes a reduction in the afterhyperpolarization following the action potential in lamprey motoneurons and premotor interneurons. Van Dongen PA, et al. **Brain Res** 1986 Feb 26;366(1-2):320-5

Induced homotypic sprouting of serotonergic fibers in hippocampus. II. An immunocytochemistry study. Zhou FC, et al. **Brain Res** 1986 May 14;373(1-2):337-48

Cerebral perivascular serotonergic fibres have a peripheral origin in the gerbil. Alafaci C, et al. **Brain Res Bull** 1986 Feb;16(2):303-4

Interaction between platelet-released serotonin and thromboxane A2 on human digital arteries. Young MS, et al. **Clin Exp Pharmacol Physiol** 1986 Feb;13(2):143-52

Measurement of whole blood serotonin as a guide in prescribing psychostimulant medication for children with attentional deficits. Saul RC, et al. **Clin Neuropharmacol** 1986;9(2):189-95

Leech Retzius cells and 5-hydroxytryptamine. Leake LD. **Comp Biochem Physiol** [C] 1986;83(2):229-39 (73 ref.)

Carbohydrate metabolism and the temporal occurrence of a serotonin-like indole in the male and female reproductive tract and its relationship with PGF and infertility: a review. van der Horst CJ. **Cytobios** 1986; 45(181):85-95 (61 ref.)

Brain 5-hydroxytryptamine and plasma testosterone in L-tryptophan treated rats. Biswas NM, et al. **Endocr Res** 1985;11(3-4):131-7

The effects of some slow channel blocking drugs on high affinity serotonin uptake by rat brain synaptosomes. Brown NL, et al. **Eur J Pharmacol** 1986 Apr 9;123(1):161-5

Antagonism by some ergot derivatives of 5-HT-induced vasoconstriction. Conolan S, et al. **Eur J Pharmacol** 1986 Apr 16;123(2):299-302

Solubilization and characterization of the 5-hydroxytryptamine transporter complex from rat cerebral cortical membranes. Habert E, et al. **Eur J Pharmacol** 1986 Mar 18;122(2):197-204

In vivo evaluation by differential pulse voltammetry of the effect of thyrotropin-releasing hormone (TRH) on dopaminergic and serotoninergic synaptic activity in the striatum and nucleus accumbens of the rat. Crespi F, et al. **Exp Brain Res** 1986;62(2):329-34

Serotonin in the human infant carotid body. Perrin DG, et al. **Experientia** 1986 May 15;42(5):562-4

Amine sulfate formation in the central nervous system. Tyce GM, et al. **Fed Proc** 1986 Jul;45(8):2247-53

Significance of calcium for the prostaglandin E2-mediated secretory response to 5-hydroxytryptamine in the small intestine of the rat in vivo. Beubler E, et al. **Gastroenterology** 1986 Jun;90(6):1972-7

Time-related response of central serotonergic function to lithium administration. Otero Losada ME, et al. **Gen Pharmacol** 1986; 17(3):333-7

GABA-induced hypothermia in rats: involvement of serotonergic and cholinergic mechanisms. Serrano JS, et al. **Gen Pharmacol** 1986; 17(3):327-32

Allometric growth of the rat peritoneal mast cell mass and of the granular constituents: heparin, histamine and 5-hydroxytryptamine. Aldenborg F, et al. **Growth** 1985 Winter;49(4):510-8

Cytological features of serotonin-containing neurons and their processes in the retina of the carp (Cyprinus carpio). An immunohistochemical study using flat-mount preparations. Hayashi T, et al. **Histochemistry** 1986;84(4-6):423-5

Response of isolated uterus of rat, hamster and guinea pig to different uterine stimulants. Mehrotra PK, et al. **Indian J Exp Biol** 1985 Oct; 23(10):572-3

Effect of graded distension of urinary bladder on arterial blood pressure and neurohumors in rabbits. Shukla M, et al. **Indian J Physiol Pharmacol** 1985 Jul-Sep;29(3):159-64

Studies on vascular permeability increasing factors involved in 48-hour homologous PCA in the mouse ear. Inagaki N, et al. **Int Arch Allergy Appl Immunol** 1986;80(3):285-90

The serotonin syndrome: case responsive to propranolol [letter] Guzé BH, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):119-20

Immunohistochemical distribution of substance P, serotonin, and methionine enkephalin in sexually dimorphic nuclei of the rat lumbar spinal cord. Micevych PE, et al. **J Comp Neurol** 1986 Jun 8; 248(2):235-44

Synaptic basis of swim initiation in the leech. III. Synaptic effects of serotonin-containing interneurones (cells 21 and 61) on swim CPG neurones (cells 18 and 208). Nusbaum MP. **J Exp Biol** 1986 May; 122:303-21

Swim initiation in the leech by serotonin-containing interneurones, cells 21 and 61. Nusbaum MP, et al. **J Exp Biol** 1986 May;122:277-302

Ultrastructural localization of serotonin and polypeptide YY (PYY) in endocrine cells of the human rectum. Lukinius AI, et al. **J Histochem Cytochem** 1986 Jun;34(6):719-26

Inter- and intracellular relationship of substance P-containing neurons with serotonin and GABA in the dorsal raphe nucleus: combination of autoradiographic and immunocytochemical techniques. Mágoul R, et al. **J Histochem Cytochem** 1986 Jun;34(6):735-42

Historical introduction: the Italian contribution to the discovery of 5-hydroxytryptamine (enteramine, serotonin). Erspamer V. **J Hypertension [Suppl]** 1986 Apr;4(1):S3-5

Three distinct subtypes of serotonergic receptors mediate the triphasic blood pressure response to serotonin in rats. Kalkman HO, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S143-5

Platelet content of serotonin and response to stress. Palermo A, et al. **J Hypertension [Suppl]** 1986 Apr;4(1):S43-5

Augmentation of vasoconstrictor responses to serotonin by acute and chronic factors: inhibition by ketanserin. Van Nueten JM, et al. **J Hypertension [Suppl]** 1986 Apr;4(1):S55-9

The specificity of ketanserin in the inhibition of serotonin-induced steroidogenesis in the rat adrenal zona glomerulosa. Williams BC, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S559-61

Effect of serotonin on murine macrophages: suppression of Ia expression by serotonin and its reversal by 5-HT2 serotonergic receptor antagonists. Sternberg EM, et al. **J Immunol** 1986 Jul 1; 137(1):276-82

Vascular responsiveness of simian digital artery to various vasoactive substances. Ito T, et al. **J Invest Dermatol** 1986 Jun;86(6):678-82

Peripheral and central short-term effects of fusaric acid, a DBH inhibitor, on tryptophan and serotonin metabolism in the rat. Chaouloff F, et al. **J Neural Transm** 1986;65(3-4):219-32

The inhibition of the cage-leaving response--a model for studies of the serotonergic neurotransmission in the rat. Rényi L, et al. **J Neural Transm** 1986;65(3-4):193-210

Regional distribution of immunoreactive-thyrotrophin-releasing hormone and substance P, and indoleamines in human spinal cord. Bennett GW, et al. **J Neurochem** 1986 Jun;46(6):1718-24

Exogenous tryptophan increases synthesis, storage, and intraneuronal metabolism of 5-hydroxytryptamine in the rat hypothalamus. Lookingland KJ, et al. **J Neurochem** 1986 Jul;47(1):205-12

Involvement of serotonin in the excitation of phrenic motoneurons evoked by stimulation of the raphe obscurus. Holtman JR Jr, et al. **J Neurosci** 1986 Apr;6(4):1185-93

Development of serotonin-containing neurons in Drosophila mutants unable to synthesize serotonin. Vallés AM, et al. **J Neurosci** 1986 May; 6(5):1482-91

Chronic clenbuterol treatment modulates a 5-hydroxytryptaminergic system. Francès H, et al. **J Pharm Pharmacol** 1986 Mar;38(3):247-8

Buspirone decreases the activity of 5-hydroxytryptamine-containing dorsal raphe neurons in-vitro. Trulson ME, et al. **J Pharm Pharmacol** 1986 May;38(5):380-2

Modification of serotonergic and noradrenergic neurotransmissions by repeated administration of monoamine oxidase inhibitors: electrophysiological studies in the rat central nervous system. Blier P, et al. **J Pharmacol Exp Ther** 1986 Jun;237(3):987-94

Voltage dependence of 5-hydroxytryptamine release at a synapse between identified leech neurones in culture. Dietzel ID, et al. **J Physiol (Lond)** 1986 Mar;372:191-205

Allosteric inhibition as a model to explain flatter displacement curves in binding experiments: application to 'heterogeneous' serotonin receptors. Gobbi M, et al. **J Recept Res** 1986;6(1):27-46

An active pathway for serotonin synthesis by renal proximal tubules. Sole MJ, et al. **Kidney Int** 1986 Mar;29(3):689-94

Serotonin uptake inhibitors and the prejunctional effects of serotonin on peripheral sympathetic nerves. Adler-Graschinsky E, et al. **Life Sci** 1986 Jul 7;39(1):61-8

Normal serotonin uptake by blood platelets and brain synaptosomes but selective impairment of platelet serotonin storage in mice with Chediack-Higashi syndrome. Lampugnani MG, et al. **Life Sci** 1986 Jun 16;38(24):2193-8

Correlations of serotonin and its metabolites in individual rat pineal glands over light:dark cycles and after acute light exposure. McNulty JA, et al. **Life Sci** 1986 Jul 7;39(1):1-6

Regional serotonin receptor studies: chronic methysergide treatment induces a selective and dose-dependent decrease in serotonin-2 receptors in mouse cerebral cortex. May PC, et al. **Life Sci** 1986 May 12;38(19):1741-7

Hepatic microvascular regulatory mechanisms. V. Effects of lodoxamide tromethamine or phentolamine-HCl on vascular responses elicited by serotonin. Reilly FD, et al. **Microcirc Endothelium Lymphatics** 1984 Dec;1(6):671-89

Serotonin-containing elements of the rat pituitary intermediate lobe. Palkovits M, et al. **Neuroendocrinology** 1986;42(6):522-5

The effect on brain 5-HT of central lysine-vasopressin administration into different cerebral ventricular compartments depends on the site of injection. Günther O, et al. **Neuropeptides** 1986 Apr;7(3):241-5

Coexistence of serotonin- and substance P-like immunoreactivity in nerve fibers apposing identified sympathoadrenal preganglionic neurons in rat intermediolateral cell column. Appel NM, et al. **Neurosci Lett** 1986 Apr 24;65(3):241-6

A spinal projection of 5-hydroxytryptamine neurons in the lamprey brainstem; evidence from combined retrograde tracing and immunohistochemistry. Brodin L, et al. **Neurosci Lett** 1986 Jun 6; 67(1):53-7

Inhibitory influence of monoamines and brainstem monoaminergic regions on the medullary swallowing reflex. Kessler JP, et al. **Neurosci Lett** 1986 Mar 28;65(1):41-6

Effect of serotonin on the dissociation of high-affinity binding of [3H]imipramine in mouse cerebral cortex. Kim SS, et al. **Neurosci Lett** 1986 Jun 18;67(2):123-8

Serotonin inhibits the depolarization-evoked release of endogenous glutamate from rat cerebellar nerve endings. Maura G, et al. **Neurosci Lett** 1986 Jun 18;67(2):218-22

Distinct functions for dopamine and serotonin in locomotor behaviour: evidence using the 5-HT1 agonist RU 24969 in globus pallidus-lesioned rats. Oberlander C, et al. **Neurosci Lett** 1986 Jun 18;67(2):113-8

Transplantation of dissociated foetal serotonin neurons into the transected spinal cord of adult rats. Privat A, et al. **Neurosci Lett** 1986 May 6; 66(1):61-6

Monoamine innervation of the oculomotor nucleus in the rat. A radioautographic study. Soghomonian JJ, et al. **Neuroscience** 1986 Apr; 17(4):1147-57

Physiological responses of guinea-pig myenteric neurons secondary to the release of endogenous serotonin by tryptamine. Takaki M, et al. **Neuroscience** 1985 Sep;16(1):223-40

Gamma-aminobutyrate, gastrin releasing peptide, serotonin, somatostatin, and vasopressin: ultrastructural immunocytochemical localization in presynaptic axons in the suprachiasmatic nucleus. van den Pol AN. **Neuroscience** 1986 Mar;17(3):643-59

Regional alterations in serotonin metabolism induced by oral exposure of rats to polychlorinated biphenyls. Seegal RF, et al. **Neurotoxicology** 1986 Spring;7(1):155-65

Comparison of the effects of the benzodiazepine midazolam and three serotonin antagonists on a consummatory conflict paradigm. Becker HC. **Pharmacol Biochem Behav** 1986 Apr;24(4):1057-64

Serotonergic mechanisms in the behavioral effects of buspirone and gepirone. Eison AS, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):701-7

Microstructural analysis of the anorectic action of peripherally administered 5-HT. Fletcher PJ, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1133-6

Recent developments in 5HT-related pharmacology of animal models of anxiety. Gardner CR. **Pharmacol Biochem Behav** 1986 May; 24(5):1479-85

5-HT and anxiety: promises and pitfalls. Johnston AL, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1467-70

Effects of serotonergic agonists and antagonists on the locomotor activity of neonatal rats. Lucot JB, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):537-41

Prenatal stress: effect on development of rat brain serotonergic neurons. Peters DA. **Pharmacol Biochem Behav** 1986 May;24(5):1377-82

Are serotonergic neurons involved in the control of anxiety and in the anxiolytic activity of benzodiazepines? Thiebot MH. **Pharmacol Biochem Behav** 1986 May;24(5):1471-7

Effects of elevated calcium on learned helplessness and brain serotonin metabolism in rats. Trulson ME, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):445-8

The effect of neonatal manipulation of hypothalamic serotonin levels on sexual activity in the adult rat. Wilson CA, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1175-83

Parachlorophenylalanine-induced serotonin depletion increases offensive but not defensive aggression in male rats. Vergnes M, et al. **Physiol Behav** 1986;36(4):653-8

Protease and cyclooxygenase inhibitors synergistically prevent activation of human platelets. Ruggiero M, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3456-9

The effect of altered 5-hydroxytryptamine levels on beta-endorphin content in rat brain. Soliman KF, et al. **Proc Soc Exp Biol Med** 1986 Jun;182(2):187-93

Prostacyclin and thromboxane formation in human umbilical arteries following stimulation with vasoactive autacoids. Bjøro K. **Prostaglandins** 1986 Apr;31(4):699-714

Dissociation of the anorectic actions of 5-HTP and fenfluramine. Fletcher PJ, et al. **Psychopharmacology (Berlin)** 1986;89(2):216-20

The effects of a 5-HT1 receptor ligand isapirone (TVX Q 7821) on 5-HT synthesis and the behavioural effects of 5-HT agonists in mice and rats. Goodwin GM, et al. **Psychopharmacology (Berlin)** 1986;89(3):382-7

Circadian rhythm of serotonin transport in human platelets. Modai I, et al. **Psychopharmacology (Berlin)** 1986;88(4):493-5

Pharmacological investigations of the mechanisms underlying the effects of peripheral 5-HT on flavour consumption and preference. Montgomery AM, et al. **Psychopharmacology (Berlin)** 1986; 89(2):192-7

Sequestration of serotonin in stored platelets. Shimizu T, et al. **Transfusion** 1986 May-Jun;26(3):274-7

[Serotonin transport by blood platelets of depressive patients] Modai I, et al. **Harefuah** 1986 Jan 15;110(2):64-7 (Eng. Abstr.) **(Heb)**

[The function of the sympathetic nervous system determined by humoral factors in the maintenance hemodialysis patients] Minami M, et al. **Hokkaido Igaku Zasshi** 1986 Mar;61(2):186-94 (Eng. Abstr.) **(Jpn)**

[The role of serotonin, histamine and prostaglandins on potentiation of hypoxic pulmonary vasoconstriction by repeated intermittent hypoxic challenges in dogs] Nakanishi S. et al. **Nippon Kyobu Shikkan Gakkai Zasshi** 1986 Jan;24(1):42-8 (Eng. Abstr.) **(Jpn)**

[The role of the sympathetic nervous system and adrenals in hemodynamic changes after intracerebroventricular administration of 5-hydroxytryptamine in rats] Kuniyoshi K, et al. **Nippon Naibunpi Gakkai Zasshi** 1986 Mar 20;62(3):188-96 (Eng. Abstr.) **(Jpn)**

[Basophil histamine and peripheral blood serotonin in metal and toxic gas poisoning] Fal W, et al. **Med Pr** 1985;36(6):377-81 (Eng. Abstr.) **(Pol)**

[Serotonin levels in the blood of patients with terminal renal failure] Myśliwiec M, et al. **Pol Tyg Lek** 1986 Jan 13;41(2):35-7 (Eng. Abstr.) **(Pol)**

[Comparison of the effect of serotonin administered into the dorsal hippocampus on conditioned passive and active avoidance in rats] Gasanov GG, et al. **Biull Eksp Biol Med** 1986 May;101(5):517-9 (Eng. Abstr.) **(Rus)**

[Mechanism of stimulation of the motor activity of the stomach by the greater splanchnic nerve] Smironov VM, et al. **Fiziol Zh SSSR** 1986 May;72(5):650-5 (Eng. Abstr.) **(Rus)**

[Dynamics of serotonin release from tissue depots in the gastrointestinal tract of the unanesthetized dog after ingesting food] Vasil'ev VP. **Fiziol Zh SSSR** 1986 Apr;72(4):544-8 (Eng. Abstr.) **(Rus)**

[Relation between glucose resorption and enzyme activity of the brush border of enterocytes in the rat and the level of endogenous serotonin] Vasil'ev VP. **Fiziol Zh SSSR** 1986 May;72(5):664-7 (Eng. Abstr.) **(Rus)**

[Effect of chorionic gonadotropin on the serotonin content in the peripheral organs and tissues] Kudriavtseva NN, et al. **Patol Fiziol Eksp Ter** 1986 Mar-Apr;(2):53-5 (Eng. Abstr.) **(Rus)**

[Immunocytochemical and autoradiographic research on the growth of serotoninergic fibers to the cerebral ventricles in the perinatal period in rats] Ugriumov MV, et al. **Tsitologiia** 1986 Feb;28(2):160-4 (Eng. Abstr.) **(Rus)**

[Isolation of liposomes containing serotonin and their effect on cAMP accumulation in the rat liver] Stefanov AV, et al. **Ukr Biokhim Zh** 1986 May-Jun;58(3):47-53 (Eng. Abstr.) **(Rus)**

[Role of the giant serotonin-containing cell of the cerebral ganglion in the edible snail in organizing its food-acquiring behavior] Galanina GN, et al. **Zh Vyssh Nerv Deiat** 1986 Jan-Feb;36(1):110-5 (Eng. Abstr.) **(Rus)**

SET (PSYCHOLOGY)

Does placebo response mediate runner's high? Hinton ER, et al. **Percept Mot Skills** 1986 Jun;62(3):789-90

SEX BEHAVIOR, ANIMAL

Gamma aminobutyric acid mediates ventromedial hypothalamic mechanisms controlling the execution of lordotic responses in the female rat. Mascó D, et al. **Behav Brain Res** 1986 Feb;19(2):153-62

Biochemical and radioautographic analysis of estrogen-inducible progestin receptors in female ferret brain and pituitary: correlations with effects of progesterone on sexual behavior and gonadotropin-releasing hormone-stimulated secretion of luteinizing hormone. Baum MJ, et al. **Brain Res** 1986 Mar 19;368(2):296-309

Dopaminergic control of male sex behavior in rats: effects of an intracerebrally-infused agonist. Hull EM, et al **Brain Res** 1986 Apr 2;370(1):73-81

Neonatal 6-hydroxydopamine lesion of forebrain norepinephrine does not eliminate critical period for behavioral effects of gonadal hormone manipulation. Pappas BA, et al. **Brain Res** 1986 May;391(2):310-4

Regulation of mating behaviour in the female rat by gonadotropin-releasing hormone in the ventral tegmental area: effects of selective destruction of the A10 dopamine neurones. Sirinathsinghji DJ, et al. **Brain Res** 1986 May 21;374(1):167-73

Changes in the immunoreactivities of an opioid peptide leumorphin in the hypothalamus and anterior pituitary during the estrous cycle of the rat and their relation to sexual behavior. Suda M, et al. **Brain Res** 1986 May 28;374(2):236-43

Removal of the vomeronasal organ impairs lordosis in female hamsters: effect is reversed by luteinising hormone-releasing hormone. Mackay-Sim A, et al. **Neuroendocrinology** 1986;42(6):489-93

Suppression of receptive and proceptive behavior in ovariectomized, estrogen-progesterone-primed rats by intraventricular beta-endorphin: studies of behavioral specificity. Wiesner JB, et al. **Neuroendocrinology** 1986;43(1):57-62

Norepinephrine infusions into the medial preoptic area inhibit lordosis behavior. Caldwell JD, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):1015-23

Lordosis behavior and GABAergic neurotransmission. Fernández-Guasti A, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):673-6

GABAergic control of masculine sexual behavior. Fernández-Guasti A, et al. **Pharmacol Biochem Behav** 1986 Apr;24(4):1065-70

Effect of beta-endorphin on sociosexual proclivity in a choice paradigm. Wiesner JB, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):507-11

The effect of neonatal manipulation of hypothalamic serotonin levels on sexual activity in the adult rat. Wilson CA, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1175-83

SLEEP

Benzodiazepines: half-life and daytime hyperarousal [letter] Soldatos CR. **Am J Psychiatry** 1986 Jun;143(6):813-4

Effects of brotizolam on the sleep-waking cycle of the cat. Kuhn FJ. **Arzneimittelforschung** 1986 Mar;36(3A):522-7

Ontogenesis of unit activity in the raphe dorsalis of the behaving kitten: its relationship with the states of vigilance. Adrien J, et al. **Brain Res** 1986 Feb 26;366(1-2):10-21

Intracerebroventricular infusion of somatostatin selectively increases paradoxical sleep in rats. Danguir J. **Brain Res** 1986 Mar 5; 367(1-2):26-30

Alpha adrenergic system in medial preoptic area involved in sleep-wakefulness in rats. Mohan Kumar V, et al. **Brain Res Bull** 1986 Apr;16(4):463-8

Alprazolam and lorazepam single and multiple-dose effects on psychomotor skills and sleep. Subhan Z, et al. **Eur J Clin Pharmacol** 1986;29(6):709-12

Influence of brown adipose tissue on deep cervical temperature during sleep in the young rabbit. Franzini C, et al. **Experientia** 1986 Jun 15; 42(6):604-6

Relationship between sleep variables and urinary excretion of adrenaline in nocturnal sleep. Nishihara K, et al. **Ind Health** 1985;23(4):279-82

Effects of melatonin and 5-methoxytryptamine on sleep-wake patterns in the male rat. Mirmiran M, et al. **J Pineal Res** 1986;3(2):135-41

Influence of some dopaminoceptor agents on nitrazepam-induced sleep in the domestic fowl (Gallus domesticus) and rats. Wambebe C. **Jpn J Pharmacol** 1986 Mar;40(3):357-65

Variation in pentobarbitone sleeping time in mice. 1. Strain and sex differences. Lovell DP. **Lab Anim** 1986 Apr;20(2):85-90

Variation in pentobarbitone sleeping time in mice. 2. Variables affecting test results. Lovell DP. **Lab Anim** 1986 Apr;20(2):91-6

Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. Ehlers CL, et al. **Neuroendocrinology** 1986;42(6):467-74

Effects of Suanzaorentang on behavior changes and central monoamines. Hsieh MT, et al. **Proc Natl Sci Counc Repub China [B]** 1986 Jan; 10(1):43-8

N,N'-diallylbarbital potentiation of drug-induced sleep and motor incoordination. Tateoka Y, et al. **Res Commun Chem Pathol Pharmacol** 1986 Apr;52(1):17-28

Effects of methylmercury on hypnotic action of hexobarbital, liver hydroxylase and cytochrome P-450 in mice. Su MQ, et al. **Toxicology** 1986 Jun;39(3):233-45

[Nocturnal prolactin (PRL) levels and PRL release by metoclopramide in normoprolactinemic anovulation, and effects of bromocriptine in induction of ovulation] Suginami H, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 Apr;38(4):603-4 **(Jpn)**

[Serum prolactin levels during sleep and in metoclopramide stimulation in normoprolactinemic anovulation and ovulation induction with bromocriptine] Suginami H, et al. **Nippon Sanka Fujinka Gakkai Zasshi** 1986 May;38(5):728-34 (Eng. Abstr.) **(Jpn)**

[Duration of the narcotic action of nembutal under hyperbarism] Sledkov AIu, et al. **Farmakol Toksikol** 1986 May-Jun;49(3):32-5 (Eng. Abstr.) **(Rus)**

SLEEP DEPRIVATION

Stress hormonal response to exercise after sleep loss. Martin BJ, et al. **Eur J Appl Physiol** 1986;55(2):210-4

The effects of REM sleep deprivation on striatal dopamine receptor sites. Zwicker AP, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):809-12

SLEEP, REM

The importance of fetal/neonatal REM sleep. Mirmiran M. **Eur J Obstet Gynecol Reprod Biol** 1986 May;21(5-6):283-91

Diurnal variations of brain noradrenaline metabolism of the methylmercury chloride-administered rat with reference to an altered circadian rhythm of paradoxical sleep. Arito H, et al. **Ind Health** 1985; 23(4):245-53

The effects of REM sleep deprivation on striatal dopamine receptor sites. Zwicker AP, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):809-12

SLEEP STAGES

Regular 48-hour cycling of sleep duration and mood in a 35-year-old woman: use of lithium in time isolation. Welsh DK, et al. **Biol Psychiatry** 1986 May;21(5-6):527-37

Behavioral changes following generic thioridazine [letter] Weber SS, et al. **J Clin Psychiatry** 1986 May;47(5):277-8

SOCIAL ADJUSTMENT

Impairment of work and leisure in depressed outpatients. A preliminary communication. De Lisio G, et al. **J Affective Disord** 1986 Mar-Apr; 10(2):79-84

Can pregnancy be a placebo effect?: Terminology, designs, and conclusions in the study of psychosocial and pharmacological treatments of behavior disorders. Paul GL. **J Behav Ther Exp Psychiatry** 1986 Jun;17(2):61-81

Predictors of outcome in schizophrenia: the process-reactive dimension. Harrow M, et al. **Schizophr Bull** 1986;12(2):195-207

SODIUM

Effect of renal nerve activity on tubular sodium and water reabsorption in dog kidneys as determined by the lithium clearance method. Abildgaard U, et al. **Acta Physiol Scand** 1986 Feb;126(2):251-7

Intra- and interindividual variability in sodium intake in normal subjects and in patients with renal insufficiency. Luft FC, et al. **Am J Kidney Dis** 1986 May;7(5):375-80

Effects of calcium antagonist TMB-8 on active Na and Cl transport in rabbit ileum. Donowitz M, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):G691-7

Tryptic modification of red-cell sodium pump behaviour. Harvey WJ, et al. **Biochim Biophys Acta** 1986 Apr 25;856(3):496-504

Na+-H+ exchange in the process of glucose-induced insulin release from the pancreatic B-cell. Effects of amiloride on 86Rb, 45Ca fluxes and insulin release. Lebrun P, et al. **Biochim Biophys Acta** 1986 May 29;886(3):448-56

The Ba2+ sensitivity of the Na+-induced Ca2+ efflux in heart mitochondria: the site of inhibitory action. Lukács GL, et al. **Biochim Biophys Acta** 1986 Jun 13;858(1):125-34

Basolateral amino acid transport systems in the perfused exocrine pancreas: sodium-dependency and kinetic interactions between influx and efflux mechanisms. Mann GE, et al. **Biochim Biophys Acta** 1986 Jun 26;858(2):263-74

Mechanism of inhibition by lithium of sodium transport in the toad bladder. Herrera FC, et al. **Biol Cell** 1985;55(3):257-63

Erythrocyte cation transport activities as a function of cell age. Hentschel WM, et al. **Clin Chim Acta** 1986 May 30;157(1):33-43

Chromium(III)ATP inactivating (Na+ + K+)-ATPase supports Na+-Na+ and Rb+-Rb+ exchanges in everted red blood cells but not Na+,K+ transport. Pauls H, et al. **Eur J Biochem** 1986 Jun 16; 157(3):585-95

Transport of ions across the blood-brain barrier. Betz AL. **Fed Proc** 1986 Jun;45(7):2050-4 (26 ref.)

Temperature sensitivity and substrate specificity of two distinct Na+-activated D-glucose transport systems in guinea pig jejunal brush border membrane vesicles. Brot-Laroche E, et al. **J Biol Chem** 1986 May 15;261(14):6168-76

Sugar binding properties of the melibiose permease in Escherichia coli membrane vesicles. Effects of Na+ and H+ concentrations. Damiano-Forano E, et al. **J Biol Chem** 1986 May 25;261(15):6893-9

Ca2+-induced down-regulation of Na+ channels in toad bladder epithelium. Garty H, et al. **J Biol Chem** 1986 Jun 5;261(16):7400-6

[3H]bumetanide binding to duck red cells. Correlation with inhibition of (Na + K + 2Cl) co-transport. Haas M, et al. **J Biol Chem** 1986 Jun 25;261(18):8434-41

Growth factors activate the bumetanide-sensitive

Na+/K+/Cl-cotransport in hamster fibroblasts. Paris S, et al. **J Biol Chem** 1986 May 15;261(14):6177-83

Early events elicited by bombesin and structurally related peptides in quiescent Swiss 3T3 cells. II. Changes in Na+ and Ca2+ fluxes, Na+/K+ pump activity, and intracellular pH. Mendoza SA, et al. **J Cell Biol** 1986 Jun;102(6):2223-33

Catecholamine-induced transport systems in trout erythrocyte. Na+/H+ countertransport or NaCl cotransport? Borgese F, et al. **J Gen Physiol** 1986 Apr;87(4):551-66

Acute volume expansion in humans releases a factor which inhibits the vascular Na+-K+ pump. Price MB, et al. **J Hypertension [Suppl]** 1984 Dec;2(3):S471-2

Activation of the voltage-sensitive sodium channel by a beta-scorpion toxin in rat brain nerve-ending particles. Bablito J, et al. **J Neurochem** 1986 Jun;46(6):1763-70

The in situ perfused spinal cord of the rat. Applicability of drugs and chemicals, sodium-lithium exchange, and calcium reduction to functional intact central nervous system tissue. Deutschmann W, et al. **J Pharmacol Methods** 1986 Apr;15(2):143-55

The interaction between the activator agents batrachotoxin and veratridine and the gating processes of neuronal sodium channels. Rando TA, et al. **Mol Pharmacol** 1986 May;29(5):467-77

The role of co-transported sodium in the effect of indirectly acting sympathomimetic amines. Bönisch H. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Feb;332(2):135-41

Sodium-dependence of the saturability of carrier-mediated noradrenaline efflux from noradrenergic neurones in the rat vas deferens. Bönisch H, et al. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Feb; 332(2):131-4

Regulation of phosphatidylinositol turnover in brain synaptoneurosomes: stimulatory effects of agents that enhance influx of sodium ions. Gusovsky F, et al. **Proc Natl Acad Sci USA** 1986 May;83(9):3003-7

Egg-laying hormone of Aplysia induces a voltage-dependent slow inward current carried by Na+ in an identified motoneuron. Kirk MD, et al. **Proc Natl Acad Sci USA** 1986 May;83(9):3017-21

SOMATOSTATIN

Plasma concentrations of motilin, somatostatin and pancreatic polypeptide before, during and after parturition. Jenssen TG, et al. **Acta Obstet Gynecol Scand** 1986;65(2):153-6

Influence on plasma levels of somatostatin, gastrin, glucagon, insulin and VIP-like immunoreactivity in peripheral venous blood of anaesthetized cats induced by low intensity afferent stimulation of the sciatic nerve. Uvnäs-Moberg K, et al. **Acta Physiol Scand** 1986 Feb;126(2):225-30

Are prostaglandins involved in somatostatin mediated inhibition of gastric secretion in the cat? Albinus M, et al. **Agents Actions** 1986 Apr; 18(1-2):205-9

Phorbol esters stimulate somatostatin release from cultured cells. Sugano K, et al. **Am J Physiol** 1986 May;250(5 Pt 1):G686-90

Specific binding and degradation of somatostatin by membrane vesicles from pig gut. Weber M, et al. **Am J Physiol** 1986 May; 250(5 Pt 1):G679-85

Somatostatin mediation of adenohypophysial secretion. Patel YC, et al. **Annu Rev Physiol** 1986;48:551-67 (100 ref.)

Gastro-intestinal tract function in sheep infused with somatostatin. Barry TN, et al. **Aust J Biol Sci** 1985;38(4):393-403

Somatostatin and cholecystokinin octapeptide differentially modulate the release of [3H]acetylcholine from caudate nucleus but not cerebral cortex: role of dopamine receptor activation. Arnerić SP, et al. **Brain Res** 1986 May 21;374(1):153-61

Intracerebroventricular infusion of somatostatin selectively increases paradoxical sleep in rats. Danguir J. **Brain Res** 1986 Mar 5; 367(1-2):26-30

Modifications in the cortical regional distribution of choline acetyltransferase, somatostatin and somatostatin binding sites in the normal rat and following lesion of the nucleus basalis. Epelbaum J, et al. **Brain Res** 1986 Apr 23;371(2):376-9

Neuropeptide Y-immunoreactive neurons in the striatum of cat and monkey: morphological characteristics, intrinsic organization and co-localization with somatostatin. Smith Y, et al. **Brain Res** 1986 May 7;372(2):241-52

Characterization of forms of immunoreactive somatostatin in sensory neuron and normal and deafferented spinal cord. Tessler A, et al. **Brain Res** 1986 Apr 9;370(2):232-40

Dopamine stimulates rat cortical somatostatin release. Thal LJ, et al. **Brain Res** 1986 May 7;372(2):205-9

Effect of hypophysectomy on somatostatin-14 and somatostatin-28 biosynthesis in the rat hypothalamus. Wetsel WC, et al. **Brain Res** 1986 Apr 9;370(2):315-20

Cysteamine effects on somatostatin, catecholamines, pineal NAT and melatonin in rats. Webb SM, et al. **Brain Res Bull** 1986 Mar; 16(3):315-20

Ultrastructural characterization of neurosecretory fibres immunoreactive for vasotocin, isotocin, somatostatin, LHRH and CRF in the pituitary of a teleost fish, Poecilia latipinna. Batten TF. **Cell Tissue Res** 1986; 244(3):661-72

Effect of somatostatin on amylase secretion from in vivo and in vitro rat pancreas. Singh M. **Dig Dis Sci** 1986 May;31(5):506-12

Growth hormone release: interaction of increased extracellular calcium and somatostatin. Stachura ME. **Endocr Res** 1986;12(1):69-92

The effect of age on somatostatin suppression of basal, growth hormone (GH)-releasing factor-stimulated, and dibutyryl adenosine 3',5'-monophosphate-stimulated GH release from rat pituitary cells in monolayer culture. Cuttler L, et al. **Endocrinology** 1986 Jul; 119(1):152-8

Inhibition of rat hypothalamic somatostatin release by somatostatin: evidence for somatostatin ultrashort loop feedback. Richardson SB, et al. **Endocrinology** 1986 May;118(5):2076-82

On the fate of centrally administered somatostatin in the rat: massive hypersomatostatinemia resulting from leakage into the peripheral circulation has effects on growth hormone secretion and glucoregulation. Tannenbaum GS, et al. **Endocrinology** 1986 May; 118(5):2137-43

Calcitonin gene-related peptide stimulates somatostatin release from isolated perfused rat stomach. Yamatani T, et al. **Endocrinology** 1986 May;118(5):2144-5

Effects of somatostatin on dopamine sensitive adenylate cyclase activity in the caudate-putamen of the rat. Moser A, et al. **Exp Brain Res** 1986; 62(3):567-71

Further studies on the inhibitory effects of somatostatin on the growth and steroidogenic capacity of rat adrenal zona glomerulosa. Robba C, et al. **Exp Pathol** 1986;29(2):77-82

Control of rat gastric somatostatin release by gamma-aminobutyric acid (GABA). Koop H, et al. **Horm Metab Res** 1986 Feb;18(2):94-7

VIP and hormone secretion from thyroidal follicular and C-cells. Laurberg P. **Horm Metab Res** 1986 Apr;18(4):230-3

Development of specific and non-specific somatostatin analogs. Nakano T, et al. **Horm Metab Res** 1986 Feb;18(2):98-102

Effect of infusion of salmon calcitonin on the secretion of somatostatin and gastrin in man. Woloszczuk W, et al. **Horm Metab Res** 1986 Mar; 18(3):197-200

Influence of beta-endorphin, somatostatin, substance P and vasoactive intestinal peptide on the proliferative response of human peripheral blood T lymphocytes to mercuric chloride. Nordlind K, et al. **Int Arch Allergy Appl Immunol** 1986;80(3):326-8

An immunohistochemical characterization of somatostatin-28 and somatostatin-281-12 in monkey prefrontal cortex. Lewis DA, et al. **J Comp Neurol** 1986 Jun 1;248(1):1-18

Somatostatin immunoreactive neurons in rat visual cortex: a light and electron microscopic study. Meinecke DL, et al. **J Neurocytol** 1986 Feb;15(1):121-36

Cyclic AMP regulates somatostatin mRNA accumulation in primary diencephalic cultures and in transfected fibroblast cells. Montminy MR, et al. **J Neurosci** 1986 Apr;6(4):1171-6

Effect of chronically administered somatostatin on the nude mouse. Johnson FE, et al. **J Surg Res** 1986 Apr;40(4):346-52

Methods for the identification of neuropeptide processing products: somatostatin and the tachykinins. Harmar AJ, et al. **Methods Enzymol** 1986;124:335-48

Somatostatin release from dissociated cerebral cortical cell cultures. Landon RM, et al. **Methods Enzymol** 1986;124:412-24

Localization of somatostatin receptors. Pelletier G, et al. **Methods Enzymol** 1986;124:607-17

Dopamine and somatostatin inhibit forskolin-stimulated prolactin and growth hormone secretion but not stimulated cyclic AMP levels in sheep anterior pituitary cell cultures. Ray KP, et al. **Mol Cell Endocrinol** 1986 May;45(2-3):175-82

Somatostatin effects on the cyclic AMP system and lipid metabolism in mouse brain. Catalan RE, et al. **Neurochem Res** 1986 Apr; 11(4):497-504

Somatostatin-sensitive neural system in the liver. Nakabayashi H, et al. **Neurosci Lett** 1986 Jun 6;67(1):78-81

Striatal neurons expressing somatostatin-like immunoreactivity: evidence for a peptidergic interneuronal system in the cat. Chesselet MF, et al. **Neuroscience** 1986 Mar;17(3):547-71

Somatostatin-immunoreactive amacrine cells of chicken retina: retinal mosaic, ultrastructural features, and light-driven variations in peptide metabolism. Ishimoto I, et al. **Neuroscience** 1986 Apr;17(4):1217-33

Somatostatin and CCK-8 modulate release of striatal amino acids: role of dopamine receptors. Arnerić SP, et al. **Peptides** 1986 Jan-Feb; 7(1):97-103

Characteristics of [D-Trp8]-somatostatin-sensitive B50 phosphorylation. Dokas LA, et al. **Peptides** 1985 Nov-Dec;6(6):1101-7

Effect of vasoactive intestinal peptide, peptide histidine isoleucine and growth hormone-releasing factor-40 on bombesin-like immunoreactivity, somatostatin and gastrin release from the perfused rat stomach. Schusdziarra V, et al. **Peptides** 1986 Jan-Feb; 7(1):127-33

Molecular forms of somatostatin, substance P and neurotensin in fresh human cerebral cortex. Bateman DE, et al. **Regul Pept** 1986 May; 14(3):211-6

Evidence for somatostatin binding sites in rabbit kidney. Roca B, et al.

Regul Pept 1986 Feb;13(3-4):273-81

Somatostatin increases the ratio between gastric mucosal blood flow and gastric acid and pepsin secretion in dogs. Bech K. **Scand J Gastroenterol** 1986 Mar;21(2):215-20

Effect of haemorrhagic shock and duodenal instillation of blood on the plasma profiles of somatostatin and motilin in pigs. A study of molecular plasma components. Jenssen TG, et al. **Scand J Gastroenterol** 1986 Apr; 21(3):281-90

Evidence of somatostatin as a humoral modulator of motilin release in man. A study of plasma motilin and somatostatin during intravenous infusion of somatostatin, secretin, cholecystokinin, and gastric inhibitory polypeptide. Jenssen TG, et al. **Scand J Gastroenterol** 1986 Apr; 21(3):273-80

[Comparative biochemical effects of the injection of cyclic and linear forms of vertebrate somatostatin on the honeybee in vivo. II. Blood lipids] Bounias M. **C R Soc Biol (Paris)** 1985;179(5):591-9 (Eng. Abstr.) **(Fre)**

[Effect of somatostatin on the rabbit Oddi's sphincter in vivo. Interrelation of somatostatin and cholecystokinin] Adami GF, et al. **Gastroenterol Clin Biol** 1986 Feb;10(2):108-11 (Eng. Abstr.) **(Fre)**

[Role of alpha-adrenoreceptors of the hypothalamus and amygdala in the response of the secretory glands of the stomach to neurotensin and somatostatin] Barashkova GM, et al. **Fiziol Zh SSSR** 1986 Apr; 72(4):498-502 (Eng. Abstr.) **(Rus)**

SOMATOTROPIN RELEASING HORMONE

TRH and GRF stimulate release of growth hormone through different mechanisms. Szabo M. **Am J Physiol** 1986 May;250(5 Pt 1):E512-7

Light and electron microscopic immunocytochemistry of GRF-like immunoreactive neurons and terminals in the rat hypothalamic arcuate nucleus and median eminence. Ibata Y, et al. **Brain Res** 1986 Apr 2; 370(1):136-43

Effects of GRF on paraventricular neurons in slices of guinea-pig hypothalamus. Poulain P, et al. **Brain Res** 1986 Apr 23;371(2):355-9

Effects of neonatal administration of monosodium glutamate on plasma growth hormone (GH) response to GH-releasing factor in adult male and female rats. Wakabayashi I, et al. **Brain Res** 1986 May 7; 372(2):361-5

Does growth hormone releasing factor desensitize the somatotroph? Interpretation of responses of growth hormone during and after 10-hour infusion of GRF 1-29 amide in man. Davis JR, et al. **Clin Endocrinol (Oxf)** 1986 Feb;24(2):135-40

Influence of dopaminergic, adrenergic and cholinergic blockade and TRH administration on GH responses to GRF 1-29. Jordan V, et al. **Clin Endocrinol (Oxf)** 1986 Mar;24(3):291-8

The interaction of growth hormone releasing hormone with other hypothalamic hormones on the release of anterior pituitary hormones. Looij BJ Jr, et al. **Clin Endocrinol (Oxf)** 1986 Feb;24(2):149-56

Desensitization to growth hormone-releasing factor (GRF) is associated with down-regulation of GRF-binding sites. Bilezikjian LM, et al. **Endocrinology** 1986 May;118(5):2045-52

Diminished pituitary responsiveness to growth hormone-releasing factor in aging male rats. Ceda GP, et al. **Endocrinology** 1986 May; 118(5):2109-14

The effect of age on somatostatin suppression of basal, growth hormone (GH)-releasing factor-stimulated, and dibutyryl adenosine 3',5'-monophosphate-stimulated GH release from rat pituitary cells in monolayer culture. Cuttler L, et al. **Endocrinology** 1986 Jul; 119(1):152-8

The effect of glucose and free fatty acids on growth hormone (GH)-releasing factor-mediated GH secretion in rats. Imaki T, et al. **Endocrinology** 1986 Jun;118(6):2390-4

Stimulation by alpha-adrenergic mechanisms of the secretion of growth hormone-releasing factor (GRF) from perifused rat hypothalamus. Kabayama Y, et al. **Endocrinology** 1986 Jul;119(1):432-4

Growth hormone (GH)-releasing factor stimulates hypothalamic somatostatin release: an inhibitory feedback effect on GH secretion. Katakami H, et al. **Endocrinology** 1986 May;118(5):1872-7

Purified chicken growth hormone (GH) and a human pancreatic GH-releasing hormone increase body weight gain in chickens. Leung FC, et al. **Endocrinology** 1986 May;118(5):1961-5

Localization of growth hormone-releasing hormone in the human hypothalamus and pituitary stalk. Werner H, et al. **J Clin Endocrinol Metab** 1986 Jul;63(1):47-50

Growth hormone-releasing factor stimulates milk production and sustains growth hormone release in Holstein cows. Enright WJ, et al. **J Dairy Sci** 1986 Feb;69(2):344-51

Synergistic interaction in bovine pituitary cultures between growth hormone-releasing factor and other hypophysiotrophic factors. Ingram CD, et al. **J Endocrinol** 1986 Apr;109(1):67-74

Stimulation of in-vivo growth hormone secretion in young chickens by rat hypothalamic growth hormone-releasing factor and synthetic analogues. Scanes CG, et al. **J Endocrinol** 1986 Mar;108(3):413-6

Measurement of growth hormone-releasing factor. Frohman LA, et al. **Methods Enzymol** 1986;124:371-89

Assay of growth hormone-releasing factor. Vale W, et al. **Methods Enzymol** 1986;124:389-401

Characteristics of the desensitization of growth hormone and cyclic AMP responses to growth hormone-releasing factor and prostaglandin E2 in rat anterior pituitary cells in culture. Simard J, et al. **Mol Cell Endocrinol** 1986 Jun;46(1):79-89

Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. Ehlers CL, et al. **Neuroendocrinology** 1986;42(6):467-74

Down-regulation of growth hormone releasing factor receptors following continuous infusion of growth hormone releasing factor in vivo. Wehrenberg WB, et al. **Neuroendocrinology** 1986;43(2):266-8

Coexpression of human growth hormone-releasing factor 1-37-like and alpha-melanotropin-like immunoreactivities in neurones of the rat lateral dorsal hypothalamus. Fellmann D, et al. **Neurosci Lett** 1986 Jul 11;68(1):122-6

Effect of vasoactive intestinal peptide, peptide histidine isoleucine and growth hormone-releasing factor-40 on bombesin-like immunoreactivity, somatostatin and gastrin release from the perfused rat stomach. Schusdziarra V, et al. **Peptides** 1986 Jan-Feb; 7(1):127-33

Stepwise evaluation of the short child. With comments on the status of growth hormone therapy. Stelling MW. **Postgrad Med** 1986 May 1; 79(6):185-7, 190-2

Effects of growth hormone-releasing factor in the brain. Wehrenberg WB, et al. **Science** 1986 Jun 6;232(4755):1271-3

[Growth hormone (GH) response to GH-releasing factor in adult female rats treated with monosodium glutamate during the neonatal period] Hatano H. **Nippon Ika Daigaku Zasshi** 1986 Apr;53(2):191-7 (Eng. Abstr.) **(Jpn)**

STARTLE REACTION

Differential effects of dopamine agonists on acoustically and electrically elicited startle responses: comparison to effects of strychnine. Davis M, et al. **Brain Res** 1986 Apr 16;371(1):58-69

STEREOTYPED BEHAVIOR

Effects of acute and chronic carbamazepine administration on apomorphine-elicited stereotypy. Barros HM, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):345-9

The effect of thioridazine on haloperidol induced behavioral hypersensitivity. Klawans HL, et al. **Life Sci** 1986 May 12; 38(19):1707-14

Selective dopamine D2 receptor reduction enhances a D1-mediated oral dyskinesia in rats. Rosengarten H, et al. **Life Sci** 1986 Jul 7; 39(1):29-35

Psychopharmacology of phencyclidine. Marwah J, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:127-33

Amphetamine-induced stereotypic responses in Roman high- and Roman low-avoidance rats. Driscoll P, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1329-32

Evidence that thioridazine enhances amphetamine-induced stereotypy via anticholinergic activity. Robertson A, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1986;10(1):33-40

[Synthesis and pharmacological studies of derivatives of 5- and 7-(O-hydroxyphenyl)-2,3-dihydro-1,4-diazepins] Kostka K, et al. **Acta Pol Pharm** 1985;42(5):442-7 (Eng. Abstr.) **(Pol)**

STRESS, PSYCHOLOGICAL

Effects of 6-hydroxydopamine-induced lesions of the paraventricular nucleus, and of prazosin, on the corticosterone response to restraint in rats. Gibson A, et al. **Neuropharmacology** 1986 Mar;25(3):257-60

Brain histamine regulation following chronic diazepam treatment and stress. Mazurkiewicz-Kwilecki IM, et al. **Pharmacol Biochem Behav** 1986 Mar;24(3):513-7

Prenatal stress: effect on development of rat brain serotonergic neurons. Peters DA. **Pharmacol Biochem Behav** 1986 May;24(5):1377-82

Biochemical and behavioral correlates of chronic stress: effects of tricyclic antidepressants. Soblosky JS, et al. **Pharmacol Biochem Behav** 1986 May; 24(5):1361-8

Norepinephrine alterations under stress conditions following the regular practice of meditation. Morrell EM, et al. **Psychosom Med** 1986 Mar-Apr;48(3-4):270-7

Unemployment stress: loss of control, reactance and learned helplessness. Baum A, et al. **Soc Sci Med** 1986;22(5):509-16

[Physical work capacity under different levels of measured stress in relation to type-A personality in intellectual workers] Mincheva L, et al. **Probl Khig** 1985;10:20-32 (Eng. Abstr.) **(Bul)**

[Histochemical, fluorescent autoradiographic study of paraganglion cells in the superior cervical ganglion of the newborn rat following maternal stress] Heym C, et al. **Acta Histochem [Suppl] (Jena)** 1986;32:59-62 (Eng. Abstr.) **(Ger)**

[Effect of stress-inducing factors on monkey behavior. II. Hormonal indices and their relation to behavior in the modelling of emotional stress in hamadryas baboons] Butovskaia ML, et al. **Biol Nauki** 1986;

(2):59-64 (Eng. Abstr.) **(Rus)**

[Indicators of catecholamine excretion in air traffic controllers] Kuprianov VA, et al. **Gig Tr Prof Zabol** 1986 Feb;(2):53-6 **(Rus)**

[Antistress and antineurotic action of psychotropic preparations in experiments on monkeys] Startsev VG, et al. **Vestn Akad Med Nauk SSSR** 1986;(3):30-3 (Eng. Abstr.) **(Rus)**

SUBSTANCE P

Design and synthesis of antagonists of substance P. Folkers K, et al. **Acta Chem Scand [B]** 1986 Apr;40(4):295-302

Antidromic nerve stimulation accelerates mucociliary activity in rabbit maxillary sinus. Lindberg S, et al. **Acta Otolaryngol (Stockh)** 1986 May-Jun;101(5-6):484-93

The effect of compound 48/80, substance P and pentagastrin on the isolated guinea pig atrium. Stanovnik L, et al. **Agents Actions** 1986 Apr, 18(1-2):197-200

Characterization of substance P effects on canine antral muscle. Mayer EA, et al. **Am J Physiol** 1986 Jul,251(1 Pt 1):G140-6

Substance P and neurotensin: their roles in the regulation of anterior pituitary function. Aronin N, et al. **Annu Rev Physiol** 1986; 48:537-49 (57 ref.)

A substance P antagonist also inhibits specific binding and mitogenic effects of vasopressin and bombesin-related peptides in Swiss 3T3 cells. Zachary I, et al. **Biochem Biophys Res Commun** 1986 May 29; 137(1):135-41

Immunocytochemical evidence for synaptic regulation of paraventricular vasopressin-containing neurons by substance P. Heike Y, et al. **Brain Res** 1986 Mar 26;369(1-2):341-6

Pharmacological characterization of the receptor mediating the adrenergic inhibition of responses to substance P in the cingulate cortex. Jones RS, et al. **Brain Res** 1986 Mar 5;367(1-2):151-61

Innervation of substance P neurons by catecholaminergic terminals in the neostriatum. Kubota Y, et al. **Brain Res** 1986 Jun 4;375(1):163-7

The localization and characterization of substance P and substance K in striatonigral neurons. Lee JM, et al. **Brain Res** 1986 Apr 16; 371(1):152-4

Colocalization of immunoreactive substance P and neurotensin in amacrine cells of the goldfish retina. Li HB, et al. **Brain Res** 1986 Feb 26;366(1-2):307-13

Immunoelectron microscopic study of substance P-containing fibers in feline cerebral arteries. Liu-Chen LY, et al. **Brain Res** 1986 Mar 26; 369(1-2):12-20

A substance P-containing hypothalamic neuronal system projects to the median eminence. Makara GB, et al. **Brain Res** 1986 May 28; 374(2):399-401

Two distinct calcitonin gene-related peptide-containing peripheral nervous systems: distribution and quantitative differences between the iris and cerebral artery with special reference to substance P. Matsuyama T, et al. **Brain Res** 1986 May 14;373(1-2):205-12

The co-occurrence of substance P-like immunoreactivity and dynorphin-like immunoreactivity in striatopallidal and striatonigral projection neurons in birds and reptiles. Reiner A. **Brain Res** 1986 Apr 16;371(1):155-61

Increased density of substance P binding sites in specific brainstem nuclei of spontaneously hypertensive rats. Shigematsu K, et al. **Brain Res** 1986 Apr 9;370(2):383-7

Distribution of substance K (neurokinin A) in the brain and peripheral tissues of rats. Takano Y, et al. **Brain Res** 1986 Mar 26; 369(1-2):400-4

Origins and distribution of calcitonin gene-related peptide-containing nerves in the wall of the cerebral arteries of the guinea pig with special reference to the coexistence with substance P. Wanaka A, et al. **Brain Res** 1986 Mar 26;369(1-2):185-92

Characterization of substance P-induced bronchoconstriction in the guinea-pig: a comparison with acetylcholine. Stewart AG, et al. **Clin Exp Pharmacol Physiol** 1986 Mar;13(3):223-32

Immunochemical evidence for substance P-like peptide in tissues of the earthworm Lumbricus terrestris: action on intestinal contraction. Kaloustian KV, et al. **Comp Biochem Physiol [C]** 1986;83(2):329-33

Substance P-induced intestinal secretion of water and electrolytes. McFadden D, et al. **Gut** 1986 Mar;27(3):267-72

Three dimensional observation of the nerve fibers along the cerebral blood vessels. Itakura T, et al. **Histochemistry** 1986;84(3):217-20

Influence of beta-endorphin, somatostatin, substance P and vasoactive intestinal peptide on the proliferative response of human peripheral blood T lymphocytes to mercuric chloride. Nordlind K, et al. **Int Arch Allergy Appl Immunol** 1986;80(3):326-8

The effects of intrathecal administration of arginine-vasopressin and substance P on blood pressure and adrenal secretion of epinephrine in rats. Riphagen CL, et al. **J Auton Nerv Syst** 1986 Jun;16(2):91-9

Dopamine antagonist haloperidol decreases substance P, substance K, and preprotachykinin mRNAs in rat striatonigral neurons. Bannon MJ, et al. **J Biol Chem** 1986 May 25;261(15):6640-2

Immunohistochemical distribution of substance P, serotonin, and methionine enkephalin in sexually dimorphic nuclei of the rat lumbar spinal cord. Micevych PE, et al. **J Comp Neurol** 1986 Jun 8; 248(2):235-44

Inter- and intracellular relationship of substance P-containing neurons with serotonin and GABA in the dorsal raphe nucleus: combination of autoradiographic and immunocytochemical techniques. Mâgoul R, et al. **J Histochem Cytochem** 1986 Jun;34(6):735-42

Substance P: binding properties and studies on cellular responses in guinea pig macrophages. Hartung HP, et al. **J Immunol** 1986 May 15; 136(10):3856-63

Effects of hypoxia on neuropeptide levels in the rabbit superior cervical ganglion. Hanson G, et al. **J Neurobiol** 1986 Jan;17(1):51-4

Regional distribution of immunoreactive-thyrotrophin-releasing hormone and substance P, and indoleamines in human spinal cord. Bennett GW, et al. **J Neurochem** 1986 Jun;46(6):1718-24

Activation of micturition reflex by substance P and substance K: indirect evidence for the existence of multiple tachykinin receptors in the rat urinary bladder. Maggi CA, et al. **J Pharmacol Exp Ther** 1986 Jul; 238(1):259-66

Motor effect of neurokinins on the rat duodenum: evidence for the involvement of substance K and substance P receptors. Maggi CA, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):341-51

Characterization of substance P-induced contractions of guinea-pig trachea. Malo PE, et al. **J Pharmacol Exp Ther** 1986 Jun; 237(3):782-6

Methods for the identification of neuropeptide processing products: somatostatin and the tachykinins. Harmar AJ, et al. **Methods Enzymol** 1986;124:335-48

Neuroleptic treatment induces region-specific changes in levels of neurokinin A and substance P in rat brain. Lindefors N, et al. **Neuropeptides** 1986 Apr;7(3):265-80

Coexistence of serotonin- and substance P-like immunoreactivity in nerve fibers apposing identified sympathoadrenal preganglionic neurons in rat intermediolateral cell column. Appel NM, et al. **Neurosci Lett** 1986 Apr 24;65(3):241-6

Neurogenic inflammation caused by wool fabric in the rat; possible mediation by substance P. Helme RD, et al. **Neurosci Lett** 1986 May 23;66(3):333-7

Substance P-immunoreactive neurons in the neocortex of the rat: a subset of the glutamic acid decarboxylase-immunoreactive neurons. Penny GR, et al. **Neurosci Lett** 1986 Mar 28;65(1):53-9

The effects of substance P on neuromuscular transmission in the frog. Akasu T. **Neurosci Res** 1986 May;3(4):275-84

Axonal transport of substance P-hydrolyzing peptidase in rat sciatic nerves. Kato T, et al. **Neurosci Res** 1986 Feb;3(3):247-52

Search for a physiological role of substance P in gastrointestinal motility. Barthó L, et al. **Neuroscience** 1985 Sep;16(1):1-32 (367 ref.)

Substance P in the human brain. Mai JK, et al. **Neuroscience** 1986 Mar; 17(3):709-39

The glutamate decarboxylase-, leucine enkephalin-, methionine enkephalin- and substance P-immunoreactive neurons in the neostriatum of the rat and cat: evidence for partial population overlap. Penny GR, et al. **Neuroscience** 1986 Apr;17(4):1011-45

Nasal absorption of substance P in rats. Karasek E, et al. **Pharmazie** 1986 Apr;41(4):289-90

Isolated plasma membranes regulate neurotransmitter expression and facilitate effects of a soluble brain cholinergic factor. Kessler JA, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3528-32

Molecular forms of somatostatin, substance P and neurotensin in fresh human cerebral cortex. Bateman DE, et al. **Regul Pept** 1986 May; 14(3):211-6

Substance P distribution and effects in the canine epicardial coronary arteries. Brum JM, et al. **Regul Pept** 1986 Mar;14(1):41-55

Catabolism of substance P and neurotensin in the rat stomach wall is susceptible to inhibitors of angiotensin converting enzyme. Orloff MS, et al. **Regul Pept** 1986 Mar;14(1):21-31

Ontogeny of substance P in the digestive tract, spinal cord and hypothalamus of the human fetus. Paulin C, et al. **Regul Pept** 1986 Apr; 14(2):145-53

Does liver-intestine significantly degrade circulating endogenous substance P in man? Henriksen JH, et al. **Scand J Gastroenterol** 1986 Apr;21(3):300-4

Flushing and plasma substance P concentration during infusion of synthetic substance P in normal man. Schaffalitzky De Muckadell OB, et al. **Scand J Gastroenterol** 1986 May;21(4):498-502

SUCKING BEHAVIOR

Conditioned aversions and their memories in 5-day-old rats during suckling. Kehoe P, et al. **J Exp Psychol [Anim Behav]** 1986 Jan; 12(1):40-7

SYMPATHOMIMETICS

Enhanced adrenergic constriction of iliac artery with removal of endothelium in conscious dogs. Young MA, et al. **Am J Physiol** 1986 May;250(5 Pt 2):H892-7

The effect of sympathomimetic drugs on bone capillaries. Döhler JR, et al. **Arch Orthop Trauma Surg** 1986;105(1):62-5

Sympathomimetic protein secretion by young and aged lacrimal gland. Bromberg BB, et al. **Curr Eye Res** 1986 Mar;5(3):217-23

Episodic patterns of luteinizing hormone and follicle-stimulating hormone release: differential secretory dynamics and adrenergic control in ovariectomized rats. Condon TP, et al. **Endocrinology** 1986 Jun; 118(6):2525-33

The role of co-transported sodium in the effect of indirectly acting sympathomimetic amines. Bönisch H. **Naunyn Schmiedebergs Arch Pharmacol** 1986 Feb;332(2):135-41

[Effect of the phospholipid composition of liposomes on the rate of release of adrenomimetics contained in them] Sazonova LIa, et al. **Fiziol Zh** 1986 May-Jun;32(3):322-7 (Eng. Abstr.) **(Rus)**

SYNAPTIC RECEPTORS

Separate purinoceptors mediate enhancement by adenosine of concanavalin A-induced mediator release and the cyclic AMP response in rat mast cells. Hughes PJ, et al. **Agents Actions** 1986 Apr; 18(1-2):81-4

Interactions of drugs and electroshock treatment on cerebral monoaminergic systems. Barkai AI. **Ann NY Acad Sci** 1986; 462:147-62

The biochemistry of electroconvulsive therapy. Discussion of Part III. Decina P. **Ann NY Acad Sci** 1986;462:172-3

Neurotransmitter receptor mapping by autoradiography and other methods. Kuhar MJ, et al. **Annu Rev Neurosci** 1986;9:27-59

N-methyl D-aspartate acts as an antagonist of the photoreceptor transmitter in the carp retina. Ariel M, et al. **Brain Res** 1986 Apr 30; 372(1):143-8

Increased density of substance P binding sites in specific brainstem nuclei of spontaneously hypertensive rats. Shigematsu K, et al. **Brain Res** 1986 Apr 9;370(2):383-7

Neurotransmitter receptor binding studies predict antiemetic efficacy and side effects. Ison PJ, et al. **Cancer Treat Rep** 1986 May;70(5):637-41

Cultured neurons as model systems for biochemical and pharmacological studies on receptors for neurotransmitter amino acids. Schousboe A, et al. **Dev Neurosci** 1985;7(5-6):252-62 (56 ref.)

[3H]imipramine displacement and 5HT uptake inhibition by tryptoline derivatives: in rat brain 5-methoxytryptoline is not the autacoid for [3H]imipramine recognition sites. Barbaccia ML, et al. **Eur J Pharmacol** 1986 Apr 9;123(1):45-52

Radioligand binding to central phencyclidine recognition sites is dependent on excitatory amino acid receptor agonists. Loo P, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):467-8

High correlation between the localization of [3H]TCP binding and NMDA receptors. Maragos WF, et al. **Eur J Pharmacol** 1986 Apr 9; 123(1):173-4

Differential effects of antidepressant drugs on [3H]dihydroalprenolol and [3H]imipramine ligand recognition sites in olfactory bulbectomized and sham-lesioned rats. Jesberger JA, et al. **Gen Pharmacol** 1986; 17(3):293-307

Substance P: binding properties and studies on cellular responses in guinea pig macrophages. Hartung HP, et al. **J Immunol** 1986 May 15; 136(10):3856-63

Activation of micturition reflex by substance P and substance K: indirect evidence for the existence of multiple tachykinin receptors in the rat urinary bladder. Maggi CA, et al. **J Pharmacol Exp Ther** 1986 Jul; 238(1):259-66

Motor effect of neurokinins on the rat duodenum: evidence for the involvement of substance K and substance P receptors. Maggi CA, et al. **J Pharmacol Exp Ther** 1986 Jul;238(1):341-51

Isolation and identification of an endogenous ligand for the phencyclidine receptor. DiMaggio DA, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986;64:24-36

Characterization of phencyclidine and sigma receptor-binding sites in brain. Gundlach AL, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:1-13

Further evidence of phencyclidine/sigma opioid receptor commonality. Sircar R, et al. **Natl Inst Drug Abuse Res Monogr Ser** 1986; 64:14-23

Chronic iminodipropionitrile (IDPN) causes no changes in the rat brain phencyclidine (PCP) receptor. Rothman RB, et al. **Neuropeptides** 1986 Apr;7(3):259-63

Dihydroergocristine-induced stimulation of the 5-HT autoreceptor in the hypothalamus of the rat. Moret C, et al. **Neuropharmacology** 1986 Feb; 25(2):169-74

Covalent labeling of neurotensin receptors in rat gastric fundus plasma membranes. Mazella J, et al. **Peptides** 1985 Nov-Dec;6(6):1137-41

Human serum Cohn fraction IV (alpha-globin enriched) inhibits ligand binding at neurotransmitter receptors in human brain. Andorn AC, et al. **Proc Natl Acad Sci USA** 1986 Jun;83(12):4572-5

[Binding of tritiated imipramine to human platelets. 1 or several binding sites?] Scotto di Tella AM, et al. **Encephale** 1986 Jan-Feb;12(1):13-7 (Eng. Abstr.) **(Fre)**

[Pharmacological analysis of the serotonin- and glutamatergic mechanisms in the suppressive effect of neuroleptics on the pedal self-stimulation of the ventral tectum of the midbrain] Talalaenko AN, et al. **Farmakol Toksikol** 1986 May-Jun;49(3):40-3 (Eng. Abstr.) **(Rus)**

TESTOSTERONE

Dissociation of the effects of castration and testosterone replacement on sexual behavior and neural metabolism of dopamine in the male rat. Baum MJ, et al. **Brain Res Bull** 1986 Feb;16(2):145-8

Brain 5-hydroxytryptamine and plasma testosterone in L-tryptophan treated rats. Biswas NM, et al. **Endocr Res** 1985;11(3-4):131-7

Evidence for activation of the central nervous system-pituitary mechanism for gonadotropin secretion at the time of puberty in the male rat. Matsumoto AM, et al. **Endocrinology** 1986 Jul;119(1):362-9

Regulation of beta-endorphin, corticotropin-like intermediate lobe peptide, and alpha-melanotropin-stimulating hormone in the hypothalamus by testosterone. Wardlaw SL. **Endocrinology** 1986 Jul; 119(1):19-24

The effect of neuroleptic drugs on serum testosterone level in the male rat. Okonmah AD, et al. **Gen Pharmacol** 1986;17(2):235-8

The influence of social cues on the reproductive endocrinology of male brown-headed cowbirds: field and laboratory studies. Dufty AM Jr, et al. **Horm Behav** 1986 Jun;20(2):222-34

Single subcutaneous doses of a luteinizing hormone-releasing hormone antagonist suppress serum gonadotropin and testosterone levels in normal men. Pavlou SN, et al. **J Clin Endocrinol Metab** 1986 Aug; 63(2):303-8

Effect of long-term infusion of an LH-releasing hormone agonist on testicular function in bulls. von Rechenberg W, et al. **J Endocrinol** 1986 May;109(2):R9-11

Testosterone metabolites do not participate in the control of hypothalamic LH-releasing hormone. Zanisi M, et al. **J Endocrinol** 1986 May; 109(2):291-6

Influence of subcutaneous melatonin implantation on gonadal development and on plasma levels of luteinizing hormone, testosterone, estradiol, and corticosterone in the pigeon. John TM, et al. **J Pineal Res** 1986;3(2):169-79

Absence of LHRH effect on testosterone production by Leydig cells from fetal mouse testis. Pointis G, et al. **J Steroid Biochem** 1986 Jan; 24(1):307-10

Effects of dopaminergic drugs on plasma levels of steroid hormones in conscious dogs. Goiny M, et al. **Life Sci** 1986 Jun 23; 38(25):2293-300

Modulation and role of Ca2+ in LH and LHRH agonist action in rat Leydig cells. Cooke BA, et al. **Med Biol** 1986;63(5-6):259-63

The different mechanisms for suppression of pituitary and testicular function. Sandow J, et al. **Med Biol** 1986;63(5-6):192-200

Interactions of testosterone and short-photoperiod exposure on the neuroendocrine axis of the male Syrian hamster. Steger RW, et al. **Neuroendocrinology** 1986;43(1):69-74

Testosterone removal in rats results in a decrease in social aggression and a loss of social dominance. Albert DJ, et al. **Physiol Behav** 1986; 36(3):401-7

The arachidonic acid cascade is involved in the masculinizing action of testosterone on embryonic external genitalia in mice. Gupta C, et al. **Proc Natl Acad Sci USA** 1986 Jun;83(12):4346-9

[Effect of tyrosine on serum concentrations of LH, FSH and testosterone in adult men] Ni J, et al. **Sheng Li Hsueh Pao** 1985 Jun;37(3):303-6 (Eng. Abstr.) **(Chi)**

[Changes in testosterone levels in rabbit embryo testes after removal of the hypothalamus (encephalectomy)] Proshliakova EV, et al. **Biull Eksp Biol Med** 1986 May;101(5):616-9 (Eng. Abstr.) **(Rus)**

[Brain monoamines and the hypophyseo-gonadal system of adult rats after the androgenization of their mothers during pregnancy] Naumenko EV, et al. **Ontogenez** 1986 May-Jun;17(3):285-92 (Eng. Abstr.) **(Rus)**

THERAPEUTIC EQUIVALENCY

Branded or generic propranolol? [letter] Garcia-Buñuel L. **Lancet** 1986 Jun 21;1(8495):1443

THIOPROPERAZINE

[Changes in plasma prolactin and magnesium in male rats treated with thioproperazine and/or bromocriptine] Marois G, et al. **Ann Endocrinol (Paris)** 1985;46(6):399-405 (Eng. Abstr.) **(Fre)**

THIORIDAZINE

Dissolution of thioridazine hydrochloride from the coprecipitate with pectin. Takahashi Y, et al. **Chem Pharm Bull (Tokyo)** 1986 Jan; 34(1):327-32

Comment: Thioridazine bioequivalence [letter] Meyer HM Jr. **Drug Intell Clin Pharm** 1986 Apr;20(4):311-2

Mesoridazine and thioridazine: clinical effects and blood levels in refractory schizophrenics. Vital-Herne J, et al. **J Clin Psychiatry** 1986 Jul;47(7):375-9

Behavioral changes following generic thioridazine [letter] Weber SS, et al. **J Clin Psychiatry** 1986 May;47(5):277-8

The effect of thioridazine on haloperidol induced behavioral hypersensitivity. Klawans HL, et al. **Life Sci** 1986 May 12; 38(19):1707–14

Evidence that thioridazine enhances amphetamine–induced stereotypy via anticholinergic activity. Robertson A, et al. **Prog Neuropsychopharmacol Biol Psychiatry** 1986;10(1):33–40

Concentrations of thioridazine and thioridazine metabolites in erythrocytes. Svensson C, et al. **Psychopharmacology (Berlin)** 1986; 89(3):291–2

[Changes in the wave composition of evoked potentials during treatment of endogenous depression] Loginov VV, et al. **Zh Nevropatol Psikhiatr** 1986;86(3):431–5 (Eng. Abstr.) **(Rus)**

THIOTHIXENE

Borderline and schizotypal personality disorders treated with low–dose thiothixene vs placebo. Goldberg SC, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):680–6

THIRST

Unilateral substantia nigra lesions and schedule–induced polydipsia. Mittleman G, et al. **Physiol Behav** 1986;36(3):437–40

THYROID HORMONES

Seasonal changes in the plasma concentration of sexual steroids, corticosterone and thyroid hormone in the hen with special respect to the moulting period. Szelényi Z, et al. **Acta Vet Hung** 1985; 33(3–4):189–98

Adrenal phenylethanolamine–N–methyltransferase activity in the young rat: influence of thyroid hormones and insulin–induced hypoglycemia. Gripois D, et al. **Biol Neonate** 1986;49(4):219–23

Influence of thyroid hormones on rat cerebellar cell aggregation and survival in culture. Sarafian T, et al. **Brain Res** 1986 May; 391(2):261–70

Thyroid neuroendocrinology: neural regulation of thyroid hormone secretion. Ahrén B. **Endocr Rev** 1986 May;7(2):149–55 (88 ref.)

Epidermal growth factor: effect on circulating thyroid hormone levels in sheep. Corcoran JM, et al. **Endocrinology** 1986 Jul;119(1):214–7

Regulation of thyrotropin (TSH) bioactivity by TSH–releasing hormone and thyroid hormone. Menezes–Ferreira MM, et al. **Endocrinology** 1986 May;118(5):2125–30

VIP and hormone secretion from thyroidal follicular and C–cells. Laurberg P. **Horm Metab Res** 1986 Apr;18(4):230–3

In vitro effects of thyroid hormones on red blood cell Ca++–dependent ATPase activity. Costante G, et al. **J Endocrinol Invest** 1986 Feb; 9(1):15–20

Serum thyrotropin by ultrasensitive immunoradiometric assay and serum free thyroid hormones in pregnancy. Pacchiarotti A, et al. **J Endocrinol Invest** 1986 Apr;9(2):185–9

[Evaluation of thyroid function (letter)] Arlet P. **Rev Med Interne** 1986 Jan;7(1):92 **(Fre)**

[Comparative histologic and hormonal studies of the thyroid gland with special reference to sudden infant death (SIDS)] Risse M, et al. **Z Rechtsmed** 1986;96(1):31–8 (Eng. Abstr.) **(Ger)**

[Hormonal and lipid changes in patients with chronic renal insufficiency in hemodialysis (letter)] Simó R, et al. **Med Clin (Barc)** 1986 Apr 5; 86(13):566–7 **(Spa)**

THYROTROPIN

Postnatal development of brain TRH, serum TSH and thyroid hormones in the male and female rat. Gayo L, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):7–11

Human foetal prolactin but not thyrotropin secretion is decreased by bromocriptine. Roti E, et al. **Acta Endocrinol (Copenh)** 1986 May; 112(1):35–42

Characterization of the pituitary response in the TRH test by kinetic modeling. Swartz CM, et al. **Acta Endocrinol (Copenh)** 1986 May; 112(1):43–8

Can neonatal treatment with a related hormone adapt the receptor for itself? Csaba G, et al. **Acta Physiol Hung** 1986;67(1):65–9

Regulation of thyrotropin (TSH) bioactivity by TSH–releasing hormone and thyroid hormone. Menezes–Ferreira MM, et al. **Endocrinology** 1986 May;118(5):2125–30

The effects of anterior hypothalamic deafferentation on thyrotropin (TSH) biosynthesis and response to TSH–releasing hormone. Taylor T, et al. **Endocrinology** 1986 Jun;118(6):2417–24

Thyrotropin and norepinephrine stimulate the metabolism of phosphoinositides in FRTL–5 thyroid cells. Philp NJ, et al. **FEBS Lett** 1986 Jul 7;202(2):193–6

The anti–oestrogen tamoxifen does not interfere with the dopaminergic control of prolactin and TSH release in normogonadotrophic oligozoospermic man. van Bergeijk L, et al. **Horm Metab Res** 1986 Apr;18(4):272–6

Thyrotrophin–releasing hormone does not accumulate glycosylated thyrotrophin, but changes heterogeneous forms of thyrotrophin within the rat anterior pituitary gland. Mori M, et al. **J Endocrinol** 1986 May; 109(2):227–31

Serum thyrotropin by ultrasensitive immunoradiometric assay and serum free thyroid hormones in pregnancy. Pacchiarotti A, et al. **J Endocrinol Invest** 1986 Apr;9(2):185–9

Age–related differences in the pituitary prolactin response to thyrotropin–releasing hormone. Arnetz BB, et al. **Life Sci** 1986 Jul 14; 39(2):135–9

THYROXINE

Postnatal development of brain TRH, serum TSH and thyroid hormones in the male and female rat. Gayo L, et al. **Acta Endocrinol (Copenh)** 1986 May;112(1):7–11

Hormones in perinatal rat and spiny mouse: relation to altricial and precocial timing of birth. Lamers WH, et al. **Am J Physiol** 1986 Jul; 251(1 Pt 1):E78–85

Role of thyroxine in functional gastric development. Tseng CC, et al. **Am J Physiol** 1986 Jul;251(1 Pt 1):G111–6

L–thyroxine, cortisol, and diet affect the postnatal development of the facial part of the skull in developing rats. Maeda N, et al. **Anat Anz** 1986;161(2):99–104

Effect on wool growth of thyroxine replacement in thyroidectomized merino rams. Maddocks S, et al. **Aust J Biol Sci** 1985;38(4):405–10

Thyroxine treatment reduces the anorectic effect of estradiol in rats. Young JK. **Behav Neurosci** 1986 Apr;100(2):284–7

Thyroxine increases neonatal mouse submandibular gland mRNA–directed synthesis of epidermal growth factor. Walker P. **Biochem Cell Biol** 1986 Apr;64(4):290–6

Studies on L–arginase in developing rat small intestine, brain, and kidney. II. Effect of hydrocortisone and thyroxine. Konarska L, et al. **Biochem Med Metab Biol** 1986 Apr;35(2):170–8

More on the Amerlex kit analog method for thyroxin. Ekins RP, et al. **Clin Chem** 1986 Jun;32(6):1243–6

One–step immunoassays for free (unbound) hormones: the effects of tracer binding by serum proteins [letter] Wilkins TA. **Clin Chem** 1986 Jun; 32(6):1238–9

Is the dilution experiment a valid technique for assessing the validity of free thyroxin assay? [letter] Wilkins TA. **Clin Chem** 1986 Jun; 32(6):1241

Familial dysalbuminaemic hyperthyroxinaemia: studies of albumin binding and implications for hormone action. Barlow JW, et al. **Clin Endocrinol (Oxf)** 1986 Jan;24(1):39–47

Cholecystographic agents and sulfobromophthalein inhibit the binding of L–thyroxine to plasma membranes of rat hepatocytes. Felicetta JV, et al. **Endocrinology** 1986 Jun;118(6):2500–4

In vivo formation of diiodotyrosine by extrathyroidal thyroxine ether–link cleavage and effects of mononitrotyrosine on this pathway in the rat. Meinhold H, et al. **Endocrinology** 1986 Jun;118(6):2305–11

Effect of different beta–blocking drugs and adrenaline on the conversion of thyroxine to triiodothyronine in isolated rat hepatocytes. Aanderud S, et al. **Horm Metab Res** 1986 Feb;18(2):110–3

Serum concentrations of prolactin, thyroxine and triiodothyronine relative to season and the estrous cycle in the mare. Johnson AL. **J Anim Sci** 1986 Apr;62(4):1012–20

The effect of environmental temperature on concentrations of thyroxine and triiodothyronine after thyrotropin releasing hormone in steers. Pratt BR, et al. **J Anim Sci** 1986 May;62(5):1346–52

Seasonal changes in concentrations of plasma hormones in the male ring dove (Streptopelia risoria). Lea RW, et al. **J Endocrinol** 1986 Mar; 108(3):385–91

Control of the development of the ipsilateral retinothalamic projection in Xenopus laevis by thyroxine: results and speculation. Hoskins SG. **J Neurobiol** 1986 May;17(3):203–29 (125 ref.)

Growth hormone treatment and circulating thyroxine [letter] Gómez–Pan A, et al. **Lancet** 1986 May 3;1(8488):1030–1

Involvement of developing sympathetic nervous system in thyroxine–mediated submandibular gland nerve growth factor and epidermal growth factor responses. Lakshmanan J, et al. **Pediatr Res** 1986 Mar;20(3):232–6

Thyroxine increases submandibular gland nerve growth factor and epidermal growth factor concentrations precociously in neonatal mice: evidence for thyroid hormone–mediated growth factor synthesis. Walker P. **Pediatr Res** 1986 Apr;20(4):281–4

Indomethacin inhibits thrombin–, but not thyroxin–stimulated resorption of fetal rat limb bones. Hoffmann O, et al. **Prostaglandins** 1986 Apr; 31(4):601–8

The effect of salivary glands extirpation, duct ligation, and thyroxine administration on body weight in rats. D'Antonio GM, et al. **Rev Odontol UNESP** 1984;13(1–2):99–104

[Effect of thyroid hormones on the nuclear–cytoplasmic transport of RNA] Adylova AT, et al. **Probl Endokrinol (Mosk)** 1986 Mar–Apr; 32(2):74–6 (Eng. Abstr.) **(Rus)**

[Effect of thyroxine on the hemoglobin affinity to oxygen and 2,3–diphosphoglycerate level in rat erythrocytes] Sukhomlinov BF, et al. **Ukr Biokhim Zh** 1986 Mar–Apr;58(2):84–6 (Eng. Abstr.) **(Rus)**

TRANQUILIZING AGENTS

Changes in popular attitudes and beliefs about tranquilizers. 1970–1979. Clinthorne JK, et al. **Arch Gen Psychiatry** 1986 Jun;43(6):527–32

Is there a trend away from tranquillizing women? Bass MJ, et al. **Can J Public Health** 1986 Mar–Apr;77(2):119–22

A comparative trial of depot pipothiazine. Steinert J, et al. **J Int Med Res** 1986;14(2):72–7

[Synthesis and pharmacological studies of derivatives of 5- and 7–(O–hydroxyphenyl)–2,3–dihydro–1,4–diazepins] Kostka K, et al. **Acta Pol Pharm** 1985;42(5):442–7 (Eng. Abstr.) **(Pol)**

TRANQUILIZING AGENTS, MAJOR

Open multicentre trial of zuclopenthixol in mania and schizophrenia based on the AMDP scales. Bobon D, et al. **Acta Psychiatr Belg** 1986 Mar–Apr;86(2):152–76

The spectrum concept of neuroleptic toxicity [letter] Conlon P. **Am J Psychiatry** 1986 Jun;143(6):811

Safety of the combination of lithium and neuroleptic drugs. Goldney RD, et al. **Am J Psychiatry** 1986 Jul;143(7):882–4

Pharmacotherapy for patients with borderline personality disorder. Gunderson JG. **Arch Gen Psychiatry** 1986 Jul;43(7):698–700

Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia. I. One–year effects of a controlled study on relapse and expressed emotion. Hogarty GE, et al. **Arch Gen Psychiatry** 1986 Jul;43(7):633–42

Within–session data [letter] Lynch MR, et al. **Biol Psychiatry** 1986 May 21(5–6):573–4

EEG asymmetry in schizophrenic patients before and during neuroleptic treatment. Merrin EL, et al. **Biol Psychiatry** 1986 May; 21(5–6):455–64

A comparison of the binding of sigma opioids and phencyclidine, and the interaction with antipsychotic drugs in rat brain membranes. Downes CP, et al. **Br J Pharmacol** 1986 May;88(1):231–7

A randomised controlled trial of prophylactic neuroleptic treatment. Crow TJ, et al. **Br J Psychiatry** 1986 Feb;148:120–7

Short–term outcome in trial entrants and trial eligible patients. MacMillan JF, et al. **Br J Psychiatry** 1986 Feb;148:128–33

Typical and atypical antipsychotic occupancy of D2 and S2 receptors: an autoradiographic analysis in rat brain. Altar CA, et al. **Brain Res Bull** 1986 Apr;16(4):517–25

Variation in the ability of neuroleptics to block the inhibitory influence of dopaminergic neurons on the activity of cells in the rat prefrontal cortex. Thierry AM, et al. **Brain Res Bull** 1986 Feb;16(2):155–60

Neuroleptic blood levels and clinical response. Rockland LH. **Can J Psychiatry** 1986 May;31(4):299–303

Early neuroleptic response in psychotic men and women: correlation with plasma HVA and MHPG. Bowers MB Jr, et al. **Compr Psychiatry** 1986 May–Jun;27(3):181–5

Characterization of the hepatic prolactin receptors induced by chronic iron deficiency and neuroleptics. Barkey RJ, et al. **Eur J Pharmacol** 1986 Mar 18;122(2):259–67

Decreased peripheral benzodiazepine binding sites in platelets of neuroleptic–treated schizophrenics. Gavish M, et al. **Eur J Pharmacol** 1986 Feb 18;121(2):275–9

Neuroleptic drugs and 5HT1 receptor: different potencies of various neuroleptic drugs on 5HT1 receptors in discrete regions of the rat brain. Harada T, et al. **Folia Psychiatr Neurol Jpn** 1985;39(4):551–7

The effect of neuroleptic drugs on serum testosterone level in the male rat. Okonmah AD, et al. **Gen Pharmacol** 1986;17(2):235–8

Patients' competency to give informed consent to medication. Beck JC, et al. **Hosp Community Psychiatry** 1986 Apr;37(4):400–2

Determination of piquindone in canine plasma and urine by high–performance liquid chromatography. Brooks MA, et al. **J Chromatogr** 1986 Mar 7;375(2):349–57

Low dose therapy: the future of neuroleptic psychopharmacology. A symposium held during the annual meeting of the American Psychiatric Association. May 1986, Washington, D.C. **J Clin Psychiatry** 1986 May; 47 Suppl:1–36

'Antipsychotic' or 'neuroleptic' [letter] Burton HB. **J Clin Psychiatry** 1986 Jul;47(7):392

Early, targeted pharmacotherapeutic intervention in schizophrenia. Carpenter W Jr. **J Clin Psychiatry** 1986 May;47 Suppl:23–9 (48 ref.)

Depot neuroleptics: a comparative review of standard, intermediate, and low–dose regimens. Kane JM, et al. **J Clin Psychiatry** 1986 May; 47 Suppl:30–3 (18 ref.)

The future of neuroleptic psychopharmacology. Ortiz A, et al. **J Clin Psychiatry** 1986 May;47 Suppl:3–11 (122 ref.)

Low–dose treatment strategies. Van Putten T, et al. **J Clin Psychiatry** 1986 May;47 Suppl:12–6 (21 ref.)

Neuroleptics and reserpine in refractory psychoses. Berlant JL. **J Clin Psychopharmacol** 1986 Jun;6(3):180–4

The prescription of discretionary antipsychotic medication by state mental hospital psychiatrists. Benson PR. **J Health Soc Behav** 1986 Mar; 27(1):28–43

Specific binding of 3H–SCH 23390 to dopamine D1 receptors in vivo. Andersen PH, et al. **Life Sci** 1986 Apr 21;38(16):1507–14

Evidence that the potential antipsychotic agent rimcazole (BW 234U) is a specific, competitive antagonist of sigma sites in brain. Ferris RM, et al. **Life Sci** 1986 Jun 23;38(25):2329–37

Involvement of extrapyramidal motor mechanisms in the suppression of locomotor activity by antipsychotic drugs: a comparison between the effects produced by pre– and post–synaptic inhibition of dopaminergic neurotransmission. Ahlenius S, et al. **Pharmacol Biochem Behav** 1986 May;24(5):1409–15

Fluperlapine vs haloperidol: a comparison of their neuroendocrinological profiles and the influence on serum lipids. Fleischhacker WW, et al. **Pharmacopsychiatry** 1986 May;19(3):111–4

Is conformational analysis a key to solve the structure––activity problem of neuroleptics? Misztal S, et al. **Pharmazie** 1986 Apr;41(4):277–81 (56 ref.)

Recent news in the chemistry and pharmacology of neuroleptics with special regard to the work carried out in Czechoslovakia. Protiva M. **Pharmazie** 1986 Apr;41(4):225–32 (179 ref.)

Relevance of polymorphic drug oxidation in the use of neuroleptics in schizophrenia. Tang SW. **Prog Clin Biol Res** 1986;214:303–11 (20 ref.)

Drug effects on serine metabolism in psychiatric patients. Waziri R, et al. **Psychiatry Res** 1986 Jun;18(2):119–26

Research methodology and the pharmacotherapy of the chronic schizophrenias. Ban TA, et al. **Psychopharmacol Bull** 1986; 22(1):36–41

An early phase II clinical trial of remoxipride in schizophrenia with measurement of plasma neuroleptic activity. Chouinard G, et al. **Psychopharmacol Bull** 1986;22(1):267–71

Pharmacological treatments of schizophrenia. Simpson GM. **Psychopharmacol Bull** 1986;22(1):33–5, 42–3

The AMDP system in international clinical trials: a double–blind comparison of fluperlapine and haloperidol. Woggon B, et al. **Psychopharmacol Bull** 1986;22(1):47–51

Involvement of different dopamine receptors in rat diphasic motility response to apomorphine. Vaccheri A, et al. **Psychopharmacology (Berlin)** 1986;89(3):265–8

First person account: a parent's view on enforcing medication. Slater E. **Schizophr Bull** 1986;12(2):291–2

[Pharmacokinetic study of isofloxythepin in animals] Poláková L, et al. **Cesk Farm** 1986 Apr;35(3):97–101 (Eng. Abstr.) **(Cze)**

[Determination of plasma concentrations in the drug treatment of psychoses] Knudsen P, et al. **Ugeskr Laeger** 1986 Mar 31; 148(14):849–52 **(Dan)**

[Pharmacokinetic aspects of the effects and interactions of various neuro– and psychotropic drugs] Melzacka M. **Postepy Hig Med Dosw** 1985 Nov–Dec;39(6):581–611 (204 ref.) (Eng. Abstr.) **(Pol)**

[Identification of neuroleptics by using the characteristics of the spatial organization of the EEG] Monakhov KK, et al. **Farmakol Toksikol** 1986 May–Jun;49(3):27–32 (Eng. Abstr.) **(Rus)**

[Pharmacological analysis of the serotonin– and glutamatergic mechanisms in the suppressive effect of neuroleptics on the pedal self–stimulation of the ventral tectum of the midbrain] Talalaenko AN, et al. **Farmakol Toksikol** 1986 May–Jun;49(3):40–3 (Eng. Abstr.) **(Rus)**

[Clinical aspects and significance of measuring concentrations of neuroleptics and antidepressants in the blood] Cheshkova E, et al. **Zh Nevropatol Psikhiatr** 1986;86(4):573–6 (Eng. Abstr.) **(Rus)**

TRANQUILIZING AGENTS, MINOR

An interim multicentre report on 677 anxious geriatric out–patients treated with buspirone. Napoliello MJ. **Br J Clin Pract** 1986 Feb;40(2):71–3

Neuroanatomical site of the inhibitory influence of anxiolytic drugs on central serotonergic transmission. Nishikawa T, et al. **Brain Res** 1986 Apr 16;371(1):123–32

Syntheses of 3,4–dihydro–2H–1,4–benzoxazine–2–acetates and related compounds. Masuoka Y, et al. **Chem Pharm Bull (Tokyo)** 1986 Jan; 34(1):130–9

Psychopharmacology and psychotherapy in the treatment of anxiety. Freedman AM. **Curr Psychiatr Ther** 1986;23:101–18 (47 ref.)

Buspirone decreases the activity of 5–hydroxytryptamine–containing dorsal raphe neurons in–vitro. Trulson ME, et al. **J Pharm Pharmacol** 1986 May;38(5):380–2

Discriminative stimulus effects of atypical anxiolytics in baboons and rats. Ator NA, et al. **J Pharmacol Exp Ther** 1986 May;237(2):393–403

Anxiolytic effects of progesterone are sexually dimorphic. Rodriguez–Sierra JF, et al. **Life Sci** 1986 May 19;38(20):1841–5

The anxiolytic but not the sedative properties of tracazolate are reversed by the benzodiazepine receptor antagonist, Ro 15–1788. File SE, et al. **Neuropsychobiology** 1985;14(4):193–7

Serotonergic mechanisms in the behavioral effects of buspirone and gepirone. Eison AS, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):701–7

The effects of Ro 15–1788 on anxiolytic self–administration in the rhesus monkey. Johanson CE, et al. **Pharmacol Biochem Behav** 1986 Apr; 24(4):855–9

Are serotonergic neurons involved in the control of anxiety and in the anxiolytic activity of benzodiazepines? Thiebot MH. **Pharmacol Biochem Behav** 1986 May;24(5):1471-7

Interaction of buspirone and dopaminergic agents on punished behavior of pigeons. Witkin JM, et al. **Pharmacol Biochem Behav** 1986 Mar; 24(3):751-6

Effects of Suanzaorentang on behavior changes and central monoamines. Hsieh MT, et al. **Proc Natl Sci Counc Repub China [B]** 1986 Jan; 10(1):43-8

Open trial of buspirone in the treatment of major depressive disorder. Schweizer EE, et al. **Psychopharmacol Bull** 1986;22(1):183-5

[Clinical methods for studying anxiolytic agents] Guelfi JD. **Therapie** 1986 Jan-Feb;41(1):37-41 (Eng. Abstr.) **(Fre)**

[Occupation of central benzodiazepine receptors and anxiety] Le Fur G, et al. **Therapie** 1986 Jan-Feb;41(1):43-7 (Eng. Abstr.) **(Fre)**

[Critical study of the clinical actions of 5-HTP] Teixeira M. **Actas Luso Esp Neurol Psiquiatr Cienc Afines** 1986 Mar-Apr; 14(2):104-12 **(Por)**

[The role of GABA-benzodiazepine receptor complex in affecting the anxiolytic effect of 3-hydroxypyridines--new non-benzodiazepine tranquilizers] Voronina TA, et al. **Biull Eksp Biol Med** 1986 May; 101(5):571-3 (Eng. Abstr.) **(Rus)**

TRANYLCYPROMINE

Synergistic action of alprazolam with tranylcypromine in drug-resistant atypical depression with panic attacks. Ries RK, et al. **Biol Psychiatry** 1986 May;21(5-6):522-6

Rapid antidepressant effect of addition of lithium to tranylcypromine. Tariot PN, et al. **J Clin Psychopharmacol** 1986 Jun;6(3):165-7

Detection and quantitation of a ring-hydroxylated metabolite of the antidepressant drug tranylcypromine. Baker GB, et al. **J Neural Transm** 1986;65(3-4):233-43

Effects of tranylcypromine enantiomers on monoamine uptake and release and imipramine binding. Tuomisto J, et al. **J Neural Transm** 1986; 65(2):135-45

Regional cerebral pharmacokinetics of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine as examined by positron emission tomography in a baboon is altered by tranylcypromine. Moerlein SM, et al. **Neurosci Lett** 1986 May 15;66(2):205-9

TRIAZOLAM

The carry-over effects of triazolam compared with nitrazepam and placebo in acute emergency driving situations and in monotonous simulated driving. Laurell H, et al. **Acta Pharmacol Toxicol (Copenh)** 1986 Mar;58(3):182-6

Repeated administration of diazepam and triazolam to subjects with histories of drug abuse. Roache JD, et al. **Drug Alcohol Depend** 1986 May;17(1):15-29

Bioavailability of two oral formulations of triazolam using radioreceptor assay. Lapka R, et al. **Pharmazie** 1986 Apr;41(4):256-7

TRIFLUOPERAZINE

Effect of trifluoperazine and other drugs on matrix vesicle formation by chicken growth plate chondrocytes in primary cell culture. Schalk EM, et al. **Biochem Pharmacol** 1986 Jul 15;35(14):2373-9

The high affinity calcium inhibition of parathyroid adenylate cyclase is not calmodulin dependent. Oldham SB, et al. **Calcif Tissue Int** 1986 May;38(5):275-81

Development and application of a specific radioimmunoassay for trifluoperazine N4'-oxide to a kinetic study in humans. Aravagiri M, et al. **J Pharmacol Exp Ther** 1986 May;237(2):615-22

Effect of trifluoperazine on rabbit cortical collecting tubular response to vasopressin. Dillingham MA, et al. **J Physiol (Lond)** 1986 Mar; 372:41-50

Effects of calmodulin antagonists Cd2+ and trifluoperazine on mixed lymphocyte culture cell-mediated lysis and antibody-dependent cell cytolysis. Wolff CH. **Scand J Immunol** 1986 Jun;23(6):663-8

Effect of heparin on platelet aggregation inhibited by PGI2, trifluoperazine and verapamil. Weber DR, et al. **Thromb Res** 1986 May 15;42(4):477-87

TRIMEPRAZINE

Relative bioavailability of trimeprazine tablets investigated in man using HPLC with electrochemical detection. Hu OY, et al. **J Pharm Pharmacol** 1986 Mar;38(3):172-6

[Biotransformation of alimemazine] Pfeifer S, et al. **Pharmazie** 1986 Feb; 41(2):111-3 (Eng. Abstr.) **(Ger)**

TRYPTAMINES

Reevaluation of the products of tryptamine catalyzed by rabbit liver N-methyltransferases. Crooks PA, et al. **Biochem Pharmacol** 1986 May 1;35(9):1600-3

Tryptamine depletion in the rat striatum following electrolytic lesions of the substantia nigra. Juorio AV, et al. **Brain Res** 1986 Apr 23; 371(2):385-9

Characterization and quantitative autoradiography of [3H]tryptamine binding sites in rat brain. Kaulen P, et al. **Brain Res** 1986 Feb 26; 366(1-2):72-88

Effect of tryptamine on the behavior of mice. Sugimoto Y, et al. **J Pharmacobiodyn** 1986 Jan;9(1):68-73

Effects of melatonin and 5-methoxytryptamine on sleep-wake patterns in the male rat. Mirmiran M, et al. **J Pineal Res** 1986;3(2):135-41

Physiological responses of guinea-pig myenteric neurons secondary to the release of endogenous serotonin by tryptamine. Takaki M, et al. **Neuroscience** 1985 Sep;16(1):223-40

TRYPTOPHAN

Tryptophan in horseradish peroxidase. Ohlsson PI, et al. **Acta Chem Scand [B]** 1986 Apr;40(4):257-61

Stability of tryptophan in total parenteral nutrient solutions [letter] Johnston SJ. **Am J Hosp Pharm** 1986 Jun;43(6):1424

Maternal dietary substrates and human fetal biophysical activity. I. The effects of tryptophan and glucose on fetal breathing movements. Devoe LD, et al. **Am J Obstet Gynecol** 1986 Jul;155(1):135-9

The adenosine triphosphate-pyrophosphate isotopic exchange reaction: a tool for determination of tryptophan. Trezeguet V, et al. **Anal Biochem** 1986 May 1;154(2):618-23

Effect of sustained exercise on concentrations of plasma aromatic and branched-chain amino acids and brain amines. Acworth I, et al. **Biochem Biophys Res Commun** 1986 May 29;137(1):149-53

Quantification of the importance of individual steps in the control of aromatic amino acid metabolism. Salter M, et al. **Biochem J** 1986 Mar 15;234(3):635-47

Tryptophanyl adenylate formation by tryptophanyl-tRNA synthetase from Escherichia coli. Merle M, et al. **Biochemistry** 1986 Mar 11; 25(5):1115-23

Detection of energy transfer between tryptophan residues in the tubulin molecule and bound bis(8-anilinonaphthalene-1-sulfonate), an inhibitor of microtubule assembly, that binds to a flexible region on tubulin. Prasad AR, et al. **Biochemistry** 1986 Jun 17;25(12):3536-40

Molecular basis for the anti-sickling activity of aromatic amino acids and related compounds: a proton nuclear magnetic resonance investigation. Russu IM, et al. **Biochemistry** 1986 Feb 25;25(4):808-15

Spin-lattice relaxation in the triplet state of the buried tryptophan residue of ribonuclease T1. Ghosh S, et al. **Biophys J** 1986 Mar; 49(3):753-60

Stimulation of tryptophan uptake into brain microvessels by D-glutamine. Gorgievski-Hrisoho M, et al. **Brain Res** 1986 Mar 5;367(1-2):395-7

Brain 5-hydroxytryptamine and plasma testosterone in L-tryptophan treated rats. Biswas NM, et al. **Endocr Res** 1985;11(3-4):131-7

Separation of tryptophan pyrrolooxygenase into three molecular forms. A study of their substrate specificities using tryptophyl-containing peptides and proteins. Camoretti-Mercado B, et al. **Eur J Biochem** 1986 Apr 15;156(2):317-25

The interaction of the trp repressor from Escherichia coli with L-tryptophan and indole propanoic acid. Lane AN. **Eur J Biochem** 1986 Jun 2;157(2):405-13

Plasma free tryptophan concentration in children with attention deficit disorder. Hoshino Y, et al. **Folia Psychiatr Neurol Jpn** 1985; 39(4):531-5

Neurotransmitter precursor therapies in affective disorders. von Lerber-Good WF. **Int J Vitam Nutr Res [Suppl]** 1986;29:69-82 (39 ref.)

Tryptophan requirement of growing swine as determined by the oxidation of an indicator amino acid. Lin FD, et al. **J Anim Sci** 1986 Mar; 62(3):660-4

Novel form of transcription attenuation regulates expression the Bacillus subtilis tryptophan operon. Shimotsu H, et al. **J Bacteriol** 1986 May; 166(2):461-71

Evidence for involvement of tryptophan residue in the low-affinity saccharide binding site of ricin D. Hatakeyama T, et al. **J Biochem (Tokyo)** 1986 Apr;99(4):1049-56

Chromatographic separation and determination of tryptophan in food-stuffs after barytic hydrolysis using Fractogel TSK HW 40 S. Huet JC, et al. **J Chromatogr** 1986 Mar 21;355(2):451-5

Influence of tryptophan loading on urinary excretion of anthranilic acid and 3-hydroxyanthranilic acid by men and women as determined by alkali flame ionization gas chromatography. van der Poll JM, et al. **J Chromatogr** 1986 Mar 7;375(2):213-23

The serotonin syndrome: case responsive to propranolol [letter] Guzé BH, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):119-20

Dissociation of depressive mood and vegetative symptoms during treatment with L-tryptophan [letter] Siddiqui AR, et al. **J Clin Psychopharmacol** 1986 Apr;6(2):118-9

Repair of tryptophan radicals by antioxidants. Jovanovic SV, et al. **J Free Radic Biol Med** 1985;1(2):125-9

Peripheral and central short-term effects of fusaric acid, a DBH inhibitor, on tryptophan and serotonin metabolism in the rat. Chaouloff F, et al. **J Neural Transm** 1986;65(3-4):219-32

Exogenous tryptophan increases synthesis, storage, and intraneuronal metabolism of 5-hydroxytryptamine in the rat hypothalamus.

Lookingland KJ, et al. **J Neurochem** 1986 Jul;47(1):205-12

L-tyrosine and L-tryptophan transport in red blood cells in normal subjects. Effects of other amino acids, temperature and medium of incubation. Widmer J, et al. **Neuropsychobiology** 1986;15(1):7-12

Interaction of tryptophan with lecithin liposomes: NMR and turbidity studies. Viti V, et al. **Physiol Chem Phys Med NMR** 1985; 17(4):413-20

[Erythrocyte membrane transport of L-tyrosine and L-tryptophan in 66 patients with depressive syndromes. Preliminary results] Pringuey D, et al. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):131-40 (Eng. Abstr.) **(Fre)**

TRYPTOPHAN HYDROXYLASE

AGN 2979 [3(3-methoxyphenyl)-3-(3-dimethylaminopropyl)-4, 4-dimethylpiperidine-2,6-dione]. An inhibitor of the activation of tryptophan hydroxylase. Boadle-Biber MC, et al. **Biochem Pharmacol** 1986 May 1;35(9):1521-6

Effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on striatal tyrosine hydroxylase and tryptophan hydroxylase in rat. Matsuda LA, et al. **Neuropharmacology** 1986 Mar;25(3):249-55

TYROSINE

Identification of tyrosine O-sulfate in proteins by reverse-phase high-performance liquid chromatography: use of base hydrolysis combined with precolumn derivatization using phenyl isothiocyanate. Christie DL, et al. **Anal Biochem** 1986 Apr;154(1):92-9

Pharmacokinetics of tiropramide after single doses in man. Arigoni R, et al. **Arzneimittelforschung** 1986 Apr;36(4):738-44

Effect of sustained exercise on concentrations of plasma aromatic and branched-chain amino acids and brain amines. Acworth I, et al. **Biochem Biophys Res Commun** 1986 May 29;137(1):149-53

The conversion of native adenylylated glutamine synthetase into phosphotyrosine enzyme by micrococcal nuclease. Kimura K, et al. **Biochem Biophys Res Commun** 1986 Jun 13;137(2):716-21

Tyr1-substituted and fluorescent Pya1-enkephalins bind strongly and selectively to mu and delta opiate receptors. Mihara H, et al. **Biochem Biophys Res Commun** 1986 May 14;136(3):1170-6

Quantification of the importance of individual steps in the control of aromatic amino acid metabolism. Salter M, et al. **Biochem J** 1986 Mar 15;234(3):635-47

K+-dependent stimulation of tyrosine hydroxylation in striatal slices: role of Ca2+/calmodulin and Ca2+/phospholipid-dependent mechanisms. Knorr AM, et al. **Biochem Pharmacol** 1986 Jun 15;35(12):1929-32

Determination of chemical properties of individual histidine and tyrosine residues of concanavalin A by competitive labeling with 1-fluoro-2,4-dinitrobenzene. Jackson GE, et al. **Biochemistry** 1986 Apr 8;25(7):1657-62

Tyrosine transport into isolated rat brain synaptosomes. Ionic dependence and kinetic studies. Diez-Guerra FJ, et al. **Biochim Biophys Acta** 1986 May 28;857(2):209-16

Radioiodination of tyrosine residue(s) of ox testis and of wheat germ calmodulins. Dutoit C, et al. **Biochim Biophys Acta** 1986 Jun 5; 871(2):130-6

The effect of tyrosine conjugation on the critical micellar concentration of free and glycine-conjugated bile salts. Mills CO, et al. **Biochim Biophys Acta** 1986 May 21;876(3):677-83

Synthesis and biliary excretion of tyrosine-conjugated bile salts in Wistar rats. Mills CO, et al. **Biochim Biophys Acta** 1986 May 21; 876(3):667-76

In vivo studies on the formation of m-tyrosine and o-tyrosine from L-phenylalanine in rats. Ishimitsu S, et al. **Chem Pharm Bull (Tokyo)** 1986 Feb;34(2):768-74

In vivo formation of diiodotyrosine by extrathyroidal thyroxine ether-link cleavage and effects of mononitrotyrosine on this pathway in the rat. Meinhold H, et al. **Endocrinology** 1986 Jun;118(6):2305-11

Fluorescence from L-tyrosine and its quenching by phosphate ions and deoxyribonucleic acid. Verma NC. **Indian J Biochem Biophys** 1985 Aug; 22(4):218-22

Neurotransmitter precursor therapies in affective disorders. von Lerber-Good WF. **Int J Vitam Nutr Res** [**Suppl**] 1986;29:69-82 (39 ref.)

Evidence of the activity of tyrosine kinase(s) and of the presence of phosphotyrosine proteins in pea plantlets. Torruella M, et al. **J Biol Chem** 1986 May 25;261(15):6651-3

High-performance liquid chromatography of tyrosine-containing peptides by pre-column derivatization involving formylation followed by fluorescence reaction with 1,2-diamino-4,5-dimethoxybenzene. Ishida J, et al. **J Chromatogr** 1986 Mar 28;356(1):171-7

Tyrosine phosphorylation of a 66,000 Mr soluble protein in lectin-activated human peripheral blood T lymphocytes. Wedner HJ, et al. **J Immunol** 1986 Jun 1;136(11):4226-31

Phosphorylation of an Escherichia coli protein at tyrosine. Cortay JC, et al. **J Mol Biol** 1986 Jan 20;187(2):305-8

L-tyrosine and L-tryptophan transport in red blood cells in normal subjects. Effects of other amino acids, temperature and medium of incubation. Widmer J, et al. **Neuropsychobiology** 1986;15(1):7-12

Two juxtaposed tyrosyl-OH groups participate in phi X174 gene A protein catalysed cleavage and ligation of DNA. van Mansfeld AD, et al. **Nucleic Acids Res** 1986 May 27;14(10):4229-38

Cholecystokinin-associated COOH-terminal peptides are fully sulfated in pig brain. Eng J, et al. **Proc Natl Acad Sci USA** 1986 May; 83(9):2832-5

Adjuvanticity of stearyl tyrosine on inactivated poliovirus vaccine. Landi S, et al. **Vaccine** 1986 Jun;4(2):99-104

Tyrosine biosynthesis in Sorghum bicolor: isolation and regulatory properties of arogenate dehydrogenase. Connelly JA, et al. **Z Naturforsch** [C] 1986 Jan-Feb;41(1-2):69-78

Tyrosine biosynthesis in Sorghum bicolor: characteristics of prephenate aminotransferase. Siehl DL, et al. **Z Naturforsch** [C] 1986 Jan-Feb; 41(1-2):79-86

[Effect of tyrosine on serum concentrations of LH, FSH and testosterone in adult men] Ni J, et al. **Sheng Li Hsueh Pao** 1985 Jun;37(3):303-6 (Eng. Abstr.) **(Chi)**

[Erythrocyte membrane transport of L-tyrosine and L-tryptophan in 66 patients with depressive syndromes. Preliminary results] Pringuey D, et al. **Acta Psychiatr Belg** 1986 Mar-Apr;86(2):131-40 (Eng. Abstr.) **(Fre)**

[Effect of tiropramide on solid gastric emptying time in man] Corinaldesi R, et al. **Minerva Med** 1986 Apr 21;77(17):675-7 (Eng. Abstr.) **(Ita)**

[Hydrophily of surface non-polar fragment in the protein molecule--a new approach to the stabilization of enzymes. Chemical modification of tyrosine residues in trypsin] Mozhaev VV, et al. **Dokl Akad Nauk SSSR** 1986;288(4):1006-9 **(Rus)**

TYROSINE AMINOTRANSFERASE

Inhibition of aromatic L-amino acid decarboxylase and tyrosine aminotransferase by the monoamine oxidase inhibitor phenelzine. Dyck LE, et al. **J Neurochem** 1986 Jun;46(6):1899-903

The effect of age on the induction of tyrosine aminotransferase and tryptophan oxygenase genes by physiological stress. Wellinger R, et al. **Mech Ageing Dev** 1986 Apr;34(2):203-17

TYROSINE HYDROXYLASE

Modulation by basic polypeptides of ATP-induced activation of tyrosine hydroxylase prepared from bovine adrenal medulla. Morita K, et al. **Arch Biochem Biophys** 1986 May 15;247(1):84-90

Relationships between catecholaminergic neurons and cholecystokinin-containing neurons in the caudal part of the dorsomedial medulla oblongata of the rat: light and electron microscopic observations by the 'mirror technique'. Kubota Y, et al. **Brain Res** 1986 Apr 9;370(2):343-8

Ultrastructural analysis of synapses involving tyrosine hydroxylase-containing neurons in the ventral periventricular hypothalamus of the macaque. Thind KK, et al. **Brain Res** 1986 Feb 26;366(1-2):37-52

Localization of the human tyrosine hydroxylase gene to 11p15: gene duplication and evolution of metabolic pathways. Craig SP, et al. **Cytogenet Cell Genet** 1986;42(1-2):29-32

Time course of the changes of TH mRNA in rat brain and adrenal medulla after a single injection of reserpine. Biguet NF, et al. **EMBO J** 1986 Feb;5(2):287-91

Evidence for a specific effect of BHT 920, an azepine derivative, on tyrosine hydroxylase in the dopaminergic system of the rat. Jennewein HM, et al. **Eur J Pharmacol** 1986 Apr 29;123(3):363-9

Electron microscopic analysis of tyrosine hydroxylase, dopamine-beta-hydroxylase and phenylethanolamine-N-methyltransferase immunoreactive innervation of the hypothalamic paraventricular nucleus in the rat. Liposits Z, et al. **Histochemistry** 1986;84(2):105-20

Distribution of tyrosine hydroxylase and neuropeptide Y-like immunoreactive neurons in rabbit medulla oblongata, with attention to colocalization studies, presumptive adrenaline-synthesizing perikarya, and vagal preganglionic cells. Blessing WW, et al. **J Comp Neurol** 1986 Jun 8;248(2):285-300

The distribution of tyrosine hydroxylase, dopamine-beta-hydroxylase, and phenylethanolamine-N-methyltransferase immunoreactive neurons in the feline medulla oblongata. Reiner PB, et al. **J Comp Neurol** 1986 Jun 22;248(4):518-31

A monoclonal antibody against tyrosine hydroxylase: application in light and electron microscopy. Semenenko FM, et al. **J Histochem Cytochem** 1986 Jun;34(6):817-21

An improved method for tyrosine hydroxylase immunolabeling of catecholamine cells in whole mounted rat retina. Versaux-Botteri C, et al. **J Histochem Cytochem** 1986 Jun;34(6):743-7

A simplified 14CO2-trapping microassay for tyrosine hydroxylase activity. Shen RS, et al. **J Neurosci Methods** 1986 Apr;16(2):163-73

Inhibitory action of hydralazine on catecholamine-synthesizing enzymes prepared from bovine adrenal medulla. Morita K, et al. **Jpn J Pharmacol** 1986 Mar;40(3):445-53

In situ activity and phosphorylation of tyrosine hydroxylase in the median eminence. Porter JC. **Mol Cell Endocrinol** 1986 Jun;46(1):21-7

Dopamine autoreceptor regulation of the kinetic state of striatal tyrosine hydroxylase. Strait KA, et al. **Mol Pharmacol** 1986 Jun;29(6):561–9

Some catecholamine inhibitors do not cause accumulation of nuclear estrogen receptors in rat hypothalamus and anterior pituitary gland. Blaustein JD, et al. **Neuroendocrinology** 1986;43(2):143–9

Effect of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) on striatal tyrosine hydroxylase and tryptophan hydroxylase in rat. Matsuda LA, et al. **Neuropharmacology** 1986 Mar;25(3):249–55

Anatomical evidence for interactions between catecholamine– and adrenocorticotropin–containing neurons. Baker H, et al. **Neuroscience** 1986 Feb;17(2):469–84

Restricted diffusion of tyrosine hydroxylase and phenylethanolamine N–methyltransferase from digitonin–permeabilized adrenal chromaffin cells. Kelner KL, et al. **Proc Natl Acad Sci USA** 1986 May; 83(9):2998–3002

[Catecholaminergic centers of the sheep encephalon. Immunocytochemistry. II. Mesencephalon and diencephalon] Tillet Y, et al. **C R Acad Sci [III]** 1986;302(5):151–6 (Eng. Abstr.) **(Fre)**

[Topography of the catecholamine neurons in the brain stem of the human fetus: an immunohistochemical study using antibodies to tyrosine hydroxylase] Takahashi H, et al. **No To Shinkei** 1986 Jan; 38(1):87–97 (Eng. Abstr.) **(Jpn)**

VASOPRESSINS

Bradykinin and vasopressin stimulate Na+–K+–Cl– cotransport in cultured endothelial cells. Brock TA, et al. **Am J Physiol** 1986 Jun; 250(6 Pt 1):C888–95

Phorbol esters, vasopressin and angiotensin II block alpha 1–adrenergic action in rat hepatocytes. Possible role of protein kinase C. Garcia–Sainz JA, et al. **Biochim Biophys Acta** 1986 Jun 16;887(1):69–72

Homologous and heterologous desensitization of one of the pathways of the alpha 1–adrenergic action. Effects of epinephrine, vasopressin, angiotensin II and phorbol 12–myristate 13–acetate. Garcia–Sainz JA, et al. **Biochim Biophys Acta** 1986 Jun 16;887(1):73–9

Vasopressin and/or glucagon rapidly increases mitochondrial calcium and oxidative enzyme activities in the perfused rat liver. Assimacopoulos–Jeannet F, et al. **J Biol Chem** 1986 Jul 5; 261(19):8799–804

Inhibition by lithium of the hydroosmotic action of vasopressin in the isolated perfused cortical collecting tubule of the rabbit. Cogan E, et al. **J Clin Invest** 1986 May;77(5):1507–14

Fastigial nucleus stimulation and concurrent activation of cardiovascular receptors; differentiate effects on arterial pressure, heart rate and vasopressin release. Del Bo A, et al. **J Hypertension [Suppl]** 1984 Dec; 2(3):S49–51

Pressor effect of centrally administered neuropeptide Y in rats: role of sympathetic nervous system and vasopressin. Vallejo M, et al. **Life Sci** 1986 May 19;38(20):1859–66

Effects of dopamine and vasopressin on histamine–induced increases in macromolecular permeability in the canine forelimb. Adamski SW, et al. **Microcirc Endothelium Lymphatics** 1985 Feb;2(1):27–39

Central adrenergic control of vasopressin release. Brooks DP, et al. **Neuroendocrinology** 1986;42(5):416–20

Dorsal medullary oxytocin, vasopressin, oxytocin antagonist, and TRH effects on gastric acid secretion and heart rate. Rogers RC, et al. **Peptides** 1985 Nov–Dec;6(6):1143–8

Role of cholecystokinin in corticotropin release: coexistence with vasopressin and corticotropin–releasing factor in cells of the rat hypothalamic paraventricular nucleus. Mezey E, et al. **Proc Natl Acad Sci USA** 1986 May;83(10):3510–2

VASOTOCIN

Ultrastructural characterization of neurosecretory fibres immunoreactive for vasotocin, isotocin, somatostatin, LHRH and CRF in the pituitary of a teleost fish, Poecilia latipinna. Batten TF. **Cell Tissue Res** 1986; 244(3):661–72

Plasma levels of arginine vasotocin, prolactin, aldosterone and corticosterone during prolonged dehydration in the domestic fowl: effect of dietary NaCl. Arnason SS, et al. **J Comp Physiol [B]** 1986; 156(3):383–97

Calcium–independent stimulation of glycogenolysis by arginine vasotocin and catecholamines in liver of the axolotl (Ambystoma mexicanum) in vitro. Janssens PA, et al. **J Endocrinol** 1986 Apr;109(1):75–84

VIOLENCE

Acute care for the violent patient. Reid GW. **J Arkansas Med Soc** 1986 Apr;82(11):541–3

VISUAL PERCEPTION

Effects of lithium on visual perception in manic–depressive patients without acute symptomatology. Kropf D, et al. **Neuropsychobiology** 1986;15(1):34–42

WAKEFULNESS

Effects of brotizolam on the sleep–waking cycle of the cat. Kuhn FJ. **Arzneimittelforschung** 1986 Mar;36(3A):522–7

Alpha adrenergic system in medial preoptic area involved in sleep–wakefulness in rats. Mohan Kumar V, et al. **Brain Res Bull** 1986 Apr;16(4):463–8

Effects of melatonin and 5–methoxytryptamine on sleep–wake patterns in the male rat. Mirmiran M, et al. **J Pineal Res** 1986;3(2):135–41

[EEG studies in rats to determine the threshold levels of chlorpromazine with respect to the state of vigilance] Bergschicker R, et al. **Biomed Biochim Acta** 1986;45(3):401–12 (Eng. Abstr.) **(Ger)**

ZIMELIDINE

Comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressed outpatients. Biochemical aspects. Nyström C, et al. **Acta Psychiatr Scand** 1986 Feb;73(2):133–8

The effects of desipramine, zimelidine, electroconvulsive treatment and lithium on rat brain biogenic amines: a comparison with peripheral changes. Karoum F, et al. **Eur J Pharmacol** 1986 Mar 4; 121(3):377–85

A double–blind comparative trial of zimelidine, amitriptyline, and placebo in patients with mixed anxiety and depression. Amsterdam JD, et al. **Pharmacopsychiatry** 1986 May;19(3):115–9

Acute effects of different antidepressant drugs on saliva secretion and accommodation range. Knorring L, et al. **Pharmacopsychiatry** 1986 May; 19(3):106–10

*U.S. GOVERNMENT PRINTING OFFICE: 1986-491-327:21004

The *Psychopharmacology Bulletin* is available on subscription from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Subscription price $19.00 per year for the United States. All other countries add $4.75 for postage. This price was in effect at time of printing. Prices are subject to change. Please make check or money order payable to the Superintendent of Documents. An annual subscription for four quarterly issues begins with the next issue following receipt of the order. Single copies and back issues may also be ordered from the Superintendent of Documents. The expiration date is printed on the top line of the address label. Change of address and complaints about non-receipt of issues should be sent to the Superintendent of Documents and should include the old address, preferably a mailing label, as well as the new address.

ORDER FORM Mail To: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

Enclosed is $________ ☐ check,
(U.S. Currency Only)
☐ money order, or charge to my
Deposit Account No.
☐☐☐☐☐☐☐–☐

Order No.______________

VISA
master charge

Credit Card Orders Only

Total charges $________ Fill in the boxes below

Credit Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiration Date Month/Year ☐☐☐☐

Please enter my subscription to **PSYCHOPHARMACOLOGY BULLETIN** [**PSBU**]

☐ $19.00 domestic. ☐ $23.75 foreign

Name—First, Last

Street address

Company name or additional address line

City **State** **ZIP Code**

(or Country)

PLEASE PRINT OR TYPE

For Office Use Only.

	Quantity	Charges
Enclosed		
To be mailed		
Subscriptions		
Postage		
Foreign handling		
MMOB		
OPNR		
UPNS		
Discount		
Refund		

**DEPARTMENT OF
HEALTH & HUMAN SERVICES**

**Public Health Service
Alcohol, Drug Abuse, and
Mental Health Administration
Rockville, MD 20857**

**Official Business
Penalty for Private Use $300**

SPECIAL FOURTH CLASS MAIL
POSTAGE AND FEES PAID
PHS/ADAMHA
PERMIT NO. G-283

DHHS Publication No. (ADM) 86-173
Printed 1986